# Differentiation Between Progressive Disease and Treatment Necrosis in Patients with Glioblastoma using Dynamic Contrast Enhancement MRI

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## TARGET AUDIENCE:

Scientists and clinicians who have an interest in DCE, tissue classification and brain tumor assessment

## PURPOSE:

Differentiation between progressive-disease (PD) and treatment related necrosis (TN) remains a major clinical challenge in patients with glioblastoma (GB), and has significant therapeutic implications[1]. PD and TN are typically indistinguishable using conventional MRI, both manifesting as enhanced areas on post contrast agent $T_1$ weighted images (WI), with surrounding edema in most cases. ***The aim*** of this study was to differentiate between PD and TN on a voxel basis, based on dynamic contrast enhancement (DCE) MRI.

## METHODS:

***Patients and MRI Protocol:*** Eighteen patients with biopsy-proven GB were longitudinally scanned on a 3.0 Tesla GE MRI, every two months, giving a total of 60 MR scans. MRI scans included: $T_1$WI acquired before and after contrast agent injection; $T_2$WI; FLAIR; DCE, acquired using multi phase spoiled gradient recalled echo (SPGR) with variable flip angles for the $T_1$ maps; and PRESS single-voxel MR spectroscopy (MRS). Patients were *retrospectively* labeled with PD or TN based on conventional MRI results at ~6 months follow-up scan.

***Data analysis:*** Preprocessing included skull stripping and realigning of all anatomical images to the DCE space. The normal appearing white matter (NAWM) was extracted from the FLAIR and post contrast $T_1$WI using FSL automatic segmentation tool. The enhanced tumor area, used as the target area for classification, was automatically segmented from the raw DCE data using independent components analysis (ICA). The DCE Pharmacokinetic (PK) parameters were calculated using DUSTER, a method for DCE Up Sampled TEmporal Resolution[2,3], based on the Extended-Tofts-Model[4,5] with correction for the $T_1$ maps and accounting for differences in the bolus-arrival-time (BAT). Model selection was applied similarly to Bagher-Ebadian[7]. A voxel-wise classification of the target tumor area was performed in all patients using support vector machine (SVM) based on the calculated PK parameters. First, a training data set was obtained from 210 voxels manually selected in each of the PD and TN groups. Differences between the PK parameters in the different tissue classes, PD, TN, and NAWM, were compared between groups using one way ANOVA with correction for multiple comparisons. Classification results were validated by a senior neuro-radiologist, verified by MRS, and sensitivity and specificity were measured based on 2-fold cross validation analysis using even odd -patient-out.

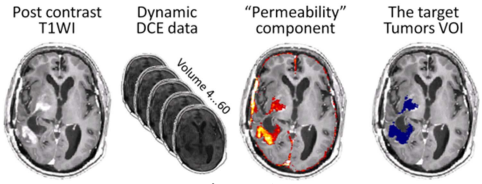

Figure 1

## RESULTS AND DISCUSSION:

Segmentation of the enhanced tumor area using ICA enabled automatic differentiation between the tumor tissue and other enhanced components such as arteries, veins and choroid plexus. Figure 1 demonstrates the classification process in one patient, with identification of the enhanced tumor area. Similar results were obtained in all patients.

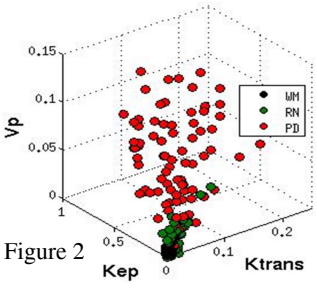

Figure 2

***DCE parameters in the different tissue classes:*** Significant differences were detected between the mean values obtained for the manually labeled PD, TN, and NAWM areas (Figure 2), with higher transfer constants ($K^{trans}$ and $k_{ep}$), extra-cellular extra-vascular volume ($V_e$) and plasma-volume ($V_p$) values, detected for the PD compared to the TN and NAWM, and prolonged BAT values for the TN relative to the PD component.

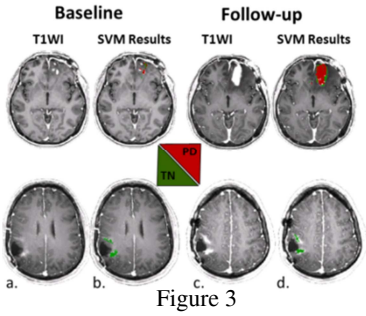

Figure 3

***Voxel-wise classification of tumor area:*** SVM algorithm classified all scans, and results were supported by MRS, consistent with radiological assessment at follow-up, and showed high sensitivity (89.3%) and specificity (89.4%) using cross validation analysis of the SVM results. Figure 3 demonstrates representative results obtained from two patients, at baseline (a, b) and at follow-up scan (c, d); In patient #1, (top row) PD was identified at baseline, and predicted the increase in tumor volume, detected 6 months later. In patient #2 (bottom row) TN was identified at baseline, with no changes in this area (volume and classification) at follow-up scans. Similar results were obtained in all patients, demonstrating the potential predictive value of the proposed method.

## CONCLUSION:

This study proposes an automatic method for differentiation betwenn PD and TN in patients with GB, based on PK parameters and provides reference values for the DCE PK parameter values. Results of this study may have major clinical importance for diagnosis and therapy response assessment in patients with GB.

**REFERENCES:** [1]Verma et al. Neuro Oncol 2013; [2]Liberman et al. ISMRM 2014; [3]Liberman et al. Journal of Magnetic Resonance Imaging 2013; [4]Sourbron et al. NMR Biomed 2013, [5]Tofts et al. MRM 1991; [6]Bagher-Ebadian et al. MRM 2012;