Permeability of Mammary Ductal Lumens to MRI Contrast Agents may be a New Marker for In Situ Mammary Cancer: An X-ray Fluorescence Microscopy Study

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Introduction: Dynamic contrast-enhanced magnet resonance imaging (DCE-MRI) is an important tool for diagnosing breast cancer. However, common pharmacokinetic models in DCE-MRI do not account for heterogeneous contrast media distribution in mammary ductal lumens, epithelia, and stroma. Here, we demonstrate, with X-ray fluorescence microscopy (XFM) of frozen tissue slices that MRI contrast agents leak into ductal lumens when in situ cancer is present, but not into lumens of normal ducts. The results suggest that increased permeability in mammary/breast ducts is an MRI-detectable marker for early cancer.

Methods: Eleven SV40Tag and eight normal FVB/N virgin female mice were studied between 19-21 weeks of age. SV40 mice were sacrificed 2-min (n=4) or 45-min (n=4) after intravenous gadodiamide (0.2 mmol/kg) injections; three were sacrificed 2-min after saline injection as controls. Five FVB/N mice were sacrificed 2-min after gadodiamide injection and three were sacrificed 2-min after saline injection as controls. These C3(1)SV40 transgenic mice develop in situ cancer that resembles ductal carcinoma in situ, DCIS, in women. Mammary tissues were harvested and frozen; 10-μm thick slices were sectioned for XFM; and adjacent 5-μm thick slices were sectioned for H&E staining. In vivo T₂-weighted MR and ex vivo H&E images guided the selection of in situ cancers for XFM. For in situ cancerous ducts in SV40 mice, typical sizes of ROIs were 9876 ± 984 μm², 2648 ± 587 μm², and 2844 ± 493 μm² for epithelium, lumen, and stroma respectively. At least two mammary tissue samples were selected per mouse to contain either normal glands (FVB/N) or glands with in situ cancer (SV40), with each sample containing epithelia, lumens, and stroma. Elemental gadolinium (Gd) concentrations in ductal epithelia, lumens and stroma in normal glands and in situ cancer were determined by XFM in 4-5 ductal regions in each mouse. A Student's t-test was performed for statistical analysis. A p-value <0.05 was considered significant.

Results: Concentrations of Gd in epithelia and stroma of normal ducts (3.35±0.75 and 1.78±0.56 mM, respectively) and in situ cancer (3.39±0.48 and 1.88±0.25 mM, respectively) were identical at 2-min after gadodiamide injection. However, Gd concentrations in lumens were dramatically different, 0.03±0.02 mM in normal lumens versus 1.15±0.16 mM in lumens with in situ cancer (p<0.001). Washout of Gd from lumens (5±2% remaining after 45 minutes) was much faster than from epithelia and stroma (18±3% remaining after 45 minutes) (p<0.003).

Conclusions: Results suggest that in situ mammary cancers are characterized by increased ductal permeability. Ductal permeability may be a marker for in situ and early invasive cancer. Rates of uptake and washout of Gd from mammary/breast ductal lumens may be an image-based biomarker for early cancer. New approaches to image acquisition and data analysis that can detect contrast media leakage into ductal lumens and subsequent washout may allow quantitative measurements of ductal permeability and significantly improve diagnostic accuracy, especially for in situ cancer.