

Magnetic resonance imaging reveals the progression, regression and indolence of *in situ* carcinoma in transgenic mice.

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Introduction: The processes that trigger progression of preinvasive ductal carcinoma *in situ* (DCIS) to invasive breast cancer remain elusive¹. Transgenic mouse models of cancer provide an experimental framework with which to begin to determine the key events in progression of breast cancer from DCIS to invasive disease. Because of the small size of *in situ* mammary cancers in mouse models, high-resolution imaging techniques are required to effectively observe how lesions develop, grow and progress over time. Heretofore, due to the challenge of detecting sub millimeter disease, there have been no imaging studies that could observe the trajectory of *in situ* to invasive cancer in mice. Here, we demonstrate that despite its sub-mm size, murine DCIS can be reliably detected by magnetic resonance imaging (MRI), which we use to track *in vivo* the transition of *in situ* to invasive cancer in transgenic mice.

Methods: A total of 24 C3(1) SV40 Tag mice, which develop mammary cancer similar to DCIS including progression to invasive tumors, were used. 12 mice were serially imaged with MRI every 2-3 weeks (FLASH TR/TE: 400/5.5, FOV = 3.0 x 3.0 cm, NEX = 2, slice thickness = 0.5 mm, in-plane resolution = 117 microns and flip angle = 30°)². Another 12 mice were used for dynamic contrast enhanced MR imaging studies (FLASH TR/TE = 30/3.5 ms, slice thickness = 1.0 mm, in-plane resolution = 256 microns, flip angle = 20°). The development and progression of DCIS lesions and early invasive tumors was followed, and several lesion features were measured, such as volume, growth rate, morphology, as well as the time to progression of DCIS to small invasive tumor. In addition, two-compartment physiologic model parameters K_{trans} and v_e (related to blood flow, capillary permeability and surface area, and extra-vascular extra-cellular space) were extracted.

Results: Overall, 31 DCIS and 18 invasive tumors were studied. Small invasive tumors demonstrated increased K_{trans} ($0.36 \pm 0.05 \text{ min}^{-1}$) compared with DCIS ($0.21 \pm 0.14 \text{ min}^{-1}$). Serial images of 16 DCIS lesions were obtained; these lesions developed at an average initial volume of $0.3 \pm 0.2 \text{ mm}^3$ with an average growth rate of $-0.15 \pm 0.66 \text{ week}^{-1}$ (Figure 1). Surprisingly, even in mice that are genetically predisposed to develop invasive carcinoma, these lesions took vastly different progression paths: (i) 9 lesions progressed to invasive tumors with an average progression time of 4.56 ± 1.9 weeks (ii) 5 were stable for over 8 weeks, and were identified by a statistical model to represent indolent disease, and (iii) 2 lesions *regressed*, i.e., the lesion was not detected on future images (Figure 2). Interestingly, larger DCIS volume was *not* a predictor of future progression to invasive tumors, but there was a trend for DCIS growth rate to be related to eventual development of invasiveness.

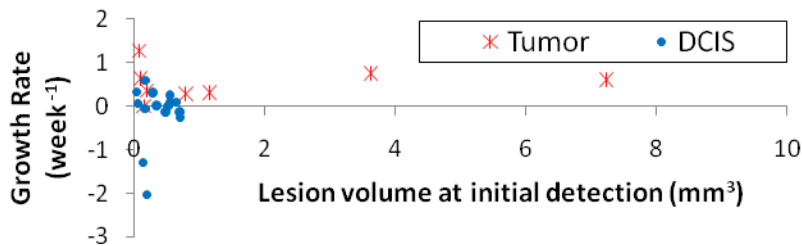


Figure 1: Scatter plot of growth rates and lesion volume at initial detection of DCIS and invasive tumors. Most DCIS lesions had growth rates near 0, and two demonstrated regression resulting in substantially negative growth rates. In contrast, all tumors exhibited positive growth rates. The initial volume of early cancers we have detected here is smaller than in any prior report.

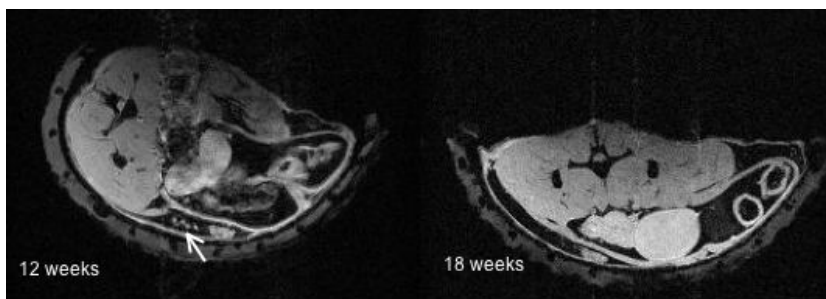


Figure 2: Example of DCIS regression. DCIS is visible at 12 weeks of age (left) beside lymph node (white arrow), but cannot be found six weeks later anywhere near the lymph node, on MR images or on histological specimens. Here, only one slice is shown demonstrating absence of a lesion near the lymph node (right). FOV is 3.0x2.0 cm, and in-plane resolution is 117 microns.

Conclusions: The results reported here are the first direct measurements of the timescales and characteristics of progression from *in situ* to invasive mammary carcinoma in mice, and provide direct evidence that DCIS may be a *non-obligate* precursor lesion. Small invasive cancers exhibited both increased vascularity and growth rates compared to preinvasive DCIS, suggesting that landmark events in disease progression, such as increased angiogenesis and dysregulation of cellular growth, occur during the transition from *in situ* to invasive disease. We have presented a new foundation for using non-invasive real-time imaging in pre-clinical studies of *early* mammary cancer progression, in particular for testing the efficacy of preventative and interventional therapies for halting *in situ* disease progression.

References: 1. Erbas B, Provenzano E, Armes J, Gertig D. The natural history of ductal carcinoma in situ of the breast: a review. *Breast Cancer Res Treat* 2006; 97:135-144. 2. Jansen SA, Conzen SD, Fan X, et al. Detection of *in situ* mammary cancer in a transgenic mouse model: *in vitro* and *in vivo* MRI studies demonstrate histopathologic correlation. *Phys Med Biol* 2008; 53:5481-5493.

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