New MRI Contrast Agent for Labeling of Tumor-Associated Macrophages that Stimulate Tumor Angiogenesis

SE Harms, T Hinton, L Manning, S Korourian
Departments of Radiology and Pathology, University of Arkansas for Medical Sciences, Arkansas Cancer Research Center, and Little Rock VA Hospital, Little Rock, Arkansas

PURPOSE
Angiogenesis is important in tumor growth and metastasis. Angiogenesis is a multistep process involving several factors including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), tumor necrosis factor α (TNFα), and basic fibroblast growth factor (bFGF), among others. In invasive breast cancers, the neoplastic cell population is often outnumbered by stromal cells such as tumor-associated macrophages (TAMs). It is thought that monocytes in the peripheral circulation are recruited to the tumor site. Once recruited, the monocytes differentiate to become TAMs and are modified in the tumor microenvironment to secrete growth factors such as EGF, VEGF, TNFα, and bFGF. An imaging method that can define the extent of this activity in vivo could have a significant impact on cancer imaging and research.

RESULTS
Ferumoxtran-10 specifically and maximally enhances on the 24-hour delayed images at the junction of the tumor margin and normal tissue corresponding histochemically with high concentrations of iron within macrophages. Factor VIII, PCNA, and VEGF were equal in the tumor center, periphery and boundary zones around the tumor but were elevated compared with normal tissue. Infiltrating cancers had avid uptake of ferumoxtran-10 maximal at the periphery, and this enhancement consistently extended over a slightly larger region than the gadolinium enhancement. One case of DCIS failed to enhance with ferumoxtran-10 but did enhance with gadolinium. Histologically, the additional area enhancing with ferumoxtran-10 corresponded to the boundary zone at the interface of infiltrating neoplastic cells and normal cells where TAM activity is high. The gadolinium boundary was within the neoplastic tissue. Immediately after injection, ferumoxtran-10 provides potent intravascular contrast. We were surprised when immediate ferumoxtran-10 images failed to demonstrate the tumor despite the significantly increased capillary density as measured on the factor VIII stains.

CONCLUSIONS
Ferumoxtran-10 may be the first contrast agent that specifically marks tumor-associated macrophage activity. This enhancement could aid in the definition of tumor margins for breast conserving surgery or minimally invasive therapy. Gadolinium-enhanced breast imaging is limited by the relatively short duration of MRI contrast agent effects. A longer imaging time would allow a longer scan time for the generation of higher resolution. Many breast procedures are limited to stereotactic positioning based upon imaging data obtained immediately after contrast injection. The dynamic manipulation of the needle with real-time guidance is limited, since the target often fades into the background of ductal tissue after about 5-10 minutes post-injection. A lasting tumor contrast would facilitate real-time imaging and demonstration of the tumor during the course of treatment.

REFERENCES