

# MRI Predicts Tumor Grade and Survival in a *tv-a* Transgenic Model of Glioma

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## MOTIVATION

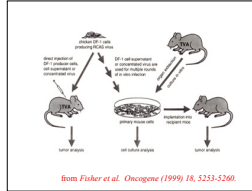
1. RCAS/*tv-a* technology provides a promising new platform for development of tissue-, and oncogenic pathway-specific mouse tumor models.
2. These models may elucidate the mechanisms of neoplastic transformation, and development of targeted treatments.
3. MRI has unique capabilities in characterization of tumor appearance, growth, heterogeneity, cellularity and vascularity in in vivo models.

## AIMS

1. To use high field (7T) MRI to characterize tumor appearance, heterogeneity and growth.
2. To characterize tumor vascularity (with contrast enhanced MRI).
3. To correlate MRI findings with tumor grade (histology) and survival.

## BACKGROUND

## METHODS



### Conventional Transgenics

- Multi-gene defects require complex breeding patterns
- Germ line mutations often lethal to developing animal
- Organ specificity difficult to control

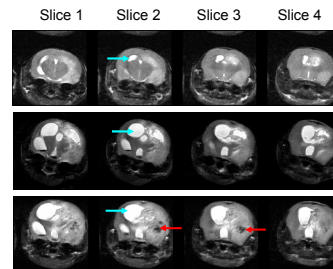
### T-va Transgenics

- Control/introduction of multiple genetic defects in same model possible
- Somatic gene changes in adult animals
- Timing of defects more easily controlled
  - Simultaneous
  - Sequential
- Organ specificity controlled at multiple levels
  - Tissue specific promoters
  - Direct tissue virus infection
- One transgenic mouse for models of multiple genetic defects
  - Simplified breeding efforts

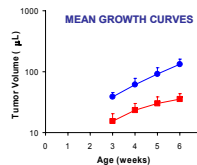
- Mice expressing *tv-a* under the control of the nestin promoter expressed in glial-progenitors (*Ntv-a* mouse) [1] were bred.
  - 40 *Ntv-a* mice that had developed tumors following intracranial injection with PDGF-encoding RCAS virus [2] underwent weekly MRI to characterize tumor growth and development.
  - T2-weighted fast spin-echo MRI was used to evaluate tumor growth.
  - T1-weighted spin-echo MRI pre- and post-contrast agent injection, was used to delineate regions of dense and/or 'leaky' microvasculature.
  - Tumor cellularity was also evaluated during the course of the study by diffusion-MRI measurement of the apparent diffusion coefficient (ADC).
  - When signs of illness were apparent, animals were sacrificed, and the brains harvested for histology.
  - 10 *Ntv-a* mice were used in a pilot studying the effect of Temozolamide in this model, as determined by the above MRI methods.
- [1] Hesselager G, Holland EC. Neurosurgery. 2003 Sep;53(3):685-94
- [2] Shih, et al. Cancer Res. 2004 Jul; 64(14):4783-9

## Tumor Growth

High Grade Glioma



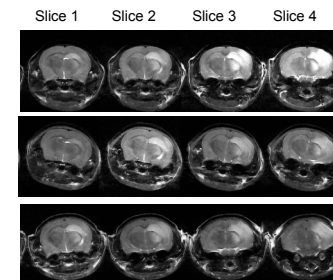
3 weeks  
4 weeks  
5 weeks



High Grade Mean Doubling Time =  $11.1 \pm 2.7$  days

Low Grade Mean Doubling Time =  $18.8 \pm 6.4$  days

Low Grade Glioma

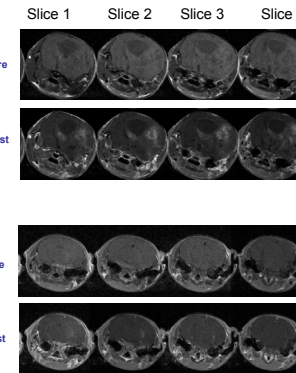


3 weeks  
4 weeks  
5 weeks

## RESULTS AND CONCLUSIONS

### Tumor Vascularity

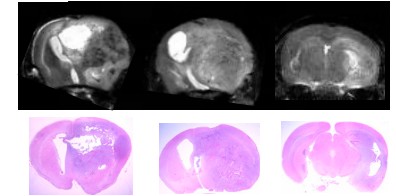
High Grade Glioma  
Low Grade Glioma



- T1-weighted pre- and post-gadolinium-enhanced images

### Histology

High Grade Low Grade

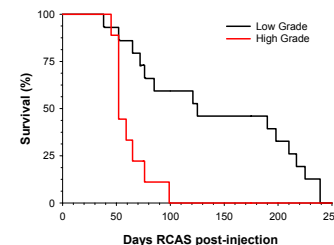


- Histology confirmed the presence of tumor cells and correlated with tumor grade as designated by MRI.
- High grade tumors showed high cellularity and regions of pseudopalisading, whereas low grade tumors showed more diffuse cellularity.

### Conclusions

- Tumors could be separated into high and low grade phenotypes, based on appearance in T2-weighted images.
- Tumors designated as high grade by MRI grew more rapidly than those designated as low grade, consistently showed invasive tendencies, the appearance of hypointense regions that may indicate necrosis and/or pseudopalisading, and the presence of hydrocephalus.
- Contrast MRI showed localized enhancement in high grade tumors, and no enhancement in low grade tumors.
- Survival and histology correlated with MRI determined tumor grade.

### Survival



- ⇒ Standard MRI methodology can be used to distinguish tumor grade in the *Ntv-a* model at the time of weaning.
- ⇒ MRI represents an efficient means of measuring growth inhibition and vascular response to therapeutics in the *tv-a* model.