Investigation of Early ADC Changes in Response to Single Dose (1000cGy) Radiotherapy in a RIF-1 Tumor Model

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Introduction

Previous studies employing diffusion MRI have shown that rapid changes in the apparent diffusion coefficient (ADC) following therapeutic intervention can indicate a positive therapeutic response.[1,2] Although tissue ADCs are known to correlate with cell density, increased ADCs at early timepoints post-treatment may be the result of therapeutically-induced changes in ADC such as vasogenic edema. In order to understand the various contributions to the ADC response, we have performed multispectral (MS) analysis using ADC, T_2 and M_0 for subdivision of tissue into regions of viable tumor and necrosis. Tissue segmentation using this methodology provides insight into the various processes whose combination yield the total ADC response over time.

Methods

Seven 6-8 week-old female C3H mice weighing 20-25g were anesthetized with an intraperitoneal injection of ketamine/zylazine (100mg/kg:10mg/kg). All mice were inoculated with 1×10^6 RIF-1 cells (0.15ml), delivered through a subcutaneous injection into the right hind leg. Tumors were allowed to develop for 3-4wks, yielding an approximate 1.0cc starting volume.

Data were acquired with a Bruker Biospin 2.0T/45cm imaging spectrometer operating at 85.56MHz for ^{1}H and equipped with ±20G/cm self-shielded gradients. Image acquisition was performed along the coronal plane [128×128, FOV=3cm, slices=8, slice thickness=1mm]. A DW-SE sequence was used to acquire the images at six b-values (15 → 760 s mm^{-2}) with TR/TE=2000/53ms, δ=4ms, Δ=35ms, resulting in an effective diffusion time t_{dif}=33.7ms. A T_2W-SE sequence was used to acquire images at six echo times (12.2 → 90 ms) with TR=2000ms. Tumors were irradiated with 1000cGy at a rate of 300cGy/min (Siemens Mevatron 77, 6 MeV electrons, Tufts University Veterinary School of Medicine). Imaging was performed 1d pre-treatment, 5hr, 1d, 2d post-treatment, and every 2d thereafter until tumor doubling (maximum 10d post-treatment).

ADC, T_2, and M_0 parameter-maps were generated using routines written in IDL® (RSI, Boulder, CO). Tissue classification was performed using the k-means (KM) clustering algorithm. KM was applied to segment data into two regions each of viable tumor (V1,V2) and necrosis (N1,N2), and one region of adipose tissue. Average ADC values were calculated on an animal-by-animal basis as well as for individual cluster volumes.

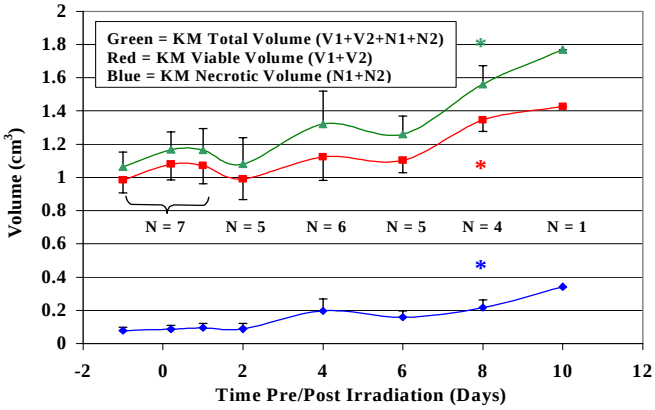

Fig.2: Plot of KM volumes versus time. Labels indicate the number of animals per timepoint. Error bars = SEM. Asterisks denote significance ($p < 0.05$), comparing each timepoint post-irradiation to pre-irradiation values.

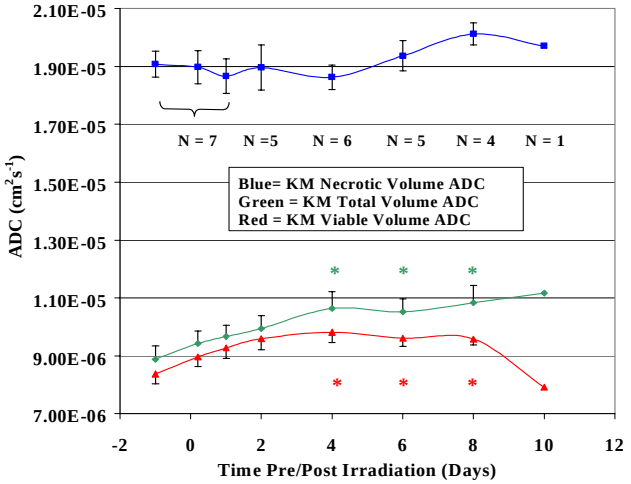

Fig.3: Plot of ADC values versus time. Error bars = SEM. Labels indicate number of animals per timepoint. Asterisks denote significance ($p < 0.05$), comparing each time point post-irradiation to pre-irradiation values.

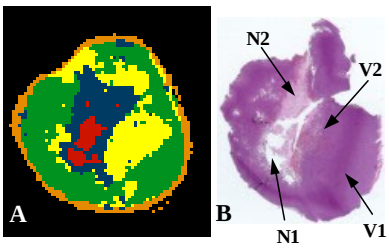

Figure 1: A multispectral (MS) image of a representative RIF-1 tumor. (A) KM map. (B) Hematoxylin-Eosin (H&E) Image. The map derived by k-means (A) depicts the segmentation of the tumor into two regions of viable tumor and two regions of necrosis. Tissue assignments are: Viable 1 (V1) = Green; Viable 2 (V2) = Yellow, Necrosis 1 = Red (N1); Necrosis 2 (N2) = Blue, Adipose Tissue = Orange.

Results

Fig.1 shows the cluster assignments for a representative RIF-1 tumor (Fig.1A) and the corresponding H&E image (Fig.1B) at 6d post-treatment. Fig.2 shows the total viable (V1+V2) and necrotic (N1+N2) tumor volumes pre- and post-irradiation as determined by the KM algorithm. There was no significant change in KM total tumor volume (V1+V2+N1+N2) until after day 6. From day 8, there was a significant increase in viable and necrotic tissue, respectively. Fig.3 shows the temporal evolution of the ADC in each tissue classification as well as the total tumor ADC.

Discussion

The trend in increased total ADC prior to day 4 is consistent with previous observations, although the radiotherapy-induced ADC increase is less than values reported in studies using chemotherapy.[1,2] An increase in ADC can result from an increase in the necrotic fraction of the tumor. However, the increase in necrosis is not observed here until after day 8 (Fig.2). In Fig.3, there is an increase in total ADC that occurs prior to the change in necrotic fraction. This trend is driven by the increase in viable tissue ADC; the necrotic tissue ADC remains constant over this period. In Fig.2, the viable tumor regrowth begins after day 6, with an increase in necrosis after day 8. Note that after the initial increase, the viable ADC becomes constant from days 2 – 8 until the point of viable tumor regrowth (day 8). The decrease in viable ADC at day 10 is consistent with an increase in cell density. These observations suggest that the early increase in total ADC is not due to a reduction in cell density, but instead may be a result of radiation-induced vasogenic edema.

References

[1] Zhao M et al. Br J Cancer 1996;73:61-64.

[2] Chenevert TL et al. J Natl Cancer Inst 2000;92:2029-2036.