MRI Predicts Survival and Correlates with Treatment Response in a *tv-a* Transgenic Model of Glioma

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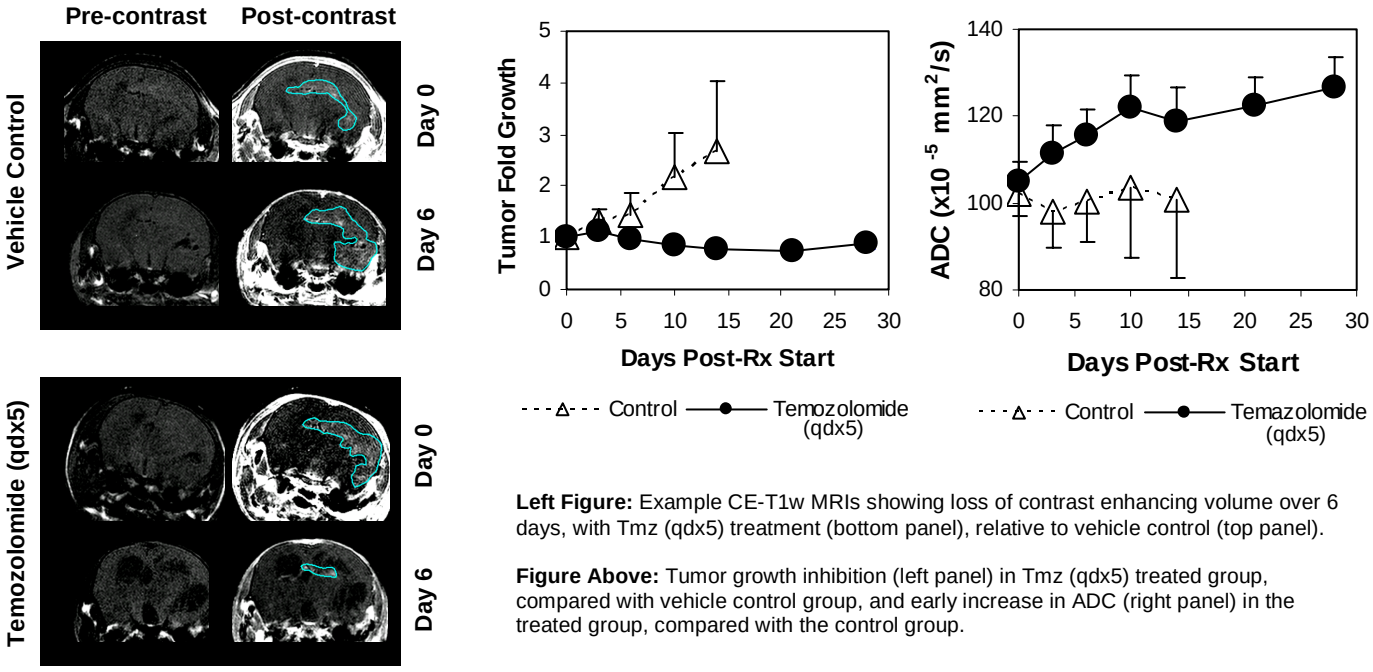
INTRODUCTION: RCAS/tv-a technology relies on somatic gene transfer through infection by RCAS viral vectors derived from the avian retrovirus (ALV-A) in mice expressing the gene for the RCAS receptor (*tv-a*). The nestin *tv-a* (N*tv-a*) mouse, which expresses tv-a under the control of the nestin promoter in glial-progenitors, when infected with ALV virus that over-expresses PDGF, spontaneously develops glioma from 0-3 weeks of age in almost 100% of cases [1]. Using this model, we correlated T2-weighted (T2w) and contrast-enhanced T1-weighted (CE-T1w) MRI with survival and histology in untreated mice, and in a separate study, quantified response to Temozolomide (Tmz) treatment using T2w, CE-T1w, and diffusion MRI (DMRI).

METHODS: 40 N*tv-a* mice with PDGF-driven brain tumors at 3 weeks of age underwent weekly T2w and CE-T1w MRI, using multi-slice fast spin-echo and spin-echo sequences, respectively. In both cases, contiguous, 0.5 mm thick, transaxial slices were used to cover the entire tumor. After 4 weeks, half of the mice were sacrificed for histology, with the remaining mice kept on study for survival. In a separate study, 20 mice were divided randomly into two groups: (1) vehicle control and (2) Tmz treated (qdx5). To quantify treatment response, T2w MRI and DMRI were used on day 0 (day of first treatment), and days 3, 7, 10, 14, then weekly thereafter, and CE-T1w MRI was used on days 0, 7, 14, 21, then bi-weekly thereafter. The DMRI sequence used a navigator echo for motion correction, and shaped gradient waveforms for motion compensation and isotropic diffusion measurement, and incorporated contiguous 0.5mm thick slices to cover the entire tumor volume.

RESULTS AND DISCUSSION: Tumors were well delineated in T2w images, showing contrast features (including solid tumor, necrosis, edema and cyst) that were typical of human glioblastoma multiforme (GBM) in about 30% of cases, and oligodendroglioma in the remaining cases. In GBMs only, CE-T1w MRI showed ring enhancement also typical of the human condition. The MRI data was confirmed by histology. By a combination of initial T2w and CE-T1w images at 3-4 weeks age, MRI was predictive of tumor grade, and ultimately survival. Gliomas in mice treated with Tmz showed an early increase in the water apparent diffusion coefficient (ADC), and later a growth delay, and decrease in enhancing volume, relative to vehicle control mice. Histology showed regions of decreased cellularity in treated tumors and the treated group of mice showed increased survival.



Left Figure: Example CE-T1w MRIs showing loss of contrast enhancing volume over 6 days, with Tmz (qdx5) treatment (bottom panel), relative to vehicle control (top panel).

Figure Above: Tumor growth inhibition (left panel) in Tmz (qdx5) treated group, compared with vehicle control group, and early increase in ADC (right panel) in the treated group, compared with the control group.

CONCLUSION: The N*tv-a* mouse constitutes a promising model of human glioma. We have shown that MRI is able to delineate heterogeneities due to localized regions of highly cellular tumor, necrosis, edema, cyst and abnormal vasculature, as in the clinical disease, and that MRI correlates with histology and survival in this model. We also demonstrated a response to Tmz in ADC, tumor growth and the contrast-enhancing volume. These MRI-determined endpoints correlated with survival. MRI methodology in the N*tv-a* mouse may provide an efficient preclinical means for testing novel therapies, and optimizing new combination strategies for treatment of glioma.

REFERENCE: [1] Shih, A. H. et al. (2004) Cancer Res, 64, 14:4783-9