Published in final edited form as:

Acad Radiol. 2018 March ; 25(3): 349–358. doi:10.1016/j.acra.2017.10.004.

Performance of Ultrafast DCE-MRI for Diagnosis of Prostate Cancer

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Abstract

Rationale and Objectives: This study aimed to test high temporal resolution dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) for different zones of the prostate and evaluate its performance in the diagnosis of prostate cancer (PCa). Determine whether the addition of ultrafast DCE-MRI improves the performance of multiparametric MRI.

Materials and Methods: Patients ($n = 20$) with pathologically confirmed PCa underwent preoperative 3T MRI with T2-weighted, diffusion-weighted, and high temporal resolution (~ 2.2 seconds) DCE-MRI using gadoterate meglumine (Guerbet, Bloomington, IN) without an endorectal coil. DCE-MRI data were analyzed by fitting signal intensity with an empirical mathematical model to obtain parameters: percent signal enhancement, enhancement rate (α), washout rate (β), initial enhancement slope, and enhancement start time along with apparent diffusion coefficient (ADC) and T2 values. Regions of interests were placed on sites of prostatectomy verified malignancy ($n = 46$) and normal tissue ($n = 71$) from different zones.

Results: Cancer ($\alpha = 6.45 \pm 4.71 \text{ s}^{-1}$, $\beta = 0.067 \pm 0.042 \text{ s}^{-1}$, slope = $3.78 \pm 1.90 \text{ s}^{-1}$) showed significantly ($P < .05$) faster signal enhancement and washout rates than normal tissue ($\alpha = 3.0 \pm 2.1 \text{ s}^{-1}$, $\beta = 0.034 \pm 0.050 \text{ s}^{-1}$, slope = $1.9 \pm 1.4 \text{ s}^{-1}$), but showed similar percentage signal enhancement and enhancement start time. Receiver operating characteristic analysis showed area under the curve for DCE parameters was comparable to ADC and T2 in the peripheral (DCE 0.67–0.82, ADC 0.80, T2 0.89) and transition zones (DCE 0.61–0.72, ADC 0.69, T2 0.75), but higher in the central zone (DCE 0.79–0.88, ADC 0.45, T2 0.45) and anterior fibromuscular stroma (DCE 0.86–0.89, ADC 0.35, T2 0.12). Importantly, combining DCE with ADC and T2 increased area under the curve by $\sim 30\%$, further improving the diagnostic accuracy of PCa detection.

Conclusion: Quantitative parameters from empirical mathematical model fits to ultrafast DCE-MRI improve diagnosis of PCa. DCE-MRI with higher temporal resolution may capture clinically

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useful information for PCa diagnosis that would be missed by low temporal resolution DCE-MRI. This new information could improve the performance of multiparametric MRI in PCa detection.

Keywords

Prostate cancer; ultrafast DCE-MRI; empirical mathematical model; mpMRI

INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer among men in the United States, with more than 200,000 men diagnosed with PCa yearly (1). Magnetic resonance imaging (MRI) is increasingly used in the detection and local staging of PCa. Dynamic contrast-enhanced (DCE) MRI is a valuable tool for clinical detection and diagnosis of PCa (2–6) and for evaluating response of therapy (7–10). DCE-MRI along with T2-weighted (T2W) and diffusion-weighted imaging (DWI) is a key component of multiparametric MRI (mpMRI) of the prostate. The addition of DCE-MRI to T2W and DWI improves the diagnostic accuracy in PCa detection (11–13).

In the recent Prostate Imaging-Reporting and Data System (PI-RADS) version 2 consensus guidelines (14), DCE is designated as secondary to DWI and T2W imaging. A temporal resolution higher than 10–15 seconds per image is recommended for clinical use (14–16). However, the full potential of DCE-MRI may not be reached and, in particular, the details of the contrast uptake kinetics may not be captured when data are acquired with relatively low temporal resolution. An investigation of the effect of temporal resolution on diagnostic performance of DCE-MRI in PCa detection showed higher temporal resolution leads to increased diagnostic performance (15). Recent studies looking at high temporal resolution (<10 seconds) DCE in the prostate showed that signal enhancement during the first 30–40 seconds after contrast media injection is very sparse, and that therefore, PCa can be detected more accurately at very early times after injection (17–21).

DCE-MRI involves acquisition of serial T1-weighted images after the bolus injection of gadolinium-based contrast agent. Qualitative visual assessment of DCE-MRI shows early focal enhancement in cancer lesions compared to benign tissue (2,3,14). Yet the DCE-MRI contrast kinetics of PCa are quite variable and heterogeneous: some lesions show early washout, whereas others retain contrast longer (14). Furthermore, enhancement alone is not definitive for clinically significant PCa, and absence of early enhancement does not exclude the possibility of lesions. Quantitative analysis of DCE-MRI is typically based on use of pharmacokinetic models such as the Tofts model (22) or pure mathematical models such as the empirical mathematical model (EMM) (23). Although the Tofts model remains the standard, a reliable arterial input function may not be easily obtained, and the assumptions made in this model may not be valid for all tissue types (17,24,25). Furthermore, the quantitative T1 values required for calculation of contrast media concentration may result in propagation of error, and may limit diagnostic accuracy. In contrast, the EMM is easy to implement and more consistent with visual assessment of DCE-MR images. Previous work has demonstrated that EMM parameters are potentially as effective as Tofts model in cancer detection (26,27). Although recent studies based on empirical modeling of DCE-MRI signal

intensity dynamics showed signal wash-in (17) and wash-out (18) are useful diagnostic parameters for PCa detection, there is no consensus regarding the optimal parameters for PCa diagnosis. In addition, these earlier studies were limited to the peripheral zone (PZ) only. Prostate is a composite organ, and the different zones are histologically different and appear different from each other in mpMRI sequences, including DCE-MRI. Much of the published work does not compare cancer detection in the various prostatic zones, and this is addressed in the present study.

The aim of the study is to test high temporal resolution DCE-MRI for different zones of the prostate and evaluate its performance in the diagnosis of PCa and determine whether the addition of ultrafast DCE-MRI improves the performance of mpMRI. An EMM (23) is used to characterize patterns of signal enhancement with a temporal resolution of DCE-MRI close to 2 seconds, which is significantly faster than clinical routine DCE-MRI of the prostate.

MATERIALS AND METHODS

Study Patients

The study was conducted after institutional review board approval, informed patient consent, and was compliant with Health Insurance Portability and Accountability Act. Twenty patients were recruited for this study, with prior biopsy-proven PCa. Among the contraindications to inclusion in the study is prior receipt of radiation or hormonal replacement therapy (leading to alterations in prostatic signal on MRI), a glomerular filtration rate measuring less than 60 mL/min/1.73 m², or any other contraindications to MRI. Patients were imaged before surgery between January and December 2016.

MRI

The MRI was performed on Philips Achieva 3T-TX scanner (Philips Healthcare, Netherlands) with d-Stream radio-frequency (RF) technology using a six-channel phased array surface coil (Medrad, Bayer Healthcare). Immediately before imaging, 1 mg of glucagon was injected intramuscularly. Axial T2W, multi-echo T2W, DWI, and DCE-MR images were taken perpendicular to the rectal wall. T1-weighted DCE-MRI data were acquired at 150 dynamic scan points with a temporal resolution of 1.0–4.3 seconds (mean 2.2 seconds) before, during, and after intravenous administration of contrast agent gadoterate meglumine (DOTAREM, Guerbet LLC, Bloomington, IN) at an injection rate of 2.0 mL/s followed by a 20-mL saline flush. Contrast dose amount was based on patient's weight (0.1 mmol/kg). DOTAREM is a macrocyclic and ionic gadolinium-based contrast agent that is extremely stable, and provides relaxivity that is comparable to that of other clinically used contrast agents. High temporal resolution was achieved by modestly decreasing spatial resolution, increasing sensitivity encoding and partial Fourier factors (sensitivity encoding factor 3.5, half scan factor 0.625), and decreasing the field of view (FOV) to allow a small amount of aliasing. The detailed MRI parameters are summarized in Table 1.

Semiquantitative MR Image Analysis

The study subjects underwent radical prostatectomy and whole-mount specimen processing of excised prostates was performed by the Pathology department. The whole prostate was

fixed in formalin and sectioned. Whole-mount sections were mounted on glass slides and were hematoxylineosin stained. Cancer outlines were marked by an expert pathologist (TA, 10 years of experience) on hematoxylineosin-stained histology images. The specimens were compared to the preoperative MRI in a retrospective fashion with the sites of known malignancy from histology identified on MRI.

MR images from different pulse sequences were registered using rigid registration in 3D Slicer (28). The MR images were analyzed by an expert radiologist (AO, 12 years' experience with prostate MRI). Regions of interest (ROIs) were drawn on T2W transaxial images and transferred to multiecho T2W, DWI, and DCE images using "PCampReview," a custom-made module for prostate mpMRI in 3D Slicer. The ROIs mask information was saved as NRRD files. The MR data were analyzed using in-house software in MATLAB (v. 2016b, MathWorks, Natick, MA) to generate apparent diffusion coefficient (ADC), T₂, and DCE parameter maps using the methods described below. The ROI mask images and the calculated maps were used to calculate the MR parameters of the ROI and used in the subsequent analysis. ROIs placed on sites of known malignancy and normal prostate tissue were compared.

T₂ values were calculated from multi-echo T2W images using a mono-exponential signal decay equation shown below:

$$S_{TE} = S_0 \exp(-TE/T_2),$$

where S_{TE} is the signal measured at each TE, and S_0 is the extrapolated signal at TE = 0 ms.

ADC was measured from DWI using a mono-exponential signal decay described below:

$$S_b = S_{SE} \exp(-b \cdot ADC),$$

where b or b -value is the diffusion-weighting factor, S_b is the attenuated spin-echo signal measured at each b -value, and S_{SE} is the maximum spin-echo signal without diffusion attenuation ($b = 0$).

DCE-MRI analysis was performed using the EMM described in Fan et al. (23). The baseline signal intensity value (S_0) of each voxel was calculated by averaging the signal intensity ($S(t)$) of the five precontrast time points. Then, the percent signal enhancement (PSE) was calculated using the following equation:

$$PSE(t) = \frac{S(t) - S_0}{S_0} \times 100$$

The PSE curve was fitted with the EMM on a voxel-by-voxel basis using a nonlinear least-squares algorithm using the following equation:

$$PSE(t) = A(1 - e^{-\alpha t})e^{-\beta t}$$

where A is the amplitude of PSE, α is the signal enhancement or uptake rate (sec^{-1}), and β is the washout rate (sec^{-1}).

To accurately determine the initial time of enhancement for each voxel, the following procedures were performed. First, the maximum intensity projections (MIPs) were generated by finding the maximum PSE value of each voxel. ROIs in the iliac artery and around the whole prostate were defined on the MIP map, to obtain mean arterial and prostatic tissue signal intensity curves with high signal-to-noise ratios. Second, the contrast media bolus arrival times (ie, the time of initial enhancement) for these two curves were found by searching the maximum derivative. Then, the following iterations of EMM fits were performed between two determined time points: the initial time of enhancement in the artery was set as the starting point ($t = 0$ in the EMM), whereas 10 time points after the mean time of prostate uptake was set as the end point in the iteration. Here, 10 time points were selected because the tissue contrast agent uptake starting time was normally delayed less than 15 seconds compared to vessel. The normalized root-mean-square error between the PSE curve and the EMM fit was calculated. The time point with the most accurate fitting result was set as the uptake start point for each voxel, and subsequently the fitted EMM parameters were obtained. For each voxel, the initial signal enhancement slope was measured as the slope of the PSE over the time period beginning at the time of initial enhancement and continuing for 10 time points. The time of arrival of contrast media in each voxel was defined as the time at which PSE achieved 20% signal enhancement. The custom MATLAB program takes approximately 5 minutes to analyze ultrafast DCE-MRI data for each slice using the Midway1 supercomputer (Intel Xeon E5-2670 processor, 2.6 GHz, 8 cores with 32 GB memory) at Research Computing Center at the University of Chicago.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM Corporation, Armonk, NY). Mean and standard deviation for quantitative mpMRI metrics: ADC, T2, DCE parameters from EMM (α , β , slope, MIP, time of arrival, and start point) were calculated. The differences between means for the quantitative mpMRI metrics for cancer and normal tissue from different prostate zones, peripheral, transition, and central zone (CZ), and anterior fibromuscular stroma, were assessed by one-way analysis of variance with post hoc Tukey honest significance test. Significance level was corrected using Bonferroni correction for four post hoc comparisons, and the significance value was set as $P < .01$ ($.05/4 = .013 \sim .01$). The Spearman correlation of quantitative mpMRI parameters with normal tissue and cancer Gleason score was estimated. Receiver operating characteristic (ROC) analysis was carried out to evaluate the parameter that best differentiates between PCa and normal tissue in the whole prostate and in different prostate zones. Logistic regression analysis was performed before ROC analysis for combining multiple MR parameters.

RESULTS

The mean age of patients was 59 years (range 42–70 years), and mean prostate-specific antigen level was 8.6 ng/mL (range 3.7–31.9 ng/mL). Forty-six ROIs from cancer (15 Gleason score 3 + 3, 25 Gleason score 3 + 4, 5 Gleason score 4 + 3, 1 Gleason score 4 + 5)

and 71 ROIs from normal tissue from different prostate zones (18 PZ, 16 transition zone [TZ], 18 CZ, and 19 anterior fibromuscular stroma [AFMS]) were analyzed in this study. Mean tumor size was $1.7 \times 0.9 \text{ cm}^2$ (range $0.6\text{--}4.3 \times 0.3\text{--}3.5 \text{ cm}^2$). Representative images showing reduced ADC and T2 values and increased α , β , and slope in ROIs denoting cancerous lesions, and corresponding histology images are shown in Figures 1 and 2.

Performance of T2 and ADC Values

One-way analysis of variance comparing the means of metrics for cancer and normal tissue shows that ADC and T2 values were significantly lower ($P < .01$) in cancer compared to normal PZ (~25%–50% lower), but not significantly lower than normal TZ and CZ. T2 values of normal AFMS were significantly lower than cancer, but no significant difference was found between ADC for cancer and normal AFMS. Figure 3 shows the box plots of quantitative ADC and T2 values for differentiation of PCa from benign prostate tissue.

DCE-MRI Characteristics of Normal Prostate and PCa

DCE parameters: signal enhancement or uptake rate (α) and initial enhancement slope were significantly higher ($P < .01$, ~2–3 times higher) in cancer compared to normal tissue from all prostatic zones except from TZ. The signal washout rate (β) was significantly higher ($P < .01$) in cancer compared to normal AFMS (7 times higher) and CZ (3.5 times higher), but not significantly different between cancer and normal PZ and TZ tissue. The enhancement starting time ($P = .28$), time of arrival ($P = .42$), and MIP ($P = .05$) showed no significant differences between cancer and normal tissue. Table 2 summarizes means of the quantitative mpMRI parameters for cancer and normal tissue from different prostate zones. Graphical representation of the data is shown in the box plots (Fig 3). The difference in the distribution of ultrafast DCE-MRI parameters, α and slope between PCa and normal tissue, shows that they can be used for diagnosis of PCa.

Correlation of Quantitative mpMRI Parameters with Gleason Score

There was no significant correlation ($P > .05$) of Gleason score with either ADC ($\rho = -0.265$), T2 values ($\rho = -0.065$), or DCE-MRI parameters: α ($\rho = -0.056$), β ($\rho = 0.089$), slope ($\rho = 0.203$), enhancement starting time ($\rho = -0.027$), and time of arrival ($\rho = 0.095$). Only MIP showed a significant, moderate correlation ($\rho = 0.337$, $P < .05$).

Diagnosis of PCa Using mpMRI with Ultrafast DCE-MRI

Results of ROC analysis for differentiation of PCa from normal tissue in different prostate zones are given in Table 3. The traditional MRI parameters, ADC and T2, have high area under the curve (AUC) in the PZ (ADC 0.80, T2 0.89, $P < .05$), but low in the CZ (ADC 0.45, T2 0.45, $P > .05$) and AFMS (ADC 0.35, T2 0.12, $P > .05$). The AUC is smaller than 0.5 as ADC and T2 values in AFMS and CZ were lower than cancer, which is opposed to our hypothesis that cancer has lower ADC and T2 compared to normal tissue. Importantly, EMM parameters obtained from ultrafast DCE-MRI, especially signal enhancement rate (α), washout rate (β), and initial enhancement slope prove to be highly effective as they have high AUC in CZ (α 0.82, β 0.79, slope 0.82, $P < .05$) and AFMS (α 0.87, β 0.86, slope 0.89, $P < .05$). However, in the PZ, AUCs for DCE parameters (α 0.74, β 0.67, slope 0.82, P

< .05) show that they are only moderately effective in PCa detection. The AUCs for all mpMRI parameters (α , 0.69; β , 0.61; slope, 0.72; ADC, 0.69; T2, 0.75) are lower in TZ compared to other prostate zones.

For the entire prostate, cancers ($\alpha = 6.45 \pm 4.71 \text{ s}^{-1}$, $\beta = 0.067 \pm 0.042 \text{ s}^{-1}$, slope = $3.78 \pm 1.90 \text{ s}^{-1}$) showed significantly ($P < .05$) faster signal enhancement and washout rates than normal tissue ($\alpha = 3.0 \pm 2.1 \text{ s}^{-1}$, $\beta = 0.034 \pm 0.050 \text{ s}^{-1}$, slope = $1.9 \pm 1.4 \text{ s}^{-1}$). MIP and enhancement start time were similar in cancer versus normal prostate. ROC analysis for pooled data for the entire prostate shows that DCE parameters (α 0.77, β 0.72, slope 0.80, $P < .05$) are more effective in PCa detection compared to ADC (0.55, $P < .05$) and T2 (0.52, $P < .05$). Importantly, combining DCE with ADC and T2 using logistic regression analysis increased AUC by ~30% compared to ADC and T2, or ~40% compared to either ADC or T2 alone, further improving the diagnostic accuracy of PCa detection.

DISCUSSION

Our results showed that high temporal resolution or ultrafast DCE-MRI is feasible and could improve the diagnosis of PCa. PCa had significantly faster signal enhancement and washout rates than normal tissue, but showed similar signal enhancement and enhancement start time. Ultrafast DCE-MRI increases sensitivity to initial rate of enhancement and initial time of enhancement. ROC analysis showed that AUCs for DCE-MRI parameters were comparable to those for ADC and T2 in the peripheral and transition zones but higher in CZ and AFMS. Importantly, combining DCE parameters with ADC and T2 further improved the diagnostic accuracy of PCa detection.

The consensus guidelines for PCa detection from PI-RADS (14) recommend use of ADC maps in conjunction with T2W images for cancer assessment. The quantitative results in this study support these recommendations as ADC and T2 values had the highest AUC in the ROC analysis in the PZ and TZ; this result is similar to those reported in literature (12,29). Although DCE-MRI plays a minor role in PI-RADS assessment, this study shows that ultrafast DCE-MRI parameters could add to conventional DWI and T2W imaging in the detection of PCa in the PZ, and is particularly effective in the CZ and AFMS.

The different prostatic zones are histologically different and appear different from each other in mpMRI sequences, including DCE-MRI. There is little published analysis comparing cancer detection in all prostatic zones. Our results show that cancer in the PZ can be identified by EMM parameters from ultrafast DCE-MRI. Signal enhancement rate (α and slope) is highly effective, whereas signal washout rate (β) is moderately effective in PCa detection in the PZ, and this is in agreement with previous literature (17,18). Although the majority of prostate malignancies occur in the PZ, up to 40% may reside in the central gland: TZ and CZ (29,30). Cancers occurring in the TZ, CZ, and AFMS are of particular clinical interest because they can often go undetected on MRI because of the similarity of imaging features to the normal gland and benign conditions, for example, benign prostatic hyperplasia (31–33). In the CZ, traditional ADC and T2 maps are not helpful in diagnosing cancer, as cancer appears the same as normal CZ tissue (32,33). However, DCE parameters, signal enhancement rate (α) and initial enhancement slope, are significantly lower in normal

CZ tissue than in cancers. Similarly, AFMS shows low signal enhancement and slow washout compared to the rest of the prostate and cancer. Therefore, DCE parameters are more useful for detecting cancers in the AFMS and CZ.

The problems of PCa detection in the TZ have been highlighted in previous studies (13,30,34,35). The results from this study showed that detecting cancers was more difficult in the TZ than in other zones. The enhancement slope and α are only nominally higher in cancer versus normal prostate in the TZ. Highly vascularized regions, for instance benign prostatic hyperplasia nodules in the TZ, have been shown to mimic PCa on DCE-MRI (2). In addition, ADC and T2 values in the TZ are similar for PCa and normal prostate. The present results are in agreement with those of previous studies, which reported similar T2, DWI characteristics, and enhancement patterns between benign prostatic hyperplasia and PCa in the TZ (2,13,30).

The DCE-MRI analysis showed that enhancement starting point and time of arrival were not significantly different between cancer and normal tissue. This information is at variance with the widely accepted notion that PCa enhances well before normal prostate. Even though contrast media arrival time to the benign prostate and PCa was similar, the faster rate of initial enhancement characterized by α leads to the wrong impression of early enhancement. This is different from results from a previous study of breast cancer patients, where ultrafast DCE-MRI showed that contrast enhancement starts earlier in cancerous tissue than in benign breast tissue (36). In addition, it takes a longer time for contrast bolus to reach the prostate (~35 seconds) as compared to breast tissue (~5–15 seconds).

Qualitative visual assessment of DCE-MRI is based on signal enhancement. Angiogenesis or increased microvessel density is generally regarded as the reason for increased contrast uptake in cancer tissue (2,37). However, the present results show that maximal signal enhancement (MIP) is not significantly different between cancerous regions and peripheral, transition, and central zones. Therefore, it would be very difficult for radiologists to accurately detect PCa using traditional DCE-MRI metrics such as the enhancement start time and MIPs. Normal TZ tissue has nominally higher MIP than other prostatic zones, and we speculate that this can be attributed to differences in the branches of the inferior vesical artery that supply prostatic blood vessels. Blood flow in the urethral artery that supplies the TZ and urethra may be greater than blood flow in the capsular artery that supplies the rest of other prostatic zones (38). On visual assessment of the MIP map, the urethra and TZ tissue surrounding the urethra have higher MIP values, and this is consistent with possible higher blood flow in the urethral artery compared to the capsular artery.

The kinetics parameters describing signal enhancement (α and slope) are the best metrics for differentiating cancer from normal tissue. High temporal resolution DCE-MRI is able to characterize these subtle changes in contrast kinetics more accurately than traditional lower temporal resolution DCE-MRI. With 10-second temporal resolution for traditional prostate DCE-MRI, there would be only three imaging phases that capture the enhancement kinetics, as compared to 10–15 images using ultrafast DCE. However, this study did not assess directly whether ultrafast sampling increases the diagnostic accuracy of DCE-MRI relative to conventional sampling. In addition, the use of the EMM was not directly compared with

the commonly used Tofts compartmental model. These are limitations of this study. Other limitations include the small sample size in this exploratory study. Other conditions that mimic PCa on mpMRI such as benign prostatic hyperplasia, prostatitis, inflammation, hemorrhage, atrophy, necrosis, and calcification (33) were not specifically considered in study. Another limitation of the proposed sequence is the relatively low signal-to-noise ratio, reduced FOV, and lower spatial resolution compared to conventional DCE-MRI. In the future, we will evaluate use of a phased-array surface coil with a higher number of channels (preferably 16 or 32 channels). This could improve signal-to-noise ratio, allow increased FOV, and increase spatial resolution. Improved detectors could also allow us to speed up scan time even further. An endorectal coil could be used if deemed necessary.

A few prior studies have used the DCE-MRI of the prostate with high temporal resolution (<5 seconds). However, their DCE-MRI scans were either in lower spatial resolution (18,21) or used Golden-angle Radial Sparse Parallel sequence (19) to achieve high temporal resolution. Although high temporal resolution can be achieved by using Golden-angle Radial Sparse Parallel sequence, it is susceptible to radially oriented streak artifacts. Our temporal resolution and Cartesian sampling of DCE-MRI is similar to the spoiled gradient echo sequence used by Somford et al. (39), but with slightly better spatial resolution and without the use of an endorectal coil. Compared to radial sampling, the conventional Cartesian sampling allows measurements that are relatively independent of feature size, shape, and internal morphology. In this study, the FOV was reduced slightly, and some aliasing was allowed to increase temporal resolution. This aliasing had no effect on the parameters that were most useful for PCa diagnosis, derived from the early phase of enhancement, that is, during the first 30–45 seconds post injection. Enhancement during the early phase of contrast media uptake is very sparse, and significantly enhancing voxels are unlikely to alias onto other significantly enhanced voxels in the prostate (40). This was demonstrated by previous work on ultrafast imaging of breast cancer (26,36). In the rare event that significantly enhancing voxels overlap in aliased images, these overlaps can be corrected using “unfolding methods” (40). This suggests that in future work, FOVs could be decreased even further by increasing the amount of aliasing even further to achieve higher temporal resolution without introducing significant errors in detection of clinically significant, rapidly enhancing voxels. In addition, other methods such as compressed sensing and radial sampling can be tested to see if these approaches to accelerated acquisition increase diagnostic accuracy.

The present results, together with previously published work, suggest that the use of higher temporal resolution increases diagnostic accuracy, and that changes in the PI-RADS recommendation (14) for the temporal resolution of DCE-MRI should be considered. In addition, computer-aided diagnosis (41,42) using ultrafast DCE-MRI could potentially further improve PCa diagnosis.

Although this study shows DCE-MRI is beneficial for patients, there are some concerns about an increase in clinical use of contrast agents because of potential adverse side effects (43–45). However, the contrast agent used in this study, DOTAREM, is both macrocyclic and ionic. This results in exceptional stability combined with low probability of allergic reactions, as demonstrated in numerous clinical trials (46–48). The relaxivity of DOTAREM

is comparable to other clinically used contrast agents. Therefore, it is likely that judicious use of DOTAREM, as well other clinically approved contrast agents, could result in improved outcomes for patients.

CONCLUSION

Quantitative parameters from EMM fits to ultrafast DCE-MRI improve diagnosis of PCa compared to ADC and T2 alone. DCE-MRI with higher temporal resolution may capture clinically useful information that would be missed by conventional, lower temporal resolution DCE-MRI. Subtle differences in contrast kinetics, specifically increased signal enhancement rate or uptake rate (α), and initial enhancement slope seen in cancer compared to surrounding normal tissue are helpful in detection of PCa. An optimal protocol could include ultrafast sampling to measure the contrast media uptake phase, combined with conventional sampling to measure washout rate (β). The comparison of contrast media dynamics in the various prostate zones shows DCE parameters are very promising for PCa detection in the CZ and AFMS. Importantly, combining DCE with ADC and T2 can further improve the diagnostic accuracy of PCa detection.

ACKNOWLEDGMENT

One of the authors (DH) wishes to acknowledge the support of China Scholarship Council (CSC) for his scholarship to study abroad.

This work was supported by Guerbet LLC, Philips Healthcare, and National Institutes of Health (NIH R01 CA172801 and NIH 1S10OD018448-01).

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Figure 1.

Representative image of ultrafast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) using empirical mathematical model (EMM): Histology image with three cancer lesions of Gleason score 3 + 4 (a), with corresponding T2 map (b). Apparent diffusion coefficient (ADC) map (c) and maps for DCE-MRI parameters: signal enhancement rate or α (d), initial signal enhancement slope (e), and wash-out rate or β (f). Patient was 68 years with prostate-specific antigen level of 10.3 ng/mL before undergoing radical prostatectomy.

Figure 2.

Representative image of ultrafast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) using empirical mathematical model (EMM): Histology image with cancer lesions of Gleason score 3 + 4 (left peripheral zone) and Gleason score 3 + 3 (right peripheral zone) (a), with corresponding T2 map (b). Apparent diffusion coefficient (ADC) map (c) and maps for DCE-MRI parameters: signal enhancement rate or α (d), initial signal enhancement slope (e), and wash-out rate or β (f). Patient was 52 years with prostate-specific antigen (PSA) level of 3.7 ng/mL before undergoing radical prostatectomy.

Figure 3.

Box plots of apparent diffusion coefficient (ADC), T2 values, and ultrafast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) parameters using empirical mathematical model (EMM) for cancer and normal tissue from different prostatic zones (AFMS, anterior fibromuscular stroma; CZ, central zone; PZ, peripheral zone; TZ, transition zone). Mean value denoted by $\blacklozenge$ mark. The median is indicated by the horizontal line

within the box, 25th and 75th percentiles are indicated by the boundaries of the box, and the 95% confidence limits of the results are indicated by the whiskers.

TABLE 1.

MR Imaging Parameters

Imaging Sequence	Pulse Sequence	FOV (mm)	Scan Matrix Size	Resolution (mm)	TE (ms)	TR (ms)	Slice Thickness (mm)	Flip Angle (°)
Axial T2WI	SE-TSE	200	256 × 256	0.8 × 0.8	38,88, 138, 188, 238, 288	8200	3	90
DWI [*]	SE-EPI	220	150 × 150	1.5 × 1.5	75	4700	3	90
Ultrafast DCE [†]	T1-FFE	200	160 × 160	1.25 × 1.25	1.4	3.8	3	10

EPI, echo planar imaging; FFE, fast field echo; FOV, field of view; SE, spin echo; TE, echo time; TR, repetition time; TSE, turbo spin echo.

^{*} *b*-values used 0, 600, 1200 s/mm².

[†] Sensitivity encoding (SENSE) factor 3.5; half scan factor 0.625; injection rate of 2.0 mL/s followed by a 20-mL saline flush. Contrast dose amount based on patient's weight (0.1 mmol/kg). Ultrafast DCE-MRI T1-weighted images were taken with temporal resolution of ~2.2 seconds (1.0–4.3 seconds) at 150 dynamic scan points over 5–12.6 minutes (DCE images were taken starting 30 seconds before contrast injection, images were taken in the first 2–5 minutes to characterize signal enhancement, followed by 0–3 minutes' gap, and imaged for another 1.6 minutes to characterize contrast washout).

TABLE 2.

Summary of Quantitative mpMRI Parameters

mpMRI Quantitative Metric	Cancer	Normal Tissue			
		Peripheral Zone	Transition Zone	Central Zone	Anterior Fibromuscular Stroma
ADC ($\mu\text{m}^2/\text{ms}$)	1.15 $\pm$ 0.41	1.55 $\pm$ 0.35	1.15 $\pm$ 0.32	0.96 $\pm$ 0.25	0.87 $\pm$ 0.37
T2 (ms)	108.7 $\pm$ 30.0	192.8 $\pm$ 69.2	118.5 $\pm$ 32.0	102.8 $\pm$ 20.8	72.1 $\pm$ 20.1
MIP (%/s)	160.6 $\pm$ 41.7	133.4 $\pm$ 46.3	159.0 $\pm$ 41.0	134.8 $\pm$ 46.3	129.9 $\pm$ 56.0
α (%/s)	6.45 $\pm$ 4.71	3.18 $\pm$ 2.00	4.28 $\pm$ 2.34	2.60 $\pm$ 1.67	2.17 $\pm$ 1.85
β (%/s)	0.067 $\pm$ 0.042	0.043 $\pm$ 0.044	0.066 $\pm$ 0.035	0.019 $\pm$ 0.061	0.010 $\pm$ 0.039
slope (%/s)	3.78 $\pm$ 1.90	1.94 $\pm$ 1.69	2.98 $\pm$ 1.49	1.62 $\pm$ 0.70	1.23 $\pm$ 1.23
Start point (s)	35.9 $\pm$ 7.6	30.9 $\pm$ 7.7	34.4 $\pm$ 7.3	33.6 $\pm$ 9.3	34.1 $\pm$ 8.3
TOA (s)	37.6 $\pm$ 7.5	33.7 $\pm$ 8.1	36.3 $\pm$ 7.7	36.0 $\pm$ 10.2	39.6 $\pm$ 13.5
<i>n</i>	46	18	16	18	19

Magnetic resonance imaging (MRI) parameters that were found to be significantly different ($P < .01$) from cancer using analysis of variance (ANOVA) with post hoc Tukey honest significance test (HSD) test are displayed in bold.

TABLE 3.
Results of ROC Analysis Between Prostate Cancer and Normal Tissue From Different Prostate Zones

	α	β	Slope	ADC	T2	ADC + T2	ADC + T2 + DCE α
Entire prostate [†]	0.770 [*]	0.719 [*]	0.800 [*]	0.550	0.522	0.601	0.765 [*]
PZ	0.739 [*]	0.667 [*]	0.819 [*]	0.803 [*]	0.891 [*]	0.902 [*]	0.922 [*]
TZ	0.689 [*]	0.605	0.715 [*]	0.693 [*]	0.745 [*]	0.767 [*]	0.797 [*]
CZ	0.824 [*]	0.792 [*]	0.878 [*]	0.446 [‡]	0.454 [‡]	–	–
AFMS	0.871 [*]	0.864 [*]	0.885 [*]	0.351 [‡]	0.116 [‡]	–	–

ADC, apparent diffusion coefficient; AFMS, anterior fibromuscular stroma; CZ, central zone; DCE, dynamic contrast-enhanced; PZ, peripheral zone; ROC, receiver operating characteristic; TZ, transition zone.

Area under the curve (95% confidence interval).

^{*} AUC values are significant ($P < .05$) for ROC analysis.

[‡] Normal tissue from the entire prostate considered as one tissue type (no zonal consideration).

[‡] AUC values < 0.5 as ADC and T2 values in AFMS and CZ were lower than cancer, which is opposed to our hypothesis that cancer has lower ADC and T2 compared to normal tissue. Further ROC analysis of performance of mpMRI parameters in PCa detection using logistic regression was not performed in these cases.