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FULL PAPER

Diagnostic value of semi-quantitative and quantitative analysis of functional parameters in multiparametric MRI of the prostate

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Objective: To determine the diagnostic value of semi-quantitative and quantitative parameters of three functional techniques in multiparametric (mp)-MRI of the prostate.

Methods: Mp-MRI was performed in 110 patients with suspicion of prostate cancer (PCA) before transrectal ultrasound (TRUS)-guided core biopsy.

Peak-enhancement, initial and post-initial enhancement, initial area under gadolinium curve, Ktrans (forward rate constant), Kep (efflux rate constant), Ve (extracellular volume), ADC (apparent diffusion coefficient) and MR spectroscopy ratio were obtained for malignant and benign lesions. For iAUGC, Ktrans, Kep and Ve we evaluated median, mean and the difference (Diff) between mean and median. For ADC we evaluated mean, median, Diff between mean and median, and min. In addition, we evaluated these parameters in dependence of Gleason score in PCA. Receiver operating characteristic analysis and area under curve (AUC) were determined.

Results: ADC min and Kep Diff were the best predictors of malignancy in all lesions (AUC: 0.765). ADC min was the best predictor of malignancy for lesions in peripheral zone (PZ) (AUC: 0.7506) and Kep Diff was the best predictor of malignancy for lesions in transitional zone (AUC: 0.7514). Peak enhancement was the best parameter in differentiation of low-grade PCA with Gleason score 6 from high-grade PCA with Gleason score ≥ 7 (AUC: 0.7692).

Conclusion: ADC min can differentiate PCA from benign prostate lesions in PZ. Kep Diff could possibly improve prostate cancer detection in. Peak enhancement might be able to differentiate low grade from high-grade PCA. Semi-quantitative and quantitative parameters may be useful for the functional techniques in mp-MRI.

Advances in knowledge: ADC min can differentiate PCA from benign prostate lesions in PZ.

Peak enhancement might be able to differentiate low grade from high-grade PCA.

INTRODUCTION

Multiparametric (mp)-MRI of the prostate including high-resolution T_2 weighted image (T_2 WI) for the morphological assessment and functional MRI techniques, such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE)-MRI and MR spectroscopy, and has been established for diagnosis and staging of prostate cancer (PCA).^{1,2}

DWI and its quantification as calculated by the apparent diffusion coefficient (ADC) has been shown to improve prostate cancer detection.³⁻⁵

DCE-MRI are usually reported semi-quantitatively with three categories of enhancement curves: increase, plateau

or decrease.^{6,7} Image interpretation of DCE-MRI can be assisted with parametric map which pixel-based colour-coded enhancement features.⁸ Another approach is the use of quantitatively pharmacokinetic modelling to determine the underlying physiologic parameter of contrast kinetics, in particular vascular permeability and extracellular volume fraction.^{6,7,9}

With MR spectroscopy the choline-plus-creatine-to citrate (Cho + Cr/Cit) ratio offers a quantitative parameter to differentiate malignant and benign prostate lesions.^{10,11}

The use of semi-quantitative and quantitative parameters in functional mp-MRI of the prostate has the potential for

standardization of image interpretation and for the comparison between different institutions.^{6,7}

Therefore the purpose of our study is to determine the diagnostic value of semi-quantitative and quantitative parameters of three functional techniques in mp-MRI to find the best predictor of malignancy in peripheral zone (PZ) and transitional zone (TZ). In addition, we evaluated these parameters in dependence of Gleason score in PCA.

METHODS AND MATERIALS

Patients

In the time interval of January 2013 to December 2015 we performed mp-MRI of the prostate before initial TRUS-guided biopsy in 110 patients (mean age: 66 years age; range: 45–82 years) in whom clinically PCA was suspected.

The average prostate specific antigen value was 8.4 ng ml^{-1} (range: $3.7\text{--}127 \text{ ng ml}^{-1}$).

Written informed consent for diagnostic MRI was obtained from each patient. This retrospective study followed the Declaration of Helsinki principles.

In mp-MRI the most suspicious lesion (index lesion) was determined in each patient and therefore we evaluated 110 lesions. We used PI-RADS v1 guidelines for classifications of the lesions.² 76/110 (69%) lesions were scored in PI-RADS 4 category (clinically significant cancer was considered as likely) and 34/110 (31%) lesions were scored in PI-RADS 5 category (clinically significant cancer was considered as highly likely).

MR imaging

MR imaging was performed on a 1.5 T scanner (Magnetom Aera®; Siemens, Erlangen, Germany), using a dedicated 16-channel phased-array body coil. An intravenous application of 1–2 ml butylscopolaminebromide (Buscopan; Boehringer, Ingelheim, Germany) was performed was given immediately before MR spectroscopic imaging.

Coronal T_2 weighted turbo-inversion-recovery-Magnitude sequence with the following parameters: TR/TE 4300/31 ms; flip angle 150° ; field of view 380 mm; matrix size $320 \times 246 \text{ mm}$; slice thickness 3 mm; duration 3.06 min.

Sagittal T_2 weighted turbo-spin-echo (TSE) sequence: TR/TE 5180/94 ms; flip angle 160° ; field of view 250 mm; matrix size $256 \times 192 \text{ mm}$; slice thickness 3 mm and duration 0.58 min. Coronal T_2 weighted TSE sequence: TR/TE 3330/99 ms; flip angle 160° ; field of view 220 mm; matrix size $320 \times 298 \text{ mm}$; slice thickness 3 mm and duration 4.08 min. Axial T_2 weighted TSE sequence: TR/TE 3540/99 ms; flip angle 160° ; field of view 220 mm; matrix size $320 \times 256 \text{ mm}$; slice thickness 3.6 mm and duration 4.23 min.

Diffusion weighted (DW) MR imaging was performed with a single-shot echo-planar imaging sequence: TR/TE 3600/61 ms; field of view 260 mm; matrix size $160 \times 120 \text{ mm}$; b values: 0, 100, 400 and 800 s mm^{-2} ; slice thickness 3 mm and duration 5.08 min.

For MR spectroscopy a 3D weighted k-space acquisition with dual-frequency selective refocusing pulses to suppress water and lipid signals was used.¹¹ The nominal voxel size was kept constant in all measurements at $8 \times 8 \times 8 \text{ mm}^3$ by adapting the matrix size and the field of view to every patient. In combination with the matrix size, the number of weighted averages was adapted to achieve a total acquisition time between 11 to 12 min (TR/TE 930/120 ms).

Dynamic contrast enhanced (DCE)-MRI was conducted using a three-dimensional axial gradient-echo sequence: TR/TE 7.39/4.76 ms; flip angle 12° ; field of view 260 mm; matrix size $129 \times 146 \text{ mm}$ and slice thickness 3 mm. 20 acquisitions of 72 slices each requiring 23 s per acquisition were obtained before and after the administration of gadolinium-based contrast medium. The contrast agent gadobutrol (Gadovist® 1.0, Bayer Pharma, Berlin, Germany) was injected, using a dose of 0.1 mmol kg^{-1} , at 1 ml s^{-1} , using an automated injector (Ulrich, Ulm, Germany) and 16 s after the beginning of the start of the dynamic image series. Total image time of DCE-MRI was 4.50 min.

Post-processing of MR imaging data

After DWI MRI the image software automatically calculated ADC maps. In addition, the image software calculated diffusion-weighted images with a b -value of 1400.

In MR spectroscopy all assigned voxels were analysed with the *syngo.via* software package (Siemens, Healthcare, Erlangen, Germany). This program uses a set of time signals of protons of the metabolites choline, creatine and citrate. Voxels with a correct automatic choice of the resonance (*syngo.via* produced signal fits at the correct parts-per-million positions), passed a quality check by the software. The choline-plus-creatine-to citrate (Cho + Cr/Cit) ratio (spectroscopy ratio) was calculated and was overlaid on the T_2 weighted axial images as colour metabolic maps.⁸

For an automated analysis of the DCE-MRI data we used a commercial software package (iCAD, Inc., Nashua, NH).^{8,12} The software allows a full-time-point analysis (analysis mode: fTP) for the semi-quantitative analysis as well as an automated application of the Tofts model to the contrast data for quantitative analysis.^{8,12,13} The fTP method codes the signal intensity changes between all time-points on a pixel-by-pixel basis, using colour intensity for the initial enhancement and colour hue for the post-initial enhancement. A fast rate of initial contrast enhancement is coded as bright; an intermediate rate is coded as medium and a slow rate of initial contrast enhancement is coded as dark. The post-initial enhancement changes are coded with three colour hues: blue for increase signal intensity to +10%, green for plateau and red for signal decrease to –10%. The final output includes colour hue- and colour intensity-coded images.

The initial area under gadolinium curve (iAUGC) and the peak enhancement (maximum signal intensity) within the lesion were determined by the software.

The pharmacokinetic analysis of the prostate module of the software package uses the four-compartment Tofts model¹³ and

allows a quantitative analysis of dynamic-enhanced MRI data. The model returns a quantitative value for Ktrans (transfer constant between plasma and extracellular space), Kep (efflux rate constant between extracellular space and plasma) and Ve (extracellular volume) for each enhancing pixel. For arterial input function the commercial software package use Weinmann's AIF as described in Tofts 1991. It was obtained from the adjacent femoral artery to normalized measurements of the gadolinium concentration-time curves. Analysis was performed on a pixel-by-pixel basis and colour maps based on the pharmacokinetic parameters were generated and overlaid on the T_1 weighted images. Motion correction, a method to reduce artifacts may cause by patient movement, was automatically performed in each examination.

Image interpretation and data analysis

Two radiologists with more than 5 years' experience in interpreting MR imaging of the prostate retrospectively reviewed the MR images in consensus.

The size of the prostate was measured on T2WI. The volume of the prostate was calculated with the formula for ellipsoid lesions: width $\times$ length $\times$ height $\times$ 0.523.

The index lesion was identified in axial T2WI (Figure 1a). The maximal diameter of the lesions was measured in axial T2WI.

Each lesion diagnosed in axial T2WI was correlated in DWI. The image slice with the maximal diameter of the lesion was identified in the ADC-map and mean, median and minimal ADC-value was evaluated by encircling the lesion (Figure 1b). The difference (Diff) between ADC mean and ADC median was calculated. Each lesion diagnosed in T2WI was correlated in DCE MRI and was identified on the parametric (colour-coded) images. The image slice with the maximal diameter of the lesion was identified (Figure 1c), and the lesion was encircled.⁸ The colour-coded area was used as the base of the semi-quantitative and quantitative analysis of contrast enhanced lesions. The software calculated the distribution of the colour intensity (initial enhancement: fast, medium, slow) and colour hue (post-initial enhancement: red, green, blue) of pixels and their percentages in the region area coloured. Consequently we differentiate between nine combined characteristics: bright red, bright green, bright blue, medium red, medium green, medium blue, dark red, dark green and dark blue. In addition, the software shows the average curve and the worst curve of the dynamic enhancement changes of lesions (Figure 1d).

The software calculated the peak enhancement, the percentage of colour hue (post-initial enhancement) and the iAUGC in the enclosed area. For quantitative analysis the mean and median of Ktrans, Kep and Ve in the enclosed area were performed (Figure 1e). The Diff between mean and median of Ktrans, Kep, iAUGC and Ve was calculated.

We used the mean and maximum MR spectroscopy ratio for our data analysis.

The standard of reference was determined by the results of systematic TRUS-guided random core biopsies. They were with an 18-gauge biopsy cut needle by two urologists and included five samples per lobe.

In all patients additional target biopsies of suspicious areas in MRI were also performed with cognitive co-registration with a mean of 2.7 tissue samples (range: 1–4). Histopathology of all obtained samples was correlated site-by-site with MRI results by the two radiologists. All lesions that were not malignant were considered for the purpose of statistical analysis as "benign".

The Gleason grading system was used to classify PCA as low grade (Gleason score of ≤ 6) and high grade (Gleason score ≥ 7).

Statistical analysis

Statistical analyses were performed with the data analysis program SAS 9.1 for Windows (SAS Institute Inc., Cary, NC) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA). A *p*-value of less than 0.05 was considered to indicate a statistically significant difference.

The Mann–Whitney *U* test and the *t*-test were applied for estimation of differences of semi-quantitative and quantitative parameters of functional MRI between malignant and benign prostate lesions. In addition to bivariate analyses logistic regression were applied for all lesions, for lesions in PZ and TZ alone and for PCA with Gleason score 6 and Gleason score ≥ 7 . The coefficient of determination R^2 was obtained. Receiver operating characteristic analysis and area under curve (AUC) were determined for quantification the diagnostic efficiency of the parameters based on the logistic regression models.

RESULTS

The mean volume of the prostate was 44.2 cm³ (range: 18–140 cm³). The mean maximal diameter of lesions was 1.5 cm (range: 0.3–4.9 cm).

The median time interval between MR imaging and TRUS-guided biopsy was 21 days (range: 2–48 days). TRUS-guided core biopsy revealed PCA in 77/110 (70%) patients, prostatitis in 14/110 (12.7%) patients, normal prostate tissue in 11/110 (10%) patients, PIN in 5/110 (4.6%) and stromal hyperplasia in 3/110 (2.7%) patients.

In 12/77 (15.6%) PCA the Gleason score was 6 (3 + 3), in 20/77 (25.9%) it was 7a (3 + 4), in 17/77 (22.1%) PCA it was 7b (4 + 3), in 24/77 (31.2%) PCA the Gleason score was 8 (4 + 4) and in 4/77 (5.2%) it was 9 (4 + 5).

Table 1 shows all results of the semi-quantitative and quantitative parameters in functional MRI in all lesions (*n* = 110).

Malignant lesions showed significant more red pixels (post-initial decrease) and more medium red pixels (intermediate rate of initial enhancement and post-initial decrease) than benign lesions. Benign lesions showed statistically significant more dark

Figure 1. Prostate in a patient with a PSA of 17 ng mL^{-1} and a lesion in right PZ with PI-RADS 5 category in mp-MRI. Histopathology revealed PCA in the right peripheral zone of the prostate with a Gleason score 7b (4 + 3). (a) Axial T2WI shows a focal lesion with low SI in the right PZ of the prostate (arrow). (b) ADC-map shows mean (average) ADC value, the median ADC value and minimal ADC-value by encircling the lesion. (c) Parametric map from DCE-MRI in the right PZ (arrow). (d) After encircling the lesion average curve and worst curve of the dynamic enhancement changes are shown. (e) The report Card after encircling the lesion shows the peak enhancement, the composition of colour hue (post-initial enhancement): red (decrease), green (plateau), blue (increase), iAUGC ($\text{mM} \times \text{s}$), Ktrans (1 min^{-1}), Kep (1 min^{-1}) and Ve within the enclosed area. MR spectroscopy reveals no suspicious ratio (choline + creatine)/citrate (not shown). ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced; iAUGC, initial area under Gadolinium Curve; DCE, dynamic contrast-enhanced; PZ, peripheral zone; PSA, prostate specific antigen; T2WI, T_2 weighted image.

blue pixels (slow rate of initial enhancement and post-initial increase) than malignant lesions.

Ktrans median, Ktrans mean and Ktrans Diff were statistically significant higher in malignant lesions than in benign lesions. Kep median, Kep mean and Kep Diff were statistically significant higher in malignant lesions than in benign lesions.

ADC mean, ADC median and ADC min were statistically significant lower in malignant lesions than in benign lesions.

In the regression model ADC min ($p = 0.016$) and Kep Diff ($p = 0.015$) were the best predictors of malignancy. The regression coefficient R^2 was 0.274. The AUC based on the logistic regression model was 0.765 [95% CI (0.6656–0.8644)].

The mean and maximum MR spectroscopy ratios were not significantly different in malignant and benign prostate lesions.

Table 1. Semi-quantitative and quantitative parameters of functional MRI in all lesions ($n = 110$)

Parameters	Malignant lesions ($n = 77$) mean $\pm$ SD	Benign lesions ($n = 33$) mean $\pm$ SD	p
Peak enhancement %	126 $\pm$ 24.5	119 $\pm$ 25.4	0.183 ^a
Blue (increase) %	49 $\pm$ 26.0	60 $\pm$ 26.0	0.052
Green (plateau) %	20 $\pm$ 12.4	24 $\pm$ 16.3	0.242 ^a
Red (decrease) %	30 $\pm$ 22.5	15 $\pm$ 16.1	0.002
Bright (fast) blue %	5.9 $\pm$ 6.4	6.1 $\pm$ 6.9	0.955
Bright (fast) green %	7.8 $\pm$ 8.1	9.4 $\pm$ 10.4	0.933
Bright (fast) red %	11 $\pm$ 14.6	6.3 $\pm$ 8.9	0.178
Medium (intermediate) blue %	14.3 $\pm$ 10.9	13 $\pm$ 10.2	0.865
Medium (intermediate) green %	8.6 $\pm$ 7.2	9.3 $\pm$ 7.7	0.685
Medium (intermediate) red %	12 $\pm$ 12.5	5.3 $\pm$ 8.3	0.002
Dark (slow) blue %	29 $\pm$ 24.3	41.58 $\pm$ 30.1	0.027
Dark (slow) green %	4.1 $\pm$ 5.8	3.7 $\pm$ 5.7	0.787
Dark (slow) red %	6.5 $\pm$ 11.1	4.1 $\pm$ 7.3	0.300
iAUGC median (mm $\times$ s)	13 $\pm$ 5.0	11 $\pm$ 5.3	0.079 ^a
iAUGC mean (mm $\times$ s)	13.5 $\pm$ 5.0	11 $\pm$ 5.8	0.167 ^a
iAUGC Diff (mean-median)	0.8 $\pm$ 0.7	0.9 $\pm$ 0.8	0.741
Ktrans median (1 min ⁻¹)	2.5 $\pm$ 2.5	2.3 $\pm$ 4.2	0.021
Ktrans mean (1 min ⁻¹)	5.5 $\pm$ 4.8	2.5 $\pm$ 2.7	0.006
Ktrans Diff [mean-median] (1 min ⁻¹)	2.9 $\pm$ 3.2	1.3 $\pm$ 3.1	0.003
Ve median	0.5 $\pm$ 0.1	0.5 $\pm$ 0.1	0.665 ^a
Ve mean	0.5 $\pm$ 0.1	0.5 $\pm$ 0.1	0.642 ^a
Ve Diff (mean-median)	0.02 $\pm$ 0.01	0.02 $\pm$ 0.02	0.484
Kep median (1 min ⁻¹)	5.2 $\pm$ 7.0	3.3 $\pm$ 5.0	0.016
Kep mean (1 min ⁻¹)	9.7 $\pm$ 8.5	4.8 $\pm$ 5.1	0.005
Kep Diff (mean-median) (1 min ⁻¹)	4.7 $\pm$ 4.8	1.6 $\pm$ 2.0	0.003
ADC mean (1 mm ⁻²)	792 $\pm$ 169.4	927 $\pm$ 242.6	0.006
ADC median (1 mm ⁻²)	786 $\pm$ 176.8	917 $\pm$ 252.7	0.013
ADC Diff (mean-median) (1 mm ⁻²)	17 $\pm$ 14.7	21 $\pm$ 21.7	0.819
ADC min (1 mm ⁻²)	535 $\pm$ 174.5	708 $\pm$ 274.8	0.002^a
MR spectroscopy ratio mean	0.8 $\pm$ 0.8	0.5 $\pm$ 0.4	0.141
MR spectroscopy ratio max	1.1 $\pm$ 1.3	0.6 $\pm$ 0.5	0.104

Note: ADC, apparent diffusion coefficient; Diff, difference between mean and median; iAUGC, area under gadolinium curve; Kep, efflux rate constant between extracellular space and plasma; Ktrans, transfer constant between plasma and extracellular space; MRS, MR- spectroscopy; p , p -value of Mann-Whitney U test; SD, standard deviation; Ve, fractional volume of extracellular space per unit volume of tissue.

Post-initial enhancement changes are coded with three colour hues: blue for increase signal intensity to +10%; green for plateau and red for signal decrease to -10%; a fast rate of initial contrast enhancement is coded as bright; an intermediate rate is coded as medium and a slow rate of initial contrast enhancement is coded as dark.

p^a , p -value of t -test.

Table 2 shows the significant semi-quantitative and quantitative parameters in functional MRI to differentiate malignant and benign lesions in PZ ($n = 69$).

Ktrans mean and Ktrans Diff were statistically significant higher in malignant lesions than in benign lesions. ADC mean, ADC

median and ADC min were statistically significant lower in malignant lesions than in benign lesions.

In the regression model ADC min was the best predictor of malignancy in PZ ($p = 0.002$). The regression coefficient R^2

Table 2. Significant semi-quantitative and quantitative parameters of functional MRI in lesions in PZ ($n = 69$)

Parameters	Malignant lesions ($n = 50$) mean $\pm$ SD	Benign lesions ($n = 19$) mean $\pm$ SD	p
Medium (intermediate) red %	12.6 $\pm$ 13.0	5.6 $\pm$ 10.8	0.008
Ktrans mean (1 min ⁻¹)	5.1 $\pm$ 4.9	2.8 $\pm$ 3.5	0.046
Ktrans Diff (mean-median) (1 min ⁻¹)	2.6 $\pm$ 3.2	1.7 $\pm$ 4.0	0.025
ADC mean (1 mm ⁻²)	796 $\pm$ 180.1	988 $\pm$ 287.6	0.018
ADC median (1 mm ⁻²)	790 $\pm$ 187.9	988 $\pm$ 299.6	0.013
ADC min (1 mm ⁻²)	532 $\pm$ 186.4	789 $\pm$ 302.9	0.003 ^a

Note: ADC, apparent diffusion coefficient; Diff, Difference between mean and median; Ktrans, transfer constant between plasma and extracellular space; p , p -value of Mann-Whitney U test; SD, standard deviation.

Post-initial enhancement changes are coded with three colour hues: blue for increase signal intensity to +10%; green for plateau and red for signal decrease to -10%; a fast rate of initial contrast enhancement is coded as bright; an intermediate rate is coded as medium and a slow rate of initial contrast enhancement is coded as dark.

p^a , p -value of t -test.

was 0.287. The AUC based on the logistic regression model was 0.7506 [95% CI (0.6095–0.8916)].

The mean and maximum MR spectroscopy ratios were not significantly different in malignant and benign lesions in PZ.

Table 3 shows the significant semi-quantitative and quantitative parameters in functional MRI to differentiate malignant and benign lesions in TZ ($n = 41$).

Ktrans mean and Ktrans Diff were statistically significant higher in malignant lesions than in benign lesions. Kep median, Kep mean and Kep Diff were statistically significant higher in malignant lesions than in benign lesions.

ADC mean, ADC median, ADC Diff and ADC min were not significantly different between malignant and benign lesions in TZ ($p = 0.193$; $p = 0.357$; $p = 0.419$; $p = 0.192$).

In the regression model Kep Diff was the best predictor of malignancy in TZ ($p = 0.018$). The regression coefficient R^2 was 0.379. The AUC based on the logistic regression model was 0.7514 [95% CI (0.5950–0.9079)].

The mean and maximum MR spectroscopy ratios were not significantly different in malignant and benign lesions in TZ.

Table 4 shows the significant semi-quantitative and quantitative parameters in functional MRI to differentiate PCA with Gleason score 6 and Gleason score ≥ 7 .

Peak enhancement, Ktrans median, mean and Diff, iAUGC median, mean and Diff, and Ve median and mean were statistically significant higher in PCA with Gleason score ≥ 7 than in PCA with Gleason score 6.

ADC mean, ADC median, ADC Diff and ADC min were not significantly different between PCA with Gleason score 6 and

Table 3. Significant semi-quantitative and quantitative parameters of functional MRI in lesions in TZ ($n = 41$)

Parameters	Malignant lesions ($n = 27$) mean $\pm$ SD	Benign lesions ($n = 14$) mean $\pm$ SD	p
Red (decrease) %	33 $\pm$ 22.5	12.5 $\pm$ 9.4	<0.001 ^a
Ktrans mean [1 min ⁻¹]	6.1 $\pm$ 4.8	2.1 $\pm$ 1.1	0.031
Ktrans Diff [mean-median] [1 min ⁻¹]	3.3 $\pm$ 3.2	0.7 $\pm$ 0.5	0.022
Kep median [1 min ⁻¹]	5.4 $\pm$ 7.1	2.5 $\pm$ 1.0	0.036
Kep mean [1 min ⁻¹]	10.3 $\pm$ 7.7	3.8 $\pm$ 1.7	0.009
Kep Diff [mean-median] [1 min]	5.4 $\pm$ 4.6	1.3 $\pm$ 0.9	0.010

Note: Diff, difference between mean and median; Ktrans, transfer constant between plasma and extracellular space; Kep, efflux rate constant between extracellular space and plasma; p , p -value of Mann-Whitney U test; SD, standard deviation.

Post-initial enhancement changes are coded with three colour hues; blue for increase signal intensity to +10%; green for plateau and red for signal decrease to -10%; a fast rate of initial contrast enhancement is coded as bright; an intermediate rate is coded as medium and a slow rate of initial contrast enhancement is coded as dark.

p^a , p -value of t -test.

Table 4. Significant semi-quantitative and quantitative parameters of functional MRI in PCA with Gleason score 6 and Gleason score ≥ 7 ($n = 77$)

Parameters	Gleason score 6 ($n = 12$) mean $\pm$ SD	Gleason score ≥ 7 ($n = 65$) mean $\pm$ SD	p
Peak enhancement %	103.7 $\pm$ 23.7	130.5 $\pm$ 22.3	0.001
Blue (increase) %	63.5 $\pm$ 27.0	46.6 $\pm$ 25.1	0.043
Red (decrease) %	16.6 $\pm$ 19.3	32.5 $\pm$ 22.3	0.026
Bright (fast) green %	2.6 $\pm$ 2.8	8.3 $\pm$ 8.4	0.029
Bright (fast) red %	2.8 $\pm$ 5.6	11.8 $\pm$ 15.1	0.026
Dark (slow) blue %	49.5 $\pm$ 30.2	23.6 $\pm$ 21.3	0.002
iAUGC median (mm $\times$ s)	8.9 $\pm$ 3.7	13.8 $\pm$ 4.9	0.002
iAUGC mean (mm $\times$ s)	9.2 $\pm$ 3.8	14.4 $\pm$ 4.8	0.002
iAUGC Diff (mean-median)	0.4 $\pm$ 0.5	0.8 $\pm$ 0.7	0.024
Ktrans median (1 min ⁻¹)	1.36 $\pm$ 1.1	2.8 $\pm$ 2.6	0.008
Ktrans mean (1 min ⁻¹)	2.80 $\pm$ 3.5	6.0 $\pm$ 4.9	0.015
Ktrans Diff (mean-median) (1 min ⁻¹)	3.1 $\pm$ 3.3	1.4 $\pm$ 2.4	0.037
Ve median	0.4 $\pm$ 0.1	0.5 $\pm$ 0.1	0.001
Ve mean	0.4 $\pm$ 0.1	0.5 $\pm$ 0.1	<0.001

Note: Diff, difference between mean and median; iAUGC, area under gadolinium curve; Ktrans, transfer constant between plasma and extracellular space; p , p -value of Mann-Whitney U test; SD, standard deviation; Ve, fractional volume of extracellular space per unit volume of tissue.

Post-initial enhancement changes are coded with three colour hues: blue for increase signal intensity to +10%; green for plateau and red for signal decrease to -10%; a fast rate of initial contrast enhancement is coded as bright; an intermediate rate is coded as medium and a slow rate of initial contrast enhancement is coded as dark.

PCA with Gleason score ≥ 7 ($p = 0.381$; $p = 0.377$; $p = 0.847$; $p = 0.716$).

In the regression model peak enhancement was the best parameter to differentiate PCA with Gleason score 6 and Gleason score ≥ 7 ($p = 0.004$). The regression coefficient R^2 was 0.319. The AUC based on the logistic regression model was 0.7692 [95% CI (0.6807–0.9118)].

The mean and maximum MR spectroscopy ratio were not significantly different in PCA with Gleason score 6 and Gleason score ≥ 7 .

DISCUSSION

Our results showed ADC mean and ADC min was statistically significant lower in malignant lesions than in benign lesions for lesions in PZ.

Li et al¹⁴ did also found significant differences in ADC values between malignant and benign lesions in PZ. Peng et al¹⁵ reported that the combination of 10th percentile ADC, average ADC and T_2 weighted skewness are effective imaging features to distinguish malignant from normal tissue in PZ. They concluded 10th percentile ADC is more effective than average ADC.

In our regression analysis ADC min was the best predictor of malignancy in all lesions and in lesions of PZ. Therefore we recommend the use ADC min in mp-MRI.

For lesions in TZ there was no significant difference in the ADC values between malignant and benign prostate lesions. Our results are in concordance with a 3T MR imaging study of Hoecks et al¹⁶ in which DWI-MRI using ADC may not improve cancer detection in TZ as with compared T2WI.

For quantitative DCE- parameters in PZ we found Ktrans mean and Ktrans Diff were statistically significant higher in malignant lesions than in benign lesions of PZ.

Van Dorsten et al¹⁷ observed higher Ktrans and higher Kep in malignant lesions compared with normal tissue in PZ. Similar results are found in a study of Ocak et al¹⁸ in which Ktrans, Kep and iAUGC were significantly higher in cancer than in normal tissue of PZ.

For lesions in TZ we observed Ktrans mean, Ktrans Diff, Kep mean, Kep median and Kep Diff were statistically significant higher in malignant lesions than in benign lesions. In our regression analysis Kep Diff was the best predictor of malignancy in TZ. In concordance Oto et al¹⁹ reported Ktrans parameter can potentially improve the detection of PCA in TZ.

In our study we performed the differences between mean and median of the parameters Ktrans, Kep, Ve, iAUGC and ADC because malignant lesions show heterogeneous histologic characteristics that may influence mean and median of these parameters and lead to different values from mean and median.

It can be explained by the heterogeneity of tumours and in the possibility that normal tissue interspersed in this tumours.²⁰ Only in homogenous tumours, densely packed with malignant cells, the differences between mean and median may be less pronounced and mean and median are nearly identical.²⁰

We observed the difference of mean and median of Ktrans and Kep showed more significant differences between malignant and benign lesions than median and mean of these parameters alone. Therefore we recommend mean and median and in addition the use of the difference between mean and median as quantitative parameters in DCE-MRI.

Our MR spectroscopy ratio was not significantly different in malignant and benign lesions of all lesions and of PZ and TZ alone. We have decided in concordance with the actual PI-RADS v2 guidelines, to eliminate MR spectroscopy in the future from our routine mp-MRI protocol.²¹

In the study ADC values have been shown to correlate with the Gleason score as a potential marker of tumour aggressiveness.^{5,15} Hötter et al⁵ found a statistically significant inverse correlation between the ADC value and all Gleason scores. This finding is attributed to the higher cellularity known to be present in higher-grade tumours.⁵ In our study ADC mean and ADC min were not significantly different between PCA with Gleason score 6 and PCA with Gleason score ≥ 7 . One reason of the different results seems to be our small number of PCA with Gleason score 6 ($n = 12$) compared to Gleason score ≥ 7 ($n = 65$).

We observed statistically higher peak enhancement, Ktrans median, mean and Diff, iAUGC median, mean and Diff, and Ve median and mean in PCA with Gleason score ≥ 7 than in Gleason score 6. Hötter et al⁵ found statistically significantly higher Ktrans for tumours with higher Gleason score, but its benefit was only in characterization more aggressive tumours. It may reflect the fact that aggressive tumours induce neovascularization to accommodate their high demand for blood supply.

Our study has several limitations. In all patients clinically prostate cancer was suspected and showed lesions were scored in PI-RADS 4 or PI-RADS 5 categories. We did not observed lesions with PI-RADS category 3 or less. Therefore selection bias

is possible. In our study DWI MRI was performed with relative low b -values $\leq 800 \text{ s mm}^{-2}$. In addition, we used only calculated high b -values images. In the future high b -value imaging ($\geq 1400 \text{ s mm}^{-2}$) should be obtained.²¹ Another limitation may be the additional costs for the quantitative software model. Our standard of reference in our study was determined by the results of systematic TRUS-guided core biopsies with additional targeted biopsies, therefore sample errors cannot be excluded. We did not use software co-registration of ultrasound and MRI, which could improve the biopsy results.

The PI-RADS v2 guidelines don't use quantitative parameters of functional techniques.²¹ In the future quantitative parameters of functional techniques of mp-MRI of the prostate could be introduced in the PI-RADS guidelines. For lesions in PZ the mean and min of ADC could be used. In addition, for DCE-MRI the mean, median and the difference of mean and median of Ktrans could be used for further differentiation of lesions with DWI score of 3.

For lesions in TZ with a T2W score of 3 the PI-RADS v2 guidelines uses DWI score for further differentiation.²¹ In contrary, we found for lesions in TZ quantitative parameters of DCE-MRI (Ktrans, Kep) are useful for further characterization of these lesions. Further investigations are necessary.

We recommend the use of DWI-MRI and DCE-MRI as the two functional techniques of mp-MRI of the prostate. We recommend the use of quantitative parameters in the analysis of DWI-MRI and DCE-MRI of the prostate. In DWI, ADC mean and min should be included as quantitative parameters in the analysis. For DCE-MRI we recommend the use of mean, median and the difference between mean and median of the quantitative parameters Ktrans, Kep, Ve.

The findings suggest that MR spectroscopy is no longer necessary in mp-MRI of the prostate.

Semi-quantitative and quantitative analysis of functional parameter in mp-MRI shows a potential to help radiologists to achieve standardized, reproducible, and more efficient interpretation of mp-MRI of the prostate to improve prostate cancer detection and improve predictive accuracy of cancer aggressiveness.¹⁵

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