3D Radial Multi Gradient Echo dynamic MRI for characterization of microvasculature in tumor models subjected to respiratory motion

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Purpose: Preclinical dynamic MRI on tumor models is typically performed with gradient- or spin-echo sequences and Cartesian k-space sampling which is not optimal for tumors affected by respiratory motion (e.g. spontaneous tumors in transgenic mice). In these cases, radial k-space sampling, rather insensitive to motion, should be more appropriate. Furthermore, simultaneous dynamic T_1 and T_2* assessment has been recently shown to be of interest to characterize vasculature of tumors at high magnetic field (1). A 2D radial multi gradient echo sequence with fast T_1 and T_2* quantification was previously developed and validated *in vitro* and *in vivo* in tumor bearing "freely breathing" anaesthetized mice (2). The purpose of this work was to extend the radial sequence to 3D and to perform a first *in vivo* study comparing 3D K^{trans} maps of motion animated subcutaneous tumors for two contrast agents (CA) of different molecular weights (MW) and structures.

Materials and Methods: A 3D-radial gradient spoiled multi gradient echo (3D-RAD-MGE) technique without slab selection was developed on a 4.7T small animal scanner (Biospec®, Bruker Biospin, Germany). A home-built quadrature birdcage coil was used (∅=52mm, length=70mm). 10 even readout echoes were acquired (TE_1 = 0.9 ms, ΔTE = 1.67 ms, TR = 18 ms, BW = 100 kHz). Flip angle was set to 12°. 5000 projections and 64 complex readout points were acquired with a total acquisition time of t_{acq} = 1m30s. Images were reconstructed using a home-written (C++) standard regridding algorithm (3) yielding, after averaging over 4 slices 64x64x16 matrix 3D images (FOV = 30x30x30 mm^3). 300 dummy scans were applied prior to acquisition to achieve steady state. Based on the SPGR signal equation and neglecting T_2* effects due to the very short first echo time, T_1 was estimated voxelwise according to

$$T_1 = \frac{TR}{\ln\dfrac{\rho_0 \sin\theta - S_{TE_1}\cos\theta}{\rho_0 \sin\theta - S_{TE_1}}}$$

Proton density ρ_0 was calculated from a variable flip angle (VFA) measurement prior to dynamic acquisition (22 angles from 1 to 90°). T_2* was estimated by mono-exponential fitting.

As VFA measurements are sensitive to B_1 heterogeneity, the local flip angle corresponding to the region of interest was calibrated using a stimulated echo localized spectroscopy sequence with the volume being positioned inside a 5 mm diameter vial placed either near the tumor or in the center of the phantom. T_1 and T_2* estimations were validated in a phantom composed of 4 vials containing ferumoxide (Endorem®, Guerbet, France) solutions at different iron concentrations yielding a range of T_1 and T_2* values similar to that observed *in vivo*. T_1 and T_2* estimations in the phantom were compared respectively to an inversion-recovery spin echo (IR-SE) T_1 measurement (MTX = 128x128, FOV = 30x30 mm^2, TR = 15 s, TE = 9 ms, slt = 2 mm) and to a "Cartesian" multi gradient echo (MGE) T_2* measurement (MTX = 64x64, FOV = 30x30 mm^2, TR = 15 s, TE_1 = 1.98 ms, ΔTE = 2.52 ms, 50 even readout echoes, slt = 2 mm).

In vivo studies were performed, without respiratory triggering, on 2 groups of 6 nude mice with subcutaneous colorectal tumor xenografts (TC302, Institut Curie, France) implanted, on purpose, next to the abdominal region. Respectively, 2 CA of different MW were used, Gd-DOTA (Dotarem®, 0.5 kDa, Guerbet, France, r_1/r_2 = 4.2/5.1 $mM^{-1}s^{-1}$ at 4.7T) and P846 (3.5 kDa, Guerbet Research, France, r_1/r_2 = 15/31 $mM^{-1}s^{-1}$ at 4.7T), at the dose of 0.32 mmol/kg and 0.089 mmol/kg respectively. CA kinetics were acquired during 30 min. Using mean strain specific AIF time constants measured on the heart in separate groups (Gd-DOTA (n = 8), P846 (n = 4)), K^{trans} values were calculated voxelwise using the Tofts-Kermode model (4) (Matlab®, The MathWorks, Natick, MA, USA). Mean K^{trans} values and standard deviations were calculated for the whole tumor and values for the 2 CA were compared using the Mann-Whitney U test (Statistica®, StatSoft Inc., Tulsa, OK, USA).

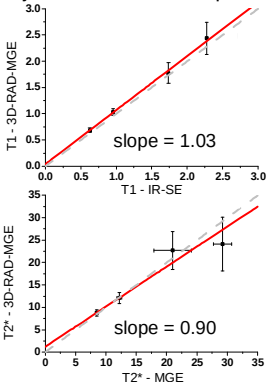

Fig. 1: Validation of T_1 (s) and T_2 (ms) estimated by 3D-RAD-MGE with respect to IR-SE and Cartesian MGE (dashed line = unity line). Both are in good agreement except for the longest T_2* due to the short echo train of 3D-RAD-MGE.*

Results and discussion: Phantom studies (Fig. 1): T_1 and T_2* values estimated by 3D-RAD-MGE were in very good agreement with respect to the standard Cartesian techniques. *In vivo* studies (Fig. 2, 3): K^{trans} was highest in the periphery of the tumors, a pattern often observed in subcutaneously implanted tumors. Mean K^{trans} values for Gd-DOTA (0.053 ± 0.016 min^{-1}) were similar to those previously obtained on the same tumor model (1). They were significantly higher than those obtained for P846 (0.030 ± 0.015 min^{-1}) ($p < 0.05$). This result is compatible with a lower capillary permeability for the high MW CA P846.

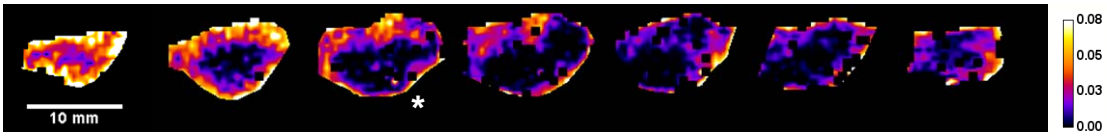

Fig. 3: Example of K^{trans} maps (min^{-1}) covering the whole tumor (CA: Gd-DOTA) generated from a 3D-RAD-MGE acquisition (slice of Fig. 2).*

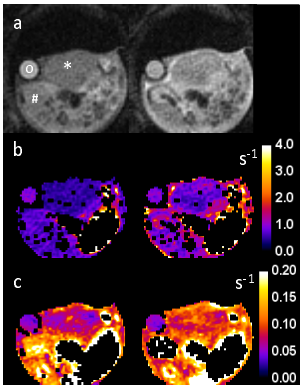

Fig. 2: Typical images and parameter maps extracted from a 3D dataset. (a) T1w images at TE = 0.9 ms. Note the absence of motion artifacts. (b) R_1 maps (c) R_2 maps. Left: pre contrast; Right: 30' post injection*

(tumor, # kidney, ° calibration vial)*

Conclusion: In this study, an optimized protocol for simultaneous dynamic T_1 and T_2* estimation by a fast 3D radial MGE technique was developed. Relaxation time estimations were validated on a phantom with respect to standard Cartesian MRI sequences. Furthermore, the *in vivo* study provided evidence for lower K^{trans} value for the higher MW CA with respect to Gd-DOTA. With this approach, particularly suited for the study of tumors subjected to respiratory motion but, more generally, optimizing dynamic MRI on experimental tumors, it is possible to combine the advantages of multiparametric, T_1 and T_2* based, dynamic MRI for characterization of tumor microvasculature with those of 3D radial acquisition techniques (e.g. sliding window, zooming possibilities).

References: (1): Heilmann M. *et al* MAGMA (2007); 20:193-203; (2): Vautier J. *et al* in Proc ISMRM 2008 3831, (3): Jackson J.I. *et al* IEEE Trans Med Imaging 1991, 10:473-8; (4): Tofts P.S.*et al* MRM 1991 17:357-367

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