Do all *in situ* cancers progress to invasive disease? A first look at progression of mammary cancer from *in situ* to invasive carcinoma *in vivo*.

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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. However, a clinical concern is whether DCIS is being overdiagnosed and overtreated, as there is evidence to suggest that not all DCIS lesions will progress into invasive cancers. The purpose of this study was to investigate the progression of DCIS into invasive cancer using a transgenic mouse model. In order to accomplish this, DCIS and early invasive cancers would need to be reliably detected in mouse mammary glands, however there have been no prior published reports demonstrating this. Therefore, the first part of this study involved demonstrating that although *in situ* and early invasive cancers are difficult and small (< 1mm) targets, they can be reliably detected by MR imaging. Then, the progression of *in situ* to invasive disease was studied using *in vivo* MRI.
Methods: The Animal Care and Use Committee approved our study of 20 C3(1) SV40 TAg mice between 10-20 weeks of age. In 12 mice, a sensitivity/specificity study was performed to determine whether conventional MR imaging techniques could be used to reliably detect early mammary cancer and DCIS *in vivo*. For this, a pair of inguinal mammary glands in each mouse was imaged using a T_1-weighted gradient echo (GE) sequence, with fat suppression. H&E sections of the glands were obtained. We used a polyethylene grid embedded in partially deuterated agar to register tissue sections and MR images. On one representative H&E section, the tumors and ducts distended with DCIS were identified by an experienced pathologist. The MR images were examined to see if correlative structures were discernable. The remaining 8 mice were selected for serial imaging every two weeks from 10-20 weeks of age. For each, the onset of DCIS, the onset of invasive tumors and the size of the lesion over time was measured.
Results: GE images were able to detect 1/1 large (~5mm) tumor, 17/18 small (~1mm) tumors, and 13/16 ducts distended with DCIS greater than 300 microns. There were no false positives—a clear MR finding corresponded to cancer in all glands. Having reliably detected DCIS with GE, we then moved to studying the progression of disease. DCIS lesions developed at an average age of 14.5 weeks of age, and small tumors developed at an average age of 17.3 weeks. 4 of 8 mice not progress from DCIS to invasive cancer within the study period (Figure 1).
Discussion: The results presented here demonstrate for the first time that i) MRI can reliably detect *in situ* cancer (300 microns) and small, non-palpable tumors (< 1 mm), ii) MRI may be used to track the progression of breast cancer through the full range of development, from *in situ* to invasive carcinoma, and iii) some DCIS lesions did not progress significantly during the study window, illustrating that this model offers the opportunity to influence factors that predict and influence DCIS progression. One significant application of this work is in pre-clinical imaging of drug evaluation. MR imaging has long been used to assess the effects of novel therapies on mammary cancers—however, the tumors imaged in these studies have been large and palpable, representing a better model for advanced rather than early human disease. With the results presented here, MR imaging could be used to assess efficacy of therapies on cancers of all stages of disease (*in situ*, early and advanced). These preliminary results point to future work performing serial imaging in larger numbers of mice, and further investigating MR markers that can predict invasion.

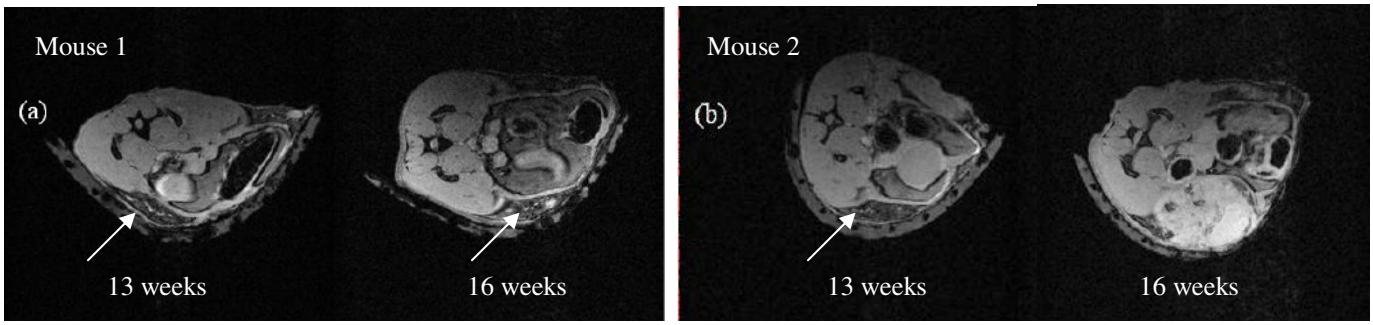

Figure 1: Axial MRI from two mice, at ages 13 and 16 weeks (a) Mouse 1: DCIS (white arrow) is present at 13 weeks and has not progressed significantly at age 16 weeks. (b) Mouse 2: DCIS is again present at 13 weeks, and at 16 weeks has progressed to a large palpable tumor.

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