ANTI-VEGF (AVASTIN) THERAPY MONITORING IN RECURRENT GLIOBLASTOMA MULTIFORME USING DYNAMIC CONTRAST-ENHANCED (DCE) MRI

J. S. Chang[1], S. N. Gupta[2], and S. Cha[3]

[1]Radiology, UCSF, San Francisco, California, United States, [2]Global Applied Science Lab, GE Healthcare, Bethesda, Maryland, [3]Radiology and Neurosurgery, UCSF, San Francisco, California, United States

Background: Dynamic contrast-enhanced MR imaging (DCEMRI) is a noninvasive tool used to estimate the degree of alteration in vascular permeability, which is represented by the endothelial permeability surface area product, and approximated by K^{trans} when the blood-brain barrier (BBB) is reasonably intact. Endothelial permeability of vessels in brain tumors provides valuable information about BBB integrity, vascular morphology and response to anti-angiogenic therapy. It is entirely unclear, however, what the most optimal metric derived from DCEMRI variables is to assess the therapeutic effect in brain tumor patients undergoing anti-angiogenic therapy.

The purpose of this study was to determine the optimal quantitative variable that represents the alterations in vascular permeability and hence serve as a surrogate marker of anti-angiogenic activity.

Methods: In this study, we quantitatively and qualitatively assessed the DCEMRI examinations of five patients undergoing anti-angiogenic therapy for recurrent glioblastoma multiforme. For each patient, anti-angiogenic treatment was administered within a week of the baseline scan, and the pre-treatment baseline exam and a 6-week follow-up examination were analyzed.

Pharmacokinetic modeling of DCEMRI data was performed using a custom research package (Cinetool, GE Healthcare). We used the 2-compartment General Kinetic Model with two rate constants K^{trans} and k_{ep}, and an explicit fractional plasma volume (f_{PV}) term. Signal-intensity versus time data was created on a pixel-wise basis. Arterial input function was measured from an ROI placed in the superior sagittal sinus. All time-intensity data was converted into Gd concentration curves using T_1 scaling. Kinetic Modeling parameters were then calculated for each pixel using an iterative, non-linear least-squares algorithm by curve-fitting the measured data to a convolution of the model impulse response with the arterial input function data. Using the CINE tool, the mean, standard deviation, minimum, and maximum k^{trans} values were produced for the patients' baseline and 6-week follow-up examination. Further, we also calculated the histograms of the kinetic model parameters within the tumor region to characterize the heterogeneity of the tumor regions and to assess and compare the frequency and distribution of pixel values.

Meanwhile, a blinded neuroradiologist reviewed the anatomic baseline and follow-up MRI examinations and based upon these, characterized the patient as: complete recovery, partial recovery, or progressive disease. We then analyzed the statistical outcomes and histograms against the anatomic imaging characterizations for relationships.

Results:

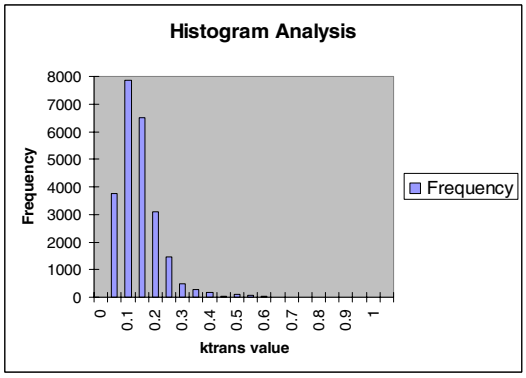

Figure 1 – Baseline MRI

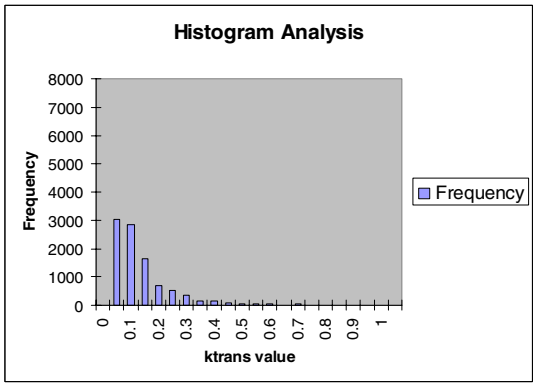

Figure 2 – 6-week Follow-up

Fig 1 & 2: *Histogram analysis of a patient characterized as partial recovery. Average K^{trans} values were similar at both time points - at baseline 0.118, and at 6 weeks, was 0.112. The histogram, however, demonstrates decreased K^{trans} intensity between time points.*

At the 6 week follow-up scan, three patients were categorized as partial recovery and two patients were shown to have progressive disease. None of our patients showed complete recovery. Based on these categories, our descriptive statistics and histograms were assessed. We found that our K^{trans} descriptive statistics had limited ability to characterize the biological change in the patients' examinations - average, minimum and maximum values did not necessarily associate with biological outcome. However, the histogram analysis demonstrating K^{trans} pixel frequency, value, and distribution, showed to represent biological change in all five of our patients (Figure 1&2).

Conclusion: DCEMRI is a promising noninvasive tool to assess therapy response following anti-angiogenic treatment for malignant brain tumor by providing a quantitative variable, K^{trans}, which reflects alteration in vascular permeability. Our study shows that a static measure of K^{trans} alone is not sufficient to assess the dynamic changes in tumor vasculature that occur during and after therapy and to determine treatment response. Our preliminary result suggests that a histogram analysis of K^{trans} on a pixel-by-pixel basis before and after therapy more accurately determines changes in tumor vasculature due to anti-angiogenic therapy.