

# Manganese-enhanced MRI of minimally gadolinium-enhancing breast tumors

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**TARGET AUDIENCE:** contrast agent developer, oncologist, radiologist

**PURPOSE:** Oncological imaging routinely requires the administration of exogenous contrast agents, as the increased vascularity of many tumors results in higher contrast agent accumulation compared with that in surrounding normal tissue. However, reliance on the vasculature for contrast distribution suggests that tumors with low vascularity or poor perfusion may not enhance appreciably relative to surrounding normal tissue. This phenomenon can be seen in some low-grade gliomas<sup>1</sup>. In this study, we investigate if manganese (Mn)-enhanced MRI can detect and delineate tumors that demonstrate little enhancement on Gd-DTPA.

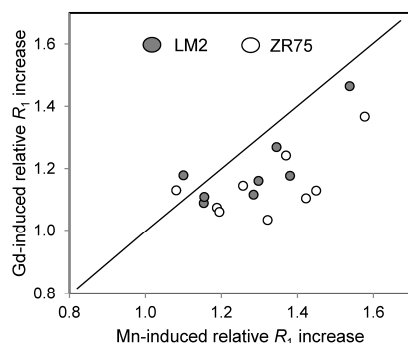
**METHODS:** Eighteen healthy female nude rats (Harlan Laboratories, Indianapolis, IN) were injected with  $\sim 10 \times 10^6$  cells in the mammary fat pad (breast cell lines: 231/LM2-4, ZR-75-1). Rats were imaged on a 3T scanner (Achieva, Philips) when tumors reached a size of 1 to 2 cm in diameter. 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. High-resolution T1-weighted spin-echo scans and T1 mapping<sup>2</sup> were acquired prior to and 10 minutes after Gd-DTPA injection. 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. T1 mapping was performed using 3D T1-FFE repeated at FA=2°, 10°, 20°. At the end of the experiment, 0.05 mmol/kg MnCl<sub>2</sub> was injected subcutaneously at the back of the neck, and the animal returned the next day for 24-hour post-MnCl<sub>2</sub> imaging. The data was analyzed by computing pixel-wise T1 maps before and after contrast administration<sup>2</sup>. Changes in T1 were compared between MnCl<sub>2</sub> and Gd-DTPA using paired-sample t-test. Tumors were also excised, fixed in 10% formalin, sectioned into 5 µm slices, stained with hematoxylin and eosin (H&E) and CD34, and observed under light microscopy (Olympus BX60, Olympus Canada, Inc).

**RESULTS:** Fig 1 compares Mn- and Gd-enhanced MRI of two different breast tumors. Fig 2 compares relative increases in R1 (1/T1) induced by MnCl<sub>2</sub> and Gd-DTPA for all tumors. Fig 3 shows gross and histopathology for a representative low Gd-enhancing tumor.

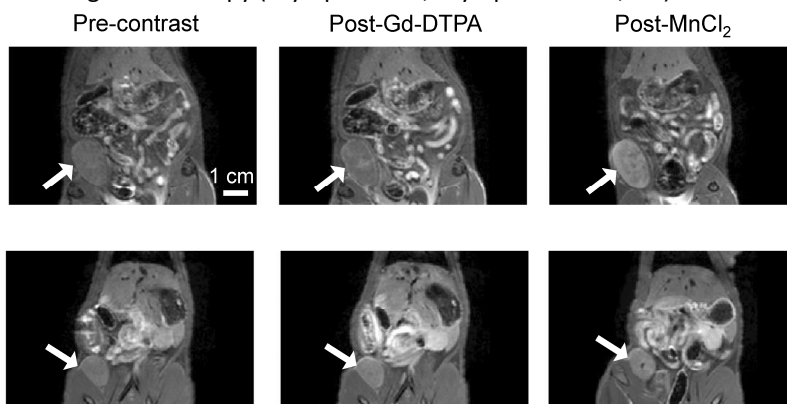
**DISCUSSION:** Most tumors (78%) demonstrated low enhancement (<20% R1 change) on Gd-DTPA. Mn-induced R1 increases were significantly greater in both ZR75 ( $p < 0.01$ ) and LM2 ( $p < 0.05$ ) tumors. Whereas Gd-enhancement was confined to the tumor periphery, Mn-enhancement was more uniform throughout the tumor mass and clearly delineated necrotic areas.

**CONCLUSION:** Mn-enhanced MRI is a promising approach for detecting low Gd-enhancing tumors.

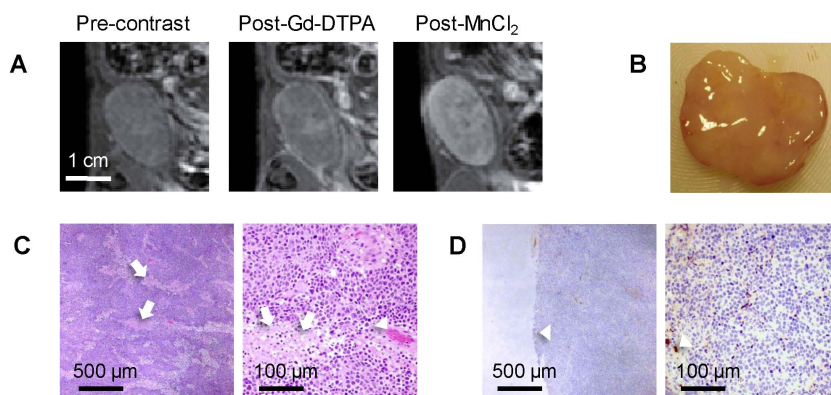
**REFERENCES:** 1. Price SJ. Adv Tech Stand Neurosurg 2010; 35:1. 2. Cheng HL and Wright GA. Magn Reson Med 2006; 55:566.



**Fig 2.** Relative increases in R1 (1/T1) post-contrast are compared between Mn- and Gd-enhanced tumors.



**Fig 1.** In-vivo Mn-enhanced and Gd-enhanced MRI of breast tumor-bearing rats at 3 T. Tumors (arrow) are shown on T1-weighted SE images acquired pre- and post-contrast for (top) ZR75 and (bottom) LM2 breast tumors.



**Fig 3.** A low Gd-enhancing ZR75 tumor is shown on (A) contrast-enhanced MRI, (B) gross pathology, (C) H&E (×4 and ×20 magnification), and (D) CD34 (×4 and ×20 magnification). Histology confirmed very low vascularity (arrowheads) and patchy necrosis (arrows) consistent with Mn-enhanced MRI.