X-ray Fluorescence Microscopy Imaging of the Normal Mouse Prostate Reveals that Intravenously Administered Gadolinium Enters the Lumen of the Prostatic Glands

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Target Audience: The study will benefit both pre-clinical and clinical investigators in DCE-MRI of prostate imaging.

Purpose: Dynamic contrast enhanced MRI (DCE-MRI) has become a standard component of multi-parametric prostate MRI protocols and its use is incorporated into current guidelines for prostate MRI. Analysis of DCE-MRI data from prostate is usually based on the model that gadolinium (Gd) distributes into two well-mixed compartments and assumes that Gd does not enter into the glandular lumen. However, this assumption has not been directly tested. The purpose of our study was to measure the concentration of Gd in the prostatic epithelium and lumens of the normal mouse prostate following intravenous (I.V.) injection, using state-of-the-art X-ray fluorescence microscopy (XFM) imaging *in situ*.

Methods: Six C57Bl6 male mice (28-weeks old) were sacrificed 10 minutes after Gd (0.13 mmol/kg) injection I.V. and three mice were sacrificed after saline injection. Prostate tissue samples from each mouse were harvested and frozen. For XFM images, 7-µm thick slices were sectioned. Adjacent to XFM slices, 5-µm thick slices were sectioned for H&E staining to facilitate lesion identification. XFM studies were performed using a high energy, synchrotron-based X-ray beamline. Images were acquired with 0.5-5 µm in-plane resolution. Average element concentrations, including Gd, in regions-of-interest (ROIs) of epithelia and lumens were determined in 32 prostatic glands in n=6 mice. Gd was administered I.V. Baseline concentrations of Gd and other elements in corresponding ROIs in 15 prostate glands were determined in n=3 mice in which no Gd was injected. Typical ROI sizes were of 2718 ± 791 μm^2 for epithelium and 4563 ± 1296 mm^2 for lumens. Quantitation and image processing were performed using MAPS software written in IDL.

Results and Discussion: Baseline concentration of Gd of 0.01 ± 0.01 mM in n=3 mice was determined from XFM measurements of prostatic tissue samples when no Gd was added and was used to determine the measurement error. In n= 6 mice when Gd was administered, average Gd concentrations in regions of epithelium and lumen were 1.00 ± 0.13 mM and 0.36 ± 0.09 mM, respectively. These values were 36- to 100-fold higher compared to similar prostatic regions in mice with no Gd injection with $p<0.0001$. The results clearly show that a significant amount of intravenously administered Gd enters into glandular lumen of the prostate. In addition, Fig. 1 demonstrates that the spatial distribution of Gd is very heterogeneous in both epithelia and lumens. The concentration of Gd in the glandular lumens was about a third of the concentration in the epithelium. Nevertheless, the concentration of 0.36 mM is sufficient to cause a significant change in contrast in T_1-weighted MR images, particularly in regions of the prostate where the fractional volume of lumens is relatively large. The effect of contrast agent molecules in the lumen on image intensity may be accentuated because the native T_1 of luminal fluid is expected to be much longer than the T_1 in epithelium and stroma. Thus the Gd detected by XFM in glandular lumens of normal prostate is likely to have a significant influence on results obtained from DCE-MRI.

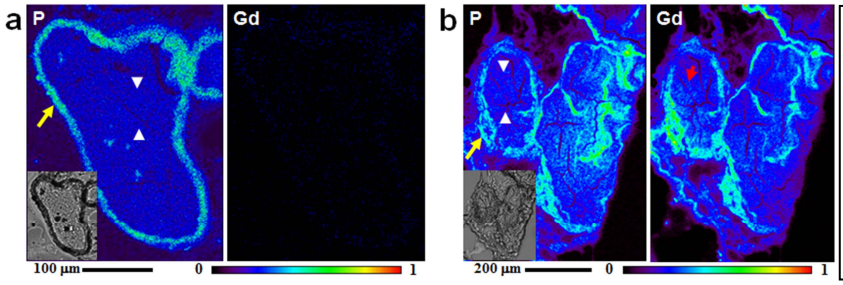

Figure 1. Distribution of Gd in prostatic epithelium and lumen. XFM images showing phosphorous (P) and Gd distributions of mouse prostate tissues without (**a**) or with (**b**) Gd administrations. In both sets of images, insets in P maps show light microscopy images; the yellow arrows indicate prostatic epithelium and the areas indicated by white arrowheads show prostatic lumen. In Fig. 1b, the red arrow indicates the accumulation of Gd in prostatic lumen. Color and scale bars are also shown.

Conclusions: Our study had several limitations: 1) the sample size was small; 2) the sacrifice time following contrast administration was fixed (10 minutes) – this limited our ability to provide temporal information on luminal Gd accumulation; and 3) there were no cancerous glands in our study population – therefore, we could not evaluate the glandular luminal uptake in cancer and compare it with the benign glands. Despite these limitations, we have demonstrated the presence of Gd in the lumens of murine prostate glands following the I.V. injection of Gd. Glandular lumen volume and its percentage in the tissue have been shown to be effective quantitative histologic biomarkers for differentiation of prostate cancer from normal prostatic tissue. These parameters also decrease as the Gleason score of the cancer increases. Distribution of Gd into the luminal compartment may allow accurate estimation of the volume of this compartment with the use of future pharmacokinetic models and image acquisition protocols that take this fact into account. The new information regarding the spatio-temporal distribution of MRI contrast agents will point the way to the development of optimal methods for acquisition and analysis of DCE-MRI data that increase diagnostic accuracy.