Why do Ductal Carcinoma in situ Lesions Enhance on Dynamic Contrast Enhanced MRI of the Breast? Using X-Ray Fluorescence and MRI to Track the Spatial Distribution of Gd-DTPA in Murine DCIS.

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Introduction: The early detection of breast cancer is a major prognostic factor in the management of the disease. In particular, detecting breast cancer in its pre-invasive form as ductal carcinoma *in situ* (DCIS) improves prognosis greatly compared with invasive tumors. Although dynamic contrast enhanced MR imaging (DCEMRI) of the breast has demonstrated high sensitivity to invasive breast cancer, the diagnostic accuracy of DCEMRI to DCIS needs improvement. Furthermore, the mechanism for contrast enhancement of DCIS lesions—which represent neoplastic cells that are still confined within the mammary ducts—on DCEMRI is not clear. The purpose of this study was to use transgenic mouse models of breast cancer to study DCEMRI of DCIS by (i) obtaining *in vivo* DCEMRI of murine DCIS lesions, (ii) use x-ray fluorescence (XRF) microscopy to identify the spatial distribution of Gd-DTPA following IV injection in mouse mammary glands, and (iii) determine if Gd-DTPA enters ducts distended with DCIS.
Methods: Fourteen C3(1) Sv40 TAg female transgenic mice were selected for DCEMRI following approval by the Animal Care and Use Committee. In this mouse model, mice develop mammary cancer similar to breast ductal carcinoma, including progression through DCIS and invasive cancer. On all fourteen mice, DCEMRI of the inguinal mouse mammary glands were obtained on a 4.7 T magnet, in conjunction with T_1 weighted gradient echo images for DCIS lesion localization. To prepare samples for XRF microscopy, mice were injected with 0.1 mM/kg Gd-DTPA, sacrificed after 2 minutes, and portions of the inguinal mammary glands were excised and frozen. Frozen sections were mounted on ~3x3mm silicon nitride "windows" for XRF; these sections contained portions of portions of lymph nodes, ducts distended with DCIS, and nearby blood vessels. Using the 2-ID XOR CAT at the Advanced Photon Source at Argonne National Laboratory, we performed XRF microscopy on the frozen section. Elemental concentrations of Gd, phosphorus (P) and iron (Fe) were determined in regions of interest in the ducts, lymph nodes and blood vessels. The DCEMRI were also compared with the XRF microscopy.
Results: DCEMRI demonstrated that ducts distended with DCIS exhibited contrast uptake along the length of the lesion (Figure 1). XRF microscopy verified that Gd-DTPA was present in lymph nodes, blood vessels as well as in portions of mammary ducts distended with DCIS (Figures 2, 3). As expected, Fe was also present in blood vessels, but not in the duct with DCIS.
Discussion: We have used transgenic mice to investigate contrast enhancement in DCEMRI. Our preliminary results indicate that: (i) murine DCIS lesions exhibit contrast uptake, which has not been observed before, and (ii) Gd-DTPA can leave blood vessels to enter ducts distended with DCIS. These ducts may have leaky basement membranes allowing gadolinium to diffuse inside. This is an important, new insight into the mechanism for contrast enhancement of DCIS lesions in DCEMRI. This observation may indicate that two compartment pharmacokinetic models may be invalid for DCIS lesions, as they ignore exchange of contrast with the mammary duct distended with DCIS (representing a 3rd compartment). These preliminary results point to future validation in more samples. Understanding the uptake of Gd in mammary ducts may lead to improvements in imaging methods, mathematical modeling of kinetic data and interpretation of DCEMRI.

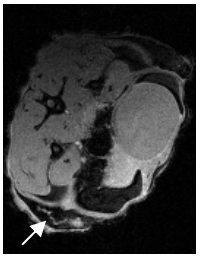

Figure 1: Axial MRI of mouse with duct distended with DCIS (arrow).

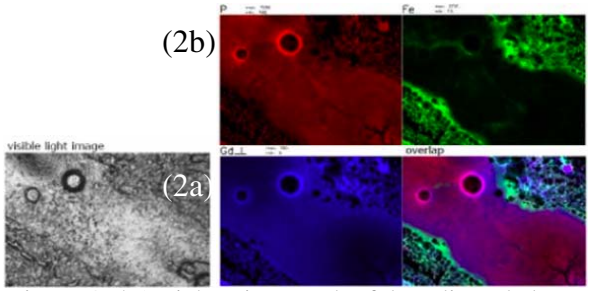

Figure 2. (a) Light micrograph of duct distended with DCIS. (b) Elemental concentration maps of P (red), Fe (green), Gd (blue) and the overlap demonstrating Gd (but not Fe) penetrated the mammary duct distended with DCIS.

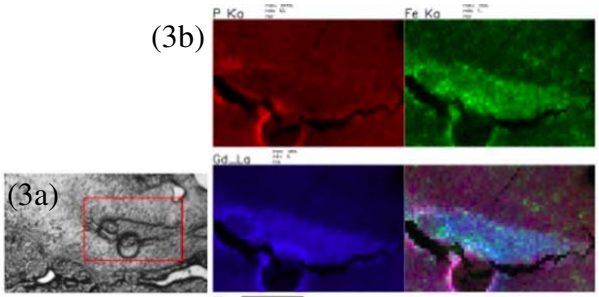

Figure 3. (a) Light micrograph of a blood vessel. (b) Elemental concentration maps of P (red), Fe (green), Gd (blue) and the overlap, demonstrating that Fe and Gd was present in the blood vessel.

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