Target audience
This study is aimed at preclinical and clinical researchers interested in using MRI to better understand drug delivery to brain tumors and the consequences of blood-tumor barrier (BTB) normalization on delivery of chemotherapy.

Purpose
The blood-brain barrier (BBB) is a key factor in limiting delivery of anti-cancer drugs to brain tumors. The compromised neovasculature of the BTB is often the only means of systemically delivering cytotoxic agents. Anti-angiogenic therapies such as bevacizumab (BEV) have been shown to “normalize” brain tumor vasculature, but the impact on chemotherapy delivery remains unclear. The goal of this pilot study was to use MRI to elucidate vascular and interstitial fluid differences that correspond with the timing of temozolomide (TMZ) chemotherapy and BEV delivery.

Methods
Rats were inoculated in the right caudate nucleus with U87MG human glioma cells (12 µl, ~10⁶ cells). When tumor volumes reached ~20-50mm³, rats were randomized to: control (n = 1), BEV (45 mg/kg IV) followed by TMZ (40 mg/kg oral) (n = 2), and TMZ followed by BEV (n = 2). MRI was performed prior to treatment and 4 and 8 days after treatment using an 11.75 T magnet system. T₂W images were acquired for detection of edema. DCE-MRI was accomplished with a fast-gradient-echo sequence. MRI sequence parameters were used from our previous work. K_trans was calculated by non-linear squared fitting to the T₁ measurements using a two-compartment model; animal-specific arterial input functions were implemented.

Results
The timing/sequencing of BEV and TMZ delivery could be important to the overall anti-tumor efficacy (Fig. 1). When BEV was delivered first, permeability (average K_trans) was decreased 65% before the delivery of TMZ (Fig. 1A); after TMZ was delivered, average K_trans increased 23%, which could represent some reversal of the BTB normalization. When TMZ was delivered first, average K_trans was increased 37% before the delivery of BEV (Fig. 1B) corresponding with edema as shown in the T₂-weighted image after this treatment. The subsequent delivery of BEV resulted in a 60% decrease of average K_trans. Average K_trans for control increased over the course of the study (Fig. 1C).

Discussion
This pilot study raises two important points: (1) When TMZ is given after BEV there is no apparent edema, which may indicate reduced delivery of TMZ; (2) When TMZ is given prior to BEV there appears to be more anti-tumor effect as shown by the hypointense regions (possible necrosis) within the tumor of Fig. 1B (day 8), while this is not observed in Fig. 1A (day 8).

Conclusion
The pilot study shows promise that it may be more effective to deliver chemotherapy before tumor vascular normalization and warrants further study. Histology can provide a path to quantify efficacy. EVAC-imaging or proton density quantification may be a better way than T₂W images to quantify changes in the interstitial fluid environment.

References