Pseudo-tumoral response of glioblastoma to anti-angiogenic treatment prematurely revealed by using Arterial spin-labeling (ASL) perfusion MRI and susceptibility weighted imaging (SWI).

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Introduction:
Angiogenesis plays a key-role in the growth and spread of solid tumors (1). This is especially true for Glioblastoma Multiforme (GBM), which is the most common and aggressive subtype of malignant glioma. New therapies involving anti-angiogenic agents may therefore now be part of the therapeutic protocol and they have been shown to dramatically improve response and survival in patients with recurrent GBM (2). However, with these agents, pseudo-response followed by a critical recurrence, may be observed. Non-responders thus need to be identified prematurely. Currently, assessment of tumor evolution after treatment is based on changes in tumor volume and extent of contrast enhancement (3). However, these morphological parameters are “late criteria” and new MR markers need to be found to provide early information on the tumor response. Recent researches thus investigate the potential role of other imaging modalities. In this study, we performed longitudinal MR follow-up of GBM treated with anti-angiogenic chemotherapy, using a multimodal MR protocol. The investigations particularly involved arterial spin-labeling (ASL) perfusion MRI and susceptibility weighted imaging (SWI). Both sequences provide vascular information that may be particularly appropriated to evaluate the anti-angiogenic response in comparison with conventional MRI.

Materials and Methods:
One patient (76 years) with pathologically proven GBM was examined before treatment (D0), and 15 (D15), 30 (D30), 90 (D90), 120 (D120) and 180 days (D180) after a treatment including chemotherapy and anti-angiogenic agent (Avastin, Genentech/Roche). All imaging studies were performed on a 3T MRI scanner (Magnetom Verio, Siemens Medical Solutions, Germany) using a 32-channel phased-array head coil. The multimodal MRI protocol included 3D pre- and post-contrast T1-weighted MRI (TR/TE 1900/2 ms, matrix 256*256, slice thickness 1mm), 3D FLAIR (TR/TE 5000/395ms, matrix 256*256, slice thickness 1mm), DWI (TR/TE 8800/95 ms, matrix 128*128, slice thickness 2.5mm), 3D chemical shift imaging (TR/TE 1500/30ms, voxel size 9*9*10mm3), 3D SWI (TR/TE 27/20ms, slice thickness 1mm), ASL perfusion MRI (TR/TE 2500/11ms, matrix 64*64, slice thickness 6mm) and DSC (TR/TE 1350/30ms, matrix 128*128, slice thickness 3mm, injection of DOTAREM, 0.2 ml/kg, 7 ml/s). All MR images were co-registered by using SPM5 software (Wellcome Trust Centre for Neuroimaging, UK). Healthy and tumoral hemispheres were outlined manually for each slice. Abnormal regions in the tumoral hemisphere were then automatically determined based on thresholds derived from the healthy control area (thresholdabnormal=(mean+2*stdevhealthyarea), using an algorithm developed with IDL (ITT Visual Information Solutions, USA). The values were afterward normalized to the contralateral hemisphere ones.

Results:
The most characteristic imaging modalities used in our multimodal protocol are illustrated on figure 1. The evolution of the tumor aggressiveness, defined as (abnormal area*abnormal value/contralateral value), is given in figure 2 for the most significative imaging modalities. During the first weeks after the beginning of the treatment, a decrease in the contrast-enhanced areas and FLAIR hyperintensity was noticed, while ASL and DSC showed a progressive increase with time and SWI no significant changes. From D90, all parameters increased. All treatments were stopped after 180 days.

Discussion:
The results observed on FLAIR and post-contrast T1-WI during the first 3 months indicated that the treatment decreases edema and contrast-enhanced areas. However, investigation with perfusion MRI and SWI demonstrated hyperperfusion and increase of the vascularization thus suggesting the absence of vascular normalization and effect of the therapy.
In this preliminary study, perfusion MRI (DSC and ASL) and SWI provided early information on the tumor evolution. From our point of view, the parameters derived from such advanced sequences could be considered as early indicators of disease progression and they may help to prematurely distinguish responder from pseudo-responder. These preliminary findings need of course to be confirmed and larger patient series are currently followed-up. Meanwhile, the potential role of MR spectroscopy and functional perfusion and diffusion maps (4) is being evaluated.

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