Evidence of Multiexponential T_2 in Rat Glioblastoma

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Introduction: The NMR signal has been shown to exhibit multiexponential T_2 (MET_2) decay in a number of tissues, arising from a combination of microanatomical water compartition and slow intercompartmental exchange. The goal of MET_2 analysis is to decompose bulk NMR signal into components that represent underlying tissue compartments that exist on a sub-voxel scale. To date, no reports have been made on MET_2 in tumors, yet such measurements may yield valuable information about the tumor microenvironment not available from conventional techniques. Thus, the goal of this preliminary study was to determine whether MET_2 analysis could be used to resolve signal arising from multiple tissue compartments in a rat glioblastoma tumor model *in vivo*.

Methods: All procedures were approved by our Institution's Animal Care and Usage Committee. Eleven male Wistar rats were immobilized and anesthetized with a 2%/98% isofluorane/oxygen mixture. The rats were inoculated with 1×10^5 C6 gliosarcoma cells using a 10-mL gastight syringe approximately one mm anterior and two mm lateral to bregma on the right side of the head, at a depth of 3 mm relative to the dural surface. C6 is a common gliosarcoma model that is widely used in experimental neuro-oncology to evaluate tumor growth, invasion, migration, and blood-brain-barrier disruptions, and has been used extensively to investigate the efficacy of various therapies including chemotherapy and radiation therapy [1].

Ten days after surgery, animals were imaged using a 7.0-T, 16-cm bore Varian Inova spectrometer and 63-mm volume RF coil. During imaging, animals were anesthetized with isofluorane and physiological signals monitored. For each rat, a single 1.5-mm axial slice through the center of the tumor volume was first selected from T_2-weighted scout images. T_2 measurements were then made using a single-slice, multiple spin-echo sequence [2] with a $\Delta TE = 8$ ms, $TR = 4$ s, number of echoes = 32, field of view = 35×35 mm^2, acquisition matrix = 64×64, and $NEX = 8$. Images were smoothed with an anisotropic filter [3] then fitted to a set of 100 decaying exponentials in a non-negative least-squares [4] sense to determine the distribution of T_2 values, or T_2 spectrum, within each voxel. An additional minimum "curvature" constraint [5], which smoothes the resultant T_2 spectrum, was incorporated into the fit in order to regularize the solution.

Results and Discussion: Sample T_2 spectra from tumor and contralateral subcortical grey matter ROIs are shown in Fig. 1. Tumor signal consistently exhibited biexponential T_2 decay, with a short-T_2 component ($T_2 = 16 \pm 12$ ms across samples) representing 6 ± 8 % of the total signal and a long-T_2 component ($T_2 = 75 \pm 12$ ms) representing the remaining signal fraction. In contrast, signal from contralateral grey matter was consistently found to be mono-exponential ($T_2 = 51 \pm 4$ ms), which is in agreement with previously published results [6].

Using T_2 spectra from each voxel, maps of the short-T_2 signal fraction were created and a representative example is displayed in Fig. 2b (Rat #3). The mean (± SD) short-T_2 signal fraction was then tabulated for tumor and contralateral grey matter ROIs, the results of which are given in Table 1. Results showed significant heterogeneity within the tumor margin, which may reflect regional differences in the tumor microenvironment due to, e.g., the presence of densely packed proliferating cells or blood clots within necrotic regions. Similar arguments might explain the observed variability across animals.

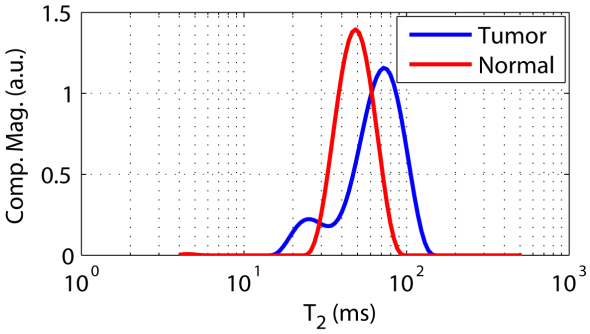

Fig 1. Sample T_2 spectra from tumor and contralateral subcortical grey matter (normal) ROIs.

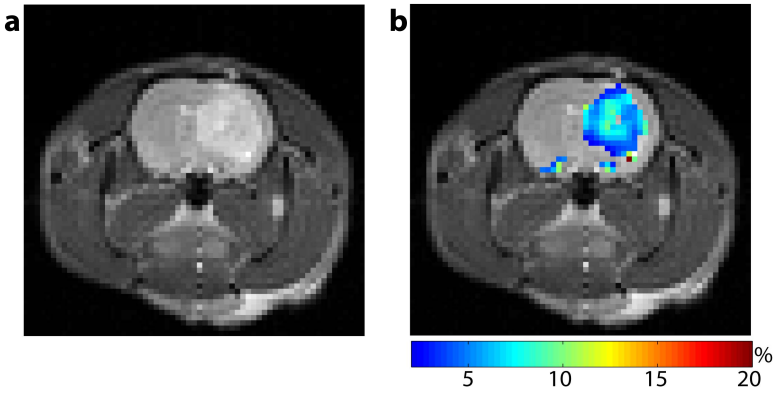

Fig 2. Sample T_2-weighted image **(a)** and short-T_2 signal fraction map **(b)**.

Conclusions: Using MET_2 analysis, two distinct signal components were resolved in rat glioblastoma. Though additional work is needed to determine the physiological origin of these components, MET_2 analysis holds promise as a non-invasive tool for characterizing tumor microenvironment *in vivo* on a sub-voxel scale.

References: [1] Barth J. Neuro-oncology 36:91–102 (1998).
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Rat #	Tumor (%)	Normal (%)
1	1.1 ± 0.7	0.1 ± 0.2
2	3.4 ± 1.9	0
3	10.7 ± 3.7	0.1 ± 0.1
4	3.5 ± 2.2	0
5	3.5 ± 0.9	0
6	0	0
7	1.7 ± 0.6	0.3 ± 0.5
8	2.7 ± 2.7	0.1 ± 0.2
9	0.4 ± 0.6	0
10	4.4 ± 4.6	0
11	0.8 ± 1.2	0.4 ± 0.8

Table 1. Mean (± SD) short-T_2 signal fraction for tumor and contralateral subcortical grey matter (normal) ROIs for each animal.