Anti-angiogenic therapy follow-up in a mouse tumor model by a novel 3D radial multi-gradient echo DCE MRI technique with individual AIF measurement

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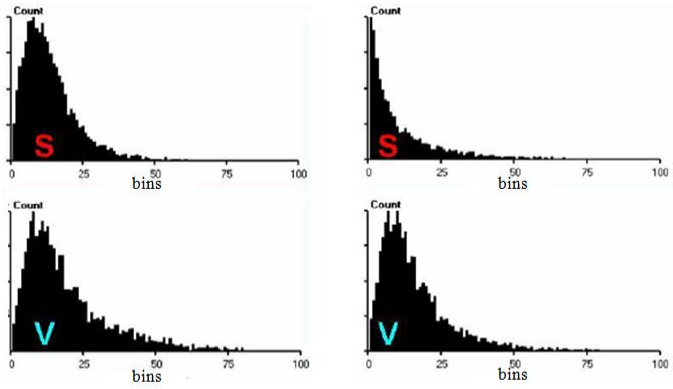
Purpose: A new quantitative DCE-MRI method was recently presented, which combines 3D tumor imaging with interleaved high time resolution 2D imaging on the heart (AIF) in mice by a radial multi gradient echo T1 weighted sequence with correction for T2* decay [1]. The purpose of the present work was to validate this method in a context of treatment follow up by evaluating its ability to assess in vivo early change of microvascular parameters under anti-angiogenic therapy.

Materials and methods: Male swiss nude mice (n=16) carrying a human colorectal tumor xenograft (TC302, Institut Curie, France; volume at day 1: 419±203 mm^3) subcutaneously implanted at the abdominal level were investigated. Animals were treated for 10 days by single daily oral administration of Sunitinib® (60mg/kg, n=9) or Vehicle only solution (n=7). Mice underwent DCE-MRI immediately prior to (day 1) and at day 4 after therapy initiation. Volume follow up by high resolution anatomical MRI was realized at these time points and at the end of the treatment period (latter performed on a 9.4T Varian system at day 11).
DCE MRI experiments were carried out on a 4.7T small animal MRI system (Bruker Biospin, Germany) with a home built quadrature birdcage probe (useful dimensions: Ø=35mm, length=50mm). Animals were anesthetized with isoflurane (AErrane®, Baxter France, France) and the body temperature was stabilized. For localization purposes pre-contrast high resolution images were acquired with the same 3D FOV as in radial DCE-MRI covering the whole tumor (respiratory triggered multi-slice spin echo sequence: TR~1s, TE=10.7ms, matrix=128x128, slice thickness=0.47mm, 64slices).
An experimental medium molecular weight contrast agent (CA) P846 (3.5 kDa, Guerbet, France) [2] was injected at a dose of 0.089mmol/kg (injection rate 600µL/min, injected volume 200µL). During DCE-MRI acquisition, 16 3D (tumor) datasets (1024 2D (AIF) datasets) were acquired continuously and simultaneously including one 3D pre-contrast image (64 2D pre contrast images). Main 3D parameters [1] were TE1=0.9ms, ΔTE=1.11ms, 10 echoes, matrix=64^3, FOV=$30^3 mm^3$, 64 readout points, 4096 projections, temporal resolution=2min. Main 2D parameters were TE1=1.9ms, ΔTE=1.11ms, 10 echoes, matrix=64^2, FOV=$30^2 mm^2$, slice thickness=2mm, 64 readouts points, 64 projections, temporal resolution=2s. TR was 31ms.
Images were reconstructed using a home-written (C++) standard regridding algorithm [3]. Sliding window reconstruction was performed for 3D data providing a virtual temporal resolution of 30s. CA concentrations in voxels (tumor) or ROI (heart) were estimated from R2* corrected R1(t) using $r_1=15 s^{-1} mM^{-1}$. AIF time constants were measured by fitting a biexponential decay to the concentration-time curve. K^{trans} and v_e values were assessed voxelwise using the Tofts-Kermode pharmacokinetic model [4].
K^{trans} and v_e histograms were generated for the whole tumor and mean, median and mode values were calculated. Parameter evolution was assessed between day 1 and day 4 using Wilcoxon's test.

Results and discussion: Volume measurement by MRI showed tumor growth inhibition in the Sunitinib® treated group, whereas a volume increase was observed in the vehicle group already at day 4. Comparing K^{trans} histograms prior to and after therapy showed a shift of the histograms' distribution towards lower value in the Sunitinib® group (figure). Change of overall histogram patterns have been reported before [5]. Accordingly, significant decrease in K^{trans} median and mode values in the Sunitinib® treated group (0.013±0.005 to 0.007±0.003 min^{-1} and 0.009±0.005 to 0.002±0.001 min^{-1} respectively) was observed between day 1 and day 4. However, mean K^{trans} values did not change significantly. Furthermore, no significant difference was seen for v_e values. For the control group, none of these parameters did change significantly. When pooling the two groups, ratio (mode K^{trans} day4/mode K^{trans} day1) was positively correlated to ratio (Volume day11/Volume day1). These results were compatible with a predictive value of mode and median K^{trans} parameters for anti-angiogenic treatment response.



Comparison of representative K^{trans} histograms of Sunitinib® (upper row) and Vehicle (lower row) treated animals on day 1 (left) and on day 4 (right)

Conclusion: The described 3D DCE MRI protocol with individual AIF measurement proved to be a potent functional imaging tool allowing to detect early K^{trans} change under anti-angiogenic therapy. This technique is expected to become a very useful preclinical research tool for investigation of tumors at arbitrary locations as it is insensitive to physiological motion, offers whole tumor coverage with the possibility of taking into account heterogeneity, and optimizes quantification issues for new high relaxivity CA.

References: 1. Vautier J. *et al.* Proc ISMRM 2010 4807; 2. Casneuf VF. *et al*. Radiat Res 2010; 3. Jackson J.I. *et al* IEEE Trans Med Imaging 1991, 10:473; 4. Tofts P.S.*et al* MRM 1991 17:357; 5.Li KL. *et al.* J Magn Reson Imag 2005, 22:511

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