Gadolinium-free extracellular MR contrast agent for tumor imaging

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TARGET AUDIENCE: contrast agent developer, oncologist, radiologist

PURPOSE: Contrast-enhanced imaging is a mainstay of tumor diagnosis and treatment monitoring, and gadolinium (Gd)-based chelates are the most common contrast agents used in clinical MRI. However, administration of Gd is associated with the risk of heavy metal poisoning from ion release when contrast clearance is delayed, as in patients with impaired kidney function [1]. In this study, we investigate the potential of a recently reported manganese porphyrin contrast agent [2], an extracellular agent that is filtered through the kidneys, for contrast-enhanced MRI of tumors.

METHODS: Six healthy female nude rats (Harlan Laboratories, Indianapolis, IN) were injected with ~10×10^6 cells in the mammary fat pad (3 different breast cell lines: MDA-MB-231, 231/LM2-4, ZR-75-1). Rats were imaged 3 to 4 weeks after inoculation on a 3T scanner (Achieva, Philips). Rats were induced on 2% isoflurane and maintained on 1.5% isoflurane during MRI. Rats were positioned prone, resting on a 36°C water blanket inside an 8-channel wrist coil. A 24-gauge angiocath was inserted into the lateral tail vein for contrast injection. Gd-DTPA was injected intravenously as a bolus (0.05 mmol/kg) followed by 2 mL saline. At least 2 hours later, the new manganese porphyrin agent, MnTCP, was injected at the same dose. High-resolution T1-weighted spin-echo scans were acquired prior to and at 20, 40, and 60 minutes after contrast injection. Dynamic T1-FFE and baseline T1 mapping [3] were also performed. Parameters for T1-weighted SE: TR=724 ms, TE=14 ms, NSA=3, FOV = 100 mm, 1 mm slices, 0.6×0.6 mm in-plane, 20 slices. Parameters for dynamic T1-FFE: TR=6.2 ms, TE=3.2 ms, NSA=8, FOV = 100 mm, 1 mm slices, 0.6×0.6 mm in-plane, 20 slices, keyhole acquisition, temporal resolution=9.1 s. The data was analyzed by first computing pixel-wise T1 maps and then performing pharmacokinetic analysis on region-of-interest averaged relative signal intensity enhancement curves to compute the peak enhancement (E_{max}), time-to-peak (TTP), steepest enhancement (ES), and area under the curve for the first 60 seconds (AUC_{60}) [4]. Differences in pharmacokinetics were evaluated using paired-sample t-test for each measured parameter.

RESULTS: Fig 1 shows relative signal enhancement curves and T1-weighted SE images of two different tumors. Fig 2 compares relative changes in T1 induced by MnTCP and Gd-DTPA. Fig 3 compares pharmacokinetic parameter estimates.

DISCUSSION: Enhancement and clearance patterns were visually similar between MnTCP and Gd-DTPA. However, relative R1 (1/T1) increases in all 11 tumors were larger for MnTCP. Pharmacokinetic analysis revealed a consistently larger (1.5 to over 2-fold) E_{max} and higher values of the ES, TTP, and AUC_{60} in all tumors with MnTCP.

CONCLUSION: MnTCP is an alternative to extra-cellular Gd-based contrast agents for tumor imaging, offering sensitive detection and rapid renal clearance.

REFERENCES: 1. Kuo PH et al. Radiology 2007; 242:647. 2. Cheng HL et al. J Magn Reson Imaging 2013 (Epub Nov 8). 3. Cheng HL and Wright GA. Magn Reson Med 2006; 55:566. 4. Jesberger JA et al. J Magn Reson Imaging 2006; 24:586.

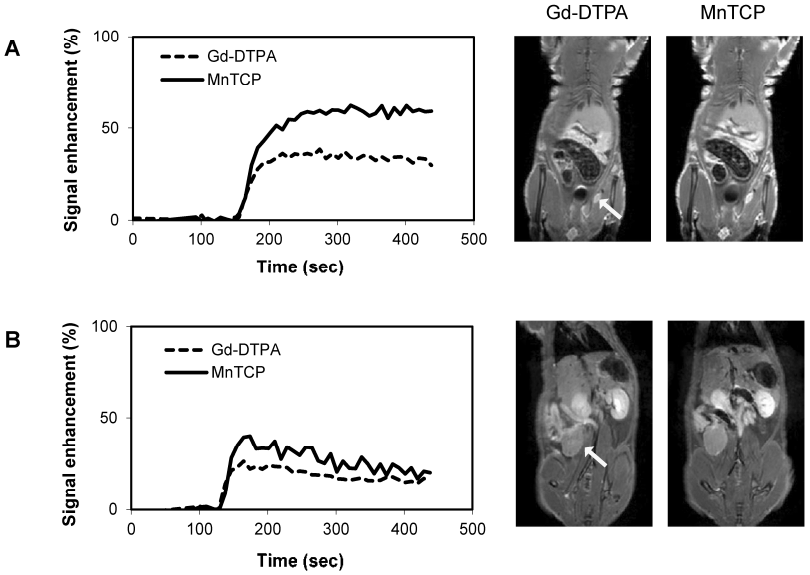

Fig 1. Relative signal enhancement during dynamic MRI and T1-weighted SE images at 20 minutes post-injection. Tumors (arrow) exhibit different pharmacokinetics.

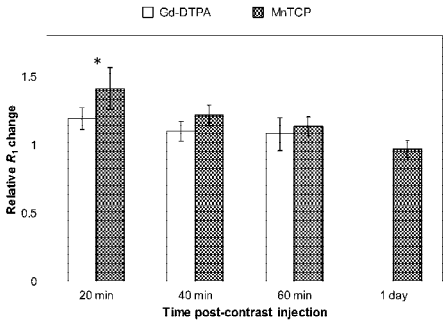

Fig 2. Contrast-induced relative R1 (1/T1) changes across 11 tumors. Shown are mean ± SD (* $p < 0.05$).

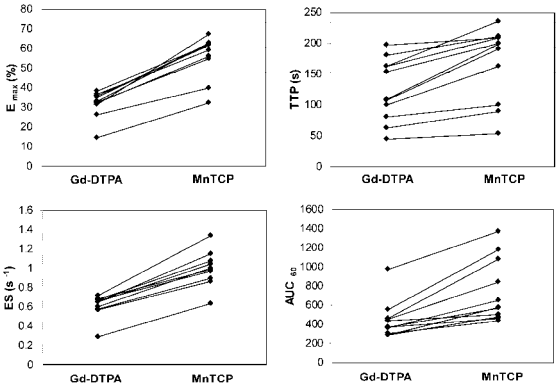

Fig 3. Pharmacokinetic parameter estimates from dynamic imaging. All parameters are significantly different between MnTCP and Gd-DTPA ($p < 0.01$).