Combination of Diffusion and Perfusion for Multi-parametric Treatment Response Mapping of Human High Grade Glioma

T. L. Chenevert[1], C. J. Galban[1], D. A. Hamstra[2], C. I. Tsien[2], L. R. Junck[3], P. C. Sundgren[1], C. R. Meyer[1], M. K. Ivancevic[1,4], T. C. Kwee[1], S. E. Rohrer[1], and B. D. Ross[1]

[1]Radiology - MRI, University of Michigan, Ann Arbor, Michigan, United States, [2]Radiation Oncology, University of Michigan, Ann Arbor, Michigan, United States, [3]Neurology, University of Michigan, Ann Arbor, Michigan, United States, [4]MRI, Philips Medical Systems, Cleveland, Ohio, United States
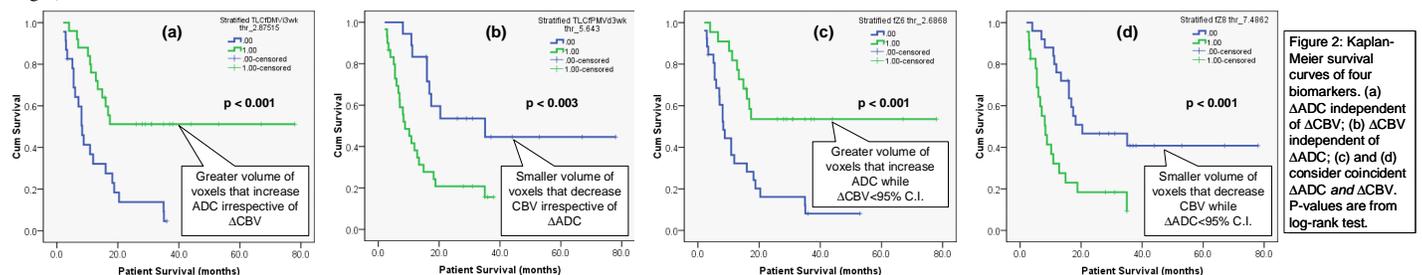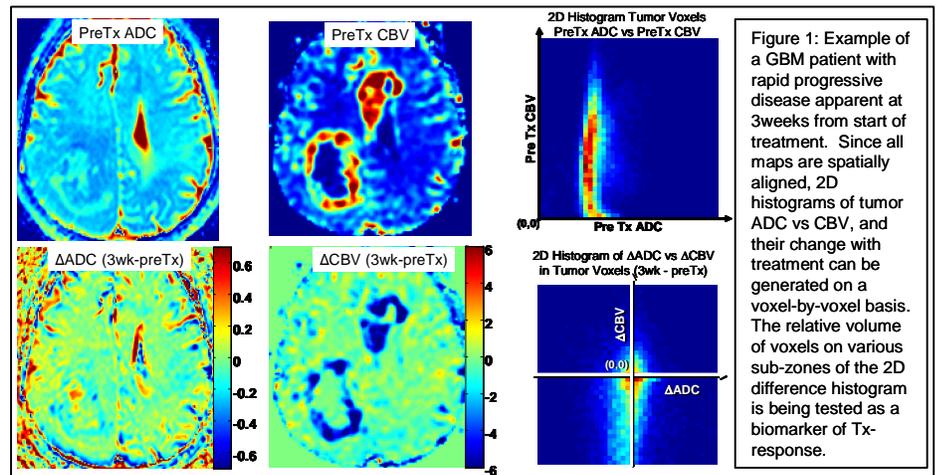
Introduction

Therapy-induced alteration of tumor cellularity and perfusion suggests diffusion and perfusion may serve as treatment-response biomarkers. Whole-tumor averages of ADC and/or perfusion are hampered by heterogeneity, whereas methods based on voxel-by-voxel differences of spatially-registered ADC and/or perfusion maps (1-3) allow regional measures of response and show promise. These prior approaches utilized ADC and perfusion as stand-alone biomarkers. In this study, we explore use of co-alignment of ADC with perfusion maps, as well as over the pre-Tx to early-Tx interval such that patterns of simultaneous change in ADC *and* perfusion within each voxel are determined. The fractional volume of tumor voxels exhibiting significant change with therapy in this dual-parameter space is tested for prognostic power.

Materials and Methods

Fourty-eight Grade III/IV glioma patients were enrolled in a prospective IRB-approved study and underwent MRI examination <2wk prior to and within 3-4 weeks from start of conventional chemo-RT treatment. MRI exams performed on 1.5T and 3T systems included anatomic, DWI, and dynamic susceptibility contrast perfusion imaging. ADC and CBV/F maps were generated for pre-Tx and early-Tx timepoints, and for each patient all maps were spatially registered to a common pre-Tx anatomic image set by way of mutual-information. Since intermodality (ADV & CBV) and interval (preTx & 3wk) maps were aligned, two-dimensional histograms of ADC vs CBV within the tumor and its temporal change could be generated. In analogy to prior voxel-difference methods (1-3), the fractional volume of tumor voxels exhibiting significant change (>95% confidence interval) defined distinct zones on the 2D histogram space of ΔADC vs ΔCBV. The fractional volumes of voxels in these zones were trialed as response biomarkers. "Tumor" was defined as voxels within Gd-enhanced VOIs on both preTx and 3wk timepoints. ROC analysis was used to derive a threshold for each potential biomarker for stratification of "non-responder" and "responder" groups. Kaplan-Meier analysis and log-rank test were used to compare potential biomarkers for prediction of overall survival.

Results

Figure 1 illustrates an example case mapping ADC vs CBV, as well as ΔADC vs ΔCBV on a voxel-by-voxel basis. For this individual whose disease progressed rapidly, most tumor rim voxels displayed a precipitous drop in CBV with a coincident slight decrease in ADC depicted on the 2D histogram. Kaplan-Meier survival plots for all 48 patients stratified by 4 potential Tx-response biomarkers are shown in Figure 2. The biomarkers correspond to: (a) fractional volume of voxels that exhibit a significant increase in ADC irrespective of ΔCBV (2, 3); (b) fractional volume of voxels that exhibit a significant decrease in CBV irrespective of ΔADC (1); (c) fractional volume of voxels that exhibit a significant increase in ADC while ΔCBV is less than 95% change threshold (eg. 2D histogram shifting right but not up or down); and (d) fractional volume of voxels that exhibit a significant decrease in CBV while ΔADC is less than 95% change threshold (eg. 2D histogram shifting down but not left or right).

Figure 1: Example of a GBM patient with rapid progressive disease apparent at 3weeks from start of treatment. Since all maps are spatially aligned, 2D histograms of tumor ADC vs CBV, and their change with treatment can be generated on a voxel-by-voxel basis. The relative volume of voxels on various sub-zones of the 2D difference histogram is being tested as a biomarker of Tx-response.

Figure 2: Kaplan-Meier survival curves of four biomarkers. (a) ΔADC independent of ΔCBV; (b) ΔCBV independent of ΔADC; (c) and (d) consider coincident ΔADC *and* ΔCBV. P-values are from log-rank test.

Conclusions

Based on log-rank p-values, there is some minor improvement in biomarker performance by combining ΔADC *and* ΔCBV features in voxel-difference approaches. This analysis indicates a lower overall survival in patients that exhibit a greater fraction of tumor that decrease CBV relative to baseline. This is particularly interesting given the fact that patients having a high baseline CBV have a poorer prognosis, thus it is reasonable to expect that a therapy-induced drop in CBV leads to a desirable outcome (ie. longer survival), yet the opposite is observed in this study. It is possible this observation stems from inherently high dynamic range of CBV in patients with highly perfused tumor. Thus, while there is greater latitude for therapy-induced CBV reduction, the therapy still fails and these persistently aggressive tumors lead to shorter overall survival.

References

1. Galban CJ, Hamstra DA, Meyer CR, et al. The Functional Perfusion Map: A Novel Imaging Biomarker for Early Prediction of Tumor Patient Response. Proceedings of the International Society of Magnetic Resonance in Medicine 2008:2194.
2. Hamstra DA, Galban CJ, Meyer CR, et al. Functional Diffusion Map As an Early Imaging Biomarker for High-Grade Glioma: Correlation With Conventional Radiologic Response and Overall Survival. J Clin Oncol 2008.
3. Moffat BA, Chenevert TL, Lawrence TS, et al. Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response. Proc Natl Acad Sci U S A 2005; 102:5524-5529.