

Apparent Diffusion Coefficient Predicts Survival in 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* (*Ntv-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]. MRI-determined apparent diffusion coefficient (ADC) is sensitive to tissue changes that occur after cell kill [2] and has been predictive of survival in human glioma patients [3]. Our hypothesis was that ADC would enable early prediction of tumor growth and survival in *tv-a* glioma after treatment with a standard chemotherapy, potentiating future use of the model in preclinical testing of much-needed new therapies for glioma.

METHODS: Tumored *Ntv-a* mice were selected for high grade glioma using T2-weighted (T2w) MRI at 4 weeks of age, and divided into two groups: (1) vehicle control (n=12) and (2) temozolomide (TMZ) treated (n=13; 100 mg/kg qdx5 ip). T2w MRI was used to monitor tumor growth and diffusion MRI (DMRI) was used to characterize cell kill from tissue ADC before treatment, and 3, 7, 10, and 14 days after treatment, then weekly thereafter. Survival was also determined to 90 days. T2w MRI was performed using a fast spin-echo sequence with TR=4s, #echoes=8, and echo spacing=12.5ms. Diffusion MRI was performed using an isotropic motion-compensated, navigator-echo motion-corrected sequence with TR=2s, TE=60ms and diffusion gradients of 1 Gauss/cm (single average) and 10 Gauss/cm (2 averages). All images incorporated contiguous, 0.5 mm thick, transaxial slices that represented the entire region of the tumor, and a 15x15mm field of view over a 128x128 matrix.

RESULTS AND DISCUSSION: Tumors were well delineated in T2w images, and showed features that were typical of human glioma (including solid tumor, necrosis, edema and cyst). These features were confirmed through histology (Figure 1). A robust, early increase in ADC (day 3) was observed, that correlated with later growth inhibition and increased survival, in the treated group, compared with controls (Figure 2). Divergence in the ADC curves for each group was evident at the first post-treatment time point (day 3), whereas the divergence in the growth curves was not clear until 10 days after the start of treatment. Median survival data was not obtained for 40 days after treatment start.

CONCLUSION: TMZ produced growth inhibition and increase in median survival in the *tv-a* model of glioma. These effects were preceded by an early increase in ADC, due to changes in effective tissue water mobility after cell kill. Consistent with previous work [2,3], ADC enabled early prediction of survival in the *tv-a* model. This may facilitate efficient screening of compounds and combination therapies in a model with close resemblance to human glioma, with clinically translatable methods. Further work to discern the viable tumor volume fraction based on the ADC images is continuing.

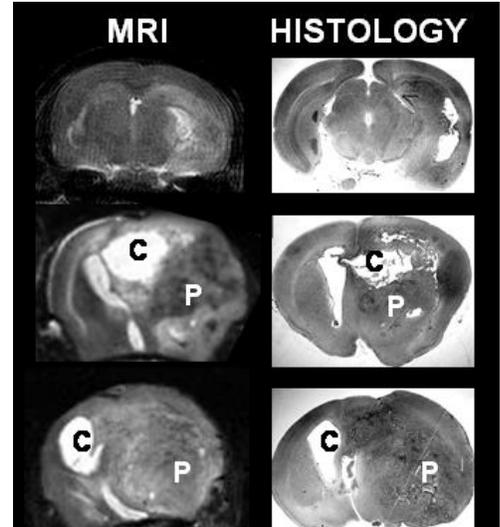


Figure 1 Histology confirmed the grade of the tumor and features such as cyst (C) and pseudopalisading (P) with similar morphology to that seen in human anatomical MRIs

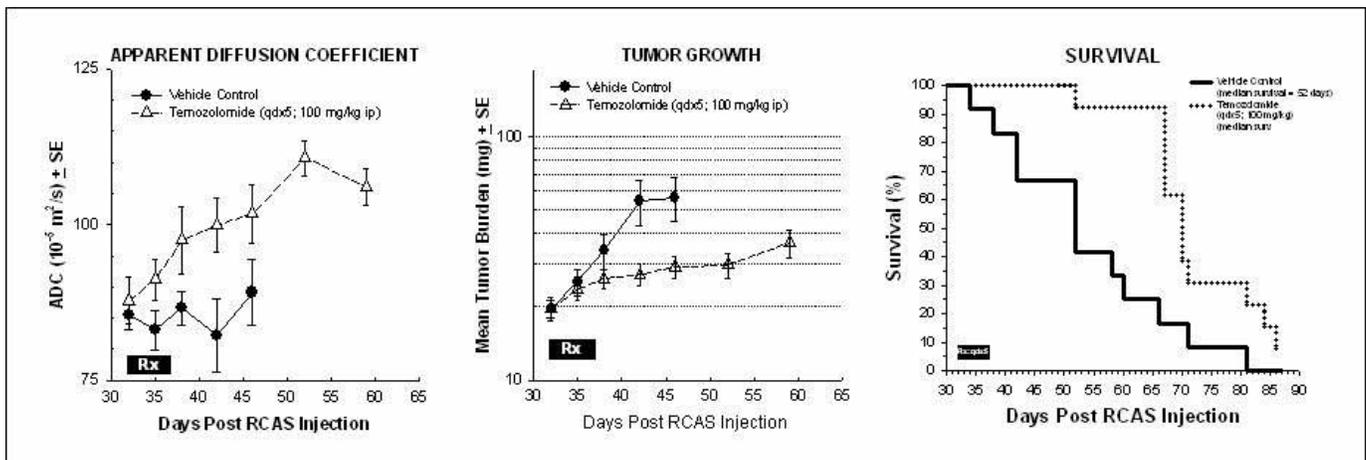


Figure 2 Mean apparent diffusion coefficient (ADC) time course (left panel), mean tumor burden time course (middle panel) and survival curves (right panel) for treated (temozolomide 100 mg/kg qdx5 IP; n=13) and control groups (n=12).

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