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Dynamic Contrast-Enhanced MRI of the Prostate: An Intraindividual Assessment of the Effect of Temporal Resolution on Qualitative Detection and Quantitative Analysis of Histopathologically Proven Prostate Cancer

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Abstract

Purpose—To assess the effects of temporal resolution (R_T) in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) on qualitative tumor detection and quantitative pharmacokinetic parameters in prostate cancer.

Materials and Methods—This retrospective Institutional Review Board (IRB)-approved study included 58 men (64 ± 7 years). They underwent 3T prostate MRI showing dominant peripheral zone (PZ) tumors (24 with Gleason 4 + 3), prior to prostatectomy. Continuously acquired DCE utilizing GRASP (Golden-angle RAdial Sparse Parallel) was retrospectively reconstructed at R_T of 1.4 sec, 3.7 sec, 6.0 sec, 9.7 sec, and 14.9 sec. A reader placed volumes-of-interest on dominant tumors and benign PZ, generating quantitative pharmacokinetic parameters (k^{trans} , v_e) at each R_T . Two blinded readers assessed each R_T for lesion presence, location, conspicuity, and reader confidence on a 5-point scale. Data were assessed by mixed-model analysis of variance (ANOVA), generalized estimating equation (GEE), and receiver operating characteristic (ROC) analysis.

Results— R_T did not affect sensitivity ($R1_{\text{all}}$: 69.0%–72.4%, all $P_{\text{adj}} = 1.000$; $R1_{\text{GS } 4+3}$: 83.3%–91.7%, all $P_{\text{adj}} = 1.000$; $R2_{\text{all}}$: 60.3%–69.0%, all $P_{\text{adj}} = 1.000$; $R2_{\text{GS } 4+3}$: 58.3%–79.2%, all $P_{\text{adj}} = 1.000$). $R1$ reported greater conspicuity of GS 4 + 3 tumors at R_T of 1.4 sec vs. 14.9 sec (4.29 ± 1.23 vs. 3.46 ± 1.44 ; $P_{\text{adj}} = 0.029$). No other tumor conspicuity pairwise comparison reached significance ($R1_{\text{all}}$: 2.98–3.43, all $P_{\text{adj}} = 0.205$; $R2_{\text{all}}$: 2.57–3.19, all $P_{\text{adj}} = 0.059$; $R1_{\text{GS } 4+3}$: 3.46–4.29, all other $P_{\text{adj}} = 0.156$; $R2_{\text{GS } 4+3}$: 2.92–3.71, all $P_{\text{adj}} = 0.439$). There was no effect of R_T on reader confidence ($R1_{\text{all}}$: 3.17–3.34, all $P_{\text{adj}} = 1.000$; $R2_{\text{all}}$: 2.83–3.19, all $P_{\text{adj}} = 0.801$;

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Disclosures

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$R1_{GS} 4+3$: 3.79–4.21, all $P_{adj} = 1.000$; $R2_{GS} 413$: 3.13–3.79, all $P_{adj} = 1.000$). k^{trans} and v_e of tumor and benign tissue did not differ across R_T (all adjusted P values [P_{adj}] = 1.000). R_T did not significantly affect area under the curve (AUC) of K^{trans} or v_e for differentiating tumor from benign (all $P_{adj} = 1.000$).

Conclusion—Current PI-RADS recommendations for R_T of 10 seconds may be sufficient, with further reduction to the stated PI-RADS preference of $R_T = 7$ seconds offering no benefit in tumor detection or quantitative analysis.

Along with diffusion-weighted imaging (DWI) and T_2 -weighted imaging, dynamic-contrast enhanced (DCE) magnetic resonance imaging (MRI) is one of the primary techniques used for tumor detection and characterization at prostate MRI.¹ Altered perfusion of prostate tumors is thought to be due to tumor angiogenesis, and both qualitative assessment of enhancement patterns as well as quantitative and semiquantitative parameters derived from DCE acquisitions have been shown to correlate histologically with markers of tumor angiogenesis, including vascular endothelial growth factor (VEGF) expression² and increased tumor microvessel density.^{2–4} Qualitatively, tumors within the peripheral zone show early and more intense enhancement relative to normal peripheral zone tissue.^{5–8} Quantitatively, pharmacokinetic parameters derived from DCE show significant differences between tumor and normal prostate tissue,^{7,9,10} and, in some studies, between high- and low-grade prostate tumors.^{11,12} Moreover, qualitative or quantitative assessment of DCE may improve the assessment of some peripheral zone (PZ) tumors compared with assessment based on DWI.^{13,14}

Until recently, there has been no clear consensus as to the temporal resolution (R_T) used for DCE acquisition, with a recent meta-analysis of DCE showing a wide range of R_T from 2–95 seconds.⁶ Insight into the optimal R_T is important given the inherent trade-off between R_T and spatial resolution for conventional DCE sequences.

In order to standardize scan acquisition parameters and reporting of prostate MRI, the American College of Radiology and European Society of Urogenital Radiology jointly developed the Prostate Imaging Reporting and Data System (PI-RADS) version 2.¹⁵ Current PI-RADS guidelines recommend a temporal resolution (R_T) for DCE acquisition of 10 seconds, with $R_T < 7$ seconds described as “preferred.”¹⁵ However, data on the optimal R_T for tumor detection and characterization is limited, predominantly reflecting simulations to assess theoretical effects of R_T upon quantitative analysis. Namely, based on the standard Tofts two-compartment model^{16,17} of tissue perfusion, Henderson et al¹⁸ used simulation data to propose an upper limit R_T of 16 seconds or faster for quantitative tissue analysis, while Heisen et al¹⁹ showed that R_T slower than 15 seconds leads to increasingly poor estimations of pharmacokinetic parameters. More recently, Othman et al²⁰ showed no significant effects of $R_T = 30$ seconds on quantitative pharmacokinetic parameters, although semiquantitative parameters had significantly poorer discrimination of lesions as R_T became longer, such that a temporal resolution of 10 seconds was proposed. However, that study lacked histopathologic correlation, solely differentiating between prostate lesions given a PI-RADS category 3 from those lesions given a PI-RADS category of >3 .

Perhaps more important than the above consideration, PI-RADS v2 has greatly simplified the process by which radiologists evaluate and interpret DCE. While PI-RADS v2 does recognize that some radiologists may choose to employ quantitative and semiquantitative analyses of DCE in their practice, the guidelines call for a simple qualitative visual assessment of early enhancement relative to the background peripheral zone as the single determining factor in categorizing detected lesions in a binary fashion in terms of the presence or absence of a DCE-abnormality. In this regard, although past studies have largely evaluated the effect of R_T on quantitative and semiquantitative parameters, the effect of varying R_T on the primary influencer of the PI-RADS assessment category for peripheral zone lesions—subjective reader detection of focal early enhancement of prostate tumors—remains unknown. Thus, the purpose of this study was to assess the effects of temporal resolution of DCE MRI on qualitative tumor detection and on quantitative pharmacokinetic parameters in prostate cancer.

Materials and Methods

Patients

This retrospective, Health Insurance Portability and Accountability Act (HIPAA)-compliant study was approved by our institution's Institutional Review Board, which waived the requirement for written informed consent. A total of 71 consecutive patients undergoing radical prostatectomy who had undergone preoperative prostate MRI utilizing the DCE sequence detailed below were assessed for inclusion into the study. Based on initial examination review (see below), 13 patients were excluded for the following reasons: dominant lesion in the transition zone ($n = 4$) (excluded given that studies have shown no clear benefit of DCE in transition zone [TZ] tumors^{21,22} and that PI-RADS v2 does not include DCE findings in determining the PI-RADS assessment category for TZ lesions¹⁵); marked PZ hemorrhage ($n = 4$) (excluded given potential impact of marked T_1 -hyperintensity on assessment of quantitative DCE metrics); lack of any DCE abnormality corresponding to the pathologically determined location of the dominant tumor during the initial unblinded case review prior to any formal qualitative or quantitative analysis ($n = 3$) (excluded given inability to perform region-of-interest [ROI]-based quantitative assessment of such tumors, as well as inability for readers to assess such lesions at any of the R_T under comparison; all had a dominant tumor Gleason score [GS] of 6); MRI performed on a 1.5T system ($n = 1$); and extensive patient motion ($n = 1$), leaving a final included cohort of 58 patients.

Mean patient age at the time of MRI was 64.6 ± 7.0 years (range 42.8–80.0 years); mean time interval between MRI and prostatectomy was 54 ± 52 days (range 2–217 days); and mean prostate-specific antigen (PSA) was 5.21 ± 78 (range 0.06–12.80). The dominant tumor had a GS of 3 + 4 in 34 patients (GS 3 + 3: $n = 10$; GS 3 + 4: $n = 24$), and a Gleason score 4 + 3 in 24 patients (GS 4 + 3: $n = 13$; GS 4 + 4: $n = 4$; GS 4 + 5: $n = 7$). Some patients from this study have been included in prior publications,^{23–28} all of which are unrelated to the current study.

Initial Examination Review and Histopathologic Correlation

All prostatectomy specimens underwent standard step-section histopathologic analysis. A genitourinary pathologist recorded on a standardized map of the prostate the location, size, and Gleason score, for all tumor foci. Two radiologists (J.M.R., an abdominal imaging fellowship trained radiologist with 2 years of prostate MRI experience and ~500 prostate MRI examinations reviewed; and A.B.R., an abdominal imaging fellowship-trained attending radiologist with 8 years of prostate MRI experience and greater than 2500 cases reviewed; neither participated in the subsequent blinded reader assessment) assessed examination prior to any qualitative or quantitative analysis by jointly reviewing the histopathologic maps in conjunction with obtained MRI sequences to localize the dominant lesion on the MRI based on standard anatomic landmarks, consistent with the approach for correlating lesions between MRI and prostatectomy findings in earlier studies.^{29,30} The dominant lesion was defined as the tumor focus having the highest Gleason score; if the highest Gleason score was shared by multiple tumor foci, then the larger such focus was selected. The reviewers recorded the following information regarding the center of the dominant lesion: zonal location (PZ or TZ), slice number on the DCE image set, position within the transverse plane (AP: anterior, posterior, or both; transverse: medial, lateral, or both). The presence of marked hemorrhage in the PZ (defined as encompassing 75% of the PZ volume based on visual assessment of precontrast T_1 -weighted fat-saturated images) was also noted.

MRI Acquisition and Reconstruction

Subjects underwent clinical prostate MRI on a 3T system (51 patients on Magnetom Trio, 6 patients on Magnetom Skyra, and 1 patient on Biograph mMR; Siemens Healthcare, Erlangen, Germany). Standard sequences of the prostate and seminal vesicles included turbo spin echo (TSE) T_2 -weighted images in axial, coronal, and sagittal planes, and axial DWI with apparent diffusion coefficient (ADC) maps.

DCE MRI was performed using the GRASP (Golden Angle RAdial Sparse Parallel)^{31,32} framework that utilizes continuously acquired small field-of-view (FOV) imaging through the prostate gland and seminal vesicles.³³ This acquisition employs continuous radial k -space filling with a “stack of stars” ordering scheme in order to allow flexible post-hoc reconstruction into different R_T following only a single acquisition and contrast injection,^{32,33} albeit with identical spatial resolution at each R_T . Scanning parameters for this acquisition included the following: total scan duration 5 minutes and 38 seconds; repetition time / echo time (TR/TE) 4.10/1.89 msec; 6/8 partial Fourier acquisition in the slice encoding direction; flip angle 12°; 3192 radial spokes; 24 slices at 3 mm slice thickness; FOV 240 × 240 mm; matrix 224 × 224; 3.0 × 1.1 × 1.1 mm voxel size. A weight-based dose of intravenous contrast (54 patients: 0.1 mmol/kg of gadobutrol [Gadavist, Bayer Schering Pharmaceuticals, Montville, NJ]; four patients: 0.1 mmol/kg of gadopentetate dimeglumine [Magnevist, Bayer Schering Pharmaceuticals]) injected at 3 cc/sec followed by a 20 cc normal saline flush was administered 20 seconds after the onset of the GRASP acquisition, such that the overall GRASP acquisition incorporated both precontrast and postcontrast timepoints.

Dynamic GRASP images were reconstructed from the continuous acquisition using the multicoil k-t SPARSE-SENSE method,^{34,35} which utilizes both parallel imaging principles and compressed sensing to take advantage of inherent data redundancy in order to achieve flexible retrospective reconstruction at variable R_T . For purposes of this study, the raw data were retrospectively reconstructed into five different R_T : 1.4 seconds, 3.7 seconds, 6.0 seconds, 9.7 seconds, and 14.9 seconds, a range which includes an R_T comparable to the lower range of reported R_T within the clinical prostate MRI literature of ~2 seconds³⁶ as well as the PI- RADS v2 recommendation of 10 seconds¹⁵ within its bounds. For $R_T < 10$ seconds, the precise number of radial spokes per dynamic timepoint was selected to be a different number within the Fibonacci series to ensure uniform k -space coverage under the stack-of-stars acquisition scheme (Table 1).³² At all R_T , each reconstructed timepoint was generated using serial nonoverlapping sets of consecutive radial spoke acquisitions, with no temporal sharing of spokes across timepoints.

Blinded Lesion Detection and Qualitative Assessment

Full DICOM datasets were generated for each R_T in each patient and loaded onto an offline DICOM image viewer (FireVoxel; <https://wp.nyu.edu/FireVoxel/>) which allowed manual 4-dimensional scrolling through each slice at each timepoint for all reconstructions. Readers 1 and 2 (R1: abdominal imaging fellowship-trained attending radiologist with 2 years of experience in prostate MRI and ~425 prostate MRI examinations reviewed; R2: body MRI fellow with 1 year experience in prostate MRI, with ~175 examinations reviewed) independently viewed each dataset in a random order, blinded to the R_T as well as to the location and Gleason score of the dominant tumor. Readers were aware that all patients had undergone prostatectomy and that patients with a dominant TZ tumor had been excluded from the investigation. A total of 290 DCE datasets (58 patients * 5 R_T per patient) were reviewed. Other clinical MRI sequences, including T_2 WI and DWI, were not available to the readers. Based on each individual DCE dataset, readers recorded the following: whether a dominant PZ lesion was visualized; the location of the identified dominant lesion; the conspicuity of the lesion using a 1–5-point scale (1 = not at all conspicuous; 5 = highly conspicuous); and reader confidence using a 1–5-point scale (1 = not at all confident; 5 = highly confident) based on the reader's confidence that the identified lesion represented a true DCE abnormality. The dominant lesion location was recorded in terms of the lesion's slice number, laterality, anterior/posterior position, and medial/lateral position within the transverse plane.

Quantitative Pharmacokinetic Analysis

A radiologist (J.M.R., previously involved in the initial unblinded examination review and identification of location of dominant tumors relative to histopathologic findings) placed 3D volumes of interest (VOIs) using in-house software package (FireVoxel, <https://wp.nyu.edu/FireVoxel/>) on DCE images for each patient as follows:

1. A whole-lesion VOI of the DCE abnormality corresponding with the dominant tumor location, as identified by the histopathologic map.
2. An equal-sized VOI in the contralateral PZ, placed at the same slice(s) of the prostate in an area confirmed to have no tumor based on the histopathologic map,

or on the nearest adjacent slice(s) if hemorrhage or a nondominant tumor was presented on the contralateral PZ at the same level as the dominant tumor (Fig. 1a).

3. The common femoral artery ipsilateral to the dominant tumor.

Mean ROI for both tumor and benign tissue was $0.96 \pm 1.21 \text{ cm}^3$. VOIs were initially drawn on the 3.7-second R_T reconstruction. A timepoint qualitatively showing strong differential enhancement between the dominant tumor and benign PZ tissue was selected in order to facilitate ROI placement. Within each patient, identical VOIs were transferred to the five different R_T reconstructions. Then, for each R_T , the VOIs were propagated across the dynamic series, and time–activity curves were generated for the dominant tumor, benign PZ, and the femoral artery. Individualized arterial input functions (AIFs) were generated for each R_T in each patient from the femoral artery VOI. A standard two-compartment model generalized kinetic model (GKM) of tissue perfusion^{16,17,37} was implemented using the individualized AIF, and the VOIs derived from the normal tissue and dominant tumor (Fig. 1). k^{trans} (the rate transfer constant of gadolinium between plasma and tissue interstitium) and v_e (the ratio of extracellular–extravascular volume to tissue volume), both of which have been shown to differ between prostate cancer and nonneoplastic prostate tissue,^{10,38} were calculated using the standard GKM as follows¹⁷:

$$dC_t/dt = K^{\text{trans}} * (C_p - C_t/v_e)$$

C_p (plasma gadolinium concentration) and C_t (tissue gadolinium concentration) were derived from signal intensity–time curves, assuming constant hematocrit of 0.45.³⁹

Gadolinium concentrations were derived from acquired signal intensity (SI) values assuming a linear relationship between SI and plasma gadolinium concentration.⁴⁰

Statistical Analysis

Readers' subjectively detected lesions were considered to be a true-positive relative to histopathology if within one slice of the tumor slice location derived from the histopathologic maps as well as having concordant anterior/posterior and medial/lateral designations, allowing for classification as either anterior or posterior or as either medial or lateral for lesions involving both regions, respectively, on histopathologic assessment.

Exact 95% confidence intervals were derived for sensitivity and positive predictive value (PPV) at each R_T . Logistic regression for correlated data was used to compare sessions in terms of the sensitivity and PPV for each reader. Specifically, generalized estimating equations (GEE) were used to model the sensitivity and PPV for each reader as a function of R_T . Post-hoc power analysis demonstrated 80% power to detect a difference of 15% in sensitivity for detection of tumor between R_T at the 5% comparison-wide significance level. Exact paired-sample Wilcoxon signed rank tests were used to compare R_T in terms of the conspicuity and confidence scores from each reader.

A mixed model two-way analysis of variance (ANOVA) with the patient as a blocking factor was used to compare the five R_T reconstructions in terms of the K^{trans} and v_e of dominant

tumors and benign tissue as well as the relative contrast (RC) of K^{trans} and v_e between tumor and benign tissue. For ANOVA, the error variance was allowed to differ among R_T to remove the assumption of variance homogeneity. The utility of K^{trans} and v_e at each R_T for discriminating tumor from benign tissue as well as for discriminating tumors with GS 3 + 4 from tumors with GS 4 + 3 was assessed in terms of the area under the receiver-operating-characteristic curve (AUC).

For GEE and ANOVA, the correlation structure was modeled by assuming results symmetrically correlated when derived for the same patient and independent otherwise. All statistical tests were initially conducted at the two-sided 5% significance level using SAS 9.3 (SAS Institute, Cary NC). The P values were then adjusted to correct for multiple comparisons using the method of Benjamini and Yekutieli, which lowers the risk of Type 1 error while maintaining statistical power to detect a true difference in comparison with other approaches for multiple comparison corrections.⁴¹ These adjustments reflected 10 possible pairwise comparisons among the five R_T and were performed using the R software environment (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org>).

Results

Lesion Detection and Qualitative Assessment

Table 2 presents sensitivity and PPV for both readers. Neither Reader 1 (range = 69.0–72.4%, all pairwise $P_{\text{adj}} = 1.000$) nor Reader 2 (range = 60.3–69.0%, all pair-wise $P_{\text{adj}} = 1.000$) showed significant differences in sensitivity for all 58 dominant tumors across all R_T . Similarly, neither Reader 1 (range = 77.8–82.0%, all pairwise $P_{\text{adj}} = 1.000$) nor Reader 2 (range = 67.3–80.0%, all pairwise $P_{\text{adj}} = 0.454$) showed a significant difference in PPV across all R_T .

For the sensitivity of the 24 GS 4 + 3 tumors, neither Reader 1 (range = 83.3–91.7%, all pairwise $P_{\text{adj}} = 1.000$) nor Reader 2 (range = 58.3–79.2%, all pairwise $P_{\text{adj}} = 0.718$) showed significantly different performance across all R_T . PPV for both Reader 1 (range = 87.0–94.7%, all pairwise $P_{\text{adj}} = 1.000$) and Reader 2 (range = 70.0–95.0%, all pairwise $P_{\text{adj}} = 0.315$) showed no significant difference across all R_T as well.

Table 3 presents readers' subjective assessment of lesion conspicuity and confidence in interpretation. For subjective ratings of lesion conspicuity among all 58 tumors, neither Reader 1 (range = 2.98–3.43, all pairwise $P_{\text{adj}} = 0.205$) nor Reader 2 (range = 2.57–3.19, all pairwise $P_{\text{adj}} = 0.059$) showed significant differences across all R_T . For the subset of 24 GS 4 + 3 tumors, Reader 1 reported increased conspicuity at the fastest R_T (1.4 sec) relative to the longest R_T (14.9 sec) with P_{adj} of 0.029. No other pairwise comparison for either Reader 1 (range = 3.46–4.29, all other pairwise $P_{\text{adj}} = 0.156$) or Reader 2 (range = 2.92–3.71, all pairwise $P_{\text{adj}} = 0.439$) was significant. Reader confidence did not significantly differ across R_T for all tumors (Reader 1 range = 3.17–3.34, all pairwise $P_{\text{adj}} = 1.000$; Reader 2 range = 2.83–3.19, all pairwise $P_{\text{adj}} = 0.801$) or for GS 4 + 3 tumors (Reader 1 range = 3.79–4.21, all pairwise $P_{\text{adj}} = 1.000$; Reader 2 range = 3.13–3.79, all pairwise $P_{\text{adj}} = 1.000$). Figure 2 provides a representative patient, showing a lesion at all R_T reconstructions.

Quantitative Pharmacokinetic Analysis

Table 4 summarizes data for K^{trans} and v_e across all R_T . There was no significant difference across all R_T in K^{trans} of benign tissue (range = 0.32–0.33; all pairwise $P_{\text{adj}} = 1.000$), v_e of benign tissue (range = 0.34–0.35; all pairwise $P_{\text{adj}} = 1.000$), K^{trans} of tumor (range = 0.88–0.97; all pair-wise $P_{\text{adj}} = 1.000$), or v_e of tumor (range = 0.39–0.41; all pairwise $P_{\text{adj}} = 1.000$).

AUC derived from ROC analysis are presented in Table 5. For differentiating benign tissue from tumor, AUC was not significantly different across all R_T or either K^{trans} (AUC range = 0.88–0.89; all pairwise $P_{\text{adj}} = 1.000$) or v_e (AUC range = 0.58–0.60; all pairwise $P_{\text{adj}} = 1.000$). Similarly, for differentiating GS 3 + 4 from GS 4 + 3 tumor, AUC was not significantly different across R_T for K^{trans} (AUC range = 0.68–0.69; all pairwise $P_{\text{adj}} = 1.000$) or v_e (AUC range = 0.59–0.61; all pairwise $P_{\text{adj}} = 1.000$).

Discussion

In this study we evaluated the potential impact effect of varying R_T during DCE MRI on both qualitative and quantitative assessment of prostate cancer. Within the studied range of R_T from 1.4–14.9 seconds, neither reader showed a significant difference in sensitivity, PPV, or confidence for all tumors or for the subset of high-grade (GS 4 + 3) tumors. The more experienced reader reported increased conspicuity of GS 4 + 3 tumors using the most rapid R_T (1.4 sec) relative to the slowest R_T (14.9 sec) within the examined R_T range, although actual sensitivity for detecting GS 4 + 3 tumors for this reader did not differ significantly. No other pairwise comparison of R_T showed significant differences in conspicuity for either all tumors or for GS 3 + 4 tumors. Finally, within the studied range, varying R_T had no significant effect upon quantitative perfusion parameters for benign tissue or prostate cancer, and there was no significant effect of R_T on the use of these quantitative parameters for differentiating benign from malignant tissue, or for differentiating tumors of varying grade.

Our findings suggest that the current PI-RADS v2 recommendation¹⁵ for an upper limit of 10 seconds for R_T during DCE-MRI acquisition in prostate MRI is sufficient, with the stated preference for further reduction of R_T to less than 7 seconds showing no significant benefit. In the current study, at all R_T less than 10 seconds (1.4–9.7 sec), neither lesion detection nor quantitative lesion assessment showed any significant difference with varying R_T . Increasing R_T to 14.9 seconds did not affect quantitative assessment of prostate tumors, nor did it affect sensitivity, although the difference in GS 4 + 3 tumor conspicuity for the more experienced reader at this longer R_T relative to the more rapid R_T suggests that there may be some subjective perceptual penalty for some readers when increasing R_T to close to 15 seconds, and suggest that the PI-RADS recommendation of $R_T \leq 10$ seconds may provide a good upper bound for R_T for DCE-MRI acquisitions. Our results complement those of Othman et al.²⁰ Similar to our findings, Othman et al reported no effect of varying R_T on quantitative pharmacokinetic parameters when comparing lesions judged to have a PI-RADS category 3 versus those lesions judged to have a PI-RADS category 4. However, their study observed significant worsening in semiquantitative parameters (wash-in and time-to-peak) for R_T greater than 10 seconds.

Based on our data, decreasing R_T further below 9.7 seconds does not appear to confer any benefit in tumor detection. Results from the current study do not support the stated preference in PI-RADS v2 for $R_T < 7$ seconds.¹⁵ Lowering R_T within that range did not cause a significant change in quantitative or qualitative tumor assessment. Given the costs of further reduction in R_T —a concomitant decrease in spatial resolution using conventional DCE sequences (in comparison with the novel continuously acquired DCE framework employed in our present study), increased processing time for quantitative analysis, and increased time in radiologist interpretation associated with the increased number of dynamic timepoints—further reduction in R_T is not warranted.

This study has several limitations. This was a retrospective study with a moderate sample size that was underpowered to demonstrate statistical significance of the observed small differences in sensitivity between R_T ; further studies with potentially much larger sample sizes would be required if wishing to demonstrate significance between a number of the investigated R_T . In addition, since the correlative histopathologic maps were derived from radical prostatectomy specimens, only patients with pathologically confirmed prostate cancer were included. Moreover, the exclusion of tumors without any corresponding DCE abnormality as well as readers' knowledge of the exclusion of patients with dominant TZ tumors would be expected to have biased their interpretations toward improved sensitivity for PZ tumor. However, such effects would be expected to be comparable across all R_T reconstructions and thus would be unlikely to impact our observations regarding comparisons among R_T . On the other hand, in this study, tumor detection was based solely on the presence of an abnormality on DCE sequences, whereas in typical clinical practice, T_2 WI and DWI are available for review and correlation at the time of DCE assessment. Tumor detection when using DCE alone would be expected to be poorer than when using all relevant sequences in combination,⁴² as reflected in the overall low sensitivity and PPV for lesions in our study. However, mitigating all of the above factors that may have impacted readers' performance (either favorably or unfavorably), is the consideration that the goal of this study was not to determine the diagnostic accuracy of DCE for prostate cancer detection, but rather to provide what may be deemed a "pure" assessment of the impact of R_T on the detection of DCE abnormalities in PZ tumors. For example, the presence of compelling correlative abnormalities on T_2 WI and DWI, had such sequences been available to the readers, may have biased the readers toward reporting lesions regardless of their actual confidence in the lesion on DCE itself, thereby hindering our evaluation of the impact of R_T on lesion detection.

Finally, given the fact that this study utilized a novel sequence that is not yet widely available, generalizability of these results to routine clinical practice may be called into question. In this study we used GRASP in the context of an experimental framework in order to assess the effects of R_T , which allowed flexible variation in temporal resolution within individual patients and lesions in a manner that would be nearly impossible with a standard DCE sequence, as it would require each patient to undergo multiple serial DCE scans with multiple separate intravenous contrast injections while introducing errors in registration and intraindividual variation across multiple scans. Additionally, the method utilized here achieves a baseline spatial resolution which does not vary with alterations in R_T , whereas the tradeoff between spatial and temporal resolution with traditional Cartesian

acquisitions⁴³ would necessitate decrements in spatial resolution in order to achieve similar reductions in temporal resolution. Although the use of compressed sensing and parallel imaging precludes the calculation of standard measures of image quality such as signal-to-noise ratio (SNR),^{44,45} the use of these techniques may mitigate some of the loss of true SNR experienced when reducing acquisition time for improved temporal resolution. Thus, GRASP provides us with an idealized framework in which to isolate the effects of temporal resolution on detection and quantitative assessment of prostate tumors. Although the actual acquisition method may not be widely available, the results obtained from this framework should be widely applicable to clinical practice—if R_T reduction below 10 seconds in this idealized framework offers no benefit for tumor detection, it is highly unlikely that a similar reduction using standard Cartesian acquisitions (with the consequent reduced spatial resolution) would offer any benefit.

In conclusion, this study using a novel DCE sequence allowing flexible retrospective reconstruction at varying R_T showed no benefit in terms of qualitative lesion detection or quantitative pharmacokinetic analysis in prostate cancer when decreasing the R_T below 10 seconds. The findings support the current PI-RADS v2 recommendation of 10 seconds for R_T during DCE-MRI acquisition, with no benefit to further reduction below this level. Thus, the theoretical advantages of faster R_T must be weighed against the inherent trade-off in terms of spatial resolution that is encountered when using conventional DCE sequences.

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FIGURE 1.

A 66-year-old man with Gleason score 3+4 tumor in the right midgland peripheral zone at prostatectomy. **(a)** Axial DCE-MRI image performed using the GRASP technique with retrospective 13 radial spoke reconstruction, providing a 1.4-second temporal resolution (R_T). Image reflects an early postinjection reconstructed timepoint and shows nodular asymmetric early enhancement in the right posterior peripheral zone (white arrow) corresponding to the dominant tumor on histopathologic assessment. **(b)** Partial volume-of-interest (VOI) placed on tumor (red) and contralateral benign peripheral zone tissue (blue).

(c–g) Normalized signal intensity curves of the arterial input function (AIF), tumor and of benign prostate tissue at R_T of (c) 1.4 seconds, (d) 3.7 seconds, (e) 6.0 seconds, (f) 9.7 seconds, and (g) 14.9 seconds. Intravenous contrast injection began 20 seconds after the onset of DCE acquisition.

FIGURE 2.

A 65-year-old man with Gleason score 4+5 tumor in the right apical peripheral zone at prostatectomy. (a) Axial DCE-MRI image performed using the GRASP technique. Image is at the level of the tumor and reflects the earliest timepoint from the 1.4-second temporal resolution (R_T) reconstruction, prior to contrast injection. (b–f) Axial GRASP images at the same level at the timepoint of tumor wash-in shows asymmetric nodular enhancement (white arrows) in the right posterior peripheral zone corresponding to the dominant tumor at R_T of (b) 1.4 seconds, (c) 3.7 seconds, (d) 6.0 seconds, (e) 9.7 seconds, and (f) 14.9 seconds. The

lesion was detected at all R_T by both readers, with identical conspicuity (five at all R_T for Reader 1 and Reader 2) and confidence (five at all R_T for Reader 1 and Reader 2) across R_T

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TABLE 1Reconstruction Parameters for Each Generated Temporal Resolution (R_T)

R_T	Number of radial k-space spokes per dynamic time point	Total number of dynamic time points	Total number of images (slices * time points)
1.4 sec	13	248	5,952
3.7 sec	34	95	2,280
6.0 sec	55	59	1,416
9.7 sec	89	36	864
14.9 sec	137	23	552

TABLE 2

Sensitivity and Positive Predictive Value (PPV) for Lesion Detection for All Tumors and for Gleason Score (GS) 4 + 3 Tumors for Reader 1 and Reader 2 at Each Temporal Resolution (R_T), With Pairwise Comparisons

R _T	Reader	1.4 sec			3.7 sec			6.0 sec			9.7 sec			14.9 sec		
		RI	R2		RI	R2		RI	R2		RI	R2		RI	R2	
All tumors (N = 58)	Sensitivity	70.7% (41/58)	67.2% (39/58)	69.0% (40/58)	60.3% (35/58)	60.3% (40/58)	70.7% (41/58)	69.0% (40/58)	60.3% (35/58)	72.4% (42/58)	60.3% (35/58)	60.3% (42/58)	69.0% (40/58)	69.0% (40/58)	69.0% (40/58)	69.0% (40/58)
	Positive predictive value	82.0% (41/50)	78.0% (39/50)	78.4% (40/51)	68.6% (35/51)	82.0% (41/50)	80.0% (40/50)	77.8% (42/54)	67.3% (35/52)	78.4% (40/51)	74.1% (40/54)					
	Pairwise comparison adjusted <i>P</i> values															
	1.4 sec Sensitivity	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	PPV	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.454	1.00	1.00	1.00	1.00
3.7 sec	Sensitivity															
	PPV															
	1.4 sec Sensitivity															
	PPV															
6.0 sec	Sensitivity															
	PPV															
	1.4 sec Sensitivity															
	PPV															
9.7 sec	Sensitivity															
	PPV															
	1.4 sec Sensitivity															
	PPV															
Gleason 4 + 3 tumors (N = 24)	Sensitivity	91.7% (22/24)	79.2% (19/24)	83.3% (20/24)	58.3% (14/24)	83.3% (20/24)	83.3% (20/24)	75.0% (18/24)	83.3% (20/24)	83.3% (20/24)	70.8% (17/24)	83.3% (20/24)	83.3% (20/24)	83.3% (20/24)	83.3% (20/24)	83.3% (20/24)
	Positive predictive value	95.7% (22/23)	95.0% (19/20)	95.2% (20/21)	70.0% (14/20)	90.9% (20/22)	90.0% (18/20)	87.0% (20/23)	77.3% (17/22)	87.0% (20/23)	77.3% (17/22)	77.3% (17/22)	77.3% (17/22)	77.3% (17/22)	77.3% (17/22)	77.3% (17/22)
	Pairwise comparison adjusted <i>P</i> values															
	1.4 sec Sensitivity															
	PPV															

R _T	Reader	1.4 sec		3.7 sec		6.0 sec		9.7 sec		14.9 sec	
		R1	R2	R1	R2	R1	R2	R1	R2	R1	R2
3.7 sec	PPV			1.00	0.351	1.00	0.770	1.00	0.351	1.00	0.351
	Sensitivity					1.00	0.718	1.00	1.00	1.00	1.00
6.0 sec	PPV					1.00	0.351	1.00	1.00	1.00	1.00
	Sensitivity							1.00	1.00	1.00	1.00
9.7 sec	PPV							1.00	0.513	1.00	0.513
	Sensitivity									1.00	1.00
PPV										1.00	1.00

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For sensitivity, percentage of lesions detected is presented, with absolute number in parentheses beneath the percentages (total N of 58 for all tumors and 24 for GS 4 + 3 tumors. *P* values are reported using Benjamini-Yekutieli adjusted *P* values. No pairwise comparison reached the significance threshold (*P*_{adj} 0.05).

Lesion Conspicuity and Confidence Ratings for Reader 1 and Reader 2 at Each Temporal Resolution (R_T) for All Tumors and for Gleason Score (GS) + 3 Tumors at Each Temporal Resolution (R_T), With Pairwise Comparisons

R_T	Reader	1.4 sec		3.7 sec		6.0 sec		9.7 sec		14.9 sec	
		RI	R2	RI	R2	RI	R2	RI	R2	RI	R2
All tumors (N = 58)	Lesion conspicuity	3.43 ± 1.73	3.19 ± 1.81	3.16 ± 1.70	2.86 ± 1.83	3.28 ± 1.65	3.00 ± 1.72	3.21 ± 1.63	2.57 ± 1.53	2.98 ± 1.57	2.60 ± 1.46
	Confidence	3.34 ± 1.69	3.19 ± 1.78	3.26 ± 1.72	2.86 ± 1.83	3.28 ± 1.67	3.16 ± 1.80	3.33 ± 1.70	2.83 ± 1.70	3.17 ± 1.69	2.90 ± 1.67
Pairwise comparison adjusted <i>P</i> values											
1.4 sec	Conspicuity			0.615		1.000		1.000		0.205	0.059
	Confidence			1.000		1.000		1.000		1.000	0.801
3.7 sec	Conspicuity					1.000		1.000		1.000	0.805
	Confidence					1.000		1.000		1.000	1.000
6.0 sec	Conspicuity							1.000		1.000	0.146
	Confidence							1.000		1.000	0.801
9.7 sec	Conspicuity									0.947	1.000
	Confidence									1.000	1.000
GS 4 + 3 tumors (N=24)	Lesion conspicuity	4.29 ± 1.23	3.71 ± 1.76	3.79 ± 1.59	3.13 ± 2.01	3.75 ± 1.54	3.54 ± 1.77	3.71 ± 1.76	3.13 ± 1.68	3.46 ± 1.44	2.92 ± 1.69
	Confidence	4.21 ± 1.28	3.67 ± 1.74	3.92 ± 1.56	3.13 ± 2.01	3.79 ± 1.53	3.79 ± 1.84	3.92 ± 1.59	3.33 ± 1.79	3.79 ± 1.50	3.29 ± 1.81
Pairwise comparison adjusted <i>P</i> values											
1.4 sec	Conspicuity			0.156		1.000		0.403		0.029*	0.439
	Confidence			1.000		1.000		1.000		1.000	1.000
3.7 sec	Conspicuity					1.000		1.000		1.000	1.000
	Confidence					1.000		1.000		1.000	1.000

R_T	Reader	1.4 sec		3.7 sec		6.0 sec		9.7 sec		14.9 sec	
		RI	R2	RI	R2	RI	R2	RI	R2	RI	R2
6.0 sec	Confidence					1.000	1.000	1.000	1.000	1.000	1.000
	Conspicuity						1.000	1.000	1.000	1.000	0.498
9.7 sec	Confidence							1.000	1.000	1.000	1.000
	Conspicuity								1.000	1.000	1.000
	Confidence									1.000	1.000
	Conspicuity										1.000

Both lesion conspicuity and confidence were rated on a 1–5 scale and are presented as mean ± standard deviation. *P* values are reported using Benjamini-Yekutieli adjusted *P* values.

* Statistically significant pairwise comparison (padj = 0.05).

TABLE 4

Mean ($\pm$ Standard Deviation) k^{trans} and v_e Values for Benign Prostate Tissue and Dominant Tumor Across Five Different Temporal Resolutions (R_T)

R_T	k^{trans}		V_e	
	Benign prostate	Tumor	Benign prostate	Tumor
1.4 sec	0.33 $\pm$.24	0.97 $\pm$.66	0.35 $\pm$.12	0.40 $\pm$.16
3.7 sec	0.33 $\pm$.26	0.99 $\pm$.69	0.35 $\pm$.13	0.41 $\pm$.16
6.0 sec	0.33 $\pm$.27	0.94 $\pm$.65	0.35 $\pm$.13	0.40 $\pm$.16
9.7 sec	0.33 $\pm$.29	0.93 $\pm$.68	0.34 $\pm$.13	0.40 $\pm$.16
14.9 sec	0.32 $\pm$.28	0.88 $\pm$.64	0.34 $\pm$.13	0.39 $\pm$.16

k^{trans} = volume transfer coefficient between plasma and tissue interstitium (min^{-1}); v_e = ratio of extracellular-extravascular volume to tissue volume (unitless).

TABLE 5

Receiver Operating Characteristic (ROC) Analysis Across All Temporal Resolutions (R_T) for Using k^{trans} and v_e to Differentiate Benign Prostate Tissue From Tumor, and to Differentiate Gleason Score (GS) 3 + 4 From GS 4 + 3 Tumors

R_T	k^{trans} AUC		v_e AUC	
	Benign tissue vs. tumor	GS 3 + 4 vs. GS 4 + 3 tumor	Benign tissue vs. tumor	GS 3 + 4 vs. GS 4 + 3 tumor
1.4 sec	0.88 (0.80–0.93)	0.69 (0.55–0.80)	0.59 (0.49–0.67)	0.59 (0.45–0.72)
3.7 sec	0.89 (0.81–0.93)	0.68 (0.54–0.79)	0.60 (0.50–0.68)	0.59 (0.45–0.72)
6.0 sec	0.88 (0.80–0.93)	0.69 (0.55–0.80)	0.59 (0.49–0.67)	0.60 (0.46–0.73)
9.7 sec	0.88 (0.80–0.93)	0.68 (0.54–0.79)	0.59 (0.49–0.67)	0.60 (0.46–0.73)
14.9 sec	0.89 (0.81–0.93)	0.69 (0.55–0.81)	0.58 (0.48–0.67)	0.61 (0.47–0.73)

R_T = AUC = area under the curve, reported as AUC with 95% confidence interval in parentheses; k^{trans} = volume transfer coefficient between plasma and tissue interstitium; v_e = ratio of extracellular-extravascular volume to tissue volume.