Molecular MR imaging of fibrin in tumors

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Introduction: In 1986, Dvorak postulated that "tumors are wounds that do not heal" [1], and pointed out that the composition of the tumor stroma strongly resembles the granulation tissue of healing skin wounds. One commonality is crosslinked fibrin in the extracellular matrix that is found in the stroma of many solid tumors [1]. Since fibrin is only found in thrombi, healing wounds, and tumors, we hypothesized that the fibrin-specific contrast agent EP-2104R may find general utility in identifying and characterizing primary and metastatic tumors. EP-2104R is a fibrin-targeted Gd-based agent with high specificity for fibrin over fibrinogen and other plasma proteins [2]. Here we compare EP-2104R and GdDTPA using dynamic and steady-state contrast enhanced imaging in a breast cancer xenograft model.

Methods: Tumors were grown in the flank of 5-6 wk old nude mice by subcutaneous injection of human breast adenocarcinoma cells (BT-20), $3x10^6$ cells in 50µl of HBSS. Mice (n=4) were imaged at 9.4T two weeks after cells were injected when the tumors were ca. 3 mm in diameter. Imaging was performed prior to and following i.v. injection of either 200 µmol/kg GdDTPA or 20 µmol/kg EP-2104R. 90 minutes after the first agent was administered, the second agent was injected i.v. and serial imaging repeated. Immediately prior to and following injection, a series of 60 multislice FLASH (TR/TE/flip=100/1.92/60; 128x128, NEX=1; acq time=13 s) were recorded. This was followed by serial high-resolution FLASH images (TR/TE/flip=100/2.3/60; 256x256, NEX=8; acq time=4 min). Regions of interest were drawn in the tumor core, tumor periphery, adjacent muscle, and air outside the animal and signal intensity (SI) and its standard deviation (SD) measured. Contrast to noise for tumor core or periphery relative to skeletal muscle was calculated as $CNR=(SI_{tumor}-SI_{muscle})/SD_{air}$. The dynamic contrast enhancement (DCE) tumor data was modeled to extract kinetic parameters. [3]

Results: DCE imaging with EP-2104R was comparable to GdDTPA, although the rate constants extracted from the kinetic data were reduced by a factor of 2, likely a result of the larger size (4 kDa) of EP-2104R. For both agents, the tumor core enhanced on first pass followed by a washout period, Fig. 1A. For GdDTPA, the tumor periphery enhanced transiently and then washed out (Fig. 1B) but when EP-2104R was injected the periphery showed persistent enhancement over the course of the study (90 min). Figure 2 shows representative images in the same animal that correspond to the data in Fig. 1.

Fig. 1: CNR relative to muscle for subsequent injections of GdDTPA and EP-2104R in the same animal. (A) Tumor Core. (B) Tumor Periphery.

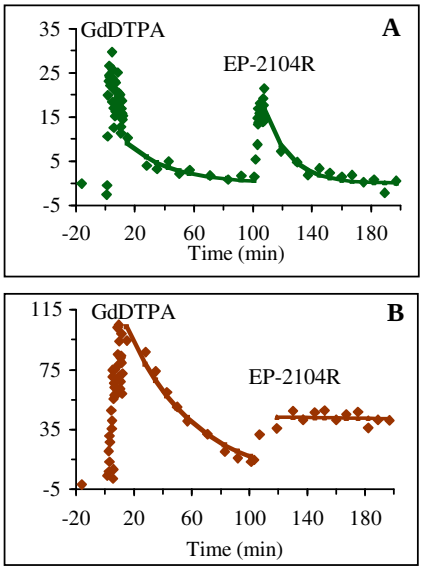
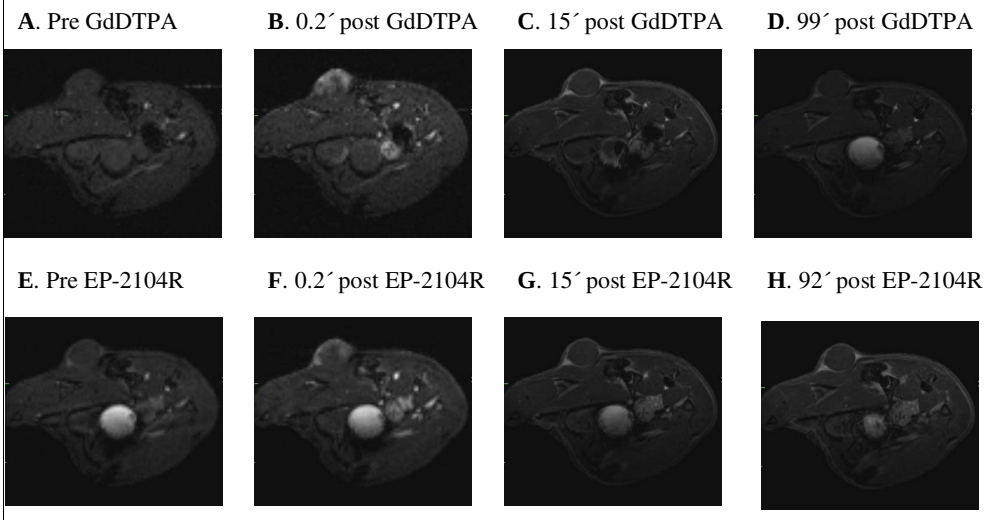


Fig. 2: Serial FLASH images pre and post injection of GdDTPA (top) and EP-2104R (bottom) show transient tumor core enhancement following contrast administration. The tumor periphery remains enhanced at least 90 min after EP-2104R injection.



Conclusions: The fibrin-targeted agent EP-2104R can be used to characterize tumors using DCE-MRI, but also shows prolonged enhancement of the tumor periphery, which may prove useful in characterizing the aggressiveness of tumors or in monitoring tumor response to therapy.

References: [1]Dvorak N. Engl. J. Med. 1986, 315:1650. [2]Overoye-Chan et al. J. Am. Chem. Soc. 2008, 130:6025. [3]Tofts et al. JMRI 1999, 10:223.