Published in final edited form as:

J Magn Reson Imaging. 2016 December ; 44(6): 1405–1414. doi:10.1002/jmri.25330.

Patient-Specific Pharmacokinetic Parameter Estimation on Dynamic Contrast-Enhanced MRI of Prostate: Preliminary Evaluation of a Novel AIF-Free Estimation Method

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Abstract

Purpose—To develop and evaluate a prostate-based method (PBM) for estimating pharmacokinetic parameters on dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) by leveraging inherent differences in pharmacokinetic characteristics between the peripheral zone (PZ) and transition zone (TZ).

Materials and Methods—This retrospective study, approved by the Institutional Review Board, included 40 patients who underwent a multiparametric 3T MRI examination and subsequent radical prostatectomy. A two-step PBM for estimating pharmacokinetic parameters exploited the inherent differences in pharmacokinetic characteristics associated with the TZ and PZ. First, the reference region model was implemented to estimate ratios of K^{trans} between normal TZ and PZ. Subsequently, the reference region model was leveraged again to estimate values for K^{trans} and v_e for every prostate voxel. The parameters of PBM were compared with those estimated using an arterial input function (AIF) derived from the femoral arteries. The ability of the parameters to differentiate prostate cancer (PCa) from benign tissue was evaluated on a voxel and lesion level. Additionally, the effect of temporal downsampling of the DCE MRI data was assessed.

Results—Significant differences ($P < 0.05$) in PBM K^{trans} between PCa lesions and benign tissue were found in 26/27 patients with TZ lesions and in 33/38 patients with PZ lesions; significant differences in AIF-based K^{trans} occurred in 26/27 and 30/38 patients, respectively. The 75th and 100th percentiles of K^{trans} and v_e estimated using PBM positively correlated with lesion size ($P < 0.05$).

Conclusion—Pharmacokinetic parameters estimated via PBM outperformed AIF-based parameters in PCa detection.

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Magnetic Resonance Imaging (MRI) is a valuable tool for detecting and localizing tumors in patients with suspected prostate cancer. Dynamic contrast-enhanced (DCE) MRI, which is useful for analyzing tissue microvasculature and angiogenesis, has been shown to facilitate improved prostate cancer detection compared to T_2 -weighted (T_2w) MRI alone.^{1–4} On DCE MRI, tumors manifest rapid and increased enhancement and early washout compared to surrounding normal prostate tissue.⁵ Pharmacokinetic analysis of DCE MRI enables the determination of parameters, such as K^{trans} (transfer constant) and v_e (extravascular-extracellular volume fraction), describing tumor vasculature perfusion and permeability.⁶ These constants are known to be elevated in prostate tumors, and a radiologist's assessment of spatial maps of these parameters have been shown to be useful for prostate cancer detection and localization.^{7–9}

There are a number of different techniques for estimating pharmacokinetic parameters on MRI, many of which rely on the Kety–Tofts pharmacokinetic model.¹⁰ In general, pharmacokinetic modeling of DCE MRI relies on knowledge of the arterial input function (AIF), which can be measured by introducing a catheter into the patient's artery and sampling blood at intervals throughout the image acquisition process or estimated in an artery in the image field-of-view (FOV).¹¹ Unfortunately, the former is not desirable due to its invasiveness, and the latter requires that the DCE MRI be acquired at a high temporal resolution, attained at the expense of lowering the spatial resolution. Thus, a method for estimating pharmacokinetic parameters that does not rely on the AIF may be valuable.

Since high spatial resolution is crucial for detecting small tumors, a variety of techniques for estimating pharmacokinetic parameters have been published that circumvent the determination of the AIF. Many of these methods involve using a population-averaged AIF¹² or parameterized AIF.^{13,14} However, AIFs vary considerably between subjects, and ignoring the inherent interpatient variation leads to errors in estimating patient-specific pharmacokinetic parameters.^{15,16} In order to avoid the AIF entirely, methods have been developed that rely on population-averaged pharmacokinetic parameter values for a reference tissue (such as skeletal muscle).¹⁷ When evaluated in canines, this approach was shown to yield more accurate pharmacokinetic parameters in the tumor compared to approaches that rely on a population-averaged AIF.¹⁸ Nevertheless, pharmacokinetic parameters vary between subjects even for well-characterized reference tissues.¹⁸ This may be a serious limitation of methods that rely on a population-averaged AIF for pharmacokinetic modeling.

To overcome the limitations of relying on population-averaged values, several groups have developed methods for estimating relative pharmacokinetic parameter values of two contrast agents that are coinjected¹⁹ or of two tissues within the image FOV.^{12,20} Without making any population-based assumptions, these methods provide patient-specific relative pharmacokinetic parameter values.^{19,20} However, the physiological interpretation of these relative pharmacokinetic parameters is not obvious, and the actual K^{trans} values cannot be estimated via these approaches.^{19,20} Furthermore, these methods were evaluated in simulations and on mice; none of these methods were evaluated on human DCE MRI data. Thus, although patient-specific AIF-free estimation of pharmacokinetic parameters seems

attractive, there is a real need to evaluate such methods in humans to identify whether AIF-free parameter estimation is as reliable as AIF-based parameter estimation.

The purpose of this work was to develop a prostate-based method (PBM) to estimate K^{trans} and v_e in the prostate without relying on any population-averaged values and to evaluate its ability to detect and grade prostate cancer on DCE MRI. Our hypothesis was that the PBM would lead to similar performance in discriminating cancer from benign tissue, discriminating cancer grades, predicting lesion size, and approximating the AIF—in spite of its nonreliance on an AIF.

Materials and Methods

Patients

This retrospective study was approved by the Institutional Review Board at University of Turku, Finland, and informed consent was waived. This study included 40 patients who underwent research MRI examination either 1) before their first biopsy, as a part of a two-institutional clinical study (clinicaltrials.org registration number NCT02002455), or 2) before robotic assisted laparoscopic prostatectomy (RALP), as a part of an ongoing single-institution clinical trial. Patient inclusion criteria are shown in Fig. 1.

MRI Acquisition

In order to suppress bowel peristalsis, 1.0 mg of glucagon (Gluca-Gen, Novo Nordisk, Bagsværd, Denmark) was given subcutaneously immediately before the start of the examination. Furthermore, patients were instructed to take laxatives in the evening before the MRI examination in order to limit rectal air (Laxoberon, Boehringer Ingelheim, Ingelheim, Germany). The MRI was performed using a 3T MR scanner (Magnetom Verio 3T, Siemens Healthcare, Erlangen, Germany). Body array and spine array coils were used as receiver coils, while whole body single channel RF coils were used as transmit coils. No endorectal coil was used. The imaging protocol consisted of triplanar T_2 w turbo spin-echo imaging, single shot spin-echo based DWI, 3D ^1H -MRS, and DCE-MRI. The 3D ^1H -MRS datasets and DWI were not analyzed in the current study. The total duration of the MRI examination was about 60 minutes.

Anatomical triplanar T_2 w images were acquired using a turbo spin-echo sequence with repetition time/echo time (TR/TE) 6400–8640/101 msec, FOV $200 \times 200\text{mm}^2$, matrix size 320×320 , slice thickness 3 mm, acquisition voxel size $0.6 \times 0.6 \times 3.0\text{mm}^3$, number of signal averages (NSA) 2, and acquisition time 2.27 minutes (transverse images), 2.47 minutes (sagittal images), 2.78 minutes (coronal images). Generalized autocalibrating partially parallel acquisitions (GRAPPA)²¹ was used with the acceleration factor of 2 and 32 reference lines for autocalibration. Axial dynamic contrast-enhanced images were acquired before, during, and after injection of contrast agent (0.1 mmol/kg Dotarem, Guerbet, France) which was injected 30 seconds after the beginning of the sequence through a peripheral vein at a rate of 2 ml/s via a mechanical injector (Spectris, Medrad, Indianola, PA). In total, 60 time points at a temporal resolution of 6.9 seconds were acquired using a 3D VIBE sequence²² with the following parameters: TR/TE 5.43/1.87 seconds, 15° flip angle, FOV

240 × 240mm², FOV in the slice direction 48mm with 25% slice oversampling factor, matrix size 192 × 192, NSA 1, slice thickness 3 mm, 16 slices, acquisition voxel size 1.25 × 1.25 × 3.0mm³, a bandwidth of 260 Hz/pixel acquiring 6/8 (75%) of *k*-space in phase-encoding direction, GRAPPA with the acceleration factor of 2 and 24 reference lines, acquisition time 6.9 seconds per frame, and overall time of 6.9 minutes. Before the contrast injection, 3D VIBE images with five different flip angles of 2, 5, 8, 10, 15° were obtained for calculation of precontrast longitudinal relaxation time (T₁₀). Dynamic contrast enhanced imaging datasets for T₁₀ maps were calculated using an Osirix DCE plugin (http://kyungs.bol.ucla.edu/software/DCE_tool/DCE_tool.html).

Histopathological Analysis

All of the histopathologic material was analyzed by one experienced genitourinary pathologist (PT, 8 years of experiences in genitourinary pathology) in consensus with another pathologist (PV, at least 4 years of experiences in genitourinary pathology). Whole-mount prostatectomy sections were processed as described previously²³ and stained with hematoxylin and eosin. The Gleason score was assigned as a combination of primary, secondary, and tertiary Gleason grade according to the 2005 International Society of Urological Pathology Modified Gleason Grading System.²⁴ A tertiary Gleason grade was assigned when a Gleason grade pattern higher than both the primary and secondary Gleason grades was present in less than 5% of the tumor.²⁵ Lesions with a Gleason score 3+3 were considered low grade, lesions with a Gleason score of 3+4 were considered intermediate grade, and lesions with a Gleason score of 4+3 were considered high grade. Among the 40 patients in our study cohort, 26 had tumors in the TZ and 38 patients had tumors in the PZ. A total of 103 individual lesions were annotated on histology, including 35 in the TZ (19 low grade, 8 intermediate grade, and 8 high grade) and 68 in the PZ (40 low grade, 14 intermediate grade, and 14 high grade).

Cancer Annotation on MRI

In order to obtain “ground truth” annotation of prostate cancer extent on MRI, coregistration of MRI and whole-mount histological sections was performed. Correspondences between histological sections and T₂w MRI slices were determined by a genitourinary pathologist (PT) and radiology research fellow (IJ - 6 years of experience in prostate MRI) working in unison. Subsequently, corresponding histological sections and MRI slices were coregistered using an interactive B-spline elastic registration scheme.²⁶ The final result was a labeling of each MRI voxel within the prostate as corresponding to cancer or benign prostate tissue. DCE MRI was spatially aligned with T₂w MRI via volumetric affine registration, which corrected interacquisition movement and interprotocol resolution differences. After interprotocol alignment, all MRI data were analyzed at the T₂w MRI resolution.

Pharmacokinetic Modeling of DCE MRI

The right and left femoral arteries, as well as the prostate capsule and TZ, were manually annotated on T₂w MRI by a research fellow (IJ) with 6 years of research experience in prostate MRI. The AIF was then obtained by averaging the concentration of contrast agent in the blood plasma across all femoral arterial pixels. Subsequently, AIF-based pharmacokinetic parameters were calculated by leveraging the AIF to solve the Kety–Tofts

model¹⁰ for each prostate voxel. In order to assess the effect of temporal downsampling of the DCE MRI data, every second DCE MRI instance was removed, thereby reducing the effective temporal resolution from 6.9 seconds to 13.8 seconds.

The PBM leverages a reference region model¹⁷ to estimate the pharmacokinetic constants associated with each prostate voxel. Assuming that two regions in the image FOV do not share the same pharmacokinetic characteristics, the reference region model provides for the estimation of 1) relative pharmacokinetic parameter ratios between the two regions or 2) pharmacokinetic parameters associated with one region provided that pharmacokinetic parameters associated with the other region are known. The reference region model¹⁷ assumes a simple two-compartment model in which the contrast agent diffuses from the blood plasma into the extravascular–extracellular spaces of two tissues. This system can be described by two differential equations:

$$\begin{aligned}\frac{d}{dt}C^{PZ}(t) &= K^{PZ}C^p(t) - \frac{K^{PZ}}{v^{PZ}}C^{PZ}(t) \\ \frac{d}{dt}C^{TZ}(t) &= K^{TZ}C^p(t) - \frac{K^{TZ}}{v^{TZ}}C^{TZ}(t)\end{aligned}$$

where $C^p(t)$ is the concentration of contrast agent in the blood plasma, also known as the AIF. $C^{PZ}(t)$ and $C^{TZ}(t)$ are the concentrations of the contrast agent in the PZ and TZ, respectively, and were computed from the signal intensities in the manner of Ref. 27. K^{PZ} and K^{TZ} are the transfer constants representing diffusion of the contrast agent from capillaries into the PZ and TZ, and v^{PZ} and v^{TZ} are the extravascular–extracellular volume fractions for the PZ and TZ. Combining these two equations and solving the resulting differential equation leads to the following expressions (17):

$$C^{PZ}(T) = \frac{K^{TZ}}{K^{PZ}}C^{TZ}(T) + \frac{K^{TZ}}{K^{PZ}} \left(\frac{K^{TZ}}{v^{TZ}} - \frac{K^{PZ}}{v^{PZ}} \right) \int_0^T C^{TZ}(t) \exp \left\{ -\frac{K^{PZ}}{v^{PZ}}(T-t) \right\} dt \quad (1)$$

$$C^{TZ}(T) = \frac{K^{PZ}}{K^{TZ}}C^{PZ}(T) + \frac{K^{PZ}}{K^{TZ}} \left(\frac{K^{PZ}}{v^{PZ}} - \frac{K^{TZ}}{v^{TZ}} \right) \int_0^T C^{PZ}(t) \exp \left\{ -\frac{K^{TZ}}{v^{TZ}}(T-t) \right\} dt \quad (2)$$

Our two-step PBM exploits the fact that the TZ and PZ do not share the same pharmacokinetic characteristics (Fig. 2); hence, the reference region model can be applied. In the first step of the PBM, Eq. 1 was implemented in an unconstrained curve-fitting routine to estimate the ratios $\frac{K^{TZ}}{K^{PZ}}$, $\frac{K^{TZ}}{v^{TZ}}$, and $\frac{K^{PZ}}{v^{PZ}}$. During this step, $C^{PZ}(T)$ and $C^{TZ}(T)$ were taken as the contrast agent concentration-versus-time curve averaged over all voxels in the PZ and TZ, respectively. The second step of the PBM used these ratios as constraints in a constrained curve-fitting routine to reimplement Eq. 1 to estimate K_{PZ} and K_{TZ} and get a more accurate estimate of $\frac{K^{PZ}}{v^{PZ}}$ and $\frac{K^{TZ}}{v^{TZ}}$. These estimates of the pharmacokinetic constants for the PZ and TZ were region-based and not voxel-specific, but they were patient-specific.

Finally, once K_{TZ} and v_{TZ} became known, these values were input as constants in Eq. 1, which was implemented on a per-voxel basis to estimate K_{PZ} and v_{PZ} for every voxel in the PZ. Similarly, once K_{PZ} and v_{PZ} were known, these values were input as constants in Eq. 2, which was implemented on a per-voxel basis to estimate K_{TZ} and v_{TZ} for every voxel in the TZ. In order to evaluate robustness of PBM method for temporal resolution of DCE MRI datasets, all analyses were performed using temporal resolutions of 6.9 and 13.8 seconds. All pharmacokinetic modeling was performed using MatLab R2015b (MathWorks, Natick, MA).

Evaluation of Pharmacokinetic Modeling Methods

Pharmacokinetic parameters were evaluated based on 1) their usefulness in discriminating prostate cancer from benign tissue, 2) their usefulness in discriminating cancer grades, 3) their association with tumor size, and 4) how well they can approximate the “true” AIF. Differences in pharmacokinetic parameter values associated with normal and cancerous prostate voxels were assessed on a perpatient level using the nonparametric Kruskal–Wallis significance test. Additionally, the accuracy of pharmacokinetic parameters for discriminating between cancerous and benign prostate voxels was assessed for each patient by the area under the receiver operating characteristic (ROC) curve (AUC).

In order to evaluate the usefulness of pharmacokinetic parameters for discriminating cancer grades (low, intermediate, high), ROC analysis was implemented on both a per-voxel and a per-lesion basis. For voxel-based ROC analysis the sensitivity and specificity of voxel-specific K^{trans} and v_e values for discriminating between low- and high-grade cancer and between intermediate- and high-grade cancer was assessed via AUC. For lesion-based ROC analysis, each lesion needed to be characterized by a single value of K^{trans} and v_e , although these parameters were computed on a per-voxel level. Therefore, each lesion was assigned a single value for K^{trans} and v_e based on the 75th or 100th percentile (maximum) of the values in each lesion. Then, AUC was leveraged to evaluate the ability of $K^{trans}(75)$, $K^{trans}(100)$, $v_e(75)$, and $v_e(100)$ to discriminate between 1) low- versus high-grade lesions, 2) intermediate- versus high-grade lesions, and 3) low- versus intermediate- and high-grade lesions.

Additionally, the strength of correlation of pharmacokinetic parameters with lesion size was explored using Pearson’s correlation coefficient. In order to evaluate the ability of pharmacokinetic parameters to approximate the “true” AIF (calculated in the femoral arteries), the mean K^{trans} and v_e values in the prostate, as well as the mean tissue contrast concentration in the prostate, were used as inputs to the Kety–Tofts model, which was solved for the AIF. This approximated AIF was compared to the true AIF calculated in the femoral arteries based on sum-of-squared differences. All statistical analyses were performed using MatLab R2015b.

Results

Discriminating Cancer From Benign Tissue

Pharmacokinetic parameters estimated on a voxel level for all patients in PCa and benign TZ and PZ are listed in Table 1 for both the PBM- and AIF-based methods. For the AIF-based method, mean K^{trans} values were 0.40 and 0.32 in normal TZ and PZ, respectively, and decreased to 0.36 and 0.29 in TZ and PZ cancer. Likewise, the mean v_e values were higher in normal TZ than cancerous TZ (0.29 vs. 0.24) but were higher in cancerous PZ than normal PZ (0.30 vs. 0.23). For the PBM, however, the mean K^{trans} values increased from 0.22 to 0.24 in cancerous TZ, compared to normal TZ, but decreased from 0.87 to 0.81 in cancerous PZ compared to normal PZ; v_e was the same in cancer and benign regions of both the TZ and PZ. When temporal downsampling decreased the temporal resolution by 50%, the average v_e increased while the average K^{trans} remained largely unaffected for the AIF-based method; this trend was reversed for the PBM.

Out of 27 patients with lesions in the TZ, significant differences between PBM estimates of K^{trans} and v_e , associated with cancerous and benign TZ, were found in 26 and 23 patients, respectively (Table 2). The one patient for which significant differences between benign and cancerous TZ were not found had a small lesion (<10 mm). Out of 38 patients with PZ lesions, 33 patients manifested significant differences in K^{trans} associated with cancerous and benign tissue, and 30 manifested significant differences in v_e between cancerous and benign PZ voxels. The five patients that did not exhibit significant differences between cancerous and benign PZ included two with low-grade cancer, one with intermediate-grade cancer, and two with high-grade cancer, all with lesions >10mm in size. Fewer patients exhibited significant differences between cancerous and benign PZ and TZ tissue when pharmacokinetic parameters were estimated via the AIF-based approach (Table 2). Additionally, K^{trans} discriminated between cancerous and benign TZ with a per-patient average AUC of 0.53 and between cancerous and benign PZ with a per-patient average AUC of 0.59, while corresponding AUC values associated with v_e were lower (0.50 in the TZ and 0.56 in the PZ). AUC values were similar when pharmacokinetic parameters estimated via the AIF-based method were used to discriminate cancerous from benign voxels (Table 2).

Figure 3 displays heat-map representations of K^{trans} for three prostate lesions. The PBM accounts for differences between enhancement patterns in the TZ and PZ; as a result, K^{trans} tended to be elevated in the TZ only when cancer was present there. In contrast, the AIF-based approach sometimes yielded ambiguous results in the TZ due to heterogeneous enhancement in the TZ. The 75th and 100th percentiles of pharmacokinetic parameters associated with lesions tended to increase significantly with lesion size (Table 3).

Association With Prostate Cancer Risk Group

The ability of voxel-wise K^{trans} and v_e values to discriminate between high-, intermediate-, and low-grade lesions was assessed by ROC analysis (Fig. 4). When the AIF-based approach was used to estimate pharmacokinetic parameters, the same AUC of 0.59 was achieved for distinguishing low-grade from high-grade lesions in the TZ on the basis of K^{trans} and v_e , respectively. When PBM was used, however, AUC values increase to 0.61 and 0.69 for

K^{trans} and v_e , respectively. When discriminating between low- and high-grade PZ lesions, AUC decreased from 0.67 to 0.61 for K^{trans} for the PBM but increased from 0.56 to 0.57 for v_e when the PBM is used. In distinguishing intermediate- from high-grade lesions, K^{trans} estimated using the AIF-based approach led to AUC values of 0.40 and 0.68 in the TZ and PZ, respectively. When the PBM was used to estimate K^{trans} , the AUC increased to 0.57 in the TZ but decreased to 0.55 in the PZ (Fig. 4b). In contrast, v_e provided lower AUC values of 0.35 and 0.52 in the TZ and PZ when the AIF-based approach was used and AUCs of 0.65 and 0.52 in the TZ and PZ when the PBM was used. Thus, whereas the PBM yields higher AUC values for all cancer grading in the TZ, the AIF-based approach yields higher AUC values for cancer grading in the PZ in most cases.

The ability of lesion-wise $K^{\text{trans}}(100)$, $K^{\text{trans}}(75)$, $v_e(100)$, and $v_e(75)$ values to discriminate between high-, intermediate-, and low-grade lesions was also assessed by ROC analysis (Table 4). $K^{\text{trans}}(100)$, $K^{\text{trans}}(75)$, $v_e(100)$, and $v_e(75)$ estimated via the AIF-based method yield higher AUC values when discriminating between low- and intermediate-grade lesions than those associated with the PBM (0.56–0.60 vs. 0.47–0.55 in the TZ and 0.56–0.62 vs. 0.37–0.50 in the PZ). In contrast, when discriminating between intermediate- and high-grade lesions, AUC values are high for the PBM (0.59–0.65) and low for the AIF-based approach (0.17–0.42). In discriminating low- from intermediate- and high-grade TZ lesions, AUC values are as high as 0.57 for the PBM; in discriminating low- versus intermediate- and high-grade PZ lesions, AUC values are as high as 0.58 for the AIF-based method.

Reverse Approximation of AIF Based on Pharmacokinetic Parameters

When pharmacokinetic parameters obtained via the PBM were used as inputs to the Kety–Tofts model to solve for the AIF, the sum-of-squared differences (SSD) between this approximated AIF and the true AIF calculated in the femoral arteries was small (SSD <0.15). In comparison, when mean pharmacokinetic parameters estimated via the AIF-based approach were used as inputs to the Kety–Tofts model to solve for the AIF, the sum-of-squared differences was higher (SSD <0.25), although this difference was not statistically significant.

Discussion

In this article we presented PBM, a novel approach for estimating pharmacokinetic parameters in the prostate without relying on knowledge of the AIF or any population-averaged values. Instead, our method leveraged differences between pharmacokinetic characteristics of the TZ and PZ in order to estimate K^{trans} and v_e on a voxel-wise basis throughout the entire prostate. Our approach involving coregistration of whole-mount histological sections with MRI allowed for an accurate mapping of lesion extent onto MRI, which enabled us to carefully develop and evaluate our approach on both a lesion- and voxel-wise basis.

Although the PBM used only patient-specific prostate voxels, pharmacokinetic parameter values estimated by PBM were similar to those estimated via the AIF-based approach and able to discriminate prostate cancer grades with comparable performance to the AIF-based approach. However, in comparison to the AIF-based approach, PBM demonstrated

statistically significant differences between cancer and benign tissues in a larger number of patients. In reality, pharmacokinetic parameters computed via different approaches are not necessarily comparable. Nevertheless, the pharmacokinetic values associated with normal and cancerous TZ and PZ tissue were similar to K^{trans} and v_e found in other studies.^{28–30} When the AIF-based method was used for parameter estimation, both K^{trans} and v_e were higher in the TZ than in the PZ; this trend was reversed for parameters estimated via the PBM. We found that for most patients both K^{trans} and v_e associated with TZ and PZ cancer were significantly higher than benign TZ and PZ, respectively, for both the PBM and the AIF-based method. This finding corroborates findings from numerous studies showing that these pharmacokinetic constants are elevated in prostate cancer^{28–30} due to their higher vascularity relative to benign prostate tissue.^{7–9}

Pharmacokinetic parameters are nonspecific for detecting cancer due to vascular leakiness associated with benign prostatic hyperplasia in the TZ and prostatitis in the PZ.³⁰ Also, postbiopsy hemorrhage in either the TZ or PZ can lead to higher pharmacokinetic parameter values. As a result, it is not surprising that benign regions, as well as cancerous regions, were associated with suspiciously high K^{trans} and v_e values and that AUC values for discriminating between cancerous and benign prostate voxels were no higher than 0.55 in the TZ and 0.59 in the PZ. K^{trans} and v_e values calculated using both PBM and AIF-based method significantly correlated with lesion size, but correlation coefficients for PBM-derived parameters were substantially higher. Moreover, we found that pharmacokinetic parameters have benefit, although limited, for discriminating between prostate cancer grades. In general, the PBM yields higher AUC values for discriminating between intermediate- and high-grade lesions, whereas the AIF-based approach yields higher AUC values for discriminating between low- and intermediate-grade lesions. K^{trans} and v_e estimated via PBM each individually distinguished between low- and intermediate/high-grade prostate cancer with AUC values up to 0.57 in the TZ and 0.55 in the PZ. Nevertheless, regardless of method, the potential of K^{trans} and v_e for distinguishing between low-, intermediate-, and high-grade prostate lesions in both the TZ and PZ was limited. This may be due to the limited benefit of pharmacokinetic parameters for distinguishing tumor grade, or it may be related to the relatively low number of patients in our study. In comparison, Vos et al³¹ achieved an AUC of 0.72 for discriminating between low- and intermediate/high-grade cancer when combining K^{trans} with several other kinetic features derived from DCE MRI. Our finding that the PBM does as well as or better than the AIF-based approach in most scenarios, while at the same time remaining completely independent of the AIF or any population-averaged measures, suggests that the PBM may be highly desirable for estimating pharmacokinetic parameters in the prostate.

There were, however, several limitations to our approach. First, this study included a diverse set of patients, including both biopsy-naïve patients and patients with biopsy-proven prostate cancer. Secondly, due to the form of Eqs. 1 and 2, if there is no difference in kinetic parameters between the TZ and PZ, then the pharmacokinetic parameters associated with these regions may not be reliably estimated. This could possibly be an issue when implementing step 1 of the PBM, which leverages average contrast agent concentration curves for the TZ and PZ, if these curves differ by only a scaling factor. However, the remaining steps of the PBM are performed on a per-voxel basis, which injects a considerable

amount of variability to the contrast agent concentration curves. Thus, even if the average curves for the TZ and PZ might differ by a scaling factor, this trend is unlikely to be the case when dealing with individual voxels. As a result, the voxel-wise pharmacokinetic parameter estimates should remain reliable.

Additionally, there is no reliable gold standard for determining the accuracy of pharmacokinetic parameters on DCE MRI. As a result, it is challenging to compare pharmacokinetic constants yielded by disparate approaches and to identify how accurately pharmacokinetic parameter estimates match up with the physiological parameters that they are supposed to measure. Nevertheless, pharmacokinetic parameter values yielded by the PBM are within the range of values obtained by other studies.^{28–30} Furthermore, when these pharmacokinetic parameters are used to estimate the AIF, the AIF is approximated with higher accuracy than when pharmacokinetic parameters estimated via the AIF-based approach are used to estimate the AIF. Also, this preliminary study involved a small cohort of only 40 patients, and further validation of the PBM is necessary on a larger cohort. Finally, we found that the effect of decreasing the temporal resolution on estimates of K^{trans} was different from its effect on estimates of v_e . Further investigation into the effect of temporal downsampling is necessary.

In conclusion, we have presented a novel approach for estimating patient-specific pharmacokinetic parameters in the prostate without relying on the AIF or any population-averaged values. We found that K^{trans} and v_e estimated using PBM performed better or equally well to corresponding parameters calculated using the AIF-based method in prostate cancer detection, characterization, and prediction of tumor size. These findings suggest that it may be possible to perform pharmacokinetic modeling on prostate DCE MRI without the need to rely on an AIF or population-averaged values for a reference region.

Acknowledgments

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under award numbers 1U24CA199374, R21CA179327; R21CA195152 the National Institute of Diabetes and Digestive and Kidney Diseases under award number R01DK098503, the DOD Prostate Cancer Synergistic Idea Development Award (PC120857); the DOD Lung Cancer Idea Development New Investigator Award (LC130463), the DOD Prostate Cancer Idea Development Award; the Case Comprehensive Cancer Center Pilot Grant VelaSano Grant from the Cleveland Clinic; the Wallace H. Coulter Foundation Program in the Department of Biomedical Engineering at Case Western Reserve University; the National Science Foundation Graduate Research Fellowship Instrumentarium Research Foundation; Sigrid Juselius Foundation; Turku University Hospital, TYKS-SAPA Research Fund; Finnish Research Fund; Finnish Cancer Foundation; and Finnish Cultural Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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FIGURE 1.

Criteria for inclusion of 40 patients with prostate cancer in this study.

FIGURE 2.

Average concentration of contrast agent in the femoral arteries (AIF), peripheral zone, and transition zone for a sample patient.

FIGURE 3.

Ground truth extent of prostate cancer is shown for three lesions on the top row. Heat-map representations of K^{trans} are displayed for the AIF-based approach (middle) and AIF-free approach (bottom).

FIGURE 4.

ROC curves illustrate the predictive power of voxel-wise K^{trans} in discriminating (a) low- from high-grade cancer voxels, and (b) intermediate- from high-grade cancer voxels, and v_e in discriminating (c) low- from high-grade cancer, and (d) intermediate- from high-grade cancer.

TABLE 1

40 Subjects and Two Methods of Pharmacokinetic Parameter Estimation

		TZ	TZ cancer	PZ	PZ cancer
AIF (6.9 s)	K^{trans}	0.40±0.50	0.36±0.53	0.32±.47	0.29±0.41
	v_e	0.29±0.22	0.24±0.20	0.23±0.22	0.30±0.22
AIF (13.8 s)	K^{trans}	0.41±0.44	0.37±0.48	0.35±0.41	0.35±0.36
	v_e	0.47±0.30	0.48±0.28	0.39±0.29	0.40±0.30
PBM (6.9 s)	K^{trans}	0.22±0.19	0.24±0.14	0.87±0.54	0.81±0.51
	v_e	0.13±0.10	0.13±0.07	0.35±0.20	0.35±0.19
PBM (13.8 s)	K^{trans}	0.12±0.12	0.13±0.07	0.44±0.35	0.55±0.28
	v_e	0.13±0.10	0.14±0.07	0.37±0.20	0.37±0.19

Voxel-wise K^{trans} and v_e parameters are listed as mean±standard deviation. TZ=transition zone; PZ=peripheral zone; AIF=arterial input function; PBM=prostate-based method.

TABLE 2

Arterial Input Function (AIF)- and Prostate-Based (PBM) Methods

	AIF-based		PBM	
	TZ	PZ	TZ	PZ
<i>N</i> patients	27	38	27	38
K^{trans} ; $p < 0.05$	26	30	26	33
K^{trans} ; $p < 0.01$	25	28	26	29
K^{trans} ; AUC	0.55 (0.18–0.82)	0.59 (0.30–0.94)	0.53 (0.18–0.76)	0.59 (0.34–0.90)
v_e ; $p < 0.05$	21	29	23	30
v_e ; $p < 0.01$	20	26	22	26
v_e ; AUC	0.50 (0.17–0.79)	0.54 (0.28–0.81)	0.50 (0.21–0.78)	0.56 (0.28–0.86)

The number of patients with significant differences between normal prostate zones and cancer, evaluated via Kruskal-Wallis significance tests. Additionally, AUC values for cancer detection on the basis of pharmacokinetic parameters are shown as mean (min-max). TZ=transition zone; PZ=peripheral zone; AIF=arterial input function; PBM=prostate-based method.

TABLE 3
Correlation Coefficients Obtained Via Pearson's Correlation Between Lesion Size and 75th and 100th Percentiles of K^{trans} and v_e

	AIF				PBM			
	$K^{trans}(100)$	$v_e(100)$	$K^{trans}(75)$	$v_e(75)$	$K^{trans}(100)$	$v_e(100)$	$K^{trans}(75)$	$v_e(75)$
TZ+PZ	0.52*	0.45*	0.24*	0.20*	0.50*	0.50*	0.50*	0.14
TZ	0.34*	0.23	-0.06	-0.05	0.64*	0.63*	0.13	0.11
PZ	0.56*	0.48*	0.31*	0.22*	0.61*	0.57*	0.27*	0.23*

TZ=transition zone; PZ=peripheral zone; AIF=arterial input function; PBM=prostate-based method. Correlations that are statistically significant at a level of $\alpha=0.01$ are shown with an asterisk.

TABLE 4

Area Under Receiver Operating Characteristic Curve (AUC) Values for Discriminating Between Lesions of Different Tumor Risk Groups Based on the 75th and 100th Percentiles of K^{trans} and v_e Associated With Each Lesion

	AIF				PBM			
	$K^{trans}(100)$	$v_e(100)$	$K^{trans}(75)$	$v_e(75)$	$K^{trans}(100)$	$v_e(100)$	$K^{trans}(75)$	$v_e(75)$
Low vs. Intermediate grade	TZ	0.60	0.57	0.57	0.55	0.54	0.47	0.47
	PZ	0.62	0.61	0.58	0.50	0.48	0.40	0.37
Low vs. intermediate and high grade	TZ	0.54	0.51	0.51	0.57	0.56	0.49	0.49
	PZ	0.58	0.55	0.51	0.55	0.52	0.46	0.43
Intermediate vs. high grade	TZ	0.18	0.17	0.20	0.60	0.58	0.62	0.65
	PZ	0.44	0.42	0.38	0.59	0.59	0.63	0.61

TZ=transition zone; PZ=peripheral zone; AIF=arterial input function; PBM=prostate-based method; Low grade=prostate cancer lesions with Gleason score of 3+3; Intermediate grade=prostate cancer lesions with Gleason score of 3+4; High grade=prostate cancer lesions with Gleason score of >3+4.