Combined Dynamic 18F-FDG PET Imaging and DCE MRI Prediction of Treatment Response in an Orthotopic Model of Glioblastoma Multiforme

Molecular Imaging, Inc., Ann Arbor, MI

Background: Glioblastomas are highly aggressive tumors. When patients are managed with the standard of care of combined radiation therapy and temozolomide (TMZ), median survival is less than 15 months. An earlier prediction of treatment response would allow these therapies to be applied sooner if efficacy is not evident. Non-invasive medical imaging provides the opportunity to link imaging-based biomarkers to treatment response. It was hypothesized that a multi-modality MRI/PET imaging protocol could allow more accurate prediction of treatment response than conventional means.

Methods: 6-7 week old female Hsd:AthymicNude-Fox1nu mice were implanted with 1x10⁶ U87MG-luc cells intracranially under isoflurane anesthesia using a stereotactic surgical apparatus. Animals were staged for treatment using a T2-weighted MRI sequence and treatment groups were populated based on a random tumor size in an interval of approximately 60 mm³ (N = 8). DCE MRI: A dynamic multi-slice gradient echo sequence was used to image the entire volume of the tumor over time. Nine consecutive transverse slices were imaged, with the slice thickness scaled to ensure complete coverage of the target (3.5-mm); 10 × 10 consecutive images were acquired over a total of 10 minutes. The first minute comprised a pre-contrast injection series. At 1 minute following the commencement of imaging, the contrast was injected as a bolus (4 times the mg/kg clinical dose equivalent) over 20 seconds, with the exact volume scaled by the body weight. The rate of injection was accordingly scaled with the body weight (mg/kg) delivered orally once a day for 5 days and PET/MRI imaging was acquired at baseline and +5 days and +15 days post treatment. Staging: Animals were staged for treatment using a T2-weighted MRI sequence and treatment groups were populated based on a random tumor size in an interval of approximately 60 mm³ (N = 8).

Results and Discussion: Control animals had a median lifespan of 59 days. Animals treated with TMZ had a significant increase in median lifespan of 87 days, as compared to controls (p<0.002) and this difference was also reflected in comparisons on tumor size (p<0.0003). Comparisons of the influx constant, Ktrans, derived from dynamic PET data showed no significant differences between control and treated groups, regardless of whether mean or maximum values were used. Similarly, there were no significant differences between groups in the SUVmax and SUVmean. Comparisons in the Ktrans between treatment groups resulted in a significant difference at +15 days post treatment (p<0.05). Finally, correlations between the Ktrans and K1 (from DCE compartmental modeling), both of which are a reflection of tumor from the vascular compartment to the extravascular compartment, did not hold in a significant manner.

Conclusions: While control and TMZ treated animal produced expected similar survival results that were significantly different as compared to historical data, this observation was confirmed in the analysis of tumor metabolic labeling derived compartmentalized 18F-FDG images. Static and dynamic analysis of 18F-FDG PET data did not demonstrate a relationship between Ktrans and the various metabolic markers, F-FLT and/or 18F-FDG uptake. Dynamic analysis of 18F-FDG PET data demonstrated a significant difference at +15 days post-treatment. Comparisons of the Ki derived from the derived parameters or that of Ktrans were not significant. Of particular note, it was expected that the Ktrans and Ki from DCE compartmental modeling would correlate with each other and not result in a significant difference between the two groups (data not shown). Based on the results of this study, it is proposed that future studies utilize later time points in evaluating tumor metabolic labeling derived compartmentalized 18F-FDG and SUVmax imaging. This could be the result of the different transport/diffusion properties of Gd versus FDG.


Figure 1. Representative images of Transverse MRI of U87 MG cancer bearing brain at baseline (A) and treated (B) PET/MRI imaging.

Figure 2. Representative images of Transverse MRI of U87 MG tumor in nude mice at baseline (A) and treated (B) PET/MRI imaging.

Figure 3. Representative images of T2-weighted MRI of U87-luc tumors in vehicle control animals (top) and temozolomide-treated animals (bottom) at baseline, +5 and +15 days post-treatment.

Figure 4. 18F-FDG derived tumor weights acquired at day 0 and +7  and +15 days post-treatment. Treament began on day 42 post-implant (baseline day 0) and continued for 5 continuous days with combined dynamic FDG PET and MRI. Tumors were measured from two dimensions at baseline and days 47 and 57 (day 15 post treatment).

Figure 5. Graphs of DCE MRI-derived Ktrans over time. (C1 vs C2) and (C1 vs C3) (N=8). Tumors treated with temozolomide showed a significant decrease in Ktrans at day 15 post treatment (p<0.0001) compared to vehicle controls.

Figure 6. Graphs of DCE MRI-derived Ktrans over time. (C1 vs C2) and (C1 vs C3) (N=8). Tumors treated with temozolomide showed a significant decrease in Ktrans at day 15 post treatment (p<0.0001) compared to vehicle controls.

Figure 7. Comparison of the DCE MRI-derived Ktrans and the dynamic 18F-FDG PET derived Ktrans (C1 vs C2) of the same animal. Ktrans is calculated from the ratio of tumor signal to that of the muscle (C1) at the opposite side of the tumor to that from the lumbar compartment in the same mouse. Dynamic analysis of 18F-FDG PET data demonstrated a significant difference at +15 days post treatment. Comparisons of the Ki derived from compartmentalized 18F-FDG PET data demonstrated a significant difference at +15 days post treatment.