A Composite Model of the Parametric Response Map Predicts Survival Independent of Radiographic Response in Patients with High Grade Glioma

C. J. Galban[1], T. L. Chenevert[1], D. A. Hamstra[2], C. R. Meyer[1], P. Sundgren[1], C. Tsien[2], T. S. Lawrence[2], A. Rehemtulla[2], T. D. Johnson[3], and B. D. Ross[1]

[1]Radiology, University of Michigan, Ann Arbor, MI, United States, [2]Radiation Oncology, University of Michigan, Ann Arbor, MI, United States, [3]Biostatistics, University of Michigan, Ann Arbor, MI, United States

Introduction: Assessment of radiographic response (RR) is critical in the management of patients with high-grade glioma. We recently developed the parametric response map (PRM), a method to quantify regional changes in tumor diffusion (apparent diffusion coefficient (ADC)) and perfusion (relative cerebral blood flow (rCBF)) MRI parameters, as an early response metric [1]. Here we evaluated if the combination of PRM_{ADC} and PRM_{rCBF} would increase their prognostic value.

Methods and Materials:

Patient

Patients (n=44) with Grade III/IV glioma were recruited for this trial. Patients underwent MRI 1-2 weeks before RT and at weeks 3-4 during RT. When MRI was performed at weeks 1-2 during RT, the patients had received a median dose of 12 Gy (range, 5-6). At Weeks 3-4, the median dose was 32 Gy (range, 26-40). MRI scans were acquired on a 1.5T GE clinical scanner (GE Medical Systems, Milwaukee, WI) or a 3T Philips clinical scanner (Philips Medical Systems, Andover, MA).

Dynamic Contrast Susceptibility- Magnetic Resonance Imaging

Dynamic contrast-susceptibility (DCS) T_2*-weighted imaging with intravenous administration of a standard dose (0.1 mL/kg) bolus of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), and post contrast T_1-weighted images were acquired by a gradient-echo echo-planar imaging pulse sequence (TR=2s, T2=60ms, field of view 220x220 mm^2, matrix 128x128, flip angle 60°, and 14 interleaved slices with 6mm thickness and 0mm gap). The relative cerebral blood flow (rCBF) in the brain and tumor were computed as described by Ostergaard [2].

Diffusion Weighted Imaging

Diffusion weighted images were acquired using a single-shot, spin-echo, diffusion-sensitized, echo-planar sequence. Sequence parameters were: TR/TE=10000/100ms; FOV=22cm; matrix=128x128; 24 slices; and slice thickness = 6mm thick. Slices were contiguous with the slice package axial-oblique. Diffusion-weighting was performed with gradients applied along all orthogonal directions with b values of 0 and 1000 s/mm^2 (b0 and b1, respectively). Scan time was approximately 40 s. The DWIs for the three orthogonal directions and b0 image were used for calculating an ADC map.

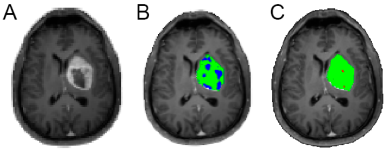

Figure 1: Patient with a glioblastoma multiforme designated by PRM_{rCBF} and PRM_{ADC} stratification as a non-responder (survival time=3.4 months). (A) Gd-enhanced T_1-weighted MR image, and (B) PRM_{rCBF} and (C) PRM_{ADC} color-encoded ROI superimposed onto a Gd-enhanced T_1-weighted MR image pre-radiotherapy.

Parametric Response Map (PRM)

All images were co-registered to Gd-enhanced T1-weighted images acquired before RT using an automated mutual information and simplex optimization module [3]. Following co-registration, brain tumors were manually contoured on the Gd-enhanced T_1-weighted images by radiologists. The rCBF and ADC values of each voxel within the tumor at weeks 1 and 3 were compared with respective pre-RT values. PRM_{rCBF} and PRM_{ADC} was performed by thresholding the absolute difference of the respective modality in a voxel into three categories: significantly increasing (V_I: red); significantly decreasing (V_D: blue); and unchanged (V_0: green). The thresholds were empirically determined to be the 95% confidence intervals calculated from normal contralateral brain tissue.

Statistics

Receiver operator characteristic analysis, assessed for 12 month survival, was used to determine the optimal cutoff for V_I and V_D generated individually from PRM_{ADC} and PRM_{rCBF} . For each PRM analysis, the parameter (V_I or V_D) that generated the largest area under the curve was used to determine the optimal cutoff. Patient population was then stratified based on these optimal cutoffs. The composite model comprised of information from both PRM_{ADC} at week 3 and PRM_{rCBF} at week 1: 1) patients found to be non-responders by both methods, 2) patients found to be responders by both methods and 3) patients where both methods conflict. PRM_{ADC} at week 3 (cutoff was V_I=4.7%) and PRM_{rCBF} at week 1 (cutoff was V_D=4.2%) were found to be most sensitive for predicting overall survival; the composite model was thus based on these measures. Kaplan-Meier survival curves and the log-rank test were used to characterize and compare the groups in terms of overall survival for RR, PRM_{ADC}, PRM_{rCBF} and $PRM_{ADC\text{-}rCBF}$. Multivariate comparisons were performed using a Cox regression analysis. Statistical significance was assessed at $p<0.05$.

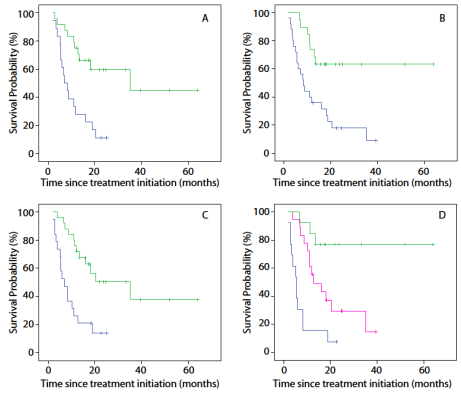

Figure 2: Kaplan-Meier survival plots of overall survival for patients stratified by (A) RR, (B) PRM_{ADC}, (C) PRM_{rCBF} and (D) $PRM_{ADC\text{-}rCBF}$.

Results: The differences between PRM_{rCBF} and PRM_{ADC} are highlighted in Fig. 1. In this figure, a representative slice is provided showing (A) contrast enhancement on a T_1-weighted image, (B) PRM_{rCBF} overlay and (C) PRM_{ADC} overlay of a patient diagnosed with a GBM (survival time of 3.4 months). Our previous work determined that large V_D (blue) in PRM_{rCBF} and small V_I (red) in PRM_{ADC} suggest a poor prognosis. It is seen here that from two separate imaging modalities, which are sensitive to different physiological and metabolic mechanisms, PRM of these modalities resulted in the same outcome. RR assessed at 10 weeks was found to have median survival times of 7 and 35.1 months for non-responders and responders (p=0.001), respectively (Fig. 2A). Similar results, presented in Figs. 2B and 2C, were observed for both PRM_{ADC} (median survival: non-responder 8.3 months and responders not reached; p=0.002) and PRM_{rCBV} (median survival: non-responder 7 and responders 35.1 months; p=0.001). $PRM_{ADC\text{-}rCBF}$ resulted in median survival times of 5.5 for non-responders (blue), 12.8 for intermediate (purple) and was not reached for responders ($p<0.0001$) (Fig. 2D). Multivariate model using the Cox regression showed that PRM_{ADC} (p=0.037) and PRM_{rCBF} (p=0.038) contributed more to the model than RR (p=0.384). Replacement of PRM_{ADC} and PRM_{rCBF} with composite model ($PRM_{ADC\text{-}rCBF}$) resulted in a strong dependence of the model to $PRM_{ADC\text{-}rCBF}$ (p=0.007). RR continued to contribute little to the model (p=0.386).

Discussion: Compared to conventional RR both PRM_{ADC} and PRM_{rCBF} provided earlier assessments of treatment response that were similarly predictive of overall survival. In addition, the combination of PRM parameters provided the best predictor of overall survival and was independent of RR.

References:

1. Moffat, B.A., et al., Proc Natl Acad Sci U S A 2005. 102, 16759-16764.
2. Ostergaard, L., et al., Magn Reson Med, 1996. 36, 715-25.
3. Meyer, C.R., et al., Med Image Anal 1997. 1, 195-206.