Dual biomarker CEST-MRI evaluates tumor pH and vascular perfusion in an orthotopic ovarian cancer model

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Introduction: A non-invasive method termed "acidoCEST-MRI" has been developed to measure extracellular tumor pH (pHe), which is a common biomarker of cancer.[1,2] This method utilizes iopromide, a contrast agent that contains two chemical exchange saturation transfer (CEST) effects. It has been shown that the magnitude of these two CEST effects changes depending on the pH of the solution/tissue where the agent is localized and that the rate of this change between the two CEST effects is independent. This allows for a $\log_{10}$ ratio of the two CEST effects to be linearly correlated with pH making measurements both independent of agent concentration and endogenous T1 relaxation time. Therefore, detecting both CEST effects of iopromide during in vivo studies can be used to accurately measure the extracellular pH in tissues. In this study, acidoCEST MRI was used to measure pHe in an orthotopic ovarian tumor model to investigate the relationship between pHe, vascular perfusion and tumor volume.

Methods: Three SCID mice were inoculated with 5 x 10^6 SKOV-3 cancer cells in sterile saline using i.p. injection of 0.2 mL per mouse. Approximately 40 and 47 days after inoculation, the mice were evaluated with acidoCEST MRI. Each mouse was given a bolus of 200 µL iopromide iv and 500 µL iopromide ip, followed by iv infusion at a rate 150 µL/hr throughout the experiment. A CEST-FISP pulse sequence with a 5 second saturation period consisting of 2.8 uT power, 90Hz bandwidth and 54 saturation frequencies between +10 and -10 ppm was used to obtain an acidoCEST MRI result in 4.8 minutes on a 7T Bruker MRI scanner. This acidoCESTMRI scan was repeated six times. To generate pixel-wise pH maps of the tumor, the six CEST spectra for a pixel were averaged, Gaussian filtering was used to smooth the CEST spectrum, each CEST spectrum was fitted to a single function with a sum of three Lorentzian line shapes using Matlab and only CEST effects greater than $2\sqrt{2}$*noise were retained (which represents a 95% probability that the CEST effect is real), and the pH was determined form a CEST-pH calibration performed using an identical acidoCEST MRI protocol. In addition, the percent of tumor volume that showed at least one CEST effect was used to calculate percent uptake of the agent, which was used as a biomarker to estimate vascular perfusion. A T2 weighted image was used to measure tumor volume, using a basic MSME sequence.

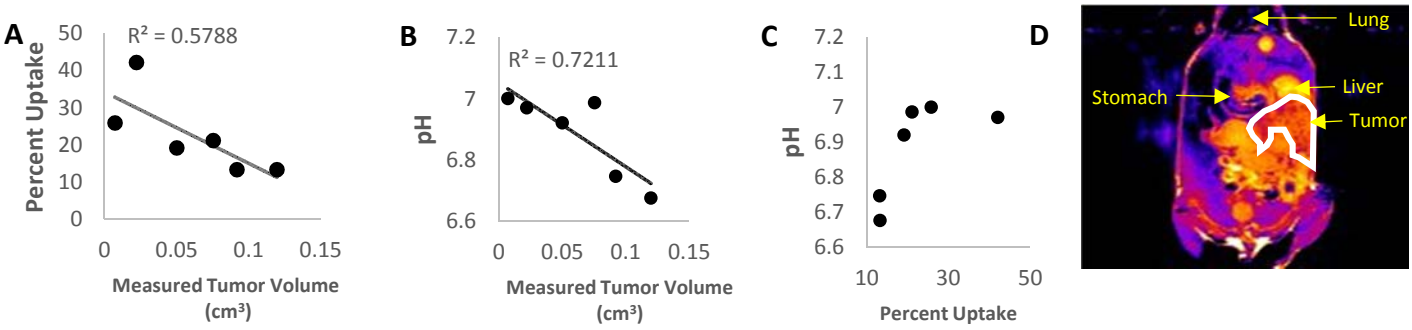

Figure 1. A-C. Correlations between pH, percent uptake, and measured tumor volume. D. Image of ovarian tumor load in the interperitoneal cavity for one representative mouse. The anatomical features are labeled.

Results: The tumor model was mildly acidic, with an average pH of 6.88. Additionally tumor acidosis was related to poor tumor perfusion (Fig. 1B). Also, tumor acidosis and lower perfusion were correlated with larger tumors (Figs. 1C).

Discussion: Results show that in combination with a CEST-FISP pulse sequence, our agent iopromide can successfully measure an orthotopic tumor model. These results support the paradigm that larger tumors are more metabolically active and therefore become more acidic and that lower vascular perfusion allows for greater lactic acid buildup causing more tumor acidosis.

References: 1) Chen LQ, et al., Magn Reson Med, 2013 2) Gillies RJ. et al., Cancer Met Rev 2007, 26:311-317. 3) Seth VR, et al., Contrast Media Mol Imaging 2012, 7 26-34.