Portable Perfusion Phantom Offers Quantitative Dynamic Contrast-Enhanced Magnetic Resonance Imaging for Accurate Prostate Cancer Grade Stratification: A Pilot Study

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Abstract

Rationale and Objectives—The study goal was to test whether the improved accuracy in quantitative dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) measurement using a point-of-care portable perfusion phantom (P4) leads to better stratification of prostate cancer grade.

Materials and Methods—A prospective clinical study was conducted recruiting 44 patients scheduled for multi-parameter MRI (mpMRI) prostate exams. All participants were imaged with the P4 placed under their pelvic regions. Tissue sampling was carried out for 25 patients at 22±18 (mean±SD) days after mpMRI. On histologic examination, a total of 31 lesions were confirmed as prostate cancer. Tumors were classified into low grade (n=14), intermediate grade (n=10), and high grade (n=7). Tumor perfusion was assessed by volume transfer constant, $K_{\text{trans}}$, before and after P4-based error correction, and the $K_{\text{trans}}$ of low, intermediate, and high-grade tumors were statistically compared.

Results—After P4-based error correction, the $K_{\text{trans}}$ of low, intermediate, and high-grade tumors were 0.109±0.026 min$^{-1}$ (95% CI: 0.094 to 0.124 min$^{-1}$), 0.163±0.049 min$^{-1}$ (95% CI: 0.129 to 0.198 min$^{-1}$) and 0.356±0.156 min$^{-1}$ (95% CI: 0.215 to 0.495 min$^{-1}$), respectively, with statistically significant difference among the groups (low vs intermediate: $p$=0.002; intermediate vs high: $p$=0.002; low vs high: $p$<0.001). The sensitivity and specificity of $K_{\text{trans}}$ value, 0.14 min...
−1, to detect the clinically significant prostate cancer were 88% and 93%, respectively, after P4 based error correction, but those before error correction were 88% and 86%, respectively.

**Conclusion**—The P4 allows to reduce errors in quantitative DCE-MRI measurement, enhancing accuracy in stratification of prostate cancer grade.

**Keywords**
Perfusion phantom; DCE-MRI; Prostate cancer; Grade stratification

**INTRODUCTION**
Prostate cancer (PCa) is the most common non-cutaneous cancer, and the second leading cause of cancer-related death in men in the United States (1). Early detection and accurate stratification of PCa grade are critical in determining the optimal treatment plan for individual patients (2). Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has been evaluated as a non-invasive diagnostic and prognostic technique for PCa (3). DCE-MRI measures microvascular perfusion by monitoring the dynamic change of MRI contrast agent in a target tissue (4). As increased perfusion is associated with tumor aggressiveness, DCE-MRI has been investigated for early prostate cancer detection (5), grade stratification (6) and therapy monitoring (7). However, the inter- and intra-scanner variability in DCE-MRI measurement remains a serious concern for its accurate and reproducible application (8). Each MRI vendor yields different pulse sequence and image reconstruction scheme based on unique hardware configuration, leading to variation in quantitating tissue contrast-agent (CA) concentration and, consequently, DCE-MRI parameters (8). Inter-scanner variability impedes the comparison of data among institutes, which prevents standardizing DCE-MRI values for quantitative analysis, while intra-scanner variability leads to errors in therapy monitoring. Inter-scanner variability can also lead to errors in therapy monitoring, as different scanner platforms may be employed in follow-up exams of the same patient even in the setting of a single institution. Thus DCE-MRI is currently utilized as a qualitative technique merely assisting the clinical interpretation of diffusion weighted imaging or T2 weighted (T2W) MRI in a standard-of-care multi-parametric MRI (mpMRI) of the prostate based on Prostate Imaging Reporting and Data System version 2.1 (9). This yields reasonable diagnostic accuracy, but it has fundamental limitation due to its nature of subjective assessment, leading to inter-observer variation (10).

A point-of-care portable perfusion phantom, P4, was recently developed to minimize the scanner-dependent error in quantitative DCE-MRI measurement (11). Unlike a static phantom, the CA concentration of the P4 varies over time, replicating a living tissue. The P4 is small enough to be imaged concurrently in the bore of a standard MRI scanner with a patient, serving as an external reference. The P4 creates constant contrast enhancement curves with high repeatability, thus CA concentration time-course in a tissue, which is a major source of error for the estimated quantitative DCE-MRI parameters, can be accurately calculated in reference to the values observed in the phantom. In a previous study, the variability in the volume transfer constant ($K^{\text{trans}}$) of various tissues across two 3T MRI scanners manufactured by different vendors was reduced approximately fivefold after P4-based error correction, whereas the static phantom used for comparison was not able to
reduce the errors (11). Furthermore, the clinical utility of the P4 has been recently demonstrated for accurate assessment of pancreatic cancer response to chemotherapy (12). The P4 is easily operable by MRI technologists with modest training and fits within the current clinical workflow. Unlike bulky and costly perfusion phantoms, the P4 was manufactured via simple assembly of a few components made of inexpensive material. Therefore, the P4 has great potential to facilitate multi-site clinical trials employing quantitative DCE-MRI to evaluate and characterize PCa in high accuracy.

We hypothesized the P4 would improve the accuracy in quantitative DCE-MRI, leading to better stratification of prostate cancer grade. In this manuscript, we describe a single-center prospective clinical study to test this hypothesis.

MATERIALS AND METHODS

IRB approval statement

Our institutional review board approved this study following the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. All participants signed informed consent to be imaged together with the P4 during DCE-MRI. Health Insurance Portability and Accountability Act was strictly observed.

Patients

Patients who are 18 years of age or older and scheduled for mpMRI prostate exam due to active surveillance or elevated prostate specific antigen (PSA) level were asked to participate in this study. Patients with safety contraindications to MRI examination (determined by standard clinical screening), and those on hemodialysis or with acute renal failure were excluded. A total of 71 patients were contacted from November 2017 to April 2019, and 44 patients agreed to participate in the study (participation rate = 62%). The median age of all participants was 65 years (age range, 50–77 years; 14 African-Americans, 30 Caucasians). Within 72 days (mean±SD: 22±18 days) after mpMRI exams, a total of 25 patients (57%) had either radical prostatectomy (n=4) or needle biopsy (MRI-transrectal ultrasound fusion biopsy (n=13); transrectal ultrasound guided systematic biopsy (n=8)). On histologic examination, a total of 31 lesions (n=19 in the peripheral zone, n=12 in the transition zone) were identified as PCa and classified into low grade (Grade Group 1: n=14), intermediate grade (Grade Group 2 or 3: n=10) and high grade (Grade Group 4 or 5: n=7). The correlation between Grade Group (GG) and Gleason Score (GS) is as follows: GG 1 = GS 3+3; GG 2 = GS 3+4; GG 3 = GS 4+3; GG 4 = GS 8; GG 5 = GS 9 or 10 (13). Tumor stage varied from T1 to T3, but no metastatic lesions were found in either lymph node or distant organs. The boundary of each lesion was delineated on the T2W MR images after consensus reads by a multidisciplinary tumor board comprised with subspecialty trained radiologist and urologist who were blinded to the histopathological findings.

Point-of-care Portable Perfusion Phantom, P4

The photograph of the P4 is shown in Fig. 1a. The detail structure and functional mechanism of the P4 were described in a previous study (11). In brief, a semipermeable membrane (pore size: 10–12 KDa) (SpectrumLabs, Rancho Dominguez, CA) was placed between top
chamber (width × height × length = 10 × 1 × 150 mm) and bottom chamber (width × height × length = 10 × 15 × 150 mm) of the P4, which was made by 3D printing with VeroClear material. Prior to use, both chambers were filled with degassed and deionized water. The P4 was triggered by infusing a MRI contrast agent, gadoteridol (100 mM), at a constant flow rate (0.06 ml/s) displacing the water in the top chamber. Then the contrast agent in the top chamber diffused to the bottom chamber over time. The increase of the CA concentration in the bottom chamber was constant for 10 minutes after infusion (0.11 mM/min), when independently analyzed using liquid chromatography with tandem mass spectrometry detection. Figure 1b shows the phantom package covering the triplicated P4 (P4a, P4b, P4c). The phantom package was framed with 9-mm thick acrylic to support the patient’s body weight. The P4 did not make direct contact with the acrylic frame so that the scanner vibration would be minimally transferred to the P4. To further absorb the scanner vibration, a 5-mm thick synthetic sponge sheet was placed under the P4. The air gap between the P4 and the top of the package was 12 mm. The polyurethane foam (pink color) was used inside the package to prevent heat transfer from the human subject to the P4. Two bars made of polyurethane foam were used to locate the P4 at the center of the package. Figure 1c illustrates the phantom package under a human subject. Two leather cushions were placed near the phantom package to match the thickness. A fiberglass cushion was placed on the top of the phantom package to comfort the human subject and to further prevent heat transfer during imaging. The P4 was placed in the MRI room for at least 30 minutes prior to imaging so that its temperature was stabilized to the MRI room temperature, 17±1°C. A phased array coil was used to wrap around the lower body and the phantom package at the same time. Endorectal coil was not used in this study.

MRI protocol

All subjects were imaged in a 3T MRI scanner (SIEMENS Prisma) equipped with a dual-channel transmit RF coil. Glucagon (1 mg/ml; Eli Lilly, Indianapolis, IN) was intramuscularly injected to all subjects to relax smooth muscle before imaging. The prostate location was initially identified using a non-contrast T1W MRI (axial view) covering entire pelvic region. Then the high-resolution T2W MRI sequences was followed for sagittal, axial, and coronal views of the prostate, respectively. DWI was implemented with four b values (0, 500, 1000, and 2000). The field of view (FOV: 180 × 180 mm) and the slice thickness (3 mm) of DWI were matched with those of axial T2W MRI. The apparent diffusion coefficient (ADC) map was automatically created using the vendor software right after DWI. Prior to DCE-MRI, B0/B1 shimming and vendor-specific B1 mapping were conducted (14). For T1 mapping, T1W MRI with a 3D fast spoiled gradient echo sequence was applied at three different flip angles (2°, 5°, and 10°) (15) with the following parameters: field-of-view = 260×260 mm; frequency/phase encoding = 154/192 (25% phase oversampling), matrix size = 192x192, slice number = 24, thickness/gap = 3.5/0 mm, TR/TE = 5.08/1.77 ms, NEX = 1, and SENSE factor = 2. The same imaging sequence and parameters were used for DCE-MRI except the fixed flip angle of 15°. DCE-MRI was applied for 7 minutes (temporal resolution = 10 sec; 42 consecutive image acquisitions). Gadoteridol (0.1 mmol/kg; 2.5 ml/s), a macrocyclic contrast agent, was i.v. injected at 20 seconds after starting DCE-MRI and followed by 20-ml saline flush using a clinical power injector (Medrad Spectris Solaris® EP; Bayer, Whippany NJ). Gadoteridol (100 mM; 0.06 ml/s) also was infused to the
triplicated P4 using a syringe pump (NE-1600, New Era Pump Systems, Inc.; Farmingdale, NY) at 30 seconds before starting DCE-MRI, as the diffusion of gadoteridol to the bottom chamber was initiated at about 60 seconds after infusion (11). The duration of DCE-MRI, 7 minutes, was determined for proper dynamic range of look-up tables (LUTs). The gadoteridol diffusion rate into the bottom chamber was 0.11 mM/min (11), and the diffusion was initiated at about 0.5 min after starting DCE-MRI. Therefore, 7 minutes of imaging allowed to create LUTs from 0 to 0.7 mM (0.11 mM/min × 6.5 min ≈ 0.7 mM). The dynamic range of CA concentration in most prostate tumors were less than 0.7 mM at full-dose injection (0.1 mmol/kg).

**Image Processing**

Image processing was implemented in eight steps as follows. (i) All 42 DCE-MRI image volume sets were co-registered using a rigid method (16). (ii) The local flip angle variation over the field of view was corrected using the B1 map (14). (iii) T1 map was created using the various flip angle method (15). (iv) CA concentration map was created using equation, \( C=\frac{1}{r_1} \log \left( \frac{M_0 \sin \theta - Scos \theta}{M_0 \sin \theta - S} \right) \), where \( r_1 \) is the longitudinal relaxivity of contrast agent (2.8 s\(^{-1}\) mM\(^{-1}\) in the P4, 3.7 s\(^{-1}\) mM\(^{-1}\) in human tissues), \( TR \) is repetition time, \( M_0 \) is the original magnetization, \( \theta \) is a flip angle, \( S \) is the MRI signal, and \( T_1(0) \) is pre-contrast T1 value (17). (v) A LUT was created, correlating the reference contrast enhancement curve obtained by liquid chromatography with tandem mass spectrometry detection (0.11 mM/min) with the one measured by MRI. (vi) The arterial input function (AIF) of each individual subject was measured from the left and right iliac arteries as described in a previous study (18). (vii) The LUT created in the fifth step was utilized to correct the AIF and CA concentration map (“Appendix B” of a previous manuscript (11) describes this procedure in detail). (viii) The extended Tofts model (ETM) was employed to create the \( K_{trans} \) map (19). A lab-made computer software package using LabVIEW v17.0 (National Instruments Co., Austin, TX) was utilized for image processing. Digital reference objects, synthetic data developed by Dr. Daniel Barboriak in Duke University and Quantitative Imaging Biomarker Alliance (20), were used to validate the software package. Time required for the entire image processing of a subject was about 30 minutes.

**Statistical Analysis**

In this manuscript, data are presented as mean ± standard deviation (SD) with 95% confidence interval (CI). Statistical difference among the groups was analyzed using one-way analysis of variance (ANOVA), and \( p \) value lower than 0.05 was considered significant at overall 5 % type I error level (21). For multiple comparisons, however, the \( p \) value to determine statistical difference was adjusted using Bonferroni method (e.g., \( p \) value lower than 0.016 (0.05 divided by 3) was considered significant between groups for three comparisons) (21). The contrast enhancement curve (CEC) repeatability of the P4 was measured using intra-class correlation coefficient (22). Sensitivity and specificity were estimated from receiver-operation characteristic (ROC) curve analysis (23). The optimal cut-point of \( K_{trans} \) (or ADC) to identify clinically significant PCa (Grade Group ≥ 2) was determined based on the Youden index (highest sensitivity and specificity) (24). SAS, version 9.4 (SAS Institute Inc., Cary, NC) was used for all statistical analyses.
RESULTS

The P4 was able to be imaged together with a human subject without inducing additional artifacts. Figure 2a shows the DCE-MRI images of a human subject bearing a prostate tumor (Grade Group 4) indicated with a white arrow in each subfigure and three P4s (bottom chamber) indicated with solid rectangles before (baseline) and at 2 and 7 minutes after gadoteridol injection. Two different gray scales (human: 0–200; P4: 0–700) were applied in order to present both the subjects in high contrast. Figure 2b shows the CA concentration maps of three P4s at 2, 5 and 7 minutes after gadoteridol injection. Figure 2c shows three CECs of the P4s together with the mean value. The CEC repeatability measured by intra-class correlation coefficient was higher than 0.99 in all measurements. No human subjects reported any pain or discomfort associated with the phantom package.

The P4 was able to reduce errors in quantitating CA concentration over different image slices. Figure 3a shows the CA concentration maps of the first, middle and last image slices of a human subject before (upper row) and after (lower row) P4-based error correction. Figure 3b shows the variation in CA concentration measurement of the gluteus maximus muscle indicated with the red arrows in Fig. 3a over 24 image slices before and after error correction. The CA concentration was overestimated particularly at the edge slices before error correction. Figure 3c shows the coefficient of variation (COV = SD/Mean%) of CA concentration in the muscle over the image slices of all 44 subjects. The box shows the interquartile range (IQR), while the midline in the box represents the median value and the “X” mark represents the mean value. Any values larger than the third quartile plus 1.5 × IQR or smaller than the first quartile minus 1.5 × IQR were considered outliers. The COVs after P4-based error correction were 5.6±2.0% (95% CI: 5.0 to 6.2%), significantly lowered than those before error correction (14.3±4.8%; 95% CI: 12.8 to 15.8%) (p<0.001). Even after the two edge slices were excluded in the analysis, the COVs after P4-based error correction remained significantly lower (5.4±1.9% (95% CI: 4.8 to 6.0%) vs 6.8±3.7% (95% CI: 5.7 to 7.9%)) (p=0.021).

The P4 was able to reduce the intra-scanner variability over time. Figure 4a shows the graphical LUTs of the P4 obtained at the center image slices from 44 MRI exams on the same scanner over approximately 1.5 years. Figure 4b shows CA concentrations in the obturator muscles of all 44 human subjects at the center image slice before and after P4-based error correction. After error correction, the muscle CA concentration was 0.064±0.006 mM (95% CI: 0.062 to 0.066 mM), which was significantly different from that before error correction (0.069±0.010 mM; 95% CI: 0.066 to 0.072 mM) (p=0.011).

The P4 was able to improve the accuracy in the stratification of PCa grade assessed by quantitative DCE-MRI. Figure 5a shows three representative T2W images of the prostates bearing low, intermediate and high-grade tumors together with the matching $K^{\text{trans}}$ maps after P4-based error correction. The matching ADC maps also were included for comparison. The tumor region was indicated with a dotted circle in each subfigure, and the same color scale (0–0.8 min$^{-1}$) was applied for all $K^{\text{trans}}$ maps, while the same gray scale (0–1.2 × 10$^{-3}$ mm$^2$/s) was applied for all ADC maps. Figure 5b shows the box plots of tumor $K^{\text{trans}}$ with low grade (0.109±0.026 min$^{-1}$; 95% CI: 0.094 to 0.124 min$^{-1}$).
intermediate grade (0.163±0.049 min\(^{-1}\); 95% CI: 0.129 to 0.198 min\(^{-1}\)) and high grade (0.356±0.152 min\(^{-1}\); 95% CI: 0.215 to 0.497 min\(^{-1}\)), when the P4 was used for error correction. The \(K_{\text{trans}}\) of low-grade tumors was significantly lower than that of intermediate-grade tumors (\(p=0.002\)) or high-grade tumors (\(p<0.001\)), and the difference between intermediate and high-grade tumors was also statistically significant (\(p=0.002\)). However, no statistical difference was detected between Grade Groups 2 and 3 (\(p=0.630\)) or between Grade Groups 4 and 5 (\(p=0.529\)). Figure 5c shows the box plots of tumor \(K_{\text{trans}}\) before P4-based error correction. The tumor \(K_{\text{trans}}\) difference before and after P4-based error correction was up to 15%. Before error correction, the tumor \(K_{\text{trans}}\) with low, intermediate and high grade were 0.109±0.027 min\(^{-1}\) (95% CI: 0.093 to 0.125 min\(^{-1}\)), 0.159±0.054 min\(^{-1}\) (95% CI: 0.120 to 0.198 min\(^{-1}\)) and 0.351±0.180 min\(^{-1}\) (95% CI: 0.184 to 0.517 min\(^{-1}\)), respectively. The difference among the groups were also statistically significant, but the significance level was lower (low vs intermediate: \(p=0.007\); intermediate vs high: \(p=0.006\)). Figure 5d shows the box plots of tumor ADC values. The ADC values of low, intermediate and high-grade tumors were 0.877±0.164 (95% CI: 0.782 to 0.972), 0.741±0.138 (95% CI: 0.642 to 0.840), and 0.668±0.058 (95% CI: 0.614 to 0.722), respectively. Statistical significance was detected only between low and high-grade tumors (\(p\) value for statistical significance: <0.016 after Bonferroni correction). The sensitivity and specificity of \(K_{\text{trans}}\) value (cut-point: 0.14 min\(^{-1}\)) to detect clinically significant PCa were 88% and 93%, respectively, after P4 based error correction, while those before error correction were 88% and 86%, respectively. The sensitivity and specificity of apparent diffusion coefficient (cut-point: 0.82×10\(^{-3}\) mm\(^2\)/s) to identify the clinically significant PCa was 88% and 71%, respectively.

Table 1 shows the \(K_{\text{trans}}\) values of normal prostate tissues before and after P4-based error correction together with ADC values in comparison to PCa. Both \(K_{\text{trans}}\) and ADC values of normal prostate tissues in the peripheral zone were significantly different from those in the transition zone as well as those of low-grade PCa (GG1) (\(p\) value for statistical significance: <0.013 after Bonferroni correction). However, no statistical difference was found between normal prostate tissues in the transition zone and low-grade PCa. The \(K_{\text{trans}}\) and ADC values of clinically significant PCa (GG ≥2) were significantly different from those of normal prostate tissues regardless of the location.

**DISCUSSION**

We demonstrated that the P4 can be utilized in clinical mpMRI exams of the prostate to reduce errors in quantitative DCE-MRI measurement, leading to the improved stratification of PCa grade. Of note, the specificity to detect clinically significant PCa increased from 86% to 93% after P4-based error correction. High specificity for grade stratification is critical to determine optimal treatment for individual PCa patients. The P4 can be used in any commercially available MRI systems without the need for adjustment, as only a simple infusion of MRI contrast agent is necessary to trigger its function.

However, the low-grade PCa was not able to be differentiated from normal prostate tissues based on \(K_{\text{trans}}\) value in the transition zone even after P4-based error correction; this demonstrates the limitation of quantitative DCE-MRI for PCa diagnosis. Other imaging
modalities in mpMRI such as T2W MRI and DWI may assist quantitative DCE-MRI to
detect and demarcate the PCa. However, as shown in this study, the ADC of low-grade PCa
was not statistically different form that of normal prostate tissue in the transition zone either.
Therefore, for detecting low-grade PCa in the central gland, other clinical indicators such as
PSA level and Gleason score would play an important role.

In this study, the LUTs correlating the reference contrast enhancement curve with the
measured ones were nearly linear. If LUTs are linear, the error in quantitating $K_{\text{trans}}$ is
mainly induced by the variation of LUTs across different image slices when linear
pharmacokinetic models such as Tofts model (26) or extended Tofts model (19) are used.
The linearity of a LUT, however, is subject to change according to imaging sequences,
imaging parameters, magnetic field strength and MRI hardware configurations. For example,
the linearity of the LUTs was markedly different between two 3T MRI scanners in a
previous study (11). Besides, the linearity of LUTs obtained from a single MRI scanner
varied over time as well (see supplemental material 1). Of interest, the extent of the intra-
scanner variability was dependent upon the MRI scanners; the COV of LUTs retrieved from
a 3T MRI scanner was 43% in a previous study (12), which was 3.6-fold higher than that
from the one used in this study (see supplemental material 2). Hence, errors in other
scanners may be even larger. Thus, for accurate quantitative DCE-MRI measurement
(particularly in a multi-institutional study), the P4 (or an equivalent device) may need to be
used as an external reference.

The current version of P4 is reusable - it requires about 30 minutes for preparation before
use, and should be cleaned after use. However, as the P4 is made by a simple assembly of
inexpensive materials, it can be readily constructed as a disposable device to expedite
efficiency for MRI personnel. The disposable P4 mass-produced via injection molding will
significantly decrease the manufacturing costs and consequently enable its routine and
widespread clinical use.

There are a few limitations in the P4-based error correction approach for quantitative DCE-
MRI of the prostate. Frist, the field-of-view should be large enough to cover from the iliac
arteries to the P4s. So, for larger patients, the field-of-view may need to be increased,
resulting in the decrease of temporal and/or spatial resolutions. Second, the phantom
package should be prepared on the patient bed before a patient walks into the MRI room.
This will delay the entire MRI exam up to 5 minutes. Third, the image processing demands
heavy computation. In order to retrieve the pharmacokinetic parameters from DCE-MRI
images, eight steps of image processing were required in this study. Currently, it takes about
30 minutes to process the data of a human subject. For routine use in clinical practice, the
entire image processing will need to be completed ideally within 10 minutes and fully
automated to minimize the operator-dependent bias.

Other limitation of this study is the fact that most histopathologic data were collected from
the needle biopsy, which could be influenced by sampling error (27, 28). For more reliable
data comparison, the whole-specimen pathologic data of all human subjects should have
been collected from radical prostatectomy, which is considered the gold-standard of prostate
pathology (29). Second, the temporal resolution of DCE-MRI in this study, 10 seconds,
might not be high enough. Ideally, the temporal resolution of DCE-MRI should be 1~2 seconds (30), and if not, the AIF could be underestimated, resulting in the overestimation of $K^{\text{trans}}$ value. Temporal resolution can be increased by reducing spatial resolution and/or the number of image slices. Alternatively, fast MRI sequences like Compressed Sensing GRASP (31) or 3D Spiral GRAPPA (32) may accelerate the imaging speed, but these new techniques will need to be further validated for prostate exam in a multi-institutional setting. Third, although 44 patients were recruited in this study, not all of them had prostate cancer, leading to reduced sample size. The sample size of 31 allowed 80–85% measurement precision of sensitivity (or specificity) of $K^{\text{trans}}$ to identify clinically significant PCa (33). To achieve higher than 90% precision, the sample size will need to be larger than 70, assuming the sensitivity (or specificity) and the prevalence of clinically significant PCa are 90% and 50%, respectively. Lastly, this study was conducted using only one MR scanner. For broader adoption of the proposed approach, it would be necessary to validate it in multiple scanners manufactured by multiple vendors.

In conclusion, the P4 is a portable, inexpensive and easily operable device improving the accuracy in quantitative DCE-MRI measurement of PCa. Accurate grade stratification will lead to better treatment decision for PCa patients. Also, quantification of absolute pharmacokinetic parameters of PCa will potentially enable data comparison across different MR scanners and different institutes, facilitating collaboration for developing advanced treatments. However, an extended clinical trial will be necessary to confirm the clinical utility of the P4 prior to being adopted in routine mpMRI exams of the prostate.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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**ABBREVIATIONS AND ACRONYMS**

| Abbreviation | Definition                          |
|--------------|------------------------------------|
| ADC          | Apparent diffusion coefficient     |
| AIF          | Arterial input function            |
| ANOVA        | One-way analysis of variance       |
| CA           | Contrast agent                     |
| CEC          | Contrast enhancement curve         |
| CI           | Confidence interval                |
| COV          | Coefficient of variation            |
DCE-MRI  Dynamic contrast enhanced magnetic resonance imaging
GG  Grade group
GS  Gleason score
IQR  Interquartile range
K^{trans}  Volume transfer constant
LUT  Look-up tables
mpMRI  Multi-parametric MRI
MRI  Magnetic resonance imaging
P4  Point-of-care portable perfusion phantom
PCa  Prostate cancer
PSA  Prostate specific antigen
ROC  Receiver-operation characteristic
SD  Standard deviation
T1W  T1 weighted
T2W  T2 weighted

REFERENCES

1. Cancer Facts & Figures 2019. American Cancer Society
2. Kuronya Z, Biro K, Geczi L, Nemeth H. Treatment strategies for advanced prostate cancer. Magy Onkol. 2015; 59(3):229–40. [PubMed: 26339912]
3. Mazaheri Y, Akin O, Hricak H. Dynamic contrast-enhanced magnetic resonance imaging of prostate cancer: A review of current methods and applications. World J Radiol. 2017; 9(12):416–25. [PubMed: 29354207]
4. Barnes SL, Whisenant JG, Loveless ME, Yankeelov TE. Practical dynamic contrast enhanced MRI in small animal models of cancer: data acquisition, data analysis, and interpretation. Pharmaceutics. 2012; 4(3):442–78. [PubMed: 23105959]
5. Tan CH, Hobbs BP, Wei W, Kundra V. Dynamic contrast-enhanced MRI for the detection of prostate cancer: meta-analysis. AJR Am J Roentgenol. 2015; 204(4):W439–48. [PubMed: 25794093]
6. Yuan Q, Costa DN, Senegas J, et al. Quantitative diffusion-weighted imaging and dynamic contrast-enhanced characterization of the index lesion with multiparametric MRI in prostate cancer patients. J Magn Reson Imaging. 2017; 45(3):908–16. [PubMed: 27442039]
7. Alonzi R, Padhani AR, Taylor NJ, et al. Antivascular effects of neoadjuvant androgen deprivation for prostate cancer: an in vivo human study using susceptibility and relaxivity dynamic MRI. Int J Radiat Oncol Biol Phys. 2011; 80(3):721–7. [PubMed: 20630668]
8. Kim H Variability in Quantitative DCE-MRI: Sources and Solutions. J Nat Sci. 2018; 4(1).
9. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1. Eur Urol 2019; 76(3):340–51. [PubMed: 30898406]
10. Tamada T, Kido A, Takeuchi M, et al. Comparison of PI-RADS version 2 and PI-RADS version 2.1 for the detection of transition zone prostate cancer. Eur J Radiol. 2019; 121:108704. [PubMed: 31669798]

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11. Kim H, Mousa M, Schexnailder P, et al. Portable perfusion phantom for quantitative DCE-MRI of the abdomen. Med Phys. 2017; 44(10):5198–209. [PubMed: 28692137]

12. Kim H, Morgan DE, Schexnailder P, et al. Accurate Therapeutic Response Assessment of Pancreatic Ductal Adenocarcinoma Using Quantitative Dynamic Contrast-Enhanced Magnetic Resonance Imaging With a Point-of-Care Perfusion Phantom: A Pilot Study. Invest Radiol 2019; 54(1):16–22. [PubMed: 30138218]

13. Gordetsky J, Epstein J. Grading of prostatic adenocarcinoma: current state and prognostic implications. Diagn Pathol. 2016; 11:25. [PubMed: 26956509]

14. Chung S, Kim D, Breton E, Axel L. Rapid B1+ mapping using a preconditioning RF pulse with TurboFLASH readout. Magn Reson Med. 2010; 64(2):439–46. [PubMed: 20665788]

15. Liberman G, Louzoun Y, Ben Bashat D. T(1) mapping using variable flip angle SPGR data with flip angle correction. J Magn Reson Imaging. 2014; 40(1):171–80. [PubMed: 24909618]

16. Klein S, Staring M, Murphy K, Viergever MA, Pluim JP. elastix: a toolbox for intensity-based medical image registration. IEEE Trans Med Imaging. 2010; 29(1):196–205. [PubMed: 19923044]

17. Bokacheva L, Rusinek H, Chen Q, et al. Quantitative determination of Gd-DTPA concentration in T1-weighted MR renography studies. Magn Reson Med. 2007; 57:1012–8. [PubMed: 17534906]

18. Kim H Modification of population based arterial input function to incorporate individual variation. Magn Reson Imaging. 2018; 45:66–71. [PubMed: 28958876]

19. Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusible tracer: standardized quantities and symbols. J Magn Reson Imaging. 1999; 10(3):223–32. [PubMed: 10508281]

20. Barboriak DP. QIBA - Digital Reference Object for Profile DCE-MRI Analysis Software Verification 2 Available at: https://scholars.duke.edu/display/gra211722.

21. Neter J, Kutner MH, Nachtsheim JC, Wasserman W. Applied linear statistical models. Fourth ed. Columbus: The McGraw-Hill Companies, Inc.; 1996.

22. Bartlett JW, Frost C. Reliability, repeatability and reproducibility: analysis of measurement errors in continuous variables. Ultrasound Obstet Gynecol. 2008; 31(4):667–71. [PubMed: 18306169]

23. Fawcett T An introduction to ROC analysis. Pattern Recognition Letters. 2006; 27(8):861–74.

24. Liu A, Schisterman EF, Zhu Y. On linear combinations of biomarkers to improve diagnostic accuracy. Stat Med. 2005; 24(1):37–47. [PubMed: 15515132]

25. Wei C, Jin B, Szewczyk-Bieda M, et al. Quantitative parameters in dynamic contrast-enhanced magnetic resonance imaging for the detection and characterization of prostate cancer. Oncotarget. 2018; 9(22):15997–6007. [PubMed: 29662622]

26. Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. J Magn Reson Imaging. 1997; 7(1):91–101. [PubMed: 9039598]

27. Elfatairy KK, Filson CP, Sandra MG, Osunkoya AO, Geller RL, Nour SG. In-bore MRI-guided biopsy: can it optimize the need for periodic biopsies in prostate cancer patients undergoing active surveillance? A pilot test-retest reliability study. Br J Radiol 2018;20170603. [PubMed: 29308912]

28. Valerio M, Donaldson I, Emberton M, et al. Detection of Clinically Significant Prostate Cancer Using Magnetic Resonance Imaging-Ultrasound Fusion Targeted Biopsy: A Systematic Review. Eur Urol. 2015; 68(1):8–19. [PubMed: 25454618]

29. McGrath DM, Lee J, Foltz WD, et al. Technical Note: Method to correlate whole-specimen histopathology of radical prostatectomy with diagnostic MR imaging. Med Phys. 2016; 43(3):1065–72. [PubMed: 26936944]

30. Parker GJ, Roberts C, Macdonald A, et al. Experimentally-derived functional form for a population-averaged high-temporal-resolution arterial input function for dynamic contrast-enhanced MRI. Magn Reson Med. 2006; 56(5):993–1000. [PubMed: 17036301]

31. Chandarana H, Feng L, Block TK, et al. Free-breathing contrast-enhanced multiphase MRI of the liver using a combination of compressed sensing, parallel imaging, and golden-angle radial sampling. Invest Radiol. 2013; 48(1):10–6. [PubMed: 23192165]

32. Chen Y, Lee GR, Wright KL, et al. Free-breathing liver perfusion imaging using 3-dimensional through-time spiral generalised autocalibrating partially parallel acquisition acceleration. Invest Radiol. 2015; 50(6):367–75.
33. Hajian-Tilaki K Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform. 2014; 48:193–204. [PubMed: 24582925]
Figure 1.
Point-of-care portable perfusion phantom, P4. (a) A photograph of the P4, when a penny serves as a size reference. (b) The phantom package covering the triplicated P4 (P4\text{a}, P4\text{b} and P4\text{c}). The polyurethane foam (pink color) was used in the package for thermal insulation. (c) An illustration of a human subject lying on the top of the phantom package. Two leather cushions were used to match thickness with the package, and the fiberglass cushion was used to comfort the patient and to prevent heat transfer from the patient to the P4s. A phased array coil was placed around the prostate and the phantom package.
Figure 2.
Representative DCE-MRI images of a patient and three P4s. (a) DCE-MRI images of a patient bearing a prostate tumor (indicated with a dotted line and a white arrow) together with the triplicated P4 (P4\textsuperscript{a}, P4\textsuperscript{b}, P4\textsuperscript{c}) (indicated with three rectangles) before (baseline) and at 2 and 7 minutes after MR contrast agent (gadoteridol) injection. (b) Contrast agent concentration maps in the bottom chambers of three P4s at 2, 5, and 7 minutes after injecting contrast agent, when the same gray scale was applied (0–1 mM). (c) Contrast enhancement curves (CECs) of three P4s and the mean value. The inter-class correlation coefficient of the CECs was higher than 0.99.
Figure 3.
The P4 corrected errors over image slices in quantitating contrast agent concentration. (a) Contrast agent concentration maps of a representative human subject at the first, middle and last image slices at 5 minutes after injecting contrast agent before (upper row) and after (lower row) P4-based error correction, when the same color scale was applied (0–0.3 mM). (b) Contrast agent concentration in the gluteus maximum muscle indicated with red arrows in the Fig. 3a over 24 image slices before and after P4-based error correction. (c) Coefficient of variation (COV = SD/mean%) of contrast agent concentration measurement over 24 image slices in the gluteus maximum muscle before and after P4-based error correction with statistical difference ($p<0.001$).
Figure 4.
The P4 reduced intra-scanner variability in quantitating contrast agent concentration. (a) Look-up tables (LUTs) of the P4 at the center image slice obtained over different imaging time (n=44). (b) Contrast-agent concentration in the obturator muscles of 44 human subjects at the center image slice and 5 minutes after injecting contrast agent before and after P4-based error correction with statistical difference (p=0.011).
Figure 5.
Prostate cancer grade stratification using $K^{\text{trans}}$ and ADC. (a) T2 weighted images, $K^{\text{trans}}$ maps and ADC maps of the prostate with low-grade (Grade Group 1), intermediate-grade (Grade Group 2) and high-grade (Grade Group 5) tumors. Tumor boundary is indicated with a dotted circle in each subfigure. The same color scale (0–0.8 min$^{-1}$) was applied for $K^{\text{trans}}$ maps, and the same gray scale (0–1.2 × 10$^{-3}$ mm$^2$/s) was applied for ADC maps. (b) Tumor $K^{\text{trans}}$ after P4-based error correction with low (Grade Group 1: n=14), intermediate (Grade Group 2 or 3: n=10) and high grade (Grade Group 4 or 5: n=7). (c) Tumor $K^{\text{trans}}$ before P4-based error correction with low, intermediate and high grade. (d) ADC values of tumors with low, intermediate and high grade. The $p$ value for statistical significance was <0.016 after Bonferroni correction.
Comparison between normal prostate tissues and prostate tumors.

Mean±SD of $K_{\text{trans}}$ before and after P4-based error correction and ADC values of normal prostate tissues (PZ: Peripheral Zone, TZ: Transition Zone) and prostate cancer (GG1: Clinically non-significant (low grade) prostate cancer, GG ≥2: Clinically significant (intermediate or high grade) prostate cancer) together with 95% confidence interval within parenthesis. The $p$ value for statistical significance was <0.013 after Bonferroni correction.

| Normal Prostate Tissue | Prostate Tumor | Statistical Comparison (ANOVA) |
|------------------------|----------------|-------------------------------|
| **Mean±SD** | **Mean±SD** | **PZ vs TZ** | **PZ vs GG1** | **TZ vs GG1** | **PZ vs GG ≥2** | **TZ vs GG ≥2** | **GG1 vs GG ≥2** |
| **K_{\text{trans}}** (min$^{-1}$) |
| (after) | 0.073±0.024(0.066~0.081) | 0.0106±0.029(0.097~0.114) | 0.109±0.026(0.094~0.124) | 0.243±0.140(0.171~0.315) | $p<0.01$ | $p<0.01$ | $p=0.671$ | $p<0.01$ | $p<0.01$ | $p<0.01$ |
| (before) | 0.072±0.026(0.064~0.080) | 0.102±0.034(0.092~0.112) | 0.109±0.027(0.093~0.125) | 0.238±0.152(0.160~0.316) | $p<0.01$ | $p<0.01$ | $p=0.073$ | $p<0.01$ | $p<0.01$ | $p<0.01$ |
| **ADC** (x10$^{-3}$ mm$^2$/s) | 1.027±0.124(0.989~1.065) | 0.870±0.089(0.843~0.897) | 0.877±0.164(0.783~0.972) | 0.711±0.116(0.652~0.771) | $p<0.01$ | $p<0.01$ | $p=0.023$ | $p<0.01$ | $p<0.01$ | $p<0.01$ |