Evaluation of Oncolytic Virus Induced Vascular Leakage in an Experimental Rat Glioma Model on 8.0 Tesla MRI: Correlation with Histopathology Result

M. Yang[1], G. A. Christoforidis[1], A. Abduljalil[1], K. Kurozumi[2], J. Zhang[1], B. Kaur[2], M. V. Knopp[1], and E. A. Chiocca[2]
[1]Radiology, The Ohio State University, Columbus, OH, United States, [2]Neurosurgey, The Ohio State University, Columbus, OH, United States

Introduction:
Oncolytic viruses (OVs) have selective ability to replicate and lyse in neoplastic cells vs. non-neoplastic cells. Therefore, OVs can increase permeability of microvessles and cause rupture of blood brain barrier (BBB). Ultra high field magnetic resonance imaging (MRI) is sensitive to magnetic susceptibility effect generated by hemosiderin-the end metabolite of hemoglobin[1]. In addition, ultrasmall particles of iron oxide (USPIO) could leak through ruptured BBB and cause prolonged negative enhancement[2]. In this study, with the aid of USPIO, we aim to identify hemorrhage and increased vascular permeability induced by OVs in an experimental rat glioma model on 8.0 Tesla (T) MR system.

Materials and Methods:
D74/HveC brain glioma cells ($2x10^5$) were stereotaxically implanted into brain of 8 Fisher rats. Ten days later, $1x10^7$pfu/ 5µl of HSV-1 derived OVs (hrR3) were injected intratumorally in 4 rats as treatment group, and 5 µl of 1 X PBS solution were injected into another 4 rats as control group. Two days after OVs injection, all rats were scanned by a T2* weighted GRE sequence on 8.0 T MR system with following parameters: TR/TE= 600/14.6 msec, field of view 4 cm, matrix 512 X 512, flip angle 22.5^0, slice thickness 1mm, gap 0.1 mm, acquisition 10 minutes 23 seconds, in-plane resolution 78 µm. Post-contrast scans were repeated at 0', 15', 30', 45', 60' and 90' after administration of USPIO at a dosage of 2 mg Fe/kg (Figure 1, & 2). A T2 weighted RARE sequence was also employed before injection of USPIO. After MRI, 250 µl FITC-Dextran was injected intravenously into each rat 15' prior to sacrifice. Rat brains were sectioned and analyzed by fluorescent microscopy, as well as hematoxylin and eosion (H & E) stain. Signal intensities (SIs) of tumor and normal hemisphere in both groups were measured using MIPAV software (MIPAV 2.6, NIH) and compared between pre- and post-contrast series at different time-points using student *t*-test. Image subtractions were also applied to enhance the identification of USPIO enhancement using an IDL based software.

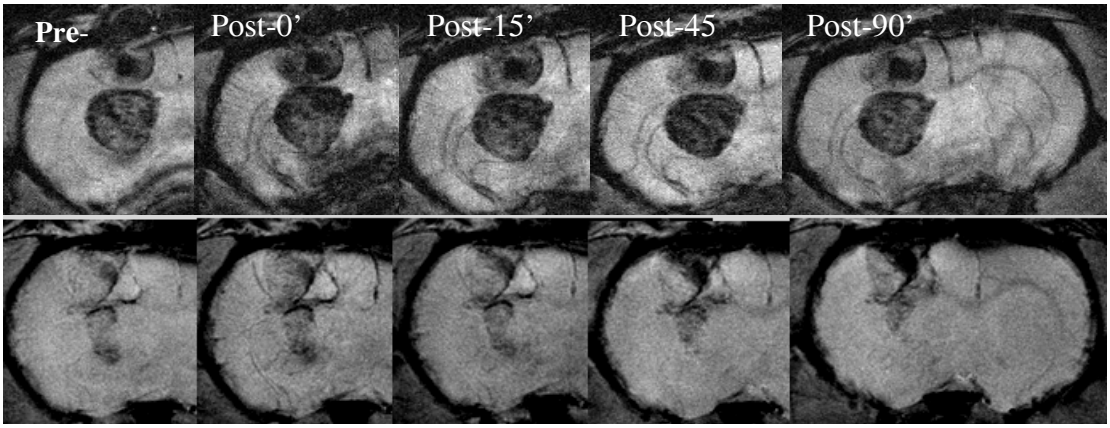

Figure 1. 8.0 Tesla GRE MRI of brain glioma rats in control group (upper row) vs OVs treatment group (lower row). There was substantial hemosiderin deposition in basal ganglian region due to tumor cell implantation and/or PBS injection in this control rat (upper row). In both groups, rat gliomas displayed as low signal occupation in right cortex in pre-contrast series and presented various patterns of signal loss after USPIO administration over 2 hrs period.

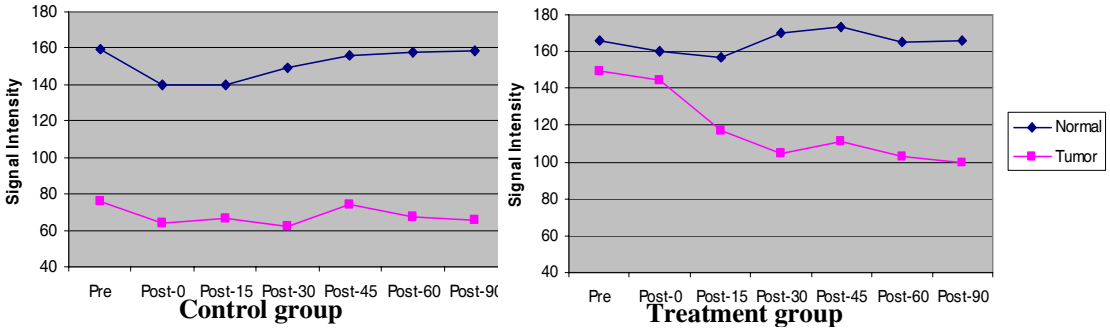

Figure 2. The patterns of signal intensity changes in tumor and normal brain of the rats in Figure 1.

Results and Discussion:
On pre-contrast GRE sequence, rat brain glioma displayed as inhomogenously low signal occupation in right hemisphere in both two groups. There was no significant difference of tumor size or SIs between these two groups ($P>0.05$). After administration of USPIO, SIs of tumor dropped consistently during the 2-hours period in OV treatment group, while dropped transiently in control group ($P<0.05$). Fluorescent photography proved substantial extravasational leakage of dye in OVs treatment group. H & E stains found more fresh hemorrhage in OVs treatment group as well. USPIO enhanced GRE at ultra high 8.0 T field is an applicable imaging method in evaluation of OVs induced vascular leakage in experimental rat glioma model.

Ref:
1. Christoforidis GA, et al. AJNR 2004; 25:756-760.
2. Yang M, et al. Invest Radiol. 2005 Oct;40 (10):655-60