Simultaneous assessment of vessel size index, relative blood volume and vessel permeability in a mouse brain tumor model using a combined spin echo gradient echo EPI sequence and viable tumor analysis

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Introduction

Anti-angiogenic therapy in tumors can be monitored by dynamic contrast enhanced MRI (DCE-MRI) or dynamic susceptibility contrast imaging (DSC-MRI) and vessel size imaging (VSI) to detect changes in tumor microvasculature. DCE-MRI (yielding permeability) is based on the measurement of a concentration time curve after injection of a Gd-based contrast agent (CA), whereas vessel size imaging and DSC-MRI (yielding blood volume) is usually performed with iron-oxide particles. In this work, which is supported by the 2010 ISMRM Seed-Grant, these biomarkers to assess therapy response are acquired simultaneously in vivo using a single shot gradient echo spin echo (GESE) EPI sequence with only one Gd-CA injection (1). To account for tumor heterogeneity tumor segmentation was performed (2). VSI and blood volume measurements using Gd-DTPA has already been demonstrated successfully (3).

Materials and Methods

To demonstrate the feasibility of the GESE sequence for measuring permeability and perfusion parameters and VSI in vivo, brain tumor bearing mice (glioblastoma cell line U-87) were imaged on a 7 T animal scanner (Bio Spec 70/20 USR, Bruker, Ettlingen, Germany) using a mouse cryo surface coil (Bruker). T_2-weighted multislice RARE scans (T_R/T_E: 4270ms/10.6ms, in plane resolution 59 µm x 59 µm) were used to localize the tumor and to select one slice of interest. Tumor tissue segmentation for viable tumor analysis was performed with multispectral k-means clustering using apparent diffusion coefficients ADC maps (multishot diffusion weighted EPI sequence, 6 b-values ranging 100-1000 s/mm^2, T_R/T_E5000ms/29.6ms, NEX=4) and T_2-maps (multi echo spin echo sequence, T_R=3s, 12 echoes with T_E=10…120ms) (2). The tumor was segmented into three tissue compartments of viable tumor and two necrotic regions. A series of single shot GESE scans (1) were acquired pre- and post-injection (i.v.) of Gd-DTPA (Magnevist, Bayer-Schering: 0.1 mmol Gd/kg) to obtain T_2 and T_2^* weighted time courses ($T_{E,SE}/T_{E,GE}$=56.6 ms/12.1 ms, temporal resolution 2.5 or 4 sec, 200 scans). All ADC, T_2-Maps and GESE data were acquired in the same geometry and resolution (1 slice of 0.8 mm thickness, FOV 14 x 14 mm, matrix 64 x 64, in plane resolution 219 µm x 219 µm).

ΔR_2^* and ΔR_2 time courses were calculated from the GE and SE signal time courses pre- and post-CA-injection. VSI maps were calculated voxel-by-voxel using the fractional blood volume map (CBV), ADC-map and the ratio of $(\Delta R_2)^{2/3}/\Delta R_2^*$ (2). CBV maps were obtained by integration of the bolus and normalizing to the whole brain CBV of 5% (3). The transfer constant (K_{trans}), volume of the extravascular and extracellular space (V_E) and plasma volume (V_P) were extracted by fitting the Tofts model (using a standardized input function) to the CA concentration time curve (4). The CA curve was derived from ΔR_2 using the relativity of Gd-DTPA at 7 T which was determined in plasma in vitro.

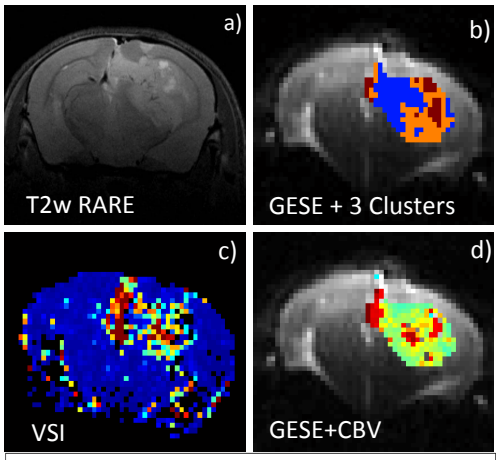

Figure 1 T2w image a), GESE SE image with segmented tumor b), VSI map c) and CBV map in tumor d) of a mouse brain with glioma (GESE temporal resolution 2.5sec.)

Results

In the morphological image necrosis and blood vessels are visible within the tumor (Fig. 1 a)). Necrotic and viable areas are correctly segmented into 3 tissue compartments (red and orange vs. blue region in Fig. 1 b)). The mean VSI values within viable tumor are higher than in the normal brain (viable tumor 63±45µm, normal brain 15±3µm) which are comparable to literature values measured with USPIO (5). The CBV values within the tumor were twice as high as in the normal brain. Time courses acquired with high temporal resolution (2.5s) showed post-contrast signal enhancement due to T_1 effects and therefore could not be used for CA concentration time course calculation. Data acquired with lower temporal resolution (4sec.) showed higher CA concentration values in tumor than in normal brain due to extravasation of CA (Fig. 2 b) and c)). Tofts fitting resulted in higher K_{trans} values in the tumor than in normal brain (tumor: K_{trans} 0.02 min^{-1}, brain: K_{trans} close to 0) as depicted in Fig. 2 a).

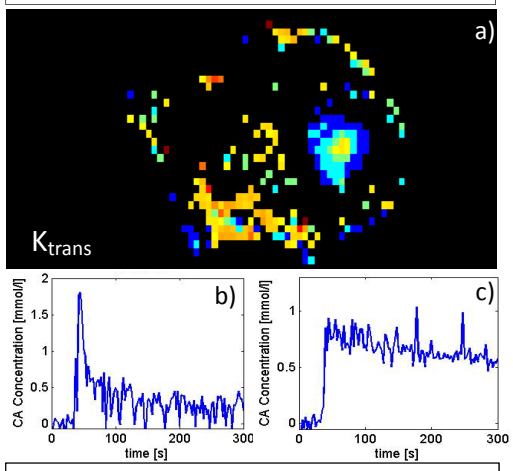

Figure 2 Ktrans map a) and CA concentration time courses in normal brain b) and within the tumor c)

Discussion and outlook

The simultaneous measurement of the biomarkers VSI, CBV, and vessel permeability (K_{trans}) using the GESE sequence with a single injection of the clinically approved Gd-based CA is feasible in mouse brain tumors in vivo. To account for tumor heterogeneity biomarkers were quantified in different tissue compartments after segmentation. Using higher temporal resolution VSI measurements are more accurate due to better sampling of the bolus whereas measurements of DCE parameters are only feasible with lower temporal resolution. Consequently we use lower temporal resolution but prolonged CA injection (to compensate decreased bolus sampling) and an adapted arterial input function in current studies.

(1) Zwick et al., *ISMRM* 2010, poster 5807 (2) Carano et al., *MRM* 51, 542-51, 2004 (3) Kiselev et al., *MRM* 53, 553-63, 2005
(4) Tofts et al., *JMRI* 7, 91-101, 1997 (5) Ungersma et al. *MRM* 63, 1637-47 2010