MRI of Ductal Carcinoma *in situ* and Other Early Mammary Cancers in Transgenic Mice

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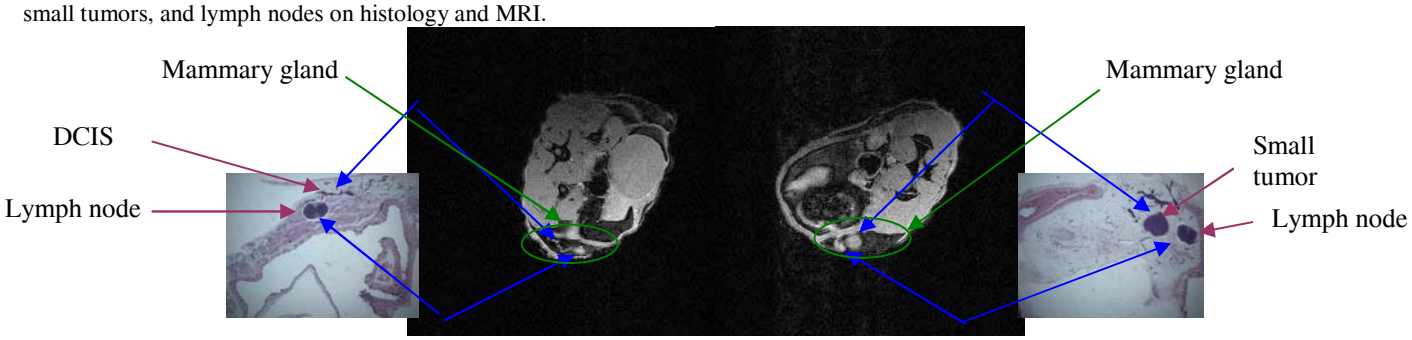
Introduction: The majority of MR studies of mammary cancer in mice focus on large, palpable tumors that are not orthotopic[1,2]. This poses significant problems for drug development and for development of improved imaging methods that target early cancer. Here, we report a novel approach to imaging rodent mammary cancer. High resolution MR was used to image early pre-invasive murine ductal carcinoma in situ (DCIS) and minimally invasive stages of mammary cancer in a transgenic model of spontaneous breast cancer, and the images were correlated with histological sections.

Methods: A pair of inguinal mammary glands was imaged in ten Sv40 large T antigen transgenic female mice. The mice were imaged and immediately sacrificed at various ages between 10-18 weeks of age. The mammary glands were then excised, fixed overnight in formalin and submitted for paraffin embedding, sectioning and H&E staining. The tissue slices were evaluated by an experienced pathologist (TK). MR imaging was performed on a 4.7 T Bruker scanner using a home built surface coil that produced high flux density in the mammary gland. FLASH GE images were obtained (TR/TE: 675/7 ms, axial orientation, slice thickness 0.5 mm, in plane resolution 117 microns, FOV=3.0x3.0cm) with and without fat suppression. High spectral and spatial resolution images were also acquired with slice thickness of 0.5 mm, in-plane resolution of 117 microns and spectral resolution of ~ 6 Hz. Dynamic contrast enhanced images were also obtained (TR/TE: 30/3.5 ms, slice thickness 1.0 mm, in plane resolution 117 microns). To facilitate comparisons with histology, a polyethylene mesh with 2.5 mm spacing was embedded in partially deuterated agar and wrapped around the mouse. The agar reduced susceptibility artifacts and also produced a pattern on MRI that was used for registration of tissue slices and images. To perform the correlation of histology with MRI, one representative H&E section was selected per mouse. On each section, the lymph node, tumors and ducts distended with DCIS were counted, and their grid locations noted. The corresponding grid positions in the MR images were examined to see if correlative structures were discernable.

Results: Fig. 1 shows FLASH GE images with fat saturation and the corresponding pathology for two different mice. The correlations indicated in the figure were made via the grid and corresponding structures are noted in the figure. In all ten cases, the mammary gland and the lymph node were accurately identified, and the position of the lymph node on histological sections correlated with MRI to within 2 mm. 'Gold standard' evaluation of the pathologist demonstrated that MRI detected 1/1 large (~5mm) tumor, 8/9 small non-palpable tumors ~0.5-1.5 mm in size, and 11/13 ducts distended with DCIS ~ 300-500 microns in diameter. These findings were clearly distinguishable from normal gland.

Discussion: To our knowledge, this is the first report of MR imaging of early, spontaneous mouse mammary cancer. The detection of very early cancers, including DCIS, in a mouse model opens new possibilities for research and for clinical applications. Because of its similarity to human breast cancer, MRI of early orthotopic murine mammary cancer will be an important tool for **a)** development of therapies that target early cancers **b)** developing improved MR imaging methods for detection of early cancers and pre-cancerous conditions **c)** discovering new MRI markers for cancer risk.

Figure 1: FLASH GE *in vivo* images with fat saturation for 12 week (left) and 16 week (right) old mice. Please note: the H&E sections are coronal slices, while the MRI are axial and a grid is used to correlate the two. Nevertheless, below close correspondence can be seen between the DCIS, small tumors, and lymph nodes on histology and MRI.



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References: [1] Cohen et al. Int J Cancer. 2006 Apr 1:118(7); 1609-17.
[2] Rodrigues et al. MAGMA. 2004 Dec; 17(3-6):260-70.