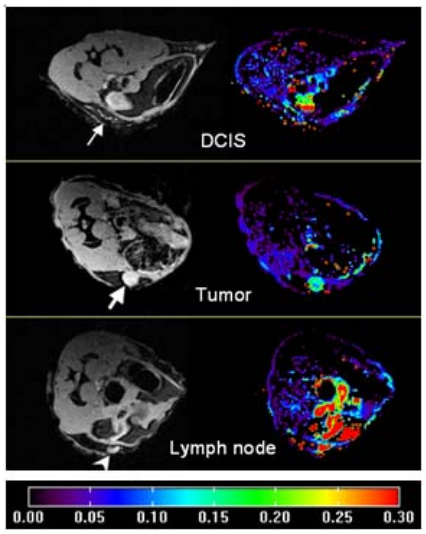
Distribution of DCE-MRI pharmacokinetic parameter maps in early murine mammary cancer

X. Fan[1], S. A. Jansen[2], E. J. Markiewicz[1], G. M. Newstead[1], and G. S. Karczmar[1]
[1]Radiology, The University of Chicago, Chicago, IL, United States, [2]Mouse Cancer Genetics Program, National Cancer Institute, Frederick, MD, United States

INTRODUCTION: Dynamic contrast enhanced MRI (DCE-MRI) has demonstrated equal or superior sensitivity and specificity for detecting early invasive cancers compared with x-ray mammography. However, this has not been consistently demonstrated for ductal carcinoma *in situ* (DCIS), a non-obligate precursor to invasive breast cancer, in which cancer cells are still confined by the basement membrane of mammary ducts. Because DCIS is the earliest stage of breast cancer with best prognosis, it is likely that improvements in detecting and characterizing breast cancers at a preinvasive stage will improve patient outcomes. In normal clinical DCE-MRI, it is very difficult to detect contrast media dynamics of pure DCIS, because of limited spatial resolution, and the diffuse anatomy of DCIS in patients. This problem is compounded by the fact that clinical DCE-MRI data are often analyzed using a region–of-interest (ROI) approach, to improve signal-to-noise ratio (SNR). This mixes signals from DCIS and other tissues and reduces sensitivity to the spatial heterogeneity of the DCIS. In high field DCE-MRI scans of a mouse model, we are able to isolate pure intraductal cancers with high SNR and high temporal resolution. This allows more accurate characterization of contrast media dynamics in these early cancers.

MATERIALS AND METHODS: Twelve C3(1) SV40 large T antigen (Tag) mice were used in DCE-MRI experiments, performed on a Bruker 4.7 Tesla magnet. Multi-slice axial gradient echo images (TR/TE = 675/7 ms, flip angle = 30°, FOV = 30 mm, array size = 256^2, slice thickness = 0.5 mm, NEX = 2) over inguinal glands with fat suppression were acquired to localize lesions. Subsequently, DCE-MRI of three slices around the lesion was acquired (TR/TE = 30/3.5 ms, flip angle = 20°, FOV = 30 mm, array size = 128^2, slice thickness = 1.0 mm, NEX = 1) for ~20 s before contrast injection (dose 0.15 mmol/kg) and followed for ~8 min. Pixel based analysis of DCE-MRI data was performed by applying the two-compartment model to generate volume transfer constant (K^{trans}) and contrast media distribution volume (v_e) maps. The arterial input function (AIF) was derived from a muscle ROI (25 pixels) by using the reference tissue method with K^{trans} = 0.07 min^{-1} and v_e = 0.09. To reduce noise propagation, muscle curves were fit with an empirical mathematical model prior to AIF calculations. To quantify the heterogeneity of parametric maps of DCIS, invasive tumors, lymph nodes (LN), and normal mammary gland (NMG), means (μ), standard deviations (σ), and coefficients of variation (cv) of kinetic parameters were calculated within each ROI. Finally, the pixel based analysis results were compared with whole ROI analysis.

Figure 1.



RESULTS: MRI-identified DCIS, invasive tumor, and lymph nodes (LN) were confirmed with histologic results. Fig. 1 shows K^{trans} (min^{-1}) maps for DCIS, tumor, and LN, which demonstrate heterogeneity in DCIS; and fairly uniform in tumor rim and LN. The averaged values of μ, σ, and cv over all the mice are given in Table 1. There were no significant differences between K^{trans} and v_e in intraductal cancers vs. invasive tumors possibly due to the small number of tumors. However, the coefficient of variation in lymph nodes (cv in LN) is significantly smaller than in DCIS ($p < 0.001$), indicating greater spatial heterogeneity in DCIS. The NMG had smallest K^{trans} and v_e values, but with comparable cv to DCIS. Finally, the whole ROI analysis results (mean ± standard deviation) are given in Table 2. For DCIS, K^{trans} ($p < 0.05$) and v_e ($p < 0.09$) values were larger in pixel-based analysis compared to whole ROI analysis.

Table 1.	K^{trans} (min^{-1})			Ve		
	μ	σ	cv	μ	σ	cv
DCIS (n=9)	0.22	0.14	0.62	0.27	0.16	0.55
Tumor (n=3)	0.18	0.11	0.60	0.35	0.20	0.53
LN (n=11)	0.23	0.07	0.30	0.24	0.08	0.32
NMG (n=8)	0.06	0.03	0.45	0.19	0.12	0.50

Table 2.	K^{trans} (min^{-1})	Ve
DCIS (n=9)	0.09±0.05	0.16±0.11
Tumor (n=3)	0.13±0.08	0.22±0.08
LN (n=11)	0.21±0.06	0.25±0.06
NMG (n=8)	0.03±0.02	0.08±0.07

DISCUSSION: This study reveals the heterogeneous physiology of DCIS and surrounding normal tissue (NMG), and illustrates the potential for murine models of early stage mammary cancer to yield insights into corresponding human disease. The lower K^{trans} values of NMG compared to DCIS, suggests that imaging with high temporal and spatial resolution may improve accurate identification of DCIS. Additionally, there were significant differences between pixel-based analysis and whole ROI analysis, and the results suggest that quantitative analysis of spatial heterogeneity of contrast kinetics may improve diagnostic accuracy. In summary, these results in preclinical mouse models point to the potential utility of pixel-based analysis for improving the differential diagnosis of early breast cancer in the clinical DCE-MRI setting. In the mouse model with a high field scanner, it was relatively easy to isolate contrast media dynamics of individual intraductal cancers, but improvements in clinical MRI technology may lead to similar diagnostic accuracy in patients.

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