Feasibility of Shutter-Speed DCE-MRI for Improved Prostate Cancer Detection

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The feasibility of shutter-speed model dynamic-contrast-enhanced MRI pharmacokinetic analyses for prostate cancer detection was investigated in a prebiopsy patient cohort. Differences of results from the fast-exchange-regime-allowed (FXR-a) shutter-speed model version and the fast-exchange-limit-constrained (FXL-c) standard model are demonstrated. Although the spatial information is more limited, postdynamic-contrast-enhanced MRI biopsy specimens were also examined. The MRI results were correlated with the biopsy pathology findings. Of all the model parameters, region-of-interest-averaged $K_{trans}$ difference [$\Delta K_{trans} \equiv K_{trans}^{FXR-a} - K_{trans}^{FXL-c}$] or two-dimensional $K_{trans}^{FXR-a}$ vs. $K_{ep}^{FXR-a}$ values were found to provide the most useful biomarkers for malignant/benign prostate tissue discrimination (at 100% sensitivity for a population of 13, the specificity is 88%) and disease burden determination. (The best specificity for the fast-exchange-limit-constrained analysis is 63%, with the two-dimensional plot.) $K_{trans}$ and $K_{ep}$ are each measures of passive transcapillary contrast reagent transfer rate constants. Parameter value increases with shutter-speed model (relative to standard model) analysis are larger in malignant foci than in normal-appearing glandular tissue. Pathology analyses verify the shutter-speed model (FXR-a) promise for prostate cancer detection. Parametric mapping may further improve pharmacokinetic biomarker performance. Magn Reson Med 000:000–000, 2012. © 2012 Wiley Periodicals, Inc.

Key words: shutter-speed, DCE-MRI, prostate

False positive screening is a major concern common to both prostate and breast cancer detection strategies. And, if anything, “overdiagnosis and overtreatment are much more common in prostate cancer screening than in … breast” (1). Although the digital-rectal examination is considered an adjunct to prostate cancer detection, the serum prostate-specific antigen test is the primary prostate screening biomarker (2). There is really no image-based screening method to compare with mammography. After more than 20 years of prostate-specific antigen screening, perhaps a million men may have been unnecessarily treated for clinically insignificant prostate cancer (1). For almost all positive screeners, the next diagnostic step is transrectal ultrasound-guided needle biopsy of the prostate gland. This is an invasive procedure that can have “a complication rate of up to 63–73% in some series” (3).

It has long been hoped that dynamic-contrast-enhanced (DCE)-MRI can make a significant contribution to reducing overdiagnosis and overtreatment of prostate cancer. Although this article concerns the latter, a brief history of DCE-MRI in breast oncology (4) is instructive. Its use started more than 20 years ago (5), and quantitative DCE-MRI studies began more than 15 years ago (6). Such work has been quite extensive in part because breast lesions generally enhance much more than surrounding normal-appearing gland (NAG) tissue, and breast malignancies manifest in DCE-MRI rather focally. However, because there are so many (and so many different subtypes of) benign breast lesions, progress in effective benign/malignant breast tumor differentiation (high specificity) has been slow. Shutter-speed DCE-MRI may change this (4,7–10)—see below.

Prostate malignancy presents an even greater challenge for DCE-MRI. The difference in maximum contrast enhancement between malignant tissue and NAG is generally very small, and often the DCE-MRI manifestation of malignancy is rather more diffuse than for breast cancer. Nonetheless, prostate DCE-MRI also began almost 15 years ago (11) and has been heavily investigated. Consequently, the indications for DCE-MRI studies of prostate disease have been increasing. Recent contributions include Refs. 12–17 and recent reviews include Refs. 18–21. The Bonekamp and Macura article (20) is particularly recommended.

Almost all of the mathematical models used for quantitative DCE-MRI are variants of the nuclear medicine radiotracer pharmacokinetic paradigm (20). However, we
have pointed out a fundamental problem in this (22). For T1-weighted $^1\text{H}_2\text{O}$ signals, the bases for DCE-MRI, the tracer paradigm carries the incorrect corollary that inter-compartmental water molecule exchange be assumed effectively infinitely fast throughout the course of the DCE-MRI acquisition—the fast-exchange-limit (FXL) MR condition. Although the contrast reagent (CR) plays the role of the tracer molecule, the signal comes from the water molecule. For classic nuclear medicine tracers, the signal molecule and the tracer molecule are one and the same, and tracer compartmentalization is not intrinsic to the signal. The shutter-speed pharmacokinetic model (SSM) was developed to correct for the tracer assumption (7–9,22,23). Relieving the FXL constraint leads to remarkable SSM performance for breast cancer diagnosis. With an SSM DCE-MRI follow-up to mammography, it is now possible to contemplate the elimination of most of the >70% of breast biopsy procedures that yield negative pathology reports (4,7–10).

The single application of the SSM to prostate DCE-MRI so far reported, in an unblinded, postbiopsy study (24), is also quite encouraging. It shows preliminary trends very much like those we see for breast malignancy. We carry the analysis further here, to include quantitative shutter-speed effect ($\Delta K^{\text{trans}}$) determinations, and slice and whole prostate mapping and histogram comparisons for disease burden measurement. In a companion article (25), we analyze prostate data extensively to determine the most appropriate SSM version. In this article, we report our preliminary experience with application of that SSM version to survey prebiopsy prostate DCE-MRI data in a partially blinded study of tumor detection.

MATERIALS AND METHODS

Patient Population

The study was approved by both the Portland VA Medical Center and Oregon Health & Science University institutional review boards. Informed consent was obtained individually. We have studied men who were referred for biopsy procedures because of standard screening indications. However, they volunteered to participate in DCE-MRI acquisitions before their biopsies. A previous prostate biopsy was an exclusion criterion. Thirteen male subjects [60 (±8.4) years] [mean (±standard deviation)] were enrolled in our DCE-MRI protocol. All presented to the Portland VA Medical Center with elevated prostate-specific antigen levels and were referred for biopsies as standard of care. DCE-MRI acquisitions were performed before a 10-core biopsy procedure, and our DCE-MRI data analyses were compared with the pathology reports consequent to the subsequent biopsy procedures. One subject found to have cancer on needle biopsy went on to have a prostatectomy in his clinical treatment plan.

MRI

Prostate $^1\text{H}_2\text{O}$ MRI data were acquired with a Siemens TIM Trio (3 T) system. Radiofrequency transmission used the instrument whole-body coil, whereas reception used a combination of flexible body and spine matrix coils. Multislice turbo spin-echo $T_2$-weighted images (repetition time/echo time/flip angle, 5000 ms/102 ms/90°) were acquired for anatomic contrast and region-of-interest (ROI) selection. To estimate pre-CR $R_1$ values for each voxel, a proton density (PD)-weighted image series of the prostate gland was obtained using a three-dimensional fast low angle shot (FLASH) pulse sequence with a 256 × 144 × 16 matrix size and a 360 × 203 mm² transverse field-of-view (FOV), resulting in a nominal in-plane resolution of (1.4)² mm². Other parameters were as follows: slice thickness, 3 or 3.2 mm and repetition time/echo time/flip angle, 200 ms/1.56 ms/8°. For DCE-MRI, the same FLASH sequence was run with the only differences being repetition time = 5.0 ms and flip angle = 15°, which yielded a 6.28 s imaging intersampling interval. The DCE-MRI imaging time was about ten and a half minutes. A bolus of 0.1 mmol/kg Prohance (Bracco, Inc.) was administered in an antecubital vein ~38 s after commencing the DCE-MRI acquisition. It was delivered in 5–10 s, at 3.0 mL/s, followed by a 20-mL saline flush.

Prostate Biopsy

Subsequent to the DCE-MRI acquisition, each subject underwent a standard 10-core prostate biopsy procedure under (exclusively) ultrasound guidance, accomplishing “geographic” coverage. Although transrectal ultrasound-guided needle biopsy is “adequate for diagnosis, it does not provide the spatial resolution needed to visualize” the malignancy (26). [Even when prostatectomy is done, “anatomic orientation in the body is lost” unless special care is taken (26).] Although we know on which side of the prostate each biopsy needle entered, we do not know if the DCE-MRI ROI chosen was actually penetrated by a needle. Therefore, we adopted the following operational criteria. We label a case malignant (five subjects) from histopathology when malignancy was found in at least one of the five biopsy core specimens from the same side of the prostate as the suspicious 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.

DCE-MRI ANALYSES

For each of the 13 subjects, an ROI boundary was manually drawn around an area in a DCE-MR image, and its location had been outlined on a $T_2$-weighted image slice by a radiologist (not involved in DCE-MRI data processing) using hypointensity and morphology criteria and the pathology laterality. The DCE-MRI analyses were performed by a researcher unaware of the pathology results. DCE-MRI pharmacokinetic modeling used the standard model (SM) and the first-generation SSM (fast-exchange-regime-allowed (FXR-a)). As presented in our breast DCE studies (4.7–10), the only difference between SM and SSM(FXR-a) is the allowance for finite transcytolemmal water exchange kinetics in SSM. The SM intrinsically assumes the mean intracellular water lifetime, $\tau_i$, in a voxel to be effectively zero.
The arterial input function (AIF) time course was obtained from a small ROI within a femoral artery that was clearly visible within the image FOV. To minimize inflow effect-introduced AIF uncertainties, each individual AIF was recursively amplitude adjusted until the $v_e(SM)$ [the interstitial (extracellular and extravascular) volume fraction] parameter from obturator muscle reference tissue (27,28) ROI DCE data converged to 0.11, with a tolerance of $0.005$. An individual AIF time course was measurable for each subject except one, due to severe motion during the DCE acquisition. A population-averaged AIF (from average of six other subjects) was used for this subject. As the PD-weighted image still carries some slight (mixed) relaxation weighting, a numerical approach is used to obtain the PD image based on the average of DCE baseline images and that of the PD-weighted image, with $T_1$ as the only variables.

All data fitting used nonlinear least-square methods with an in-house software package written in Matlab (MathWorks, Natick, MA). CR relaxivity was assumed to be $3.8 \text{mM}^{-1} \text{s}^{-1}$ for both plasma and interstitium.

**RESULTS**

**ROI DCE-MRI Analyses**

Figure 1a shows a transverse DCE (3-min post-CR injection) pelvic image slice (#5) from subject no. 10 at 3-min post-CR injection. The perspective is inferior–anterior up. b: A $T_2$-weighted image of the same slice. c: A zoomed section of (a)—the four ROIs represent suspicious and NAG prostate tissues, obturator muscle tissue, and the femoral artery yielding the AIF. Subsequent biopsy/pathology indicated malignant adenocarcinoma in three left prostate (image right) core specimens, and benign tissue in the other seven. f: Inset shows the AIF determined using the (c) muscle ROI for reference. d: Points trace the normalized ($S/S_{pre}$) suspicious ROI time course. The solid curve represents the best SSM (FXR–a) fitting, whereas the lower dashed curve is the best SM(FXL–c) analysis. The signature mismatch (temporally correlated residuals) of the FXL fitting is that commonly seen. This systematic error is even more clearly indicated with the upper dashed curve, expected by SM (FXL–c) (i.e., with $\tau_i = 0$) for the SSM(FXR–a)-returned $K^{trans}$ and $v_e$ values. e: Analogous results for the (c) NAG ROI. Those for the (c) muscle ROI are shown in (f).

FIG. 1. a: A transverse DCE pelvic image slice (#5) from subject no. 10 at 3-min post-CR injection. The perspective is inferior–anterior up. b: A $T_2$-weighted image of the same slice. c: A zoomed section of (a)—the four ROIs represent suspicious and NAG prostate tissues, obturator muscle tissue, and the femoral artery yielding the AIF. Subsequent biopsy/pathology indicated malignant adenocarcinoma in three left prostate (image right) core specimens, and benign tissue in the other seven. f: Inset shows the AIF determined using the (c) muscle ROI for reference. d: Points trace the normalized ($S/S_{pre}$) suspicious ROI time course. The solid curve represents the best SSM (FXR–a) fitting, whereas the lower dashed curve is the best SM(FXL–c) analysis. The signature mismatch (temporally correlated residuals) of the FXL fitting is that commonly seen. This systematic error is even more clearly indicated with the upper dashed curve, expected by SM (FXL–c) (i.e., with $\tau_i = 0$) for the SSM(FXR–a)-returned $K^{trans}$ and $v_e$ values.

e: Analogous results for the (c) NAG ROI. Those for the (c) muscle ROI are shown in (f).

The arterial input function (AIF) time course was obtained from a small ROI within a femoral artery that was clearly visible within the image FOV. To minimize inflow effect-introduced AIF uncertainties, each individual AIF was recursively amplitude adjusted until the $v_e(SM)$ [the interstitial (extracellular and extravascular) volume fraction] parameter from obturator muscle reference tissue (27,28) ROI DCE data converged to 0.11, with a tolerance of $0.005$. An individual AIF time course was measurable for each subject except one, due to severe motion during the DCE acquisition. A population-averaged AIF (from average of six other subjects) was used for this subject. As the PD-weighted image still carries some slight (mixed) relaxation weighting, a numerical approach is used to obtain the PD image based on the average of DCE baseline images and that of the PD-weighted image, with $T_1$ as the only variables.

All data fitting used nonlinear least-square methods with an in-house software package written in Matlab (MathWorks, Natick, MA). CR relaxivity was assumed to be $3.8 \text{mM}^{-1} \text{s}^{-1}$ for both plasma and interstitium.

**RESULTS**

**ROI DCE-MRI Analyses**

Figure 1a shows a transverse DCE (3-min post-CR injection) pelvic image slice (#5) from subject no. 10. [A different subject is shown in Fig. 1 of (25).] The image is viewed from the inferior perspective and has the anterior side up. A $T_2$-weighted image of the same slice is shown in Fig. 1b. Based on the Fig. 1b image, four ROIs, representing suspicious (15 pixels) and NAG (16 pixels) prostate tissues, obturator muscle (75 pixels) tissue, and the femoral artery (4 pixels) used to obtain the AIF, are indicated with arrows and white borders in the zoomed Fig. 1a image section, Fig. 1c. Following the DCE-MRI study, a 10-core transrectal prostate biopsy procedure was conducted on the subject. The 10 biopsy needles were inserted so as to representatively (geographically) sample the entire gland peripheral zone. The pathology analyses indicated malignant adenocarcinoma in three left prostate (image right) core specimens, and benign tissue (NAG) in the remaining core specimens. The Figure 1f inset shows the AIF (in the form of the plasma CR concentration, $[CR_p]$) determined from the femoral artery $S/S_{pre}$ time course, using muscle as reference tissue to adjust the amplitude (27–29). The Figure 1d points trace the normalized ($S/S_{pre}$) time course for the suspicious Fig. 1c ROI, which was on the same side as the biopsy-confirmed malignancy. The solid curve represents the best fitting with the SSM(FXR-a) model, whereas the lower dashed curve is that with the SSM(FXL-c) analysis. The signature mismatch (temporally correlated residuals) of the FXL fitting is the same as we have previously reported for breast malignancy (4,7,8,9,30) and other tissues (30), and others for prostate cancer (24). It is (slightly) more noticeable here because of the larger $K^{trans}$ value and reflects systematic SM model insufficiency.
This is also indicated by the parameter values returned by these fittings: $K_{\text{trans}}^{\text{SSM}} = 0.462 \text{ min}^{-1}$; $K_{\text{trans}}^{\text{SM}} = 0.263 \text{ min}^{-1}$; $v_0^{\text{SSM}} = 0.475$; $v_0^{\text{SM}} = 0.229$; and $\tau_i^{\text{SSM}} = 394 \text{ ms}$. The SSM and SM difference is even more clearly indicated with the upper dashed curve, expected by SM(FXL-c) (i.e., with $\tau_i \rightarrow 0$) for the SSM(FXR-a)-returned $K_{\text{trans}}$ and $v_0$ values. Analogous results for the Fig. 1c prostate NAG ROI are shown in Fig. 1e. The maximum enhancement is not very different from that of the suspicious ROI (Fig. 1d). The differences in the $S/S_{\text{pro}}$ time courses for the suspicious (Fig. 1d) and NAG (Fig. 1e) ROIs are seen to be almost exclusively in their shapes. Propitiously, the SSM is especially sensitive to this feature (23). Consequently, Fig. 1e SM/data mismatch, though of similar magnitude as in Fig. 1d, gives altered systematic parameter changes: $K_{\text{trans}}^{\text{SSM}} = 0.177 \text{ min}^{-1}$, $K_{\text{trans}}^{\text{SM}} = 0.124 \text{ min}^{-1}$, $v_0^{\text{SSM}} = 0.475$, $v_0^{\text{SM}} = 0.226$, and $\tau_i^{\text{SSM}} = 598 \text{ ms}$. Finally, the analogous plots for the Fig. 1c muscle ROI are shown in Fig. 1f. The SM/data mismatch is not large: $K_{\text{trans}}^{\text{SSM}} = 0.081 \text{ min}^{-1}$, $K_{\text{trans}}^{\text{SM}} = 0.063 \text{ min}^{-1}$, $v_0^{\text{SSM}} = 0.093$, $v_0^{\text{SM}} = 0.057$, and $\tau_i^{\text{SSM}} = 615 \text{ ms}$. With decreasing $K_{\text{trans}}$ values, the shutter-speed (water exchange) effects in these DCE data decrease, reflected as decreasing SSM(FXR-a) – SM(FXL-c) parameter differences. This is exactly as predicted by shutter-speed theory (22) and observed in breast DCE-MRI (4, 7–10). As we will see below, the signal-to-noise (S/N) ratio afforded by the coil arrays used here is also sufficient for parametric mapping.

The subsequently performed 10-core clinical biopsy results are summarized in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Pathology report (Gleason scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–8</td>
<td>No malignancy found</td>
</tr>
<tr>
<td>9</td>
<td>Malignancy found in three right cores (4 + 4; 4 + 3; 4 + 3) and one left core (3 + 3)</td>
</tr>
<tr>
<td>10</td>
<td>Malignancy found in three left cores (3 + 4)</td>
</tr>
<tr>
<td>11</td>
<td>Malignancy found in five right cores (3 + 3)</td>
</tr>
<tr>
<td>12</td>
<td>Malignancy found in five left cores (3 + 4)</td>
</tr>
<tr>
<td>13</td>
<td>Malignancy found in one right core (3 + 3)</td>
</tr>
</tbody>
</table>

In Fig. 1f, the SSM/data mismatch is not large: $K_{\text{trans}}^{\text{SSM}} = 0.081 \text{ min}^{-1}$, $K_{\text{trans}}^{\text{SM}} = 0.063 \text{ min}^{-1}$, $v_0^{\text{SSM}} = 0.093$, $v_0^{\text{SM}} = 0.057$, and $\tau_i^{\text{SSM}} = 615 \text{ ms}$. With decreasing $K_{\text{trans}}$ values, the shutter-speed (water exchange) effects in these DCE data decrease, reflected as decreasing SSM(FXR-a) – SM(FXL-c) parameter differences. This is exactly as predicted by shutter-speed theory (22) and observed in breast DCE-MRI (4, 7–10). As we will see below, the signal-to-noise (S/N) ratio afforded by the coil arrays used here is also sufficient for parametric mapping.

The one-dimensional scatter plots of four ROI-averaged FXL-c and FXR-a parameters for all 13 subjects are shown in Fig. 2: panel a, $K_{\text{trans}}$; panel b, $v_0$; panel c, $k_{\text{ep}}$; and panel d, $\tau_i$. Triangles represent the eight benign cases and circles represent the five malignant cases. From FXL-c to FXR-a, larger $K_{\text{trans}}$ increases are seen for the malignant than for the benign cases (Fig. 2a). The $v_0$ parameter (Fig. 2b) shows similar increases from FXL-c to FXR-a for both malignant and benign prostate tissues. However, the largest increase is seen for a benign case, making $v_0$ alone an unsuitable predictor for discriminating lesions. The $k_{\text{ep}}$ [the unidirectional rate constant for passive CR intravascularation (8)] values generally decrease from FXL-c to FXR-a (Fig. 2c). This FXL-c overestimation of $k_{\text{ep}}$, relative to the value from FXR-a, is seen to occur mostly for the benign cases. The $\tau_i$ values increase from FXL-c to FXR-a (Fig. 2d): they are effectively zero in the FXL condition. It is important to note that it is not malignant/benign $k_{\text{ep}}$ differences that cause malignant/benign ROI $K_{\text{trans}}$ and/or $k_{\text{ep}}$ differences in the two model analyses. The malignant/benign capillary CR permeation differences

![FIG. 2. One-dimensional scatter plots of four ROI-averaged FXL-c and FXR-a parameters for 13 subjects: (a) $K_{\text{trans}}$, (b) $v_0$, (c) $k_{\text{ep}}$, and (d) $\tau_i$. Triangles represent the eight benign cases and circles represent the five malignant cases. From FXL-c to FXR-a, larger $K_{\text{trans}}$ increases are seen for the malignant cases. The $v_0$ parameter exhibits similar increases from FXL-c to FXR-a for the benign cases. The $\tau_i$ parameter exhibits similar increases from FXL-c to FXR-a for malignant and benign cases. Benign $k_{\text{ep}}$ values decrease from FXL-c to FXR-a (Fig. 2c). The $\tau_i$ values increase from FXL-c to FXR-a; they are treated as effectively zero by the FXL-c analyses. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]](image-url)
are genuine. In general, these results are quite similar to those seen for breast tumors (8).

Figure 3 is a scatter plot of ROI $\Delta K^{trans}$ values for all 13 subjects ($\Delta K^{trans} \equiv K^{trans}(FXR-a) - K^{trans}(FXL-c)$). The abscissa measures the percentage of biopsy core specimens found malignant. As all benign cases had zero malignant core specimens (by definition), the triangles are clustered at 0%. The malignant cases (circles) are scattered from 10 to 50%. One can see that there is a rough supralinear positive correlation of $\Delta K^{trans}$ with disease burden. A binary classifier cutoff line (dashed) is drawn at $\Delta K^{trans} \approx 0.085 \text{ min}^{-1}$, which yields no false negatives and only one false positive for this group. The points for subject nos. 7, 10, and 12 are labeled. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

**Feasibility of Prostate Shutter-Speed DCE-MRI**

**Parametric Mapping and Histographic Analysis**

Figure 5 shows parametric maps for subject no. 12 who had malignant foci found in the left peripheral zone (image right). The prostate is indicated in yellow on a post-CR DCE image in panel a. Zoomed $K^{trans}(FXL-c)$ and $K^{trans}(FXR-a)$ color maps are shown in panels b and c, respectively. The corresponding $\Delta K^{trans}$ map is shown in panel d. A “ring” enhancing lesion is seen clearly in the $\Delta K^{trans}$ map. This provides complementary contrast to that seen in the common $K^{trans}$ map (Fig. 5b). There is also a clear $\Delta K^{trans}$ hot spot in the central zone. Such hot spots show precisely where systems depart the FXL condition during the CR bolus passage. This is the only difference between the FXR-a and FXL-c analyses. Although parametric maps can ultimately be validated only via histopathology coregistered with the use of individualized prostate molds (26), our results are very encouraging that these could ultimately be useful for a DCE-MRI follow-up to serum prostate-specific antigen determination.

Figure 6a shows normalized histograms of pixel-by-pixel FXL-c-fitted prostate $K^{trans}$ values for single image
slices from a benign (pink) and a malignant (gray) subject, nos. 7 and 10, respectively. The benign case has a narrower $K_{\text{trans}}(\text{FXL-c})$ distribution compared with that of the malignant one. The FXR-a-fitted $K_{\text{trans}}$ histograms of the same data are shown in Fig. 6b. Although the benign histogram is not much affected, portions of the malignant histogram are significantly shifted to larger $K_{\text{trans}}$ values. The $\Delta K_{\text{trans}}$ histograms are shown in Fig. 6c. The benign $\Delta K_{\text{trans}}$ histogram is quite narrow, with the majority of its values close to zero. The malignant $\Delta K_{\text{trans}}$ histogram is rather broad. This could be a key characteristic for prostate DCE-MRI.

Based on the biopsy/pathology findings, whole prostate (9–14 slices) voxel-by-voxel $\Delta K_{\text{trans}}$ histograms were combined into malignant [5] and benign [8] subgroups of the 13 subjects. The normalized, averaged results are plotted in Fig. 7. The averaged malignant subgroup $\Delta K_{\text{trans}}$ values are shown as black bars and the benign subgroup values as pink. As there is tremendous partial volume averaging here, over the entire gland, the two distributions are very similar. However, for all values of $\Delta K_{\text{trans}} > 0$, the black bars are larger than the pink bars. Pairwise t-test shows this difference to be highly significant ($P < 10^{-3}$). Negative $\Delta K_{\text{trans}}$ values can occur only because of random noise and when the $K_{\text{trans}}$ value itself is small (see Fig. 6c). Interestingly, for all $\Delta K_{\text{trans}} < 0$ in Fig. 7, the pink bars are larger than the black bars. This is also statistically significant ($P = 0.024$). Even with the extensive partial volume averaging here, the malignant histogram is slightly more skewed to larger $\Delta K_{\text{trans}}$ values. With the mode ($\Delta K_{\text{trans}}$ value for the maximum probability distribution) set at zero for prostate DCE-MRI histograms, statistical tools can be used for simple distribution and shape comparisons. Thus, within the $K_{\text{trans}}$ domain, intersubject or intrasubject results can be directly examined for shutter-speed effects.

DISCUSSION
Surface Coil Prostate DCE-MRI

As an ultimate goal is to minimize biopsy and prostatectomy procedures, a large FOV can be very important for nonsurgical treatments, such as radiation therapy. Although it yields excellent signal strength, an endorectal receive radiofrequency coil provides: (1) an extremely

FIG. 5. Parametric maps for subject no. 12 who had malignant foci in the left peripheral zone (image right). a: The prostate is indicated in yellow on a post-CR DCE image. b and c: Zoomed $K_{\text{trans}}(\text{FXL-c})$ and $K_{\text{trans}}(\text{FXR-a})$ color maps, respectively. d: The corresponding $\Delta K_{\text{trans}}$ map. A ‘ring’ enhancing lesion is evident in the $\Delta K_{\text{trans}}$ map. This provides complementary contrast to that seen in the standard $K_{\text{trans}}$ map (b).

FIG. 6. a: Normalized histograms of voxel-by-voxel FXL-c-fitted $K_{\text{trans}}$ values for image slices from representative benign (pink) and malignant (gray) subject nos. 7 and 10, respectively. The benign case has a narrower $K_{\text{trans}}(\text{FXL-c})$ distribution compared with that of the malignant one. The FXR-a-fitted $K_{\text{trans}}$ histograms of the same data. Although the benign distribution is not much affected, portions of the malignant histogram are significantly shifted to larger $K_{\text{trans}}$ values. The $\Delta K_{\text{trans}}$ histograms are shown in Fig. 6c. The benign $\Delta K_{\text{trans}}$ histogram is quite narrow, with the majority of its values close to zero. The malignant $\Delta K_{\text{trans}}$ histogram is very broad. This could be a key characteristic for prostate DCE-MRI.
Although transrectal ultrasound-guided needle biopsy provides scant spatial resolution, our results show that FXR-a SSM provides a near optimal analysis for DCE-MRI discrimination of malignant from benign prostate tissue (Figs. 3 and 4b). As the angiogenic capillaries in malignant tissues are expected to be more CR permeable, the elevated \( k_{\text{trans}} \) (Fig. 2a) values found only by SSM(FXR-a) argue that these are closer to “truth.” Recall that we know only that one or more positive biopsy core specimens are on the same side of the prostate as the suspicious ROI, but not whether a positive core actually penetrated the ROI selected. Given this significant partial volume uncertainty, our results are extremely encouraging. The \( k_{\text{trans}} \) and \( k_{\text{ep}} \) parameters are separate measures of transcapillary CR permeability.

In addition, most quantitative pharmacokinetic models conceptually divide the extracellular in vivo system into simply a CR-accessible compartment \( (v_c) \) and a compartment inaccessible to CR \( (1 - v_c) \). Any prostate tissue compartment that may normally be sequestered from direct CR access, even if it is not intracellular [e.g., the normal glandular-ductule lumen spaces (17,24)], will be reflected in the \( (1 - v_c) \) value and possibly in \( \tau_i \) (25). Any pathological changes that also change compartmental CR accessibility will result in pharmacokinetic model parameter changes (particularly \( v_c \) ) (36).

Our results suggest that SSM DCE-MRI may have the potential to eliminate a large fraction of prostate biopsy procedures or at least to help guide them more effectively. Also, as the use of a surface coil array avoids a small pelvic FOV and prostate shape deformation, both of which are detrimental for radiation therapy planning, combining SSM DCE-MRI with such a coil setup has the potential to reduce the number of prostatectomies.

Limitations of this study include the small sample size and the use of only biopsy for verification. It is necessary to expand the population to further investigate the usefulness of our protocol. Furthermore, to provide maximal verification, DCE parametric maps should be used for biopsy guidance and/or coregistered with appropriately stained histopathology slides obtained after prostatectomy. The coregistration is best achieved through the use of a customized mold, produced from MR images, made to hold the individual excised gland (26).

CONCLUSIONS

When S/N is optimized with acquisition parameters, prostate DCE-MRI data become sensitive to water exchange effects, and the \( \Delta k_{\text{trans}} \) and/or \( k_{\text{trans}} \) vs. \( k_{\text{ep}} \) 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. The promise for prostate cancer detection is encouraging.

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