Evaluation of Dispersion MRI for Improved Prostate Cancer Diagnosis in a Multicenter Study

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OBJECTIVE. The purpose of this study is to compare dispersion MRI and Tofts model (TM) for analysis of quantitative dynamic contrast-enhanced (DCE) MRI (DCE-MRI) for localization of prostate cancer and to assess the correlation between quantitative DCE-MRI parameters and tumor grade.

MATERIALS AND METHODS. This retrospective multicenter study included 80 patients with biopsy-proven prostate cancer who underwent DCE-MRI followed by radical prostatectomy. DCE-MRI parameters were extracted from dispersion MRI analysis (the dispersion parameter \(k_d\)), the flux rate \(k_{\text{ep}}\), and the intravascular mean transit time) and TM analysis (the forward volume transfer constant \(K^\text{trans}\), \(k_{\text{ep}}\), and the extravascular extracellular volume fraction \(v_e\)). ROIs representing benign and malignant tissue were drawn on each DCE-MRI slice according to the histopathologic findings, and the diagnostic performance of the estimated parameters for the diagnosis of prostate cancer was evaluated using fivefold cross-validation and ROC curve analysis. Further analysis was conducted for the two most relevant parameters (i.e., \(k_d\) [for dispersion MRI] and \(k_{\text{ep}}\) [for TM]), to investigate the correlation between DCE-MRI parameters and tumor grade.

RESULTS. DCE-MRI parameters were significantly different between benign and malignant prostate tissue \((p < 0.0001)\). The dispersion MRI parameter \(k_d\) outperformed all other DCE-MRI parameters for prostate cancer diagnosis, showing the highest area under the ROC curve value \((p < 0.0001)\). Only a weak linear correlation (Pearson \(r = 0.18; p < 0.05\)) was found between the dispersion parameter and the Gleason grade group.

CONCLUSION. Dispersion MRI outperformed TM analysis, improving the diagnostic performance of quantitative DCE-MRI for prostate cancer localization. Of the DCE-MRI parameters, \(k_d\) [for dispersion MRI] and \(k_{\text{ep}}\) [for TM] provided only poor characterization of tumor grade.
that inclusion of DCE-MRI in mpMRI protocols improves the performance of mpMRI [3, 12, 13], the added value of DCE-MRI to prostate mpMRI has been debated [10, 14], and the role of DCE-MRI in the updated Prostate Imaging and Reporting Data System version 2 (PI-RADSv2) is marginal [15].

Because of angiogenesis (i.e., the chaotic formation of a vascular network to support tumor growth), cancer tissue is typically characterized by abnormal vessels, exhibiting higher tortuosity, permeability, and microvascular density than in benign tissue [16]. DCE-MRI is used to probe tissue vascularity by dynamic acquisition of T1-weighted images before, during, and after the injection of a contrast agent [16]. After IV injection, the commonly adopted gadolinium-based MR agents flow from large arteries to the microvasculature and extravasate into the interstitium, thus providing an opportunity to assess microvascular perfusion and permeability, which typically are altered in cancer angiogenic vasculature.

Quantitative analysis of DCE-MRI is frequently performed using pharmacokinetic (PK) analysis with the Tofts model (TM) [17], which enables the estimation of PK parameters related to the microvascular permeability (the forward volume transfer constant [Ktrans]) and flux rate (kep) and leakage space (extravascular extracellular volume fraction [ve]). TM analysis requires separate estimation of the arterial input function (AIF), which is the contrast concentration used as input to the capillary-tissue exchange. The AIF is typically measured in a large artery present in the FOV or is obtained from population-averaged models as found in the literature [16]. This represents a limitation both theoretically (because of the effects of delay and dispersion on the AIF caused by transport from the sampling site [the large artery] to the exchange site [the capillaries] are neglected) [18, 19] and practically (because measurement of the AIF is notoriously affected by several sources of error, which can considerably influence parameter estimation) [16, 20, 21]. Moreover, quantitative analysis of DCE-MRI with use of the TM has failed to prove substantial improvements, compared with qualitative or semiquantitative DCE analysis [22, 23]. As a result, DCE-MRI quantification is rarely performed in mpMRI protocols.

Dispersion MRI has been proposed as an alternative for quantitative DCE-MRI analysis, with promising initial results obtained for the prostate cancer localization [19]. In dispersion MRI, the transport of the contrast agent from the injection site to the leakage sites is included in the model by describing it as a convective dispersion process, thus providing an opportunity to also characterize the microvascular architecture. In addition, dispersion MRI eliminates the hurdle of the extra measurement of the AIF, thus offering a simpler quantification protocol that may improve clinical workflow.

In the present study, we analyzed the diagnostic performance of dispersion MRI and TM for prostate cancer localization, and we investigated the correlation of PK parameters with histologic assessment of tumor grade.

**Materials and Methods**

**Pharmacokinetic Modeling of Contrast Agent Transport**

A schematic diagram comparing dispersion MRI with TM is presented in Figure 1. In prostate DCE-MRI, after peripheral IV injection is performed, a bolus of gadolinium-based contrast agent spreads through the vasculature and leaks across the vascular endothelium, especially in areas of increased microvascular permeability.

In dispersion MRI, the transport of the contrast agent within the vasculature is described by a distributed convective dispersion model. According to this model, the contrast bolus translates at a velocity (v), is dragged by the carrier fluid (blood), and spreads (dispersion) through the multipath trajectories defined by the microvascular network [24]. A local solution of this model, known as the modified local density random walk, provides the intravascular contrast concentration, C(t), at the capillary-tissue exchange site as shown in the following equation [25]:

\[
C(t) = \alpha \sqrt{\frac{k_{ep} \tau}{2 \pi T_i}} e^{-\frac{k_{ep} \tau}{2 \pi T_i}},
\]

where \(t\) is the time variable, \(\alpha\) is the Euler number, \(T_i\) is the intravascular mean transit time between the injection and detection sites, \(\alpha\) is the time integral of \(C(t)\), \(k_{ep}\) is the theoretical injection time, and \(k_{ep}\) is the dispersion parameter given by the local ratio of the squared velocity (v2) and the dispersion coefficient (D). Similar to a dispersion process through a porous medium, where the dispersion coefficient is mainly determined by the porosity and tortuosity of the medium [24], the dispersion coefficient is adopted to characterize the microvascular architecture, providing an option for assessing the vascular changes induced by cancer angiogenesis [16, 19, 25].

With the adoption of a simple monocompartmental representation of the extravascular extracellular space, as was done in the study by Tofts et al. [17], the contrast concentration \(C(t)\) in the extravascular extracellular space can be described by the following partial differential equation:

\[
\frac{\partial C(t)}{\partial t} = k_{ep} [C_0(t) - C(t)],
\]

**Fig. 1**—Comparison of Tofts model (TM) and reduced dispersion MRI model. A and B, Schematics show that, in TM (A), intravascular concentration at capillary-tissue exchange site \(C(t)\) is represented by arterial input function (AIF) measured in large artery, whereas, in reduced dispersion model (B), \(C(t)\) is represented by modified random walk solution of distributed convective dispersion model. In both cases, extravascular extracellular space is modeled as single compartment, which is mathematically described by monoeponential decay. \(e\), Euler number, \(k_{ep}\) = flux rate.
Dynamic Contrast-Enhanced MRI Acquisition

MRI examinations were performed using different protocols, depending on the institution. For patients at the Amsterdam Medical Centers (n = 13), DCE-MRI was performed on a 1.5-T clinical scanner (Achieva, Siemens Healthcare) equipped with an endorectal coil, with use of IV injection of gadobutrol (0.1 mmol/kg; Gadovist, Bayer Healthcare) and the following parameters: TR/TE, 50/3.9; flip angle, 70°; temporal resolution, 3.1 seconds; number of repetitions, 45–60; spatial resolution, 1.7 mm; and slice thickness, 4 mm. For patients at the Netherlands Cancer Institute (n = 34), DCE-MRI was performed using a 3-T clinical scanner (Achieva, Philips Healthcare) that was equipped with an endorectal coil, with use of IV injection of gadoterate meglumine (0.1 mmol/kg, Dotarem, Guerbet) and the following parameters: TR/TE, 4–5.5/1–2; flip angle, 8–15°; temporal resolution, 2.9–3.7 seconds; number of repetitions, 80–100; spatial resolution, 1–2 mm; and slice thickness, 6 mm. For patients at the Radboudumc Nijmegen (n = 33), 19 of the DCE-MRI examinations were performed using a 3-T clinical scanner (Magnetom Skyra, Siemens Healthcare) with a body coil, with use of IV injection of gadobutrol (0.1 mmol/kg) and the following parameters: TR/TE, 3.6/1.4; flip angle, 14°; temporal resolution, 3.3 seconds; number of repetitions, 45–70; spatial resolution, 1.5 mm; and slice thickness, 3–4 mm. An additional 14 DCE-MRI examinations were performed using a 3-T clinical scanner (Magnetom Trio Tim, Siemens Healthcare) with a body coil, with use of IV injection of gadobutrol (0.1 mmol/kg) with the following parameters: TR/TE, 3.2–3.85/1.4–1.5; flip angle, 10–14°; temporal resolution, 3.3–4.5 seconds; number of repetitions, 45–70; spatial resolution, 1.5–1.8 mm; and slice thickness, 3–4 mm.

Histopathologic Findings

All patients underwent radical prostatectomy at their respective institutions. All histopathologic analyses were thus performed on prostate specimens after resection. After fixation in formalin, the prostate specimens were cut into slices with a thickness of approximately 4 mm by a pathologist who marked cancer areas on the basis of the microscopic analysis of cellular differentiation (Fig. 2). For each patient, at least the index lesion was graded by the pathologist according to the 2005 International Society of Urological Pathology Gleason grading system [27], and the corresponding Gleason score was noted. On the basis of the Gleason score, the lesions were stratified...
Dispersion MRI for Prostate Cancer Diagnosis

Pharmacokinetic Analysis

All DCE-MRI data were imported to a workstation and processed using Matlab (Matlab, version 2017a, MathWorks). The prostate contours were manually drawn on each MRI slice by a technical expert with more than 4 years of experience in DCE imaging of prostate cancer. Signal intensity curves were extracted at each pixel within the contours and were converted into concentration-time curves, in accordance with the study by Schabel and Parker [29], setting the contrast agent relaxivity to 5.2 mmol\(^{-1}\)s\(^{-1}\) at 1.5 T and 5.0 mmol\(^{-1}\)s\(^{-1}\) at 3 T for gadobutrol and to 3.5 mmol\(^{-1}\)s\(^{-1}\) at 3 T for gadoterate meglumine [30]. Because a quantitative measurement of the native tissue relaxation time \(T_1\) was not always available, population-averaged values of 939 ms at 1.5 T and 1540 ms at 3 T for prostate \(T_1\) were used [31, 32].

Each concentration-time curve was fitted using the reduced dispersion model in equation 4 through nonlinear least-squares curve fitting with the Trust Region Reflective algorithm. Parameter estimation was optimized as explained in Turco et al. [33]; to reduce the computational burden given by the presence of the convolution integral in equation 4, a time-efficient solution exploiting the computational advantages of the fast-Fourier transform was used. To decrease the risk of incurring in local minima, a grid-search for \(t_0\) was implemented, and the parameters were constrained to physiologically sensible values (for the dispersion parameter, \(k_g = 0.0005 + 4\) s\(^{-1}\); for the flux rate, \(k_{vp} = 0.0005 \times 3\) min\(^{-1}\); and for the mean transit time, \(T_M = 5 + 60\) s). Parametric maps of \(k_g\), \(k_{vp}\) and \(T_M\) were thus obtained and compared with the TM parameters \(K^{TM}\) and \(v_v\).

For estimation of the TM parameters, the Tofts model was applied as follows:

\[
C_i(t) = K^{TM} C_p(t) \times e^{-\frac{t}{T_{ep}}},
\]

where \(C_i(t)\) is the tissue concentration at time \(t\), \(v_v\) is the extravascular volume fraction, and \(C_p(t)\) is the AIF. To measure the AIF, an ROI in the iliac artery was manually selected in multiple sections of the scan. An arterial concentration-time curve, \(C_{blood}(t)\), as proposed by Schnabel and Parker [29], was determined by use of a native blood relaxation time \((T_{1blood})\) of 1540 ms at 1.5 T and 1700 ms at 3 T [34]. The plasma concentration in the capillary \(C_p\) was estimated using the equation \(C_p = C_{blood}(t)(1 - Hct)\), where Hct denotes the hematocrit level, for which a value of 0.45 was used.

To avoid partial volume effects, only the pixels with the highest enhancement were used to generate the arterial signal. Because of unavoidable flow artifacts in the arteries, the AIF needed adjustment before being used for the PK analysis. The AIF peak amplitude was thus corrected according to a previously published method [35]. The resulting \(C_i(t)\) was fitted by the analytic function (model 2) proposed by Orton et al. [36], and equation 5 was solved in closed form as described by Orton et al. [36]. The TM parameters \(K^{TM}\) and \(v_v\), and \(k_{vp} = K^{TM} / v_v\) were thus calculated by nonlinear fitting using the lsqcurvet algorithm in Matlab.

To evaluate the ability of PK parameters to localize prostate cancer, ROIs representing benign and malignant tissue (hereafter referred to as “benign ROIs” and “malignant ROIs”) were drawn on the DCE-MRI grey-scale slices at baseline, according to the corresponding histopathologic slices, by a technical expert with more than 4 years of experience in DCE imaging of prostate cancer. To avoid any possible bias, the expert was blinded to the results of the pharmacokinetic analysis. Visual matching between histopathologic slices and MRI was performed by comparing the apex-base orientation, the prostate shape, and the number of slices. Given the inherent uncertainty in the matching, ROIs were drawn only when malignant or benign tissue was present in consecutive pathologic slices. Figure 3 shows an example of MRI slices with benign and malignant ROIs, which correspond to the histopathologic slices in Figure 2.

Statistical Analysis

The values of DCE-MRI quantitative parameters in malignant and benign ROIs, expressed as median values (± SD), were compared using the Wilcoxon signed rank test.

ROC curve analysis performed using the upper left corner criterion evaluated the diagnostic performance of each PK parameter on the manually drawn benign and malignant ROIs. To simulate an independent validation dataset, a fivefold cross-validation strategy was used: the 80 patients were divided into five groups of 16 patients; the optimal cutoff threshold was determined for four groups (the training set), and the predictive performance was validated for the remaining group (the validation set), with rounding done five times so that each group was included in the validation set once; the whole procedure was repeated for 100 random partitions of the 80 patients into the five groups. To avoid any bias toward a negative or positive result, the number of samples in each class was balanced at each repetition by randomly subsampling the class with a higher number of samples. The classification performance was evaluated in terms of sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, and optimal cutoff, with all data presented as mean (± SD) values.

Diagnostic performance was also assessed by standard ROC analysis on the full dataset. ROC curves were obtained, and the AUC values (with CIs) were calculated for each parameter. Given the larger number of benign ROIs, the benign samples were randomly subsampled to create a group of 217 samples, to balance the number of malignant samples. Pairwise comparison between the AUC values was performed for each couple of DCE-MRI parameters by use of the Hanley and McNeil method [37].

Further subanalysis was performed for the two most relevant parameters (i.e., \(k_g\) for dispersion MRI and \(k_{vp}\) for TM). The correlation with Gleason grade group was evaluated by calculating the Pearson \(r\) (the linear correlation) and Spearman \(r\) (the rank correlation) values and by performing one-way ANOVA with a post hoc Tukey honestly significant difference test comparing the group means.

Standard values with a significance level of \(\alpha=0.05\) and a statistical power of \(1 - \beta=0.80\) were used.
PK parameters. The dispersion model outperformed all the other models in all cases (as evaluated by fivefold cross-validation, and in the benign ROIs for different magnetic field strength ($p = 0.01$), contrast agents ($p = 0.03$), and institutions ($p = 0.01$). These results are summarized in Table S2 (which can be viewed in the AJR electronic supplement to this article, available at www.ajronline.org).

Discussion and Conclusion

In the present study, we evaluated the diagnostic performance of quantitative DCE-MRI for prostate cancer localization by dispersion MRI and TM analysis. The parameter $k_d$ from dispersion MRI significantly outperformed all the other PK parameters, providing the best diagnostic performance, as evaluated by fivefold cross-validation, and the highest AUC value in the ROC analysis.

In dispersion MRI, the contrast concentration in tissue is described as a convolution between the modified local density random walk model, which describes the contrast transport from large arteries to the capillary-tissue exchange site as a convective dispersion process, and a monoexponential decay, which characterizes contrast leakage in tissue. Dispersion MRI thus provides an option to characterize the microvascular architecture by estimation of the dispersion parameter $k_d$. In fact, as described by Taylor [24] for convective transport through porous media, dispersion in the microcirculation is mainly determined by the multipath trajectories across the microvascular bed. In particular, the increased tortuosity typically exhibited by angiogenic microvessels may constrain the transported contrast agent in space, leading to reduced dispersion.

Several studies using DCE-ultrasound have shown dispersion-related parameters to be a promising option for prostate cancer diagnosis, outperforming perfusion-related parameters [25, 40, 41]. In the present study, we showed that dispersion may be a better biomarker for cancer than permeability-related parameters, confirming the results of a previous preliminary validation of dispersion MRI [19]. In addition, we also confirm that the presence of cancer correlates well with lower values of dispersion, because $k_d$ is inversely proportional to the dispersion coefficient. This enforces the hypothesis that microvascular tortuosity, constraining the
TABLE 3: Results of Fivefold Cross-Validation Evaluating Diagnostic Performance of Dispersion MRI and Tofts Model

<table>
<thead>
<tr>
<th>Result</th>
<th>$k_d$ (Dispersion MRI)</th>
<th>$k_{ep}$ (Tofts Model)</th>
<th>$K^{trans}$ (Tofts Model)</th>
<th>$k_d$ (Dispersion MRI)</th>
<th>$T_i$ (Dispersion MRI)</th>
<th>$v_e$ (Tofts Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>78 ± 9</td>
<td>72 ± 14</td>
<td>63 ± 14</td>
<td>60 ± 14</td>
<td>58 ± 14</td>
<td>54 ± 17</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>91 ± 7</td>
<td>75 ± 14</td>
<td>74 ± 14</td>
<td>68 ± 15</td>
<td>64 ± 15</td>
<td>61 ± 20</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>85 ± 5</td>
<td>73 ± 6</td>
<td>68 ± 6</td>
<td>64 ± 7</td>
<td>61 ± 7</td>
<td>58 ± 6</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>90 ± 7</td>
<td>76 ± 9</td>
<td>72 ± 9</td>
<td>66 ± 10</td>
<td>63 ± 9</td>
<td>60 ± 10</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>81 ± 6</td>
<td>74 ± 8</td>
<td>67 ± 7</td>
<td>63 ± 7</td>
<td>61 ± 7</td>
<td>57 ± 7</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>8.46 ± 1.0</td>
<td>2.89 ± 0.6</td>
<td>2.38 ± 0.5</td>
<td>1.84 ± 0.5</td>
<td>1.63 ± 0.5</td>
<td>1.39 ± 0.5</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>4.18 ± 0.4</td>
<td>2.67 ± 0.5</td>
<td>1.99 ± 0.5</td>
<td>1.67 ± 0.5</td>
<td>1.54 ± 0.5</td>
<td>1.33 ± 0.6</td>
</tr>
<tr>
<td>Optimal cutoff value*</td>
<td>&gt; 0.17</td>
<td>&gt; 1.12</td>
<td>&gt; 0.25</td>
<td>&gt; 0.06</td>
<td>&gt; 15.01</td>
<td>&lt; 0.24</td>
</tr>
</tbody>
</table>

Note—Except where otherwise indicated, data are mean (± SD) values. $k_d$ = dispersion parameter, $k_{ep}$ = flux rate, $K^{trans}$ = forward volume transfer constant, $T_i$ = mean transit time, $v_e$ = extravascular extracellular volume fraction.

*Unit of measurement is that of the corresponding parameter.

In addition to relying on strong modeling assumptions, the estimation of a reliable AIF is, in general, challenging. Patient-specific AIFs can be obtained from a large artery present in the FOV of the DCE-MRI acquisition or by a lower-dose pre-bolus injection followed by a separate DCE acquisition tailored to the sampling and amplitude requirements of the AIF; however, both are prone to several sources of error, which may lead to poor estimation accuracy and poor repeatability [16, 20, 21]. The population-averaged AIFs available in the literature can be used to improve repeatability, but they fail to account for interpatient variability. The hurdles for a reliable AIF estimation, together with the complexity of PK analysis and the lack of consensus on a standard method have resulted in a limited use of quantitative DCE-MRI.

Recently, with the objective of providing a simpler and standardized method of reporting prostate mpMRI, the updated version of PI-RADS (PI-RADSv2) has greatly limited the influence of DCE-MRI: it contributes only to upgrade a PI-RADS score from 3 to 4 in peripheral zone tumors by qualitative evaluation of focal early enhancement [14]. Although a recent study comparing PI-RADSv2 with the original version of PI-RADS has shown a significant decrease in the overall diagnostic performance with PI-RADSv2 and (semi-)quantitative DCE analysis to be superior to a qualitative approach [14]. Although a simpler and standardized method for mpMRI scoring is highly desirable, the study by Auer et al. [14] suggests that PI-RADSv2 is still not optimal and that the role of quantitative DCE analysis needs to be reviewed. In this context, dispersion MRI may improve mpMRI performance and workflow by providing a quantitative DCE-MRI method with higher diagnostic accuracy and a simpler quantification protocol. Moreover, it would be interesting to evaluate the potential added value that dispersion MRI might provide to mpMRI, by comparing the diagnostic performance of PI-RADS, dispersion MRI, and the combination of the two. However, this comparison would require an inherently different validation strategy. In fact, although the present study estimated quantitative parameters at each voxel and assessed their classification performance for malignant and benign tissue on a voxel level, a comparison with PI-RADS would require qualitative assessment of the parametric maps on a sector or lesion level, possibly in a PI-RADS–like fashion, as well as evaluation of the diagnostic performance on the basis of sector-level agreement with the histologic findings.

The correlation analysis of PK parameters and tumor grade, as defined by stratification of the Gleason score in Gleason grade groups [28], showed only a weak but significant linear correlation between $k_d$ and the Gleason grade and only a significant ability to distinguish grade group 5 from grade group 3 or lower for $k_{ep}$ and grade group 1 from grade group 2 for $k_{ep}$. These results could be influenced by the unbalanced distribution of the lesions: although 40% of the lesions had a Gleason score of 3 + 4 (grade group 2), only 7% and 10% had a Gleason score of 8 (grade group 4) or 9 or less (grade group 5), respectively. As a result, the number of lesions included in the present study may not have been sufficient to fully characterize the PK parameter distribution within each grade group. In addition, the Gleason score is based on the microscopic analysis of cellular differentiation of resected tumors, whereas $k_{ep}$, which is related to the microvascular architecture, and $k_{ep}$, which assesses microvascular permeability, reflect the in vivo changes occurring in tumor vasculature as a result of cancer angiogenesis. In the future, it would be interesting to investigate the correlation of PK parameters with different immunohistologic markers quantifying the microvascular density and expression level of angiogenic biomarkers.

Analysis of the influence of the acquisition protocol on the diagnostic performance showed that dispersion MRI was, in general, robust with respect to the acquisition settings. A significant decrease in specificity was observed only for decreasing temporal resolution and for the comparison of the
TABLE 4: Pairwise Comparison of Area Under ROC Curve

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$k_p$ (Tofts Model)</th>
<th>$K^{\text{trans}}$ (Tofts Model)</th>
<th>$k_{ep}$ (Tofts Model)</th>
<th>$T_i$ (Tofts Model)</th>
<th>$v_e$ (Tofts Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_p$ (Dispersion MRI)</td>
<td>0.093 ($p &lt; 0.0001$)*</td>
<td>0.165 ($p &lt; 0.0001$)*</td>
<td>0.225 ($p &lt; 0.0001$)*</td>
<td>0.259 ($p &lt; 0.0001$)*</td>
<td>0.279 ($p &lt; 0.0001$)*</td>
</tr>
<tr>
<td>$k_p$ (Tofts model)</td>
<td>—</td>
<td>0.073 ($p &lt; 0.0001$)*</td>
<td>0.132 ($p &lt; 0.0001$)*</td>
<td>0.166 ($p &lt; 0.0001$)*</td>
<td>0.186 ($p &lt; 0.0001$)*</td>
</tr>
<tr>
<td>$K^{\text{trans}}$ (Tofts model)</td>
<td>—</td>
<td>—</td>
<td>0.059 (0.0302)</td>
<td>0.094 (0.0034)*</td>
<td>0.114 (0.0002)*</td>
</tr>
<tr>
<td>$k_{ep}$ (Dispersion MRI)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.034 (0.3020)</td>
<td>0.054 (0.1408)</td>
</tr>
<tr>
<td>$T_i$ (Dispersion MRI)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.020 (0.5694)</td>
</tr>
</tbody>
</table>

Note—Data are the difference in the ROC areas for each parameter (as specified at the start of each row) compared with other parameters (as specified in column headers), with the corresponding $p$ value shown in parentheses. $k_p$ = dispersion parameter, $k_{ep}$ = flux rate, $K^{\text{trans}}$ = forward volume transfer constant, $T_i$ = mean transit time, $v_e$ = extravascular extracellular volume fraction.

*Statistically significant difference ($p < 0.05$).
Amsterdam University Medical Centers with Radboudumc Nijmegen. However, comparison of institutions may have been influenced by the difference in temporal resolution, which was high for the Amsterdam University Medical Center and (on average) low for the Radboudumc Nijmegen. In fact, the influence of each acquisition setting was considered separately in the present study. Because of the limited dataset resulting from sub-grouping, the co-influence of a combination of settings could not be further investigated. Ideally, through more extensive clinical experience, an optimal combination of acquisition settings should be found, and a standardized clinical protocol should be proposed.

Previous studies have established that a temporal resolution of 6 seconds may be sufficient for accurate estimation of PK parameters from TM, whereas temporal resolution of 1 second is suggested to accurately capture the fast dynamics of the AIF [16]. Because of dispersion effects during the transport from the artery to the capillary-tissue exchange site, incorporated in the reduced dispersion model, slower dynamics are expected at the exchange site, possibly relaxing the high temporal resolution requirements for dispersion MRI. In fact, we infer the faster intravascular kinetics from the slower extravasation process. A simple noise-free simulation using worst-case scenario values for the time constants in the reduced dispersion model led to a signal with a bandwidth of approximately 0.12 Hz. Therefore, according to the Shannon sampling theorem, a temporal resolution of 4.2 seconds would theoretically be sufficient to fully capture the dispersion dynamics of DCE-MRI–derived concentration-time curves in the prostate. However, although this suggests that the temporal resolution used in the present study may be sufficient for accurate parameter estimation, a significant decrease in the diagnostic performance was observed for a temporal resolution longer than 3.2 seconds. A simulation study including the effects of noise should be performed in the future to accurately evaluate the sampling requirements of dispersion MRI. The robustness of the parameter estimation toward uncertainties in the contrast relaxivity and tissue certainties in the parameter estimation toward uncertainties in the contrast relaxivity and tissue could also be tested by simulations.

The present study has some limitations. No distinction was made between peripheral zone and transition zone lesions. Because DCE-MRI has shown poor performance in the transition zone [14, 15], this may affect the overall diagnostic performance obtained in the present study and may represent a confounding factor in the analysis of correlation of PK parameters with tumor grade. Another limitation is the use of a population-averaged value of $T_{1\text{r}}$ due to the lack of acquisition of T1 mapping for most patients. However, although this may affect the parameter estimation, the same values were used for both methods, and therefore the comparison should still be considered valid. In addition, the validation was performed by comparing the DCE-MRI parametric maps with the corresponding histologic analysis. Because of the adopted validation strategy, only patients who underwent radical prostatectomy could be enrolled in this study, and patients with inflammatory conditions such as prostatitis were not included. As a consequence, the results may be biased toward the presence of cancer, and the potential ability of dispersion MRI to distinguish between angiogenesis in inflammation and tumor tissue could not be investigated. Moreover, matching of MRI and histopathologic findings was performed visually, on the basis of the known order and thickness of the pathologic slices. Although attention was given to selecting only those ROIs for which malignant or benign tissue was consistent in adjacent slices, this approach is inherently affected by the risk of mismatching errors, which may influence the classification results. In the future,
coregistration of 3D histopathologic models onto the DCE-MRI 3D volumes may provide more reliable lesion matching and may also permit the inclusion of smaller and isolated lesions. Finally, no comparison was performed using other MRI sequences, such as T2-weighted and DWI sequences, and the correlation of the estimated parameters with PI-RADS scoring was not addressed. Although the objective of the present study was to validate dispersion MRI for quantitative DCE-MRI of the prostate, in the future these comparisons should be performed to assess the potential added value of dispersion MRI to mpMRI in the context of PI-RADS scoring.

The clinical experience with dispersion MRI is currently limited to the prostate. Considering that dispersion MRI is based on the assessment of cancer angiogenesis, which is a fundamental process in the growth and development of several solid tumors, it would be interesting in the future to test the performance of dispersion MRI in other organs in which angiogenesis also plays a role.

In conclusion, dispersion MRI improves the diagnostic performance of quantitative DCE-MRI for prostate cancer localization with use of a simpler quantification protocol that does not require the measurement of the AIF. In the context of prostate mpMRI, dispersion MRI may thus represent a valuable option for quantitative DCE-MRI, possibly improving standardization and overall performance of mpMRI scoring.

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Fig. 6—Graphs of mean values of parameters (circles on vertical lines, A; diamonds on vertical lines, B) according to Gleason grade groups. Error bars denote 95% CIs. Significant differences, as evaluated by post hoc ANOVA with Tukey honest significant criterion, are denoted by asterisks. Single asterisk denotes \( p < 0.05 \), and double asterisk denotes \( p < 0.01 \).  \( k_e \) = flux rate, \( TM \) = Tofts model.

References

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65:1670–1679


35. Lavini C. Simulating the effect of input errors on the accuracy of TofTs' pharmacokinetic model parameters. Magn Reson Imaging 2015; 33:222–235


39. Chan Y, Walmsley RP. Learning and understanding the Kruskal-Wallis one-way analysis-of-variance-by-ranks test for differences among three or more independent groups. Phys Ther 1997; 77:1755–1762
