Investigating MRI Biomarkers as Indicators of Early Treatment Response in a Triple Negative Model of Breast Cancer

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Target Audience: Those interested in the use of MRI-based biomarkers for evaluating early treatment response.

PURPOSE The current standard-of-care method for evaluating treatment response relies on measuring a change in the physical size of the tumor (1). As a change in size is a temporally downstream result of changes at the cellular level, it may not be the most sensitive measure for the early evaluation (or prediction) of treatment response. The purpose of this study is to evaluate the potential of diffusion-weighted (DW) MRI and dynamic contrast enhanced (DCE) MRI to serve as early, non-invasive indicators of treatment response in a mouse model of triple negative breast cancer (TNBC).

METHODS Four to five-week old female nude mice were injected subcutaneously in the hind limb with approximately 1×10^7 MDA-MB-231 cells. Tumors were allowed to grow until they reached a volume of approximately 346 mm^3 (average, range: 150-750 mm^3), at which point the mice were entered into the imaging study. The study consisted of three imaging sessions (baseline, day 2, and day 4) and the animals were treated at two time points: once immediately following the baseline imaging session, and once on the third day. The study consisted of three treatment groups: control, which received i.p. saline injections, a "low" dose treatment group which received 15 mg/kg of Abraxane (a chemotherapy used clinically for treatment of TNBC), and a "high" dose treatment group, which received 25 mg/kg of Abraxane. All groups consist of at least 10 mice on each day (range: 10-13). The imaging protocol was implemented on a Varian 7.0T scanner and included an anatomical scan followed by DW-MRI and DCE-MRI. The DW-MRI protocol employed a respiratory gated and navigated pulsed gradient spin echo sequence with b-values of 150, 500, and 800 s/mm^2. The ADC value was calculated on a voxel-by-voxel basis using standard methods. The DCE-MRI protocol employed a T_1-weighted, gradient echo sequence. After approximately 3 minutes of baseline collection, a bolus injection of 120 μL of 0.05 mmol/kg Gd-DTPA was given and data was collected for an additional 20 minutes after injection. The data was then fit on a voxel-wise basis to the standard Kety-Tofts equation to extract K^{trans}. The volume of each tumor was measured from the anatomical image. For each of the parameters (ADC and K^{trans}), the median value over the entire tumor volume was calculated for each imaging time point. The median values for each time point were then normalized to the baseline value, so as to calculate a percent change from baseline, and the average value was calculated for each of the three treatment groups.

RESULTS The results for the study are shown in **Figure 1**. The panels show the percent change from baseline ± the standard error for each treatment group at day 2 and day 4 for tumor volume, ADC, and K^{trans} (from top to bottom). The percent change in tumor volume at day 2 was not significantly different from control for either treatment group, but on day 4 the 25 mg/kg treatment group was significantly different from the control ($p<0.05$). The percent change in ADC was indicative of treatment response for both doses; in particular, the change in ADC was significantly different than the change in the control group for both day 2 and day 4 ($p<0.05$). K^{trans} was also indicative of treatment response on day 2; for both doses, the percent change in K^{trans} was significantly different from control ($p<0.05$). On day 4, neither group was significantly different than control, though both show a trend towards significance ($p=0.09$ and 0.08 for 15 mg/kg and 25 mg/kg, respectively).

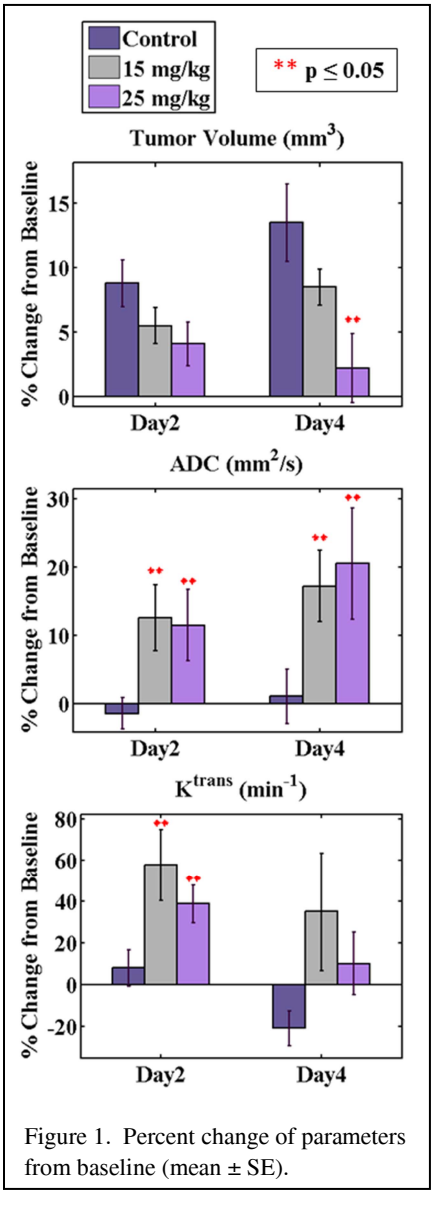

Figure 1. Percent change of parameters from baseline (mean ± SE).

DISCUSSION The literature regarding monitoring treatment response in a preclinical model of TNBC is limited, with few articles focusing on preclinical models of TNBC, and fewer yet monitoring treatment response via MRI. This work serves to fill that void. Ongoing work is focused on histological analysis of the tissues for validation of the imaging findings.

CONCLUSION In this preclinical model of triple negative breast cancer, both ADC and K^{trans} are indicative of response to treatment with Abraxane as early as 20 hours after the initial treatment. Hence, these parameters could potentially find use as imaging biomarkers of patient-specific evaluation of response early in the course of therapy.

REFERENCES (1) Eisenhauer et al. *European Journal of Cancer* 2009; 45: 228-247.

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