

Longitudinal Monitoring of Low-Grade Glioma Transformation: A Fully-Automatic Method using Quantitative DSC-MRI

K. E. Emblem^{1,2}, P. Due-Tonnessen^{1,3}, I. A. Rasmussen Jr¹, and A. Bjornerud^{2,4}

¹The Interventional Centre, Rikshospitalet, Oslo University Hospital, Oslo, Norway, ²Department of Medical Physics, Rikshospitalet, Oslo University Hospital, Oslo, Norway, ³Clinic for Imaging- and Intervention, Rikshospitalet, Oslo University Hospital, Oslo, Norway, ⁴Department of Physics, University of Oslo, Oslo, Norway

Purpose: To evaluate a fully-automatic method for longitudinal monitoring of low-grade glioma transformation by quantitative dynamic susceptibility contrast (DSC) MR imaging and to compare the method with conventional criteria for malignant glioma progression.

Background: Recently, relative cerebral blood volume (CBV) values from DSC-based MR imaging has been suggested as a marker for low-grade glioma progression, demonstrating significant differences in relative CBV values in transforming gliomas up to 12 months prior to conventional criteria such as T1-w contrast enhancement [1]. With such exciting results, the need for a robust, reproducible and user-independent analysis method is evident. In our study, we have introduced a fully-automated analysis method using quantitative DSC tumor imaging and monitoring of baseline perfusion in unaffected brain tissue, thereby allowing inter- and intra-patient comparisons across MR machines and institutions.

Methods: The study was approved by the regional medical ethics committee. Thirteen patients with a histopathological confirmed (7 patients), or an untreated, suggestive (6 patients) diagnosis of a low-grade (WHO grade II) glioma have so far been included in the study (aged 15-69 yrs, mean age 41; 8 males, 5 females). During the study, all patients were treated conservatively (observation only) and no patient received radiation treatment or surgery. All patients were imaged at least three times, and the average time between two consecutive MR exams was 283 days (range 56-842 days). Imaging was performed at 1.5 T (Siemens Sonata or Avanto, Siemens AG, Germany). The MR imaging protocol consisted of axial T2-w images, axial T1-w images (pre- and post-contrast) and coronal FLAIR images. The MR perfusion images were acquired using a first-pass gradient echo (GRE)-EPI sequence with TR=1.5s, voxel size 1.8x1.8x6.5mm³ and i.v. bolus injection of 0.2 mmol/kg of Gadovist (Schering AG, Germany). Quantitative CBV maps were derived using established methods [2] and the arterial input function was automatically detected in each DSC image slice using K-means cluster analysis [3] and corrected for potential partial volume effects [4]. Areas of normal-appearing gray- and white-matter tissue were automatically derived from the DSC images only, using K-means cluster analysis of the first pass response [5]. Areas of tumor tissue was automatically segmented from the anatomical MR images using knowledge-based Fuzzy C-means cluster analysis [6]. For each time point (i.e. MR exam), mean gray- and white-matter quantitative CBV values were derived and a normalized histogram peak height value was derived from the distribution of quantitative CBV values in the segmented tumor area. From this, a relative perfusion index (rPI) assessing the relationship between the gray/white matter values in combination, and the tumor histogram peak heights were derived and compared to conventional criteria for glioma progression as seen on the anatomical MR images (i.e. tumor growth, contrast enhancement) and also neurological/clinical status [1]. Image analysis was performed using Matlab R2008a (MathWorks, Natick, US) and nordicICE (NordicImagingLab, Norway). Statistical analysis was performed using SPSS 15 (SPSS, Chicago, Ill).

Results: The rPI values at time points with tumor transformation (Yes/No) using conventional criteria were significantly lower compared to the non-transformers (Mann-Whitney; $P=0.03$). There was also a borderline significant relationship between the rPI values at time points with (a) no visible tumor growth or contrast enhancement, (b) visible tumor growth but no contrast enhancement and (c) visible tumor growth and contrast enhancement (Kruskal-Wallis; $P=0.049$). Figure 1 shows post-contrast T1-w images and quantitative CBV maps of a patient diagnosed with a malignant transforming glioma. Using linear mixed models, the rPI curves as a function of time was significantly different for the transformers compared to the non-transformers ($P=0.011$). Resulting rPC curves of transforming and non-transforming gliomas are shown in Figure 2. For the two patients that were diagnosed as transformers during the study because of visible contrast enhancement and moderate function impairment (Neurological performance scale; NPS = 2), the rPI curves predicted tumor progression 289 and 363 days prior to conventional diagnosis.

Discussion: Early detection of malignant glioma transformation in longitudinal tumor monitoring is of high clinical importance. Our preliminary results suggest that the rPI value is associated with glioma transformation. Also, as confirmed by others [1], our study suggests that DSC imaging can detect glioma transformation up to one year prior to visible changes in contrast enhancement and reduced NPS status. By having a method more sensitive to glioma progression than conventional methods, the decision making process as to whether an ongoing treatment strategy should be continued, terminated or changed, could potentially be accelerated to the benefit of the patient. The added value of using quantitative CBV values in the analysis is standardized perfusion metrics with reduced sensitivity to patient-, site- and scanner-specific variations. Finally, the fully-automatic procedure improves speed and reproducibility of the measurements, thereby removing user-induced bias and making the technique clinically feasible.

Conclusion: In our study, we have shown that a fully-automatic method for longitudinal monitoring of malignant glioma transformation using quantitative DSC imaging provides a sensitive marker for tumor progression at an early stage compared to conventional imaging criteria. The quantitative analysis is attractive in that it simplifies inter- and intra-patient comparisons. Combined with the fully-automatic procedure, it is expected that the availability of the proposed method will increase the acceptability and clinical utility of DSC imaging for the benefit of health care.

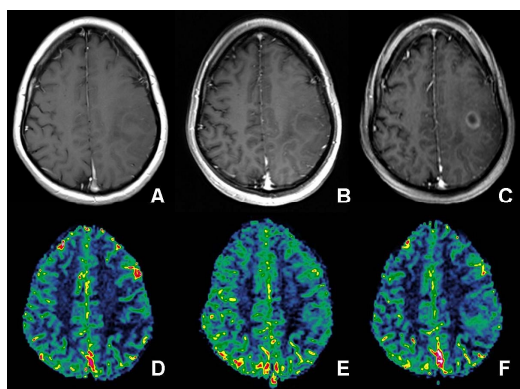


Figure 1: Axial T1-w post-contrast MR images (A-C) and corresponding quantitative CBV maps (D-F) of a 42-year old female patient with a transforming glioma. The images (A,D), (B,E) and (C,F) were acquired with ~1 year intervals and areas of high CBV values are visible in the tumor area in (E) 289 days prior to the contrast enhancement in (C).

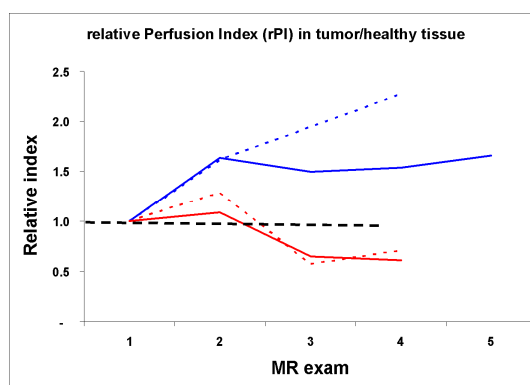


Figure 2: Relative perfusion index (rPI) curves of two non-transforming glioma patients (blue lines) and two transforming glioma patients (red lines). Compared to the reference value (1.0), the transforming gliomas convey malignant signatures at time point 3 and onwards.

References:

- [1] Danchaivijitr et al. Radiology 2008;247:170-178
- [2] Ostergaard et al, MRM 1996;36:715-725
- [3] Mouridsen et al. MRM 2006;55:524-531
- [4] Ziegelitz et al. MRM 2009;62:56-65
- [5] Emblem et al. AJNR 2009;Oct 8;Epub
- [6] Emblem et al. JMIR 2009;30:1-10