Feasibility of Assaying Prostate Cancer Disease Burden with Shutter-Speed DCE-MRI

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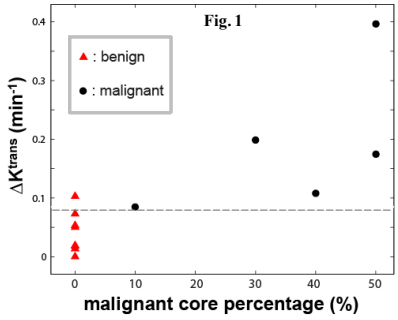
Introduction: Standard Dynamic-Contrast-Enhanced MRI (DCE-MRI) pharmacokinetic modeling, SM (1), assumes inter-compartmental water exchange kinetics to be always effectively infinitely fast. Though it is physically impossible that such processes be truly infinitely rapid, in many tissue regions they seem so as far as DCE-MRI ^1H_2O signals are concerned: the exchange MR systems remain in their fast-exchange-limit [FXL] conditions. However, there are tissue *loci* where these systems transiently depart their FXLs during DCE-MRI contrast reagent (CR) bolus passage (2) – because of high microvessel CR permeability. Using an exchange-sensitized DCE-MRI acquisition and analytical "shutter-speed" model, SSM (2), we demonstrate the feasibility of prostate cancer detection with water exchange allowed DCE-MRI pharmacokinetic modeling. The influence of the shutter-speed effect in prostate disease burden monitoring and objective lesion categorization may provide clinical benefits.

Methods: Prostate ^1H_2O MRI data were acquired from 13 subjects with a Siemens TIM Trio (3T) system under an IRB-approved protocol. RF transmitting was through the whole body coil and RF receiving was with Spine Matrix and flexible Body Matrix coil arrays. The DCE-MRI acquisition employed a 3D FLASH pulse sequence with a 256*144*16 matrix size and a 360*203 mm^2 FOV, resulting in (1.4)^2 mm^2 axial-plane resolution. Other parameters are: slice thickness: 3 or 3.2 mm; TR/TE/FA: 5.0 ms/1.57 ms/15º, inter-image sampling interval: 6.3 s. A 0.1 mmol/kg CR (Prohance; Bracco) bolus was administered starting ~30 s after commencing the DCE-MRI sequence. Other details are given in (3).

DCE data were analyzed using the first generation shutter-speed model (SSM1), which focuses on cell membrane water exchange kinetics and allows τ_i (the mean intracellular water molecule lifetime) estimation (2). For prostate tissue, τ_i is often the 3rd most influential parameter [after K^{trans} (a CR extravasation rate measure) and v_e (the extracellular, extravascular volume fraction)] (4), even more sensitive than the blood volume fraction. With the inclusion of τ_i, the water exchange effect on K^{tran} can be quantified using the difference of a parameter magnitude returned by sequential SSM and SM analyses of a given DCE-MRI time-course. The new biomarker ΔK^{trans} [$\Delta K^{trans} \equiv K^{trans}(SSM) - K^{trans}(SM)$] is investigated for its potential in prostate cancer.

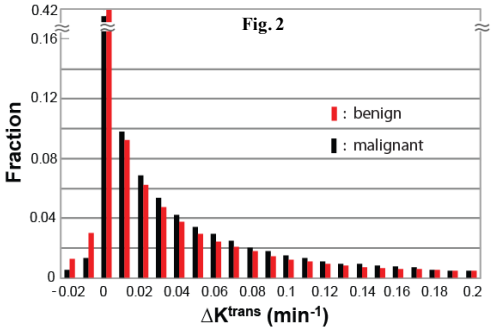
All subjects underwent subsequent standard ten-core prostate biopsies with ultrasound (US) guidance. We label a case malignant (five subjects) from histopathology if malignancy was found in at least one of the five biopsy core specimens from the same side of the prostate as the suspicious DCE-MRI ROI. A case is benign (eight subjects) from histopathology if no malignancy was found in any of the 10 biopsy core specimens. For positive biopsy specimens, the Gleason scores ranged from 6 to 8.



Results: **Figure 1** is a scatter plot of ROI ΔK^{trans} values for all 13 subjects. The abscissa measures the percentage of biopsy core specimens found malignant. Since all benign cases had zero malignant core specimens (by definition), the red triangles are clustered at zero percent. The malignant cases (black circles) are scattered from 10% to 50%. One can see that there is a rough supra-linear positive correlation of ΔK^{trans} with disease burden. A binary classifier cut-off line (dashed) can be drawn at $\Delta K^{trans} \approx 0.085$ min^{-1}, which yields no false negatives and only one false positive (89% specificity), for this small study group. This is particularly encouraging since it was not possible for us to know if a biopsy core passed through our chosen ROI or not.

Based on the biopsy/pathology findings, whole prostate (9 – 14 slices) voxel-by-voxel ΔK^{trans} histograms were combined into malignant and benign sub-groups of the 13 subjects. The normalized, averaged results are plotted in **Figure 2**. The averaged malignant group ΔK^{trans} values are shown as black bars and the benign group values as red. Since there is tremendous partial volume averaging here, over the entire gland, the two distributions are very similar. However, for all values of $\Delta K^{trans} > 0$, the black bars are larger than the red bars. Negative ΔK^{trans} values can occur due only to random noise, and when the K^{trans} value itself is small. Interestingly, for all ΔK^{trans} values ≤ 0, the red bars are larger than the black bars. Even with the extensive partial volume averaging here, the malignant histogram is slightly more skewed to larger ΔK^{trans} values. With the mode (ΔK^{trans} value for the maximum probability distribution) set at zero for prostate DCE-MRI histograms, sensitive statistical tools can be used for simple distribution and shape comparisons. Thus, within the ΔK^{trans} domain, inter- and/or intra-subject results can be directly examined for shutter-speed effects.

Discussion: When signal-to-noise ratio is optimized with acquisition parameter values, prostate DCE-MRI data become sensitive to water exchange effects, and the ΔK^{trans} SSM parameter values become useful biomarkers for discriminating malignant from benign tissue. Furthermore, these parameters can be mapped with high resolution using surface coil arrays, making it readily translational. Limitations of the current study include the small sample size, and the use of only US-guided biopsy for verification. To further investigate our protocol usefulness, it is necessary to expand the population. Furthermore, to provide maximal verification, DCE-guided biopsy and/or parametric map co-registration with appropriately stained histopathology slides obtained after prostatectomy (when clinically indicated) should be employed. Such co-registration is best achieved through the use of a customized mold, produced from MR images, made to hold the individual excised gland (5).



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Reference: **1.** Tofts, Brix, Buckley, *et al. J Magn Reson Imaging,* 10:223-232 (1999). **2.** Yankeelov, Rooney, Li, Springer *Magn Reson Med.* **50**:1151-1169 (2003). **3.** Priest, Li, Tagge, Woodward, Beer, Springer, Garzotto, *Proc.Int Soc Magn Reson Med*. **18**: 2809 (2010). **4.** Li, Rooney, Springer, *Proc. Int Soc Magn Reson Med*. **18**: 3392 (2010). **5.** Shah, Pohida, Turkbey, Mani, Merino, Pinto, Choyke, Bernardo, Rev Sci Instrum. 80(10):104301 (2009).