A Combined Gradient-Echo/Spin-Echo DSC Method: A Surrogate Marker for Brain Tumor Histologic Grade and Angiogenesis in Patients

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Synopsis: In 45 patients, diagnosed with gliomas, a simultaneous GE/SE echo planar imaging sequence was used to obtain GE ("total") and SE ("microvascular") relative cerebral blood volume (rCBV) maps while enabling the calculation of the GE:SE ratio, a marker of mean vessel diameter (mVD). A significant correlation between GE rCBV and grade, and mVD and grade is observed for whole tumor. Only when evaluating rCBV "hot spots" is a significant correlation between SE rCBV and grade observed. Combining the GE and SE data results in a distinct classification boundary between lower grade (II/III) and high grade (IV) tumors emerges suggesting that this approach will provide relevant information regarding tumor grade and potentially angiogenesis on a per-patient basis.

Introduction: As indicated by several initial studies (eg. (1-5)), dynamic susceptibility contrast (DSC) MRI methods, which allow the creation of relative cerebral blood volume (rCBV) maps, have the potential to evaluate novel cancer drugs that target a tumor's new blood vessel growth (ie angiogenesis). While the standard approach has been to acquire rCBV maps using either gradient-echo (GE) or spin-echo (SE) imaging methods, our approach was to acquire GE and SE rCBV maps simultaneously, since each has a different sensitivity to vessel diameter, which itself has been shown to be a relevant marker of angiogenesis. While SE is maximally sensitive to microvessels, GE is sensitive to vessels of all diameters, thus providing "microvascular" and "total" blood volume maps. Also, the GE:SE relaxation rate ratio ($\Delta R2^*/\Delta R2$) may serve as a direct index of vessel diameter, as demonstrated in animal tumor models using long-lived contrast agents (6, 7). In the present analysis of 45 patients, we test the hypothesis that these measurements provide relevant information about tumor angiogenesis by testing their correlation with tumor grade, a known correlate of brain tumor angiogenesis. The work presented here represents an update of the results reported at a recent ISMRM workshop (8).

Methods: A total of 170 rCBV studies have been performed to date, with informed written consent, under guidelines approved by the Institutional Review Board at our Institution. The rCBV analysis has been completed on 123 of these studies. Of these 45 were gliomas that had tissue confirmation of diagnosis and are presented here. All MRI studies were performed on a 1.5T GE Signa System fitted with a 12" local gradient coil and a quadrature transmit-receive birdcage RF coil (IGC-Medical Advances, Milwaukee, WI). A 0.05-0.10 mmole/kg dose of Gadodiamide (Omniscan; Nycomed Amersham, Princeton, NJ) was administered to diminish T1 effects that might result from agent extravasation. Next, simultaneous GE/SE-EPI images, were acquired for 1 minute before and 2 minutes after a 0.15-0.25 mmole/kg bolus injection. Five, 7 mm slices were acquired at TE(GE)/TE(SE) = 30ms/109.1ms with fat suppression, TR=1s, a FOV=24cm and matrix = 64x64. Finally, conventional post-contrast T1-weighted images were acquired (SE, TE/TR = 11 ms/500 ms, matrix = 256x256). The ratio, GE and SE rCBV maps, corrected for agent extravasation were determined as previously described (3). Data was extracted from ROIs of the whole tumor (avoiding areas of necrosis), contralateral brain and from tumor "hot spots" defined as the areas of highest SE rCBV. All results are normalized to contralateral brain. A correlation between the MRI-derived parameters and tumor grade was evaluated with the Spearman rank correlation test. Fisher's linear discriminant analysis was applied to determine if a classification boundary, separating grade II-III from grade IV tumors, could be determined.

Results: The results from 42 patients (excluding 3 statistical outliers) include those with grade II (n=12), grade III (n=7) and grade IV (n=26) tumors. The rCBV and mVD measurements were significantly different between whole tumor and contralateral brain parenchyma (GE: p=0.0002; SE: p=0.003; mVD: p=0.0002). Data from whole tumor (Fig. 1), showed a significant correlation between GE rCBV and tumor grade (p=0.003) and ratio ($\Delta R2^*/\Delta R2$) and grade (p=0.0007), but not between SE rCBV and grade (p=0.86). Considering areas of highest SE rCBV (microvascular "hot-spots") only, a significant correlation with grade emerged (p=0.001) for SE rCBV. Using GE and SE rCBV data together, a good distinction between grade II-III and grade IV tumors resulted with apparent and expected-actual misclassification rates of 19%-24% (Fig 2).

Figure 1.

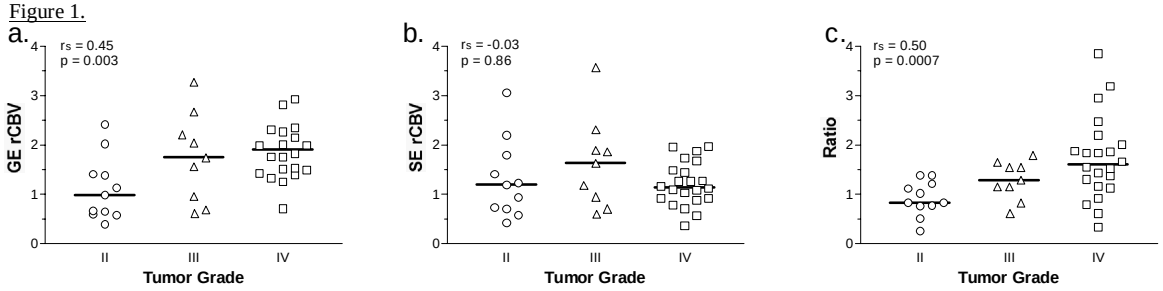
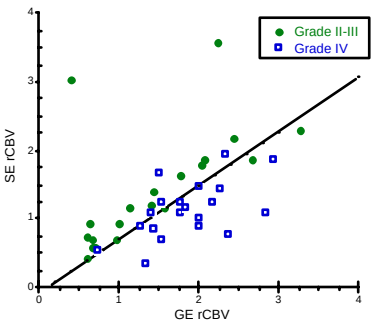


Figure 2.



Summary: In this study of 45 patients, whole tumor, "total" and "microvascular" blood volume are increased relative to contralateral brain, and the "mean vessel diameter" is enlarged. For whole tumor, the "total" rCBV and mVD are predictive of tumor grade, while the "microvascular" rCBV is not. Yet, when considering tumor microvascular hot spots only, the "microvascular" blood volume is predictive of tumor grade. This is consistent with the standard histologic approach of using the highest microvessel count to predict angiogenesis and grade. The fact that $\Delta R2^*/\Delta R2$ did not correlate with grade when evaluating hot-spots is consistent with the idea that it is a marker of the mean vessel diameter, since in this case we are pre-selecting for vessels of a given diameter. Finally, a good delineation between tumor grades was established when combining the GE and SE data, an indication that this approach provides relevant information on a per-patient basis.

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