Supporting Information

Characterization of tumor vascular permeability using natural dextrans and CEST MRI

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S1. Sizes of dextrans

Table S1. Mean size (z-average) and polydispersity index (PDI) of dextrans

MW (kD)	Diameter (nm)	PDI
10	5.9	0.3
70	12.9	0.15
150	27.3	0.3
2000	77.0	0.55

S2. Comparison of the CEST effects of dextrans of different MWs at 0.9 ppm.

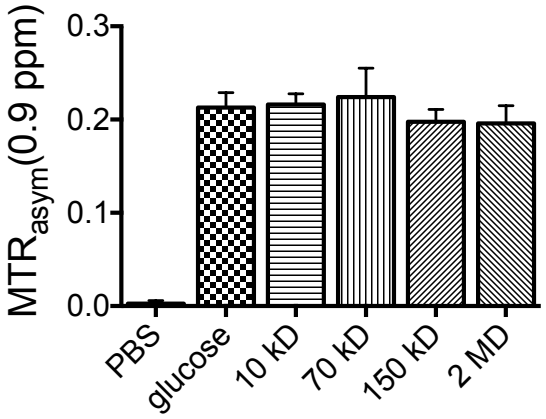

Figure S1. Comparison of the CEST MRI contrast of dextrans of different MWs at 0.9 ppm. All samples were prepared at pH=7.3 in 10 mM PBS, and the CEST MRI was acquired using a 4-second long CW RF pulse (B_1=3.6 μT) at 37 °C.

S3. DCE MRI data processing

A single-slice FLASH gradient echo sequence was used for DCE imaging. The parameters were TR/TE= 18/3 ms and flip angle =15. Temporal resolution was 4.61 s. Images were acquired rapidly for 120 seconds before a bolus of 0.1 mmol/kg body weight Gd-DTPA was i.v. injected. DCE imaging continued for about 15 min. Data analysis was performed using a custom Matalb program modified based on a "fitdcemri" matlab function as used previously (1). A region of leg muscle was chosen as the reference region. Signal change in tumour and reference region was documented for each pixel. Concentration of contast agent in tumor (Ctoi) and reference region (Crr) was calculated based on the following equations:

$$S_0 = S_- \frac{(1-e^{-\frac{TR}{T_{10}}}cos\alpha)}{\left(1-e^{-\frac{TR}{T_{10}}}\right)sin\alpha} \quad (1)$$

$$R_1(t) = \frac{1}{TR}\ln\left(\frac{S_0 sin\alpha - Scos\alpha}{S_0 sin\alpha - S}\right) \quad (2)$$

$$Ctoi(t)\ or\ Crr(t) = \frac{1}{r1}[R_1(t) - R_1(1)] \quad (3)$$

where S_0 is the average signal intensity in tumor or reference region in the absence of contrast agent. S_- is the steady-state signal intensity. T_{10} is the T_1 of the tumor ROI or reference region in the absence of contrast agent, and r_1 and the relaxivity of the contrast agent, which is 2.8 $mM^{-1}s^{-1}$. $R_1(1)$ is the relaxation rate in tumor or reference region in absence of contrast agents, which was estimated based on previous T_1 mapping experiments. R1(1) of 0.382 and 0.5 s^{-1} was used for tumor and reference region, respectively. Crr and Ctoi were next used to fit the non-linear reference region (NLRR) model(2) to calculate R^{Ktrans}. To calculate K^{trans} for tumor, reference region K^{trans} ($K^{trans}RR$) of 0.1 min^{-1} was used and $K^{trans}tumor = R^{Ktrans} \times K^{trans}RR$.

S4. Fluorescence microscopic images of whole tumors

As shown in Figure S3, the fluorescence microscopic images of whole tumors (DAPI and dextran) clearly reveal the difference in the distribution of 10 KD and 70 kD dextrans.

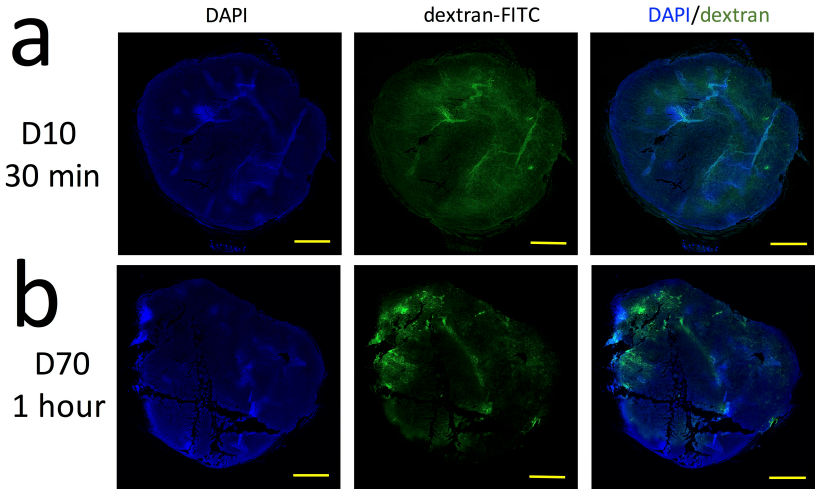

Figure S2. Fluorescence microscopy of the distribution of 10 kD and 70 kD dextrans in two representative tumor slices. Blue: nuclei (stained with DAPI) and green: FITC-dextrans. Scale bar= 1 mm.

S5. Change in B0 inhomogeneity over time

A series of B0 maps over 90 minutes after the injection of 300 μL saline. Our results showed that the changes in B0 after injection are very subtle (< 25 Hz) most the time, indicating the B0 inhomogeneity didn't change significantly over time.

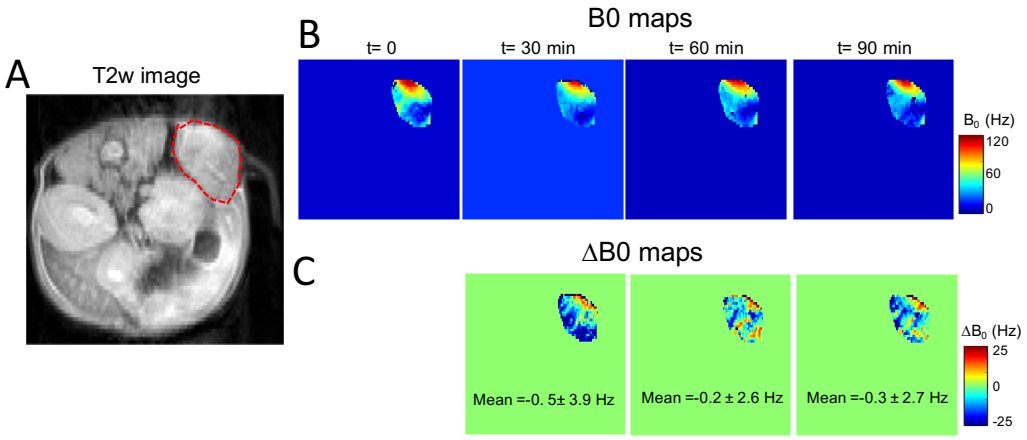

Figure S3. Change in B0 maps in a representative tumor. A) T2w image showing the region of tumor (red dashed circle); B) B0 maps at different time points after saline injection; and C) The corresponding ΔB0 maps at different time points, with the mean and standard deviation of ΔB0 in the tumor labeled on the bottom.

Refs:

1. Cardenas-Rodriguez J, Howison CM, Pagel MD. A linear algorithm of the reference region model for DCE-MRI is robust and relaxes requirements for temporal resolution. Magn Reson Imaging. 2013;31(4):497-507.

2. Yankeelov TE, Luci JJ, Lepage M, et al. Quantitative pharmacokinetic analysis of DCE-MRI data without an arterial input function: a reference region model. Magn Reson Imaging. 2005;23(4):519-29.