Initial Area Under the Curve (IAUC) is an objective, pragmatic and translatable MRI biomarker for quantifying human brain tumor perfusion: Correlation with histopathology.

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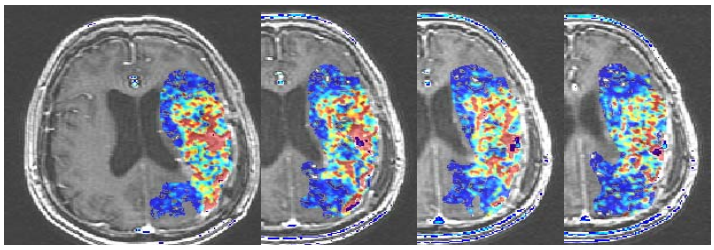
Introduction: The purpose of this study was to investigate a model free analysis of dynamic contrast enhanced (DCE) MRI data for its potential as a non-invasive imaging biomarker of brain tumor perfusion. Quantitative perfusion imaging has wide ranging potential for both non-invasive diagnosis of tumor grade [1] and quantifying response to anti-angiogenic therapies [2]. It is most common in brain perfusion imaging to quantify perfusion characteristics such as permeability (Ktrans), blood volume (CBV) and flow (CBF) by fitting mathematical models of contrast agent effect on DSC MRI data and de-convolving with an arterial input function (AIF). While these methods produce parameters that are theoretically specific to a biological marker of interest there is much confusion and little consensus as to the best models to use. In addition there is often a significant degree of subjectivity in the calculation of the critically important AIF. The hypothesis of this study was: *that model free analyses of DCE-MRI data without de-convolution of an AIF can quantitatively and objectively characterize the perfusion of high grade malignant brain tumors (WHO grade III and IV).*

Aim: With this hypothesis in mind the aim of this study was to determine whether the initial area under the gadolinium time curve (IAUC) [3] can be used to pragmatically and consistently produce useful perfusion maps of high grade malignant brain tumors. To test the hypothesis the IAUC from WHO grade IV tumors were statistically compared to those from grade III tumors.

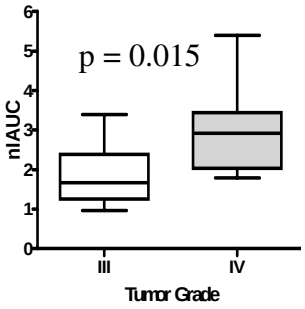
Materials and Methods: Twenty three histopathologically confirmed high grade (III or IV) were entered into a prospective MRI study on a 1.5T GE MRI scanner. The imaging consisted of anatomical T2, FLAIR and T1 weighted imaging, as well as diffusion tensor, T1 mapping and perfusion imaging. Perfusion imaging was performed by acquiring 12 x 3mm multi-slice SPGR images at a time resolution of 8s for between 2 and 5 minutes following a 15s bolus injection of GdDTPA contrast agent. IAUC was calculated on a pixel by pixel basis by converting the SPGR images into Gd concentration maps (based on change in T1) and integrating over the first 60 seconds. The tumors were segmented manually based on T2 or Flair enhancement. The mean IAUC for the entire tumor was then normalised by dividing by the mean IAUC from a contra lateral gray matter ROI (nIAUC).

Results: DCE MRI data was successfully acquired on 21 out of 23 patients (13 grade III and 8 grade 4 tumors). Below is an example of a nIAUC map from a grade IV GBM patient. It can be seen that the tumor is significantly and heterogeneously perfused consistent with high CBV, CBF and Ktrans. Using a "bar and whiskers" plot (below) it can be seen that in general grade IV tumors have greater perfusion than grade III brain tumors. This was confirmed statistically using a two-tailed t-test. The mean nIAUC from grade IV tumors (2.99 ± 0.42) was significantly (p=0.015) greater than that from grade III tumors (1.87 ± 0.21). In addition, receiver operating curve analysis (AUC = 0.82± 0.14) showed that nIAUC showed great promise in distinguishing tumor grade.



DCE MRI results from a 65 year old male with a heterogeneous Glioblastoma Multiforme (WHO grade IV) tumor. Mean nIAUC = 5.9

Discussion: Analysis of MRI perfusion data using nIAUC has been proposed and utilized for quantifying perfusion in various human tumors and animal tumor models. The results of this study are novel in that we believe this is the first time that nIAUC analysis has been shown to correlate with a biologically relevant end point (histopathology) in human brain tumors. Such a correlation is an important first step in the development and validation of any biomarker. While nIAUC may lack some specificity for a biological end point (eg CBV), the simplicity of the analysis suggests that it has great potential for standardisation across multiple centers and field strength. Standardisation is critical for the translation of perfusion imaging as an endpoint in clinical trials of novel antiangiogenic agents or into clinical diagnostic and follow-up procedures. It is interesting to note that CBV has previously been shown to discriminate between low an high grade brain tumors but not between grade III and IV tumors.



Conclusion: In this study we have shown that the model free (nIAUC) analysis is a pragmatic, useful and clinically relevant method for analysing DCE-MRI data from human brain tumors. Its pragmatism and correlation with histopathology suggest it has great potential for translation as a validated imaging biomarker for non-invasive assessment of assessment of brain tumor angiogenesis.

References: 1. LAW M et a. 2006, **AJNR,** 27(9), p 1975-82.
2. Batchelor et al. 2007**, Cancer Cell,** 11, p 83-95.
3. Evelhoch JL, 1999, **Magn. Reson. Med.**, 10(3), 254.