Objective: The aim of this study was to evaluate the effect of sampling duration on pharmacokinetic parameters from dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) and their diagnostic accuracy regarding the detection of potentially malignant prostate lesions.

Materials and Methods: Sixty-six consecutive male patients (mean [SD] age, 65.4 [10.8] years) with clinically suspected prostate cancer were included. All patients underwent multiparametric MRI of the prostate (T2-weighted imaging, diffusion-weighted imaging, and DCE-MRI) on a 3 T MRI scanner. Patients were divided into 2 groups depending on the prostate imaging and data system (PI-RADS) score of the detected lesions (group A: PI-RADS 53, n = 32; group B: PI-RADS >3, n = 34). In all patients, DCE-MRI was performed using a CAIPIRINA-Dixon-TWIST volume interpolated breath-hold examination sequence (spatial resolution, 3 × 1.2 × 1.2 mm; temporal resolution, 5 seconds; total sampling duration, 4-10 minutes [250 seconds]) with body weight–adapted administration of contrast agent (gadobutrol, Bayer Healthcare, Berlin, Germany). Five DCE-MRI series with different acquisition durations ranging from 50 to 250 seconds were retrospectively generated from the original data sets. Pharmacokinetic parameters (ie, $K_{\text{trans}}$, $K_{\text{ep}}$, Ve, and iAUC60) were calculated for the different sampling durations using the Tofts model. Both lesion groups and all 5 DCE-MRI series were compared regarding pharmacokinetic parameters. Diagnostic accuracy for the detection of potentially malignant lesions was calculated for all 5 series using receiver operating characteristic analysis.

Results: For all 5 series, $K_{\text{trans}}$, $K_{\text{ep}}$, and iAUC60 in patient group B were significantly higher than the respective parameters in patient group A (all $P \leq 0.008$). In both groups, $K_{\text{trans}}$, $K_{\text{ep}}$, and iAUC60 remained constant at 200 and 150 seconds acquisition duration and did not significantly differ from parameters estimated from the original data sets (250 seconds; all $P \geq 0.310$). Ve did not differ significantly between the 2 groups ($P \geq 0.337$) and acquisition time did not have a significant effect on this parameter ($P \geq 0.275$). Receiver operating characteristic analyses showed consistent diagnostic accuracy for the different series; only diagnostic accuracy of $K_{\text{trans}}$ decreased with lowered sampling duration, showing lowest accuracy for the 50-second series (0.682; 95% confidence interval, 0.553–0.811).

Conclusions: Using fast optimized DCE-MRI of the prostate, a minimum sampling duration of 150 seconds is required for sufficient pharmacokinetic parameter estimates, providing a high diagnostic accuracy regarding the discrimination between benign and potentially malignant lesions.

Key Words: magnetic resonance imaging, dynamic imaging, DCE-MRI, CDT-VIBE, prostate, prostate cancer, sampling duration

Magnetic resonance imaging (MRI) of the prostate is a widely used and accurate diagnostic tool for the identification and localization of prostate tumors. Typically, multiparametric MRI consisting of T2-weighted sequences, diffusion-weighted imaging, and dynamic contrast-enhanced (DCE) MRI is performed. Prostate cancer, like many other tumors, is characterized by a more pronounced contrast enhancement than normal prostate tissue, which has been related to tumor angiogenesis. Characteristic findings of DCE-MRI in prostate cancer are an earlier and faster enhancement (wash-in) and an earlier wash-out of the contrast agent compared with normal prostate tissue. There are 3 different approaches for the assessment of DCE-MRI: a qualitative, semiquantitative, and quantitative approach, with the quantitative assessment being the most objective method. Quantitative assessment methods provide direct information about vascular pharmacokinetic features such as vascular permeability, volume, and perfusion of the extravascular/extracellular space (EES). For assessment of pharmacokinetic parameters in DCE-MRI, both high temporal and high spatial resolution are mandatory. International working groups recently stressed the importance of a high temporal resolution for DCE-MRI of the prostate and recommended a temporal resolution of less than 10 seconds for characterization of prostatic vascular pharmacokinetic features. Overall, a sampling duration of 5 to 10 minutes is recommended. Concerning the appropriate temporal resolution, 10 to 15 seconds per time point has been proposed as minimum requirement for DCE-MRI of the prostate, whereas a temporal resolution of 5 seconds per time point and a total sampling duration of 5 minutes have been discussed as optimal requirements in addition to a high temporal resolution. However, no dedicated studies have systematically assessed the effect of sampling duration on DCE-MRI of the prostate. Recent developments enabled the acquisition of dynamic MRI images with both high temporal and spatial resolution. Long sampling durations in DCE-MRI frequently cause motion artifacts, which are a major source of error. On the other hand, short sampling durations may lead to insufficient estimation of perfusion parameter. To reduce motion artifacts and maintain reliable parameter estimates, it is of high importance to identify the minimum total sampling duration required for sufficient and exact perfusion estimates in prostate lesions.

In this study, we aimed to evaluate the minimum sampling duration required for the generation of reliable perfusion estimates from fast optimized DCE-MRI in patients with suspected prostate cancer. We therefore utilized a novel CAIPIRINA-Dixon-TWIST volume interpolated breath-hold examination (CDT-VIBE), a dynamic MR angiography sequence, which has been recently presented for dynamic imaging of the abdomen and the breast, providing a high spatial and temporal resolution.

MATERIALS AND METHODS

Patients

In this study, the institutional review board waived the requirement of informed patient consent. From August 2014 to April 2015, 84 consecutive patients with elevated prostate-specific antigen levels and suspicious or inconclusive findings on transrectal ultrasonography...
 Patients were then divided into 2 groups, depending on lesion's PI-RADS scores (group A: PI-RADS ≤3; group B: PI-RADS >3).

were referred for multimodal prostate MRI. Of those 84 patients, 18 were excluded because of small lesion size (maximum diameter, <0.5 cm; 12 patients) and negative MRI findings (6 patients), resulting in a final sample size of 66 patients (age, 65.4 [10.8] years; prostate-specific antigen, 6.24 [2.32] μg/L). Two radiologists rated the likelihood of malignancy of detected lesions on multiparametric MRI using the American College of Radiology prostate imaging reporting and data system (PI-RADS) Version 2, that is, applying a 5-point rating scale for the likelihood of tumor presence (1, highly unlikely; 2, unlikely; 3, equivocal; 4, likely; 5, highly likely). Patients were then divided into 2 groups, depending on PI-RADS score of the detected lesions (group A: PI-RADS ≤3; group B: PI-RADS >3). This procedure is shown in Figure 1.

Data Acquisition

Magnetic resonance imaging examinations were performed on a 48-channel 3 T scanner (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany) using a 30-channel coil setup (18-channel body coil + 12 channels from the spine coil) with patients in supine position. Prostate MRI, consisting of T2-w Turbo Spin Echo (TSE) (refocusing coil + 12 channels from the spine coil) with patients in supine position.

Dynamic contrast-enhanced MRI was acquired using a prototyp-

FIGURE 1. Flowchart of patient inclusion and assignment into both groups, depending on lesion's PI-RADS scores (group A: PI-RADS ≤3; group B: PI-RADS >3).

Perfusion Data Analysis

To examine the effect of sampling duration on pharmacokinetic parameters, we retrospectively generated 5 DCE-MRI series from the original data sets with different durations (10 phases, 50 seconds' duration; 20 phases, 100 seconds' duration; 30 phases, 150 seconds' duration; 40 phases, 200 seconds' duration; 50 phases, 250 seconds' duration).

Pharmacokinetic perfusion analyses for the 5 DCE-MRI series were performed using a dedicated postprocessing software (MR Tissue 4D, Syngo.via; Siemens Healthcare; Erlangen, Germany) with “soft” constraints (ie, values exceeding the respective limit are penalized in the cost function; limits: Ve_max = 1.0, Kep_max = 4000, Ktrans_max = 4.0). T2-weighted images were used for defining regions of interest (ROIs). As recommended by Braunagel et al, the ROIs were set covering the prostate lesions on T2-weighted images and saved as templates. After automated motion correction was performed, time intensity curves were calculated in all 5 DCE-MRI series for all ROIs. Pharmacokinetic parameters (ie, influx volume transfer constant from plasma to EES [Ktrans], efflux rate constant from EES to the plasma [Kep], EES volume fraction [Ve], initial area under the curve [iAUC60]) were obtained using a Tofts model and a population average arterial input function as provided in Tissue 4D. A flow chart of the perfusion data acquisition and analysis is given in Figure 2.

Statistical Analyses

Statistical analyses were performed using SPSS version 20 (IBM Corp, Armonk, NY). Student t tests were performed to assess differences of pharmacokinetic parameters between both groups. For each group, repeated measures (rm) analysis of variance (ANOVA) with “series” as rm-factor were conducted to compare pharmacokinetic parameters from the 5 different DCE-MRI series. Multiple comparisons were accounted for using Bonferroni correction. Results were considered significant at $P < 0.05$. Receiver operating characteristic (ROC) curve analysis with areas under the curve (AUCs) and the corresponding 95% confidence intervals were calculated using MedCalc (Medcalc Soft, Belgium).

FIGURE 2. Flowchart of data acquisition and parameter estimation.
intervals (95% CIs) were used for assessment of diagnostic accuracy of the different series for the differentiation between likely benign (ie, PI-RADS 1–3) and likely malignant lesions (ie, PI-RADS 4–5).

RESULTS

Patients

Lesions with low likelihood of malignancy (ie, PI-RADS ≤3) were found in 32 patients (group A). Lesions with high likelihood of malignancy (ie, PI-RADS >3) were identified in 34 patients (group B). From 22 of the 34 patients with a PI-RADS score of more than 3 (group B), biopsy results were available, confirming the malignancy of the lesions. In 12 of the 34 patients with suspected malignant lesions (group B) and in all 32 patients with PI-RADS ≤3 (group A), biopsy results were not available.

Effect of Sampling Duration on Pharmacokinetic Parameters

An example of enhancement curves from the different series is given in Figure 3. Descriptive values (means and standard deviations) of the pharmacokinetic parameters $K_{\text{trans}}$, $K_{\text{ep}}$, $V_e$, and $i\text{AUC}_60$ are shown in Table 1. $K_{\text{trans}}$ and $K_{\text{ep}}$ were lowest in the original data sets with 250 seconds sampling duration and highest in the 50-second series ($K_{\text{trans}}$ 0.13 vs 0.18 for group A and 0.26 vs 0.25 for group B; $K_{\text{ep}}$ 0.53 vs 1.60 for group A and 1.08 vs 2.26 for group B). In both groups, $i\text{AUC}_60$ was highest for the original series and lowest in the 50-second series ($i\text{AUC}_60$ 9.2 vs 5.0 for group A and 15.9 vs 8.9 for group B).

Student $t$ tests revealed significant differences between the 2 groups regarding the pharmacokinetic parameters $K_{\text{trans}}$, $K_{\text{ep}}$, and $i\text{AUC}_60$ for all 5 series with significantly higher values in group B (all $P \leq 0.008$; see Table 1). For $V_e$, no significant differences were found between the 2 groups in any of the series (all $P \geq 0.337$; see Table 1).

For group A, rm-ANOVAs revealed the following results: the effect of sampling duration on $K_{\text{trans}}$ was significant ($F_{1,31} = 12.5$, $P < 0.001$); post hoc comparisons revealed significant differences between 50 seconds and every other sampling duration (all $P < 0.001$) as well as between 100 and 250 seconds ($P < 0.001$). Similar patterns were found for $K_{\text{ep}}$ and $i\text{AUC}_60$: rm-ANOVA revealed a significant effect of sampling duration on $K_{\text{ep}}$ ($F_{1,31} = 47.7$, $P < 0.001$). In this case, post hoc comparisons also confirmed significant differences between

FIGURE 3. A 77-year-old patient with potentially malignant lesion in the left peripheral zone of the prostate (red arrows), presenting with low T2 signal, bulging of the organ capsule, diffusion restriction on ADC map, and typical DCE-MRI pattern (early wash-in and wash-out). Lesion was classified as PI-RADS IV. Perfusion enhancement curves from original data sets with sampling durations ranging between 50 and 250 seconds were generated. Note that the wash-out of the lesion is first clearly seen using the 150 seconds data sets. Figure 3 can be viewed online in color at www.investigativeradiology.com.
50 seconds and every other sampling duration (all \( P < 0.001 \)) as well as significant differences between 100 and 150 seconds (\( P < 0.001 \)) and between 100 and 250 seconds (\( P < 0.001 \)). Likewise, the rm-ANOVA showed a significant effect of sampling duration on iAUC60 (\( F_{1,31} = 195.4, P < 0.001 \)). Significant differences were confirmed between 50 seconds and every other sampling duration (all \( P < 0.001 \)), between 100 and 150 seconds (\( P = 0.047 \)), and between 100 and 200 seconds (\( P < 0.001 \)).

For group B, rm-ANOVA revealed the following similar results pattern: the effect of sampling duration on \( K_{\text{trans}} \) was significant (\( F_{1,33} = 11.4, P < 0.001 \)); post hoc comparisons revealed significant differences between 50 seconds and every other sampling duration (all \( P < 0.023 \)). Repeated measures ANOVA revealed a significant effect of sampling duration on \( K_{\text{ep}} \) (\( F_{1,33} = 38.2, P < 0.001 \)). In this case, post hoc comparisons also confirmed significant differences between 50 seconds and every other sampling duration (all \( P < 0.001 \)) as well as a significant difference between 100 and 150 seconds (\( P = 0.004 \)).

Likewise, rm-ANOVA showed a significant effect of sampling duration on iAUC60 (\( F_{1,33} = 75.5, P < 0.001 \)). Significant differences were confirmed between 50 seconds and every other sampling duration (all \( P < 0.001 \)).

For both groups, rm-ANOVA revealed no significant effect of sampling duration on \( V_e \) (group A: \( F_{1,31} = 1.3, P = 0.275 \); group B: \( F_{1,33} = 0.2, P = 0.930 \)). Detailed results of all post hoc comparisons are given in Table 2.

### ROC Analyses

The AUC and the corresponding 95% CIs of all pharmacokinetic parameters for the different sampling durations are given in Table 3. The ROC curves are depicted in Figure 4. For \( K_{\text{trans}}, V_e, \) and iAUC60, diagnostic accuracy did not differ significantly between the different sampling durations due to an overlap of the corresponding 95% CIs. In contrast, diagnostic accuracy of \( K_{\text{ep}} \) decreased with lowered sampling duration, showing lowest accuracy for the 50-second series (0.682; 95% CI, 0.553–0.811), which was significantly lower than diagnostic accuracy of 150-, 200-, and 250-second series. Optimal thresholds for discrimination between both groups differed between the different series with greater differences for the 50- and 100-second series (Fig. 5).

### DISCUSSION

In this study, we aimed to assess the effect of sampling duration on pharmacokinetic parameters from DCE-MRI and to identify an

<p>| TABLE 1. Descriptive Statistics and Results of Student’s t Test for Pharmacokinetic Parameters Between Groups A and B |</p>
<table>
<thead>
<tr>
<th>Acquisition Duration, s</th>
<th>A</th>
<th>B</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The values are presented as mean (SD). Significant differences are captured in bold.

<p>| TABLE 2. Results of Post Hoc Comparisons for Effect of Scan Duration on Pharmacokinetic Parameters for Groups A and B |</p>
<table>
<thead>
<tr>
<th>Acquisition Duration, s</th>
<th>( K_{\text{trans}} ) (Bonferroni Corrected)</th>
<th>( K_{\text{ep}} )</th>
<th>( V_e )</th>
<th>iAUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>200</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>150</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>100</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The values are presented as mean (SD). Significant differences are captured in bold.
optimal sampling duration. New technologies in medical imaging and particularly in MRI such as parallel imaging\cite{19} and view-sharing techniques\cite{20,21} allow for a faster image acquisition while preserving spatial image resolution. In the present study, we utilized a novel CDT-VIBE sequence for DCE-MRI, which combines view sharing (ie, TWIST) and parallel imaging (ie, CAIPIRINHA) with a spatial resolution of $3 \times 1.2 \times 1.2$ mm and a temporal resolution of 5 seconds per time point. The CDT-VIBE has previously been assessed for dynamic imaging of the liver\cite{15,22} and breast,\cite{16} yielding satisfactory results. For DCE-MRI of the prostate, a total scan duration of 5 to 10 minutes is recommended.\cite{1,8} However, this recommendation is only based on consensus of expert groups, yet no dedicated studies have systematically investigated this issue. In the present study, pharmacokinetic parameters derived from benign and potentially malignant lesions did not significantly differ between sampling durations from 150 to 250 seconds. In benign lesions, sampling durations shorter than 150 seconds caused significant alteration, that is, overestimations, of $K_{trans}$ and $K_{ep}$. Only sampling durations lower than 100 seconds led to significant alteration of iAUC in benign lesions. In potentially malignant lesions, pharmacokinetic parameters were consistent for sampling duration between 100 and 250 seconds. Only sampling durations lower than 100 seconds cause significant changes in $K_{trans}$, $K_{ep}$, and iAUC in malignant lesions. Given that $iAUC_{60}$

### TABLE 3. Effect of Acquisition Duration on Diagnostic Accuracy of Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Acquisition Duration, s</th>
<th>$K_{trans}$</th>
<th>$K_{ep}$</th>
<th>Ve</th>
<th>iAUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>0.827 (0.715–0.938)</td>
<td>0.952 (0.898–1.00)</td>
<td>0.484 (0.342–0.626)</td>
<td>0.827 (0.721–0.934)</td>
</tr>
<tr>
<td>200</td>
<td>0.850 (0.746–0.953)</td>
<td>0.917 (0.837–0.997)</td>
<td>0.498 (0.356–0.640)</td>
<td>0.835 (0.730–0.939)</td>
</tr>
<tr>
<td>150</td>
<td>0.866 (0.768–0.964)</td>
<td>0.922 (0.854–0.990)</td>
<td>0.483 (0.341–0.625)</td>
<td>0.830 (0.724–0.936)</td>
</tr>
<tr>
<td>100</td>
<td>0.857 (0.758–0.955)</td>
<td>0.858 (0.764–0.952)</td>
<td>0.537 (0.396–0.678)</td>
<td>0.835 (0.731–0.940)</td>
</tr>
<tr>
<td>50</td>
<td>0.810 (0.699–0.921)</td>
<td>0.682 (0.553–0.811)</td>
<td>0.645 (0.510–0.780)</td>
<td>0.780 (0.668–0.893)</td>
</tr>
</tbody>
</table>

AUC indicates areas under the curve; CI, confidence interval.
integrates the area under the kinetic curve during the first 60 seconds, significant alterations of iAUC60 in the 50 seconds data sets are considered as artifacts. Ve was consistent among all scan durations, without significant differences for sampling durations ranging from 50 to 250 seconds. We furthermore found that short sampling duration (ie, lower than 100 seconds) might affect the diagnostic accuracy of $K_{ep}$ for distinguishing potentially malignant from benign prostate lesions. Diagnostic accuracy of $K_{trans}$, Ve, and iAUC60 was not affected by shortened scan durations. In conclusion, our finding support the assumption that a sampling duration of 150 seconds provides sufficient estimation of pharmacokinetic parameters in optimized fast DCE-MRI of the prostate. The reduction of sampling duration can increase patient comfort and reduce motion artifacts, which usually occur in longer acquisitions, especially in later phases of image acquisition. Before applying the shortened protocol, further confirmational studies (eg, using MRI scanners from different vendors) in larger populations are needed.

For pharmacokinetic parameter estimates, compartment models such as the Tofts model used in the present study assume an immediate equilibrium of contrast agent between plasma and EES, neglecting the first-pass effect of contrast bolus injection. The first-pass effect includes contrast agent arrival via arteries and homogeneous mixing into the plasma and into the EES and might take up to 2 minutes. Therefore, the inhomogeneous contrast agent contribution in the first 2 minutes might have caused the altered parameter estimates in the present study. These results should thus be taken with caution when using different DCE-MRI software packages because fitting results obtained with other software packages may vary due to different initial estimates and constraints. Furthermore, increased image noise might decrease the reliability of pharmacokinetic parameters. This also should be considered when applying different sequence acquisition parameters.

Despite the standardized injection rate of contrast agent (2 mL/s) as well as the fixed delay after contrast injection applied in this study, contrast agent arrival in prostate tissue is dependent on further factors such as blood circulation, which varies among patients. A substantial delay of contrast agent can lead to insufficient parameter estimation. However, in this study, we observed consistent length of the baseline phase among the included patients and therefore acceptable variability in contrast agent arrival.

FIGURE 5. Optimal thresholds for discrimination between both lesion groups among the different series. Below each data point, corresponding sensitivity and specificity are given.
The European Society of Urogenital Radiology recommends a sampling duration of 5 minutes for DCE-MRI. In the present study, an acquisition duration of only 2.5 minutes was required for sufficient parameter estimation. In a simulation study, Aerts et al.\(^1\)\(^3\) stated that duration of more than 120 seconds is required for sufficient parameter estimation. Similar results were reported in a further simulation study using an in vivo arterial input function by Jaspers et al.\(^1\)\(^4\) With a sampling frequency of 12 seconds per time point, Hao et al.\(^1\)\(^6\) reported that a sampling duration of 4 to 6 minutes might be essential for sufficient parameter estimation, especially in malignant breast lesions. In contrast to Hao et al., results of the present study indicate that scan durations of 150 seconds (2.5 minutes) are adequate for parameter estimation in prostate lesions, when a high sampling frequency is used.

Although the focus of this study was to assess the effect of sampling duration in DCE-MRI on pharmacokinetic parameters and diagnostic accuracy based on PI-RADS scoring (American College of Radiology PI-RADS v2\(^1\)\(^7\)), the lack of histological correlation in a number of suspected malignant findings (12 of the 34 suspected malignant lesions) might be considered as a limitation.

A further limitation is the potential effect of view-sharing by the integrated TWIST technique, which is known to cause underestimation of signal intensity due to sharing the k-space data among the different time points of the DCE-MRI measures.\(^8\)\(^9\) Nonetheless, in previous studies assessing the effect of view-sharing techniques on signal intensity, variation of malignant lesions with a diameter of 0.5 mm or greater was not higher than 5%. Based on this knowledge and to minimize the effects of view-sharing, we included only lesions with diameters larger than 5 mm.

**CONCLUSIONS**

Using fast optimized DCE-MRI of the prostate, a minimum sampling duration of 150 seconds is required for sufficient pharmacokinetic parameter estimates with high diagnostic accuracy regarding the discrimination between benign and potentially malignant lesions.

**REFERENCES**


