Tissue Cell Fraction (TCF) from Quantitative Sodium MR Imaging Measures Real-time Tumor Response to Fractionated Radiation Therapy

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Purpose:

If sodium ion homeostasis is used as the operational definition of tissue viability [1], increases in tissue sodium concentration (TSC) can be used to calculate loss of cell density. TSC measured by quantitative sodium MR imaging (qNaMRI) and the two-compartment model of the distribution of sodium in brain tissue between the intra- and extracellular compartments can be used to derive the tissue cell fraction (TCF) [2]. The temporal sensitivity of TCF measured by qNaMRI has been investigated for detecting early changes in TCF in high-grade human brain tumors during fractionated intensity modulated radiation therapy.

Methods:

Under an IRB approved protocol with signed consent, qNaMRI using 3-D flexible twisted projection imaging [2], with B_0 and B_1 corrections and a separate signal calibration using the same protocol on a phantom, has been applied weekly to patients (N=28 at 3T; N=4 at 9.4T) undergoing fractionated radiation therapy (total of 60Gy over 6 weeks with 5/7 day schedule) for high grade (grade III or IV) brain tumors (Figure 1a & 2a). The acquisition parameters (3T: T_E/T_R = 0.36/160 ms 1529 projections, 90° tip angle, radial fraction = 0.25, gradient strength = 4G/cm, 2 averages; 9.4T: T_E/T_R = 0.26/160 ms, 3760 projections, 90° tip angle, radial fraction = 0.31, gradient strength = 5.47 G/cm, 1 average) provided spatial resolutions of nominal isotropic 5 and 3.5 mm at 3T and 9.4T, respectively, in about the same 10 minute acquisition time. Sodium images were reconstructed and aligned to the first dataset by finding the transformation coefficients in image space, applying those coefficients to the k-space data during image reconstruction to avoid image blurring [3]. These aligned sodium images were used to calculate weekly TSC and TCF maps. The maps were then analyzed for voxel-wise weekly and accumulated changes in TCF from before, during and after radiation treatment. The 95% confidence limits for significant positive and negative changes were established in normal brain away from the tumor and treatment site. These limits were then applied to the tumor to determine the positive (decreasing edema) and negative (cell kill) changes in TCF. Numbers of voxels with changing TCF were plotted over time (Figure 1b & 2b). The weekly and accumulated medians of the TCF changes in responding voxels were then plotted over time (Figure 1c &2c).

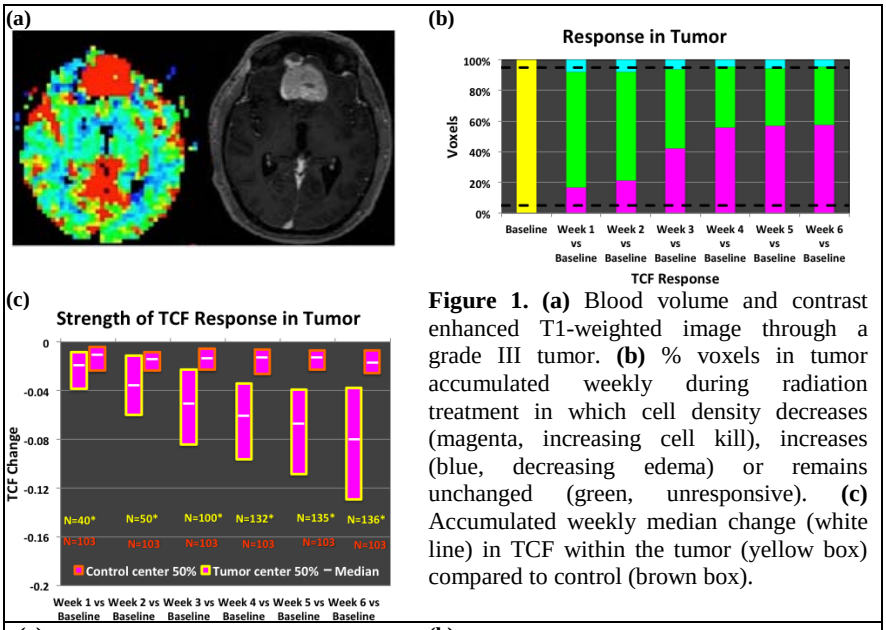

Figure 1. (a) Blood volume and contrast enhanced T1-weighted image through a grade III tumor. **(b)** % voxels in tumor accumulated weekly during radiation treatment in which cell density decreases (magenta, increasing cell kill), increases (blue, decreasing edema) or remains unchanged (green, unresponsive). **(c)** Accumulated weekly median change (white line) in TCF within the tumor (yellow box) compared to control (brown box).

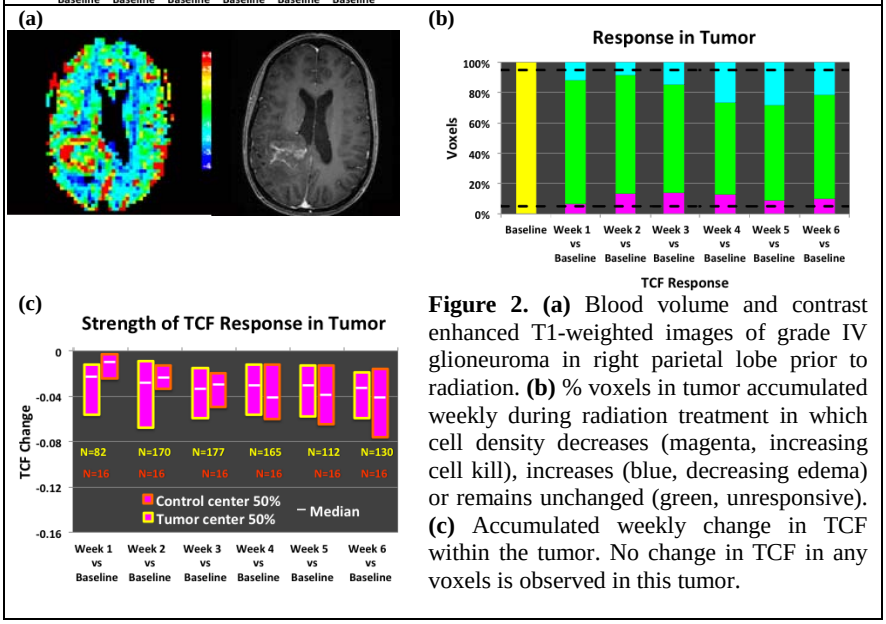

Figure 2. (a) Blood volume and contrast enhanced T1-weighted images of grade IV glioneuroma in right parietal lobe prior to radiation. **(b)** % voxels in tumor accumulated weekly during radiation treatment in which cell density decreases (magenta, increasing cell kill), increases (blue, decreasing edema) or remains unchanged (green, unresponsive). **(c)** Accumulated weekly change in TCF within the tumor. No change in TCF in any voxels is observed in this tumor.

Results:

Different patterns of TCF change are found (Figures 1 & 2). Figure 1 shows weekly TCF changes for a young adult patient with a grade III tumor showing cell kill in up to 60% of tumor voxels. However the magnitude of the cell kill at 60Gy is only about 15% of the tumor cellularity. The distribution of cell kill is not uniform but shows marked regional differences. Figure 2 shows equivalent plots for another patient with a grade IV tumor showing no weekly or accumulated change in TCF indicating minimal cell kill in any region of the tumor.

Conclusion:

TCF measured from qNaMRI detects different patterns of weekly cell density changes in high-grade human brain tumors during radiation treatment. Such information could be used to triage patients towards more effective treatments thereby avoiding continued needless ineffective but expensive therapy. Regions of ineffective treatment are identified early for prompt immediate additional treatment. The surprising result is that radiation does not achieve large cell kills in human high grade brain tumors.

References: [1] Neuroimag Clin N Am 2005 15:639-653, [2] Magn Reson Med 2010 63:1583–1593, [3] Magn Reson Med. 2012; 68(3):751-61.

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