# Dynamic Contrast Magnetic Resonance Imaging Detects Premalignant High-Grade Dysplasia In Epithelial Carcinogenesis

J. R. Garbow[1], J. Engelbach[1], K. Olson[2], J. Arbeit[2]

[1]Radiology, Washington University, St. Louis, MO, United States, [2]Surgery, Washington University, St. Louis, MO, United States

**Introduction:** Worldwide, cervical cancer is the second most common malignancy in women and accounts for nearly 200,000 deaths annually. Human papillomavirus (HPV) is the initiator of cervical carcinogenesis, a disease characterized by progression through stages of increasing epithelial neoplastic pre-malignancy, termed cervical intraepithelial neoplasia (CIN), eventually resulting in invasive cervix cancer in a subgroup of patients. The ability to non-invasively detect, stage, and then treat patients with pre-malignant CIN would be a tremendous boon to therapy and prevention of invasive malignancies. Here, using a combination of a unique transgenic model of cervical carcinogenesis[1-3] and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), we are able to identify transgenic mice harboring high-grade CIN based on differential microvascular biology associated with these lesions.

**Materials and Methods:** MR images were collected in an Oxford Instruments 4.7 tesla magnet (40 cm, clear bore) equipped with 10-cm, inner-diameter, actively shielded Magnex gradient coils. The magnet/gradients are interfaced with a Varian INOVA console and data were collected using a 2.0-cm quadrature birdcage RF coil (Stark Contrast). Mice were maintained on isoflurane/O2 (1-1.5% v/v) throughout all experiments. DCE-MRI data were collected as 2-D, multi-slice gradient echo images with Tr = 60 ms; TE = 3 ms; FOV = 2.5 × 2.5; slice thickness = 0.5 mm; 2 transients). Transgenic mice (TG, n=7) with the human papillomavirus Type 16 early region targeted for basal squamous epithelial cell expression (K14-HPV16 TG mice) and non-transgenic mice (NTG, n=5) were treated with continuous-release estrogen pellets for three months, This treatment induces high-grade squamous epithelial dysplasia of the cervical transformation zone in the TG animals. Serial dynamic contrast enhanced magnetic resonance images were obtained with 15 s time resolution following intravenous injection of Gadomer contrast agent, 200 µl/kg (Schering, AG; MW 17 kD). Microvascular density was determined in separate sub-cohorts (n=4 each group) by image analysis of the microvascular area of MECA32 immunoperoxidase stained tissue sections. Statistical differences between means ± S.D. were tested using the Mann-Whitney U test.

**Results:** Typical image intensity *vs*. time curves are shown in the top of Figure 1 for an arterial region located within the female pelvis (left) and for a region of interest within the cervical-uterine transformation zone (right). Image intensities for the tissue ROI were converted into relaxivities and relaxivity *vs*. time curves were then quantified using standard kinetic models.[4] DCE-MRI data were analyzed on a pixel-by-pixel basis to derive parametric maps of fractional blood volume (fBV) and vascular permeability ($K^{PS}$). $K^{PS}$ measured at the cervical transformation zone was elevated in the TG mice (2.9 ± 0.4 ml/min/100cc tissue) compared to NTG mice (1.9 ± 0.2 ml/min/100cc tissue, p=0.03). Sub-epithelial microvascular area was elevated in the TG (7.68 ± 2.01) compared to the NTG mice (4.58 ± 2.13, p=0.057).

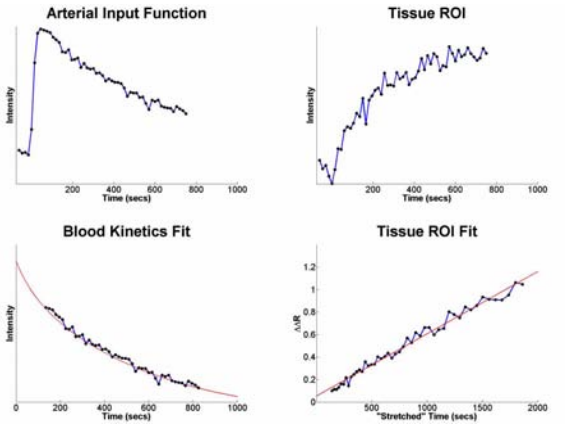


**Figure 1.** Image intensity *vs*. time curves for: within the female reproductive tract (top, left) and a region of interest within the cervical uterine transformation zone (top, right) for a TG mouse. A fit of the intensity *vs*. time curve for the blood (bottom, left) yields the arterial input function. Images intensities for a region of interest within the cervical transformation zone were converted into relaxivities and modeled using standard kinetic equations.

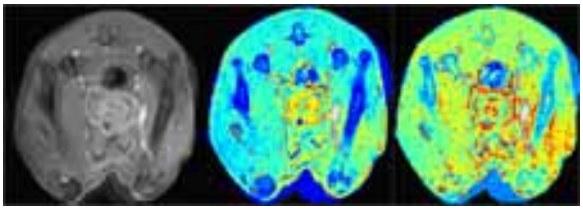

**Figure 2.** Parametric maps for a TG mouse derived from DCE-MRI data: anatomic, gradient-echo image (left); permeability (KPS) map (center); fractional blood volume (fBV) map (right).

**Conclusion:** DCE-MRI identifies TG mice harboring high-grade dysplasia *via* noninvasive determination of microvascular biology. Delineation of these lesions will facilitate development of chemoprevention strategies based on therapies targeted either directly to the angiogenic endothelium or to the overlying neoplastic epithelium.

**Acknowledgments.** We gratefully acknowledge Joseph J. H. Ackerman for helpful discussions, Schering AG (Berlin, Germany) for supplying the Gadomer contrast agent, and funding from an NIH/NCI Small Animal Imaging Resource Program (SAIRP) grant (R24 CA83060) and the Alvin J. Siteman Cancer Center at Washington University in St. Louis, an NCI Comprehensive Cancer Center (P30 CA91842).

**References.** 1. Elson, DA, Riley, RR, Lacey, A; Thordarson, G; Talamantes, FJ; Arbeit, JM. *Cancer Research* (2000), **60**, 1267.

2. Arbeit, JM. *Cancer Surveys*, Volume **26**: Skin Cancer, pp. 7-32.
3. Riley, RR; Duensing, S; Brake, T; Munger, K; Lambert, PF; Arbeit, JM. *Cancer Research* (2003), **63**, 4862.
4. Tofts, PS; *J. Magn. Reson. Imaging*, (1997) **7**, 91.