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Quantification of serial changes in cerebral blood volume and metabolism in patients with recurrent glioblastoma undergoing antiangiogenic therapy

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ABSTRACT

Objectives: To evaluate the usefulness of quantitative advanced magnetic resonance imaging (MRI) methods for assessment of antiangiogenic therapy (AAT) response in recurrent glioblastoma multiforme (GBM).
Methods: Eighteen patients with recurrent GBM received bevacizumab and 18 patients served as control group. Baseline MRI and two follow-up examinations were acquired every 3–5 months using dynamic susceptibility-weighted contrast (DSC) perfusion MRI and ^{1}H-MR spectroscopic imaging (^{1}H-MRSI). Maps of absolute cerebral blood volume (aCBV) were coregistered with choline (Cho) and N-acetyl-aspartate (NAA) concentrations and compared to usually used relative parameters as well as controls.
Results: Perfusion significantly decreased in responding and pseudoresponding GBMs but also in normal appearing brain after AAT onset. Cho and NAA concentrations were superior to Cr-ratios in lesion differentiation and showed a clear gap between responding and pseudoresponding lesions. Responders to AAT exceptionally frequently (6 out of 8 patients) showed remote GBM progression.
Conclusions: Quantification of CBV reveals changes in normal brain perfusion due to AAT, which were not described so far. DSC perfusion MRI seems not to be suitable for differentiation between response and pseudoresponse to AAT. However, absolute quantification of brain metabolites may allow for distinction due to a clear gap at 6–9 months after therapy onset.

1. Introduction

Glioblastoma multiforme (GBM) are highly vascularized brain tumours with an elevated expression of vascular endothelial growth factor (VEGF) protein, which has been identified as a critical regulator of tumour angiogenesis, endothelial cell proliferation, and migration [1]. GBMs are therefore attractive targets for antiangiogenic therapies (AAT) [2]. The VEGF-specific antibody bevacizumab was approved by the Food and Drug Administration (FDA) for this purpose in 2009 [3]. Preclinical studies demonstrated that AAT not only can lead to a temporary reduction in vascular permeability and oedema [4], but also to an increase of tumour cell invasiveness [2]. Increasing administration of bevacizumab in humans has shown that standard MRI is no longer adequate for assessment of therapy response in GBMs [5] even though its criteria has been updated by the Response Assessment in Neuro-Oncology (RANO) working group [6]. The major challenge based on a decreased vessel permeability [7], which results in diminished contrast agent extravasation [8] but does not necessarily reflect biological tumour response [9]. Alternatives that may offer additional information are measurement of cerebral blood volume (CBV) with dynamic susceptibility-weighted contrast (DSC) perfusion MR imaging [10,11] and determination of brain metabolites with MR spectroscopy [12,13]. Relative parameters (normalized to contralateral side, e.g. rCBV) are generally used in clinical practice. However, for monitoring of perfusion in apparently unaffected brain tissue

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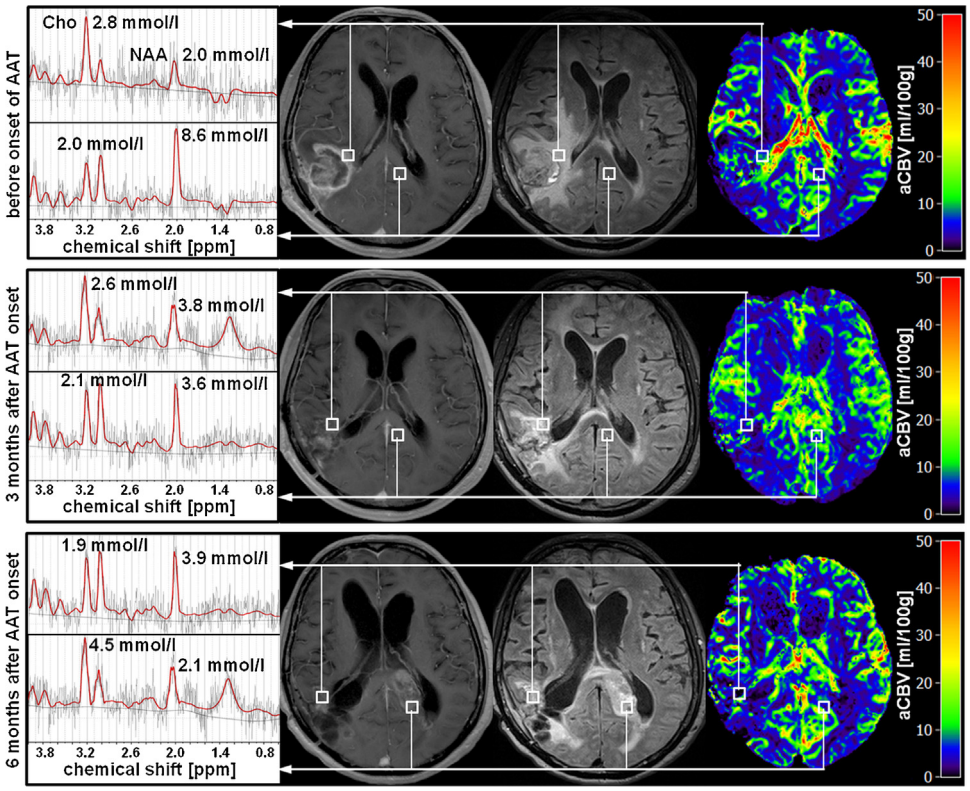

Fig. 1. Quantitative analysis of serial DSC perfusion MR and ^{1}H-MRSI examinations of a 65-year-old male patient with a recurrent GBM (right, parietal) showing response but remote progression under AAT. The results for the baseline (1st) examination before onset of AAT is shown in the upper row, those for the 2nd (3 months after AAT onset) and the 3rd examination (6 months after AAT onset) are presented in the middle and lower row, respectively. A spectrum in the initial lesion (above) and one in the brain region where a remote progression has been developed over time (below) are shown leftmost for each examination. The corresponding axial post-CE T1w MR and FLAIR images are presented in the middle as well as the parametric aCBV maps, which are on the right-handed side. For the initial lesion the spectra demonstrate a decrease in Cho (from 2.8 to 1.9 mmol/l) and an increase in NAA concentration (from 2.0 to 3.9 mmol/l). Anatomical MR images show a reduction in contrast enhancement and oedema, and the aCBV maps a reduction in perfusion as well. For the new lesion the spectra demonstrate an increase in Cho, especially between the 2nd and 3rd examination (from 2.1 to 4.5 mmol/l) and a decrease in NAA (from 8.6 to 2.1 mmol/l) over all three examinations. However, increase in contrast enhancement, oedema and perfusion is only minor. *Note*: White squares are voxel positions in the lesion and in remote progression of the GBM. The numbers overlaid on the spectra are the absolute concentrations for Cho and NAA in mmol/l. The colour codes for the aCBV maps are included rightmost; aCBV values are in units of ml/100 g.

or longitudinal inter- and intra-patient comparisons quantitative perfusion analysis is required but challenging as well [14,15]. The common used strategy for evaluation of metabolite values from ^{1}H-MR spectroscopy is the calculation of ratios using creatine (Cr) as denominator under assumption of stable Cr-concentrations [16]. Few studies [17,18] have discussed the problems that arise with use of metabolite ratios: a loss in metabolic information, artificial variability of metabolic values, and potentially misleading results.

The purpose of this study was to quantitatively investigate serial changes in absolute cerebral blood volume (aCBV) and metabolite concentrations using DSC perfusion MR and ^{1}H-MR spectroscopic imaging (^{1}H-MRSI) in patients with recurrent GBM undergoing antiangiogenic therapy in order to assess the utility for therapy monitoring and to distinguish response from pseudoresponse.

2. Materials and methods

2.1. Patient selection

In this Institutional Review Board – approved study, 67 patients with recurrent glioma after radiation therapy and chemotherapy with temozolomid (Temodal) were retrospectively evaluated (MRI between April 2010 and May 2014). Thirty-one patients were excluded due to tumour pathologic findings other than GBM ($N = 13$) or inadequate imaging available (i.e. incomplete data or insufficient quality; $N = 18$). From the remaining 36 patients, 18 patients (6 women, 12 men; mean age ± standard deviation, 53.1 ± 14.7 years) had not been eligible for AAT because of bevacizumab specific criteria (uncontrolled hypertension, active vascular disease, bleeding, intestinal perforation). These patients received no further chemotherapy. Eighteen patients (8 women, 10 men; 54.4 ± 11.0 years) with recurrent GBMs have been obtained 3–15 cycles (mean, 9 ± 4cycles) of antiangiogenic therapy (Avastin; every 2 weeks 10 mg/kg-bodyweight).

2.2. MRI protocol

MRI was performed on a 3 Tesla whole-body MR unit (Tim Trio; Siemens, Erlangen, Germany) equipped with an 8-channel head coil. MR examinations were performed prior to AAT (baseline or 1st examination) and every 3–5 months after therapy onset. Time to 2nd examination: 107 ± 13 days for AAT-patients and 99 ± 16 days for controls (no AAT); time between 1st and 3rd examination: 234 ± 41days for AAT-patients and 219 ± 47 days for control group. There were no significant differences in time intervals between the subgroups.

The MRI protocol included an axial fluid-attenuated inversion-recovery (FLAIR) sequence (TR/TE/TI, 5000/458/1800 ms; voxel size, 0.5 mm × 0.5 mm × 5 mm), as well as pre- and post-contrast enhanced T1-weighted gradient-echo sequences (TR/TE, 1550/2.6 ms; voxel size, 0.5 × 0.5 × 5 mm). FLAIR images were used for planning of ^{1}H-MRSI experiments and coregistration with anatomic MRI [19]. ^{1}H-MRSI was performed prior to the application of contrast material using a point-resolved spectroscopy sequence