Accelerated evaluation of tumor treatment response by Diffusion MRI

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INTRODUCTION Numerous studies have demonstrated the correspondence between the apparent diffusion coefficient (ADC) in tumor and tumor cell density [1]. Changes in tumor ADC due to therapy reflect changes in tumor cellularity with the development of necrosis and/or apoptosis, and precede gross tumor regression. However, tumor heterogeneity can hinder accurate and consistent quantification of tumor response to therapy by diffusion MRI. Recent progress has been made in MR tumor characterization through the use of novel segmentation approaches [2,3]. We present here an alternative approach to characterizing tumor heterogeneity by diffusion MRI which provides an *in vivo* estimate of net log cell kill (*NK)*. Moreover, we demonstrate that diffusion MRI-based *NK* is significantly correlated with conventional estimates of *NK* based on tumor growth delay (TGD).

METHODS Four subcutaneous human tumor xenograft models and seven standard chemotherapeutics were evaluated: A-375 melanoma (dacarbazine, paclitaxel), PC-3 prostate (cyclophosphamide, mitoxantrone), HT-29 colon (irinotecan, 5-fluorouracil); Panc-1 (gemcitabine). Animals were imaged twice weekly using an isotropic diffusion-weighted pulse sequence that included gradient moment nulling and navigator echo correction. Tumor growth was also followed by caliper measurements. Tumor ADC maps were automatically segmented using a Markov random field algorithm, and the serial viability, V_t , was calculated at each time point according to the relation, $V_t = \log10(f_t) - \log10(f_0)$, where f_t is the viable tumor fraction at time t, and f_0 is the median pretreatment viable fraction. Diffusion MRI-*NK* was defined as $-\min(V_t)$ over the imaging time course for each animal. Diffusion MRI-*NK* was compared to conventional TGD-*NK* using Pearson's product moment correlation coefficient (significance level, $p < 0.10$).

RESULTS A representative example of the serial viability versus time is shown in Figure 1. In this case, an A-375 tumor was treated with dacarbazine on days 14-18, and the minimum V_t occurred on day 24, yielding a diffusion MRI-*NK* of 0.62 (TGD-*NK* was 0.65). Each tumor type and treatment group demonstrated a significant linear correlation between diffusion MRI-*NK* and TGD-*NK,* as did pooled data from all groups (Fig 2, slope=0.949, intercept=0.003). The median number of days after start of treatment for determination of *NK* was 9 days (diffusion MRI) and 63 (TGD).

DISCUSSION Diffusion MRI-based *NK* was significantly correlated with *NK* derived from TGD. An important advantage of efficacy evaluation by D-MRI-*NK* is that it could be determined more than seven weeks before *NK* was available from TGD. In addition, diffusion MRI-*NK* was determined directly from *in vivo* estimates of viable tumor fraction. This renders the *NK* estimate more robust in cases when tumor growth is not log-linear or when regrowth is altered by tumor bed effects. The use of diffusion MRI-*NK* to quantify *in vivo* efficacy in drug development may significantly accelerate preclinical evaluation of novel therapeutics.

REFERENCES **[1]** H. Lyng, et al. *Magn Reson Med*, 43(6): 828, 2000. **[2]** B.A. Moffat, et al. *Proc Natl Acad Sci USA*, 102(15): 5524, 2005. **[3]** R.A. Carano, et al., *Magn Reson Med*, 51(3): 542, 2004.

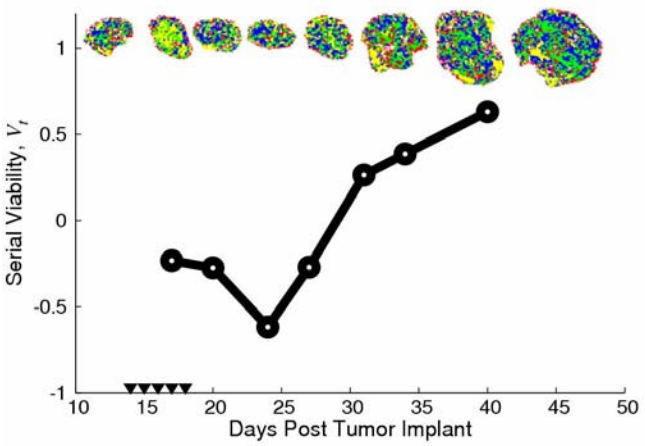

Figure 1: Example of serial viability as a function of time derived from diffusion MRI. Representative slices from segmented tumor ADC maps are shown above each plot for the pre-treatment (first on left) and each subsequent imaging time point.

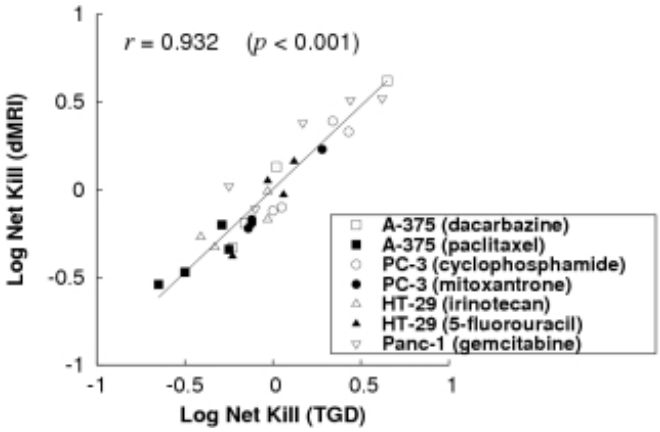

Figure 2: Linear correlation between diffusion MRI and tumor growth delay-based net kill for pooled data of all tumors and treatments (N=29).