Gas-Challenge Blood Oxygen Level Dependent (BOLD) MRI for quantitative assessment of tumor necrosis in rodent hepatoma model

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INTRODUCTION

Assessment of tumor necrosis is important for evaluating tumor treatment response (1). A non-invasive surrogate for pathology providing tumor necrotic fraction would permit timely assessment of tumor response, ideally prior to tumor size changes. Gas-challenge (GC) blood oxygen level dependent (BOLD) MRI may permit tissue characterization without the need for exogenous contrast agents. GC-BOLD MRI has been used for monitoring tumor progression (2), neo-vascularization (3) and oxygenation (4). For our study, the main purpose was to test the feasibility of using GC-BOLD MRI to assess tumor necrosis fraction and compare to reference standard histological measurements in a rodent N1-S1 hepatoma model.

METHOD

Animal Model 9 adult male Sprague Dawley rats (weighting 301-325g) were used for our ACUC-approved experiments. $1x10^6$ N1-S1 rat hepatoma cells (ATCC, Manassas, VA) were implanted in the left medial hepatic lobe with 7 rats developing N1-S1 hepatoma.

MRI Rats were anaesthetized with a high limb injection of ketamine (75-100mg/kg) and xylazine (2-6mg/kg). All experiments were performed using a 3.0T clinical MR scanner (Magnetom Trio, Siemens) with custom rodent receiver coil (Chenguang Med. Tech. Co., Shanghai, China). After initial localization, 3-5 axial slices passing through the N1-S1 hepatoma were selected for our BOLD studies. For T2* measurements we used a multiple gradient-echo (MGRE) sequence with parameters: TR=150ms, ETL=12 (4ms spacing), FA=30°, 3mm slices, 150mm FOV, 192 matrix, averages=25. Room air (78% N2/20% O2) or carbogen (95%O2/5%CO2) was administered via a rat nose-cone. MGRE images were first acquired during air breathing; then the animal was given carbogen for ten minutes for transition, and a second set of MGRE images were acquired while the animal continued to breathe carbogen. After image acquisition, rats were euthanized and the tumors were harvested for histological evaluation.

Images Analysis T2* maps were calculated by employing the nonlinear Levenberg-Marquardt algorithm to fit the mono-exponential function $S(TEi) = S(0)\cdot\exp(-R2^*\cdot TEi)$ using Matlab software (The Math Works Inc., Natick, MA). Maps of the absolute value of T2* change were calculated as |R2* air – R2* carbogen|. The tumor region-of-interest (ROI) was manually selected at each slice position on the absolute T2* change maps. The absolute T2* change values of all voxels within the tumor region were classified into two tissue populations using the K-means (KM) clustering algorithm (5,6). High and low absolute T2* change populations were assumed to represent viable and necrotic tissues, respectively. These two populations were displayed as gray or bright voxels, respectively, within our spatially resolved liver tumor viability maps.

Histology Each rat was euthanized 24 hours post-IRE. Liver specimens were fixed in formalin and paraffin embedded and H&E staining was performed. Histological slides were digitized using a multi-channel automated imaging system. The areas of necrotic tumor tissue were measured based upon cell morphology.

Statistical Analysis All statistics were performed using SPSS (SPSS, Chicago, IL, USA). The Spearman's correlation coefficient was calculated to assess the correlation between GC-BOLD MRI-measured tumor necrosis fraction and percentage of necrotic tissues within the tumor region on H&E staining slides. Test was considered statistically significant with a p-value < 0.05.

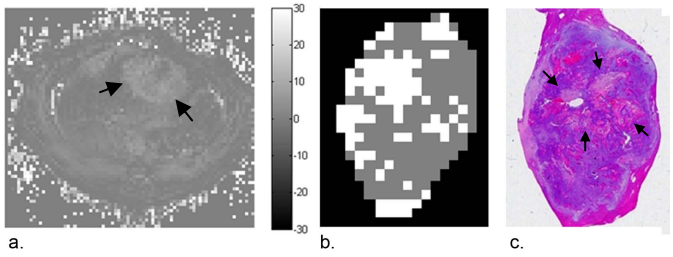

Fig. 1 Full FOV absolute T2* change maps (arrow, tumor)(**a**), tumor viability maps with gray regions classified as viable tissues and white regions classified as necrotic tissues (**b**) and corresponding tumor H&E histology image from the same axial slice position (arrow, necrosis) (**c**).

RESULTS

Representative example of absolute T2* change maps, tumor viability and corresponding H&E stain slide are shown in **Fig. 1**. A significant positive correlation was observed between gold-standard histology and GC-BOLD measured necrotic fraction (r = 0.829, p= 0.042).

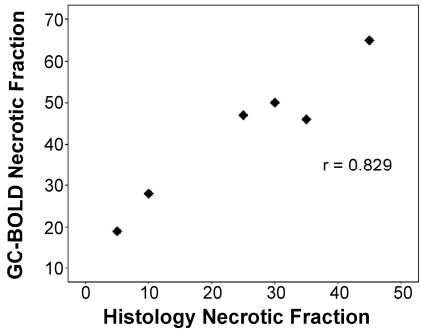

Fig. 2 A significant positive correlation between histology and GC-BOLD measured necrotic fraction was found (r = 0.829, p= 0.042).

CONCLUSION

Functional gas challenge-BOLD MRI provided resolved hepatic tumor viability maps for the assessment of tumor necrosis in N1-S1 hepatoma. GC-BOLD MRI might serve as a non-invasive surrogate for early assessment of therapy response (prior to conventional anatomic size changes).

Reference:

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