Blood Flow Increase in 9L Brain Tumors in Response to Radiation Therapy and Chemotherapy as Detected by Arterial Spin Labeling MRI

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Introduction: Tumor blood flow (BF) affects its survival, metastatic potential, and sensitivity to radiotherapy and chemotherapeutic agents. Steady BF and high oxygen levels within a tumor are crucial for effective treatments. Detection of tumor BF is thus important for characterizing tumor microenvironment, evaluating its response to therapies, and assisting in the design of new therapeutic trials. Arterial spin label (ASL) technique[1] is able to non-invasively measure blood flow in humans and experimental animal models[2,3]. This is important for study of tumors as it obviates the need for contrast injection. For ASL, an MRI RF pulse magnetically labels arterial blood outside the imaging section. Subtraction of a control image without labeling results in a perfusion-weighted image, and BF can also be quantified. In this work, the T_1 and T_2 relaxation times, apparent diffusion coefficients (ADC), and BF were quantified in the rat model of 9L brain tumors, and the responses of therapy was evaluated with respect to treatment method, dosage, and tumor age.

Materials & Methods: Fisher 344 rats (n = 44) received 9L gliosarcoma cells (25,000 cells/2 µl) by stereotactic injection to right caudate/putamen. On post-implantation day (PID) 7 or 9, twenty-two tumor-bearing rats received either 15 Gy cranial irradiation as a single fraction (Shepherd Mark I 137) under ketamine + xylazine sedation or BCNU diluted in saline at a dose of 10 mg/kg body weight as a single i.p. injection. Starting PID 9, isoflurane anesthetized rats were imaged using a horizontal bore 4.7 T Biospec animal imager. Single-shot SE EPI was used for data acquisition (matrix 64×64, FOV 28×28 mm^2, slice thickness 2 mm). Four MRI scripts are: (i) Perfusion map (continuous arterial spin-labeling (CASL)[1], saturation time 2 s, power 5.9 µT, TR 5 s, TE 30 ms, the distance between labeling and imaging slice 10-20 mm, NA 16); (ii) T_2 map (spin echo, TR 3 s, TE 30-90 ms, NA 4); (iii) T_1 map (inversion recovery, TR 3 s, TE 30 ms, TI 0.05-3.5 s, NA 4); and (iv) ADC map (single-shot trace diffusion weighting, TR 3 s, TE 80 ms, b-value 0-1000 s/mm^2, NA 8). Quantitative analysis was performed on three treatment groups (radiotherapy on PID 7, radiotherapy on PID 9, BCNU on PID 9) including control animals of the same age, which are called group 1, 2, or 3, respectively.

Results & Discussion: Fig. 1 shows an example of the comparison of the acquired maps on post-treatment day (PTD) 5 from group 1. The effect of treatment is obvious with respect to control, although tumor volume following treatment remains the same or increases slightly with time for most animals. Fig. 2 summarizes the experimental results for group 1. There is a significant decrease in T_1 and significant substantial increase in BF, but there are no significant changes in T_2 and ADC, when comparing treated and untreated tumors. This increased BF starts earlier than T_1, peaks on PTD 5, and persists till PTD 7 when the surviving animals were euthanized. The difference in T_1, T_2, and ADC is very small for the treated and untreated contralateral normal appearing brain tissue, but a large increase in BF can also be detected for contralateral regions in radiated animals. Finally, when comparing the three treatment groups, the results show that the tumor changes in response to the therapies have a different trend for these four MR measures, as shown in Table 1 for PTD 4. Note that the statistical interpretation is based on limited animals, especially for group 2 & 3. Although further studies are required, the trend from preliminary data indicates that BF increases consistently for all treated tumors. Changes in T_1, T_2, and ADC in the tumor associated with the treatment[4] depend on water content and necrosis. Previous studies[5,6] in the RIF-1 tumor model have indirectly demonstrated an increase in BF post-irradiation by a fall in intra-tumoral lactate levels as seen by ^{31}P and ^{1}H MR spectroscopy. The decreased lactate levels in response to radiation dose of 20 Gy persisted for 48 hours and was attributed to improvement in BF leading to re-oxygenation of the tumor and subsequent fall in lactate concentration due to its decreased production, better clearance, or both.

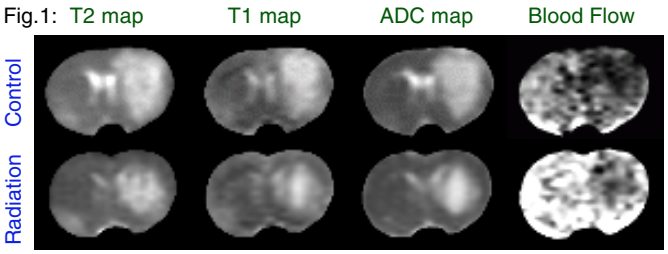
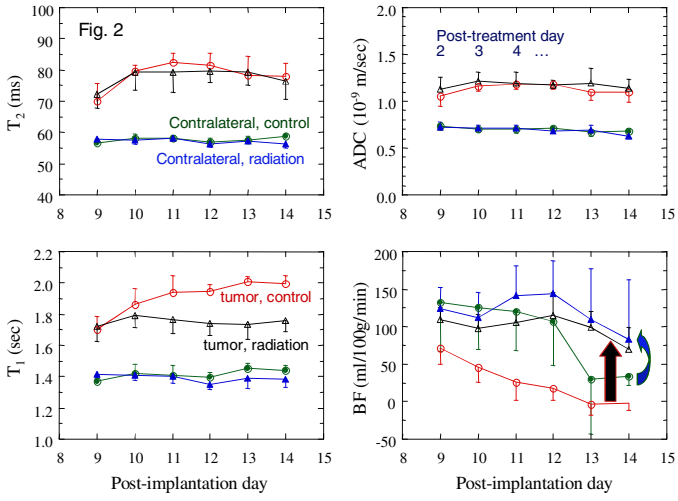


Table 1. Treated compared to untreated tumors, increase (+) and decrease (-), significant (blue) and insignificant (black), PTD 4.

	T2	T1	ADC	BF
Group 1	-4%	-9%	+0.4%	+315%
Group 2	+3%	-5%	+14%	+338%
Group 3	+10%	-6%	+6%	+65%



Conclusion: ASL imaging offers a novel method to assess the tumor response to therapy by detecting an increase in BF in tumor that occurs more consistently than other MR measures.

References: 1) Williams et al. PNAS 1992;89:212. 2) Silva et al. MRM 2000;44:169. 3) Moffat et al. JMRI 2005;21:290. 4) Chenevert et al. Mol Imag 2002;1:336. 5) Tozer et al. Int J Rad Oncol Biol Phys 1989;16:155. 6) Bhujwalla et al. Int J Rad Oncol Biol Phys 1996;36:635.