Received:
25 May 2015

Revised:
4 August 2015

Accepted:
11 August 2015

doi: 10.1259/bjr.20150422

Cite this article as:

Hauth E, Hohmuth H, Cozub-Poetica C, Bernand S, Beer M, Jaeger H. Multiparametric MRI of the prostate with three functional techniques in patients with PSA elevation before initial TRUS-guided biopsy. *Br J Radiol* 2015; **88**: 20150422.

FULL PAPER

Multiparametric MRI of the prostate with three functional techniques in patients with PSA elevation before initial TRUS-guided biopsy

¹ELKE HAUTH, MD, PhD, ²HORST HOHMUTH, MD, ¹CORINA COZUB-POETICA, MD, ²STEFAN BERNAND, MD, ³MEINRAD BEER, MD, PhD and ¹HORST JAEGER, MD

¹Radiologische Praxis, Ulm, Germany

²Uropraxis, Ulm, Germany

³Department of Diagnostic and Interventional Radiology, University Hospital, Ulm, Germany

Address correspondence to: Dr Elke Hauth

E-mail: ehauth@t-online.de

Objective: Multiparametric MRI (mp-MRI) of the prostate is increasingly being used for local staging and detection of recurrence of prostate cancer (PCA). In patients with elevated prostate-specific antigen (PSA), mp-MRI could provide information on the position of the cancer, allowing adjustments to be made to the needle depth and direction before repeat transrectal ultrasound (TRUS)-guided biopsy to ensure accurate sampling of lesions. The purpose of the prospective study was to evaluate mp-MRI of the prostate in patients with PSA elevation before initial TRUS-guided biopsy.

Methods: mp-MRI was performed in 94 patients using a 1.5-T scanner (MAGNETOM Aera®; Siemens Healthcare, Erlangen, Germany) and 16-channel phased-array body coil (Siemens Healthcare). T_2 weighted images (T2WI), diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) MRI and MR spectroscopy were obtained. TRUS-guided random biopsies and additional targeted biopsies of suspicious MRI areas were performed.

Results: Additional targeted biopsies were obtained in 17 of 43 (40%) patients with PCA. 11 of 17 targeted biopsies contained PCA. 5 of 11 PCAs were diagnosed only by additional targeted biopsies. Sensitivity of mp-MRI in patients was 97.7% and specificity was 11.8%. mp-MRI was false negative in one patient. Sensitivity of mp-MRI in 207 lesions was 80.9% and specificity was 44.7%. In a logistic regression model, the apparent diffusion coefficient value was the only significant parameter to differentiate malignant and benign lesions.

Conclusion: mp-MRI should be performed in patients with PSA elevation before initial TRUS-guided biopsy to allow additional targeted biopsies from suspicious areas of MRI. We recommend mp-MRI with T2WI, DWI, DCE MRI and MR spectroscopy. DWI as the most reliable technique should be used in every mp-MRI.

Advances in knowledge: DWI is the most reliable technique in mp-MRI of the prostate.

INTRODUCTION

Multiparametric MRI (mp-MRI) as a combination of morphological and functional MRI techniques is increasingly being used for local staging of prostate cancer (PCA), follow-up after treatment of PCA and detection of recurrence of PCA.¹ mp-MRI includes a combination of high-resolution T_2 weighted images (T2WI) and at least two functional MRI techniques to provide better diagnosis of PCA than T2WI alone or with only one functional technique.²

In patients with elevated prostate-specific antigen (PSA) ($>3\text{--}4\text{ ng ml}^{-1}$) or suspicious digital rectal examination, transrectal ultrasound (TRUS)-guided biopsy will be performed to detect potential PCA.² Because of the poor

sensitivity for detection and localization of malignant lesions in TRUS, a random biopsy is usually performed in a systematic six, eight or ten pattern. It is possible that cancer located outside the routine biopsy site may be missed or that sampling error occurs. For these reasons, mp-MRI may allow a better detection and localization of PCA for guidance of biopsy.

Studies,^{3,4} reported on the results of mp-MRI before repeat TRUS-guided biopsy in patients in whom PCA was still suspected, revealed that this technique could provide information on the position of the cancer, allowing adjustments to be made to the needle depth and direction before TRUS-guided biopsy to ensure accurate sampling of lesions.²

However, only a few studies^{5–7} reported on the role and benefit of mp-MRI in patients with elevated PSA before initial TRUS-guided biopsy.

Therefore, the purpose of this prospective study was to evaluate mp-MRI of the prostate in patients with PSA elevation before initial TRUS-guided biopsy.

METHODS AND MATERIALS

Patients

In the time interval of January 2011 to May 2013, we performed mp-MRI of the prostate before initial TRUS-guided biopsy in 94 consecutive patients (mean age: 63 years; range: 43–83 years) in whom PCA was suspected owing to an elevated PSA value (≥ 3 ng ml⁻¹).

MRI

MRI was performed on a 1.5-T scanner (MAGNETOM Aera®; Siemens Healthcare, Erlangen, Germany), using a dedicated 16-channel phased-array body coil (Siemens Healthcare). Peristalsis was suppressed with an intravenous application of 1- to 2-ml butylscopolaminebromide (Buscopan®; Boehringer, Ingelheim, Germany), which was given immediately before MR spectroscopic imaging. Table 1 shows MRI protocol of the prostate.

Diffusion-weighted MRI

Diffusion-weighted MRI was performed with a single-shot echo-planar imaging sequence (Table 1). The image software automatically calculated apparent diffusion coefficient (ADC) maps.

MR SPECTROSCOPY

Axial T2WI served as background images for the 3-dimensional (3D) MR spectroscopy measurement. A 3D weighted *k*-space acquisition with dual-frequency selective refocusing pulses to suppress water and lipid signals was used.⁸ The surrounding lipid tissues were additionally suppressed by manual placement of saturation slabs. The nominal voxel size was kept constant in all measurements at $8 \times 8 \times 8$ mm³ 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 and 12 min (repetition time/echo time 930/120 ms). Post-processing data involved 3D using Hamming filter in *k*-space to reduce intervoxel signal contamination and zero filling to the nearest power of two before spatial Fourier transformation. Zero filling and filtering of the MR spectroscopy matrix artificially increase the spatial resolution beyond the actual spatial resolution of the measurement.⁸

Dynamic contrast-enhanced MRI

Dynamic contrast-enhanced (DCE) MRI was conducted using a 3D axial gradient echo sequence (Table 1). 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 Schering Pharma AG, Berlin, Germany) was injected, using a dose of 0.1 mmol kg⁻¹, 16 s after the beginning of the start of the dynamic image series. Contrast agent was administrated at 1 ml s⁻¹, using an automated injector (Ulrich Medical, Ulm, Germany). After the dynamic series, image subtraction of the contrast-enhanced images from the images before the administration of contrast agent was performed.

Post-processing of dynamic MRI data

We used a commercial software package for an automated analysis of the DCE MRI data (iCAD Inc. Nashua, NH). The software allows a pixel-based semi-quantitative analysis. The analysis is based on the assumption of three common dynamic curve types after initial uptake: a persistent increase is coded as blue pixels, a plateau is coded as green pixels and washout is coded as red pixels. Detailed information of the analysis process has been published in earlier publication.⁹

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

Table 1. MRI protocol of the prostate

Sequence	Imaging plane	Repetition time/echo time (ms)	Flip Angle (°)	Field of view (mm)	Matrix size (mm)	Slice thickness (mm)	Imaging time (min)
<i>T</i> ₂ weighted turbo inversion recovery magnitude	Coronal	4300/31	150	380	320 × 246	5	3.06
<i>T</i> ₂ weighted turbo spin echo	Sagittal	5180/94	160	250	256 × 193	3	0.58
	Coronal	3330/99	160	220	329 × 298	3	4.08
	Axial	3540/99	160	220	320 × 256	3.6	4.23
Single-shot echoplanar imaging <i>b</i> -values: 0, 100, 400, 800 s mm ⁻³	Axial	3600/61		260	160 × 120	3.7	5.08
3-dimensional gradient echo: 20 acquisitions	Axial	7.39/4.76	12	260	129 × 146	3	0.23

citrate (Cho + Cr/Ci) ratio was calculated and was overlaid on the T2WI axial images as colour metabolic maps.

Image interpretation and data analysis

T2WI, diffusion-weighted imaging (DWI), DCE MRI and MR spectroscopy were successfully performed in all patients. Two radiologists with more than 3 years' experience in interpreting MRI of the prostate reviewed the MR images.

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 radiologists described the lesions and their signal intensity (SI) in the peripheral zone (PZ) of the prostate on T2WI as follows: focal nodular mass with low SI, segmental low SI area, diffuse low SI area.¹⁰ Suspicious lesions located in the transitional zone (TZ) of the prostate were described on T2WI as low SI mass with indistinct margins (erased charcoal sign).²

Each lesion diagnosed in T2WI was correlated in DWI. The ADC value was evaluated in ADC maps with positioning of a predetermined region of interest (ROI) within the lesion. An ADC value $<1000 \text{ s mm}^{-3}$ was defined as suspicious of malignancy.³

Each lesion diagnosed in T2WI was correlated in DCE MRI. We differentiated three post-initial dynamic characteristics of lesions in which the most suspicious colour hue was the basis criterion of the lesion.

When a lesion showed any red pixels (washout characteristic), it was coded as red. When a lesion showed green (plateau characteristic) and blue pixels (increasing characteristic), it was classified as green. When a lesion showed only blue pixels and no green or red pixels, it was classified as blue. A lesion with red pixels was defined as suspect for malignancy.

In MR spectroscopy, voxels were considered as suspicious when the ratio of (choline + creatine)/citrate was ≥ 1.0 .¹¹

We used a sum of prostate imaging reporting and data system (PI-RADS) score, including all information of morphological and functional MRI data to classify a lesion. Each lesion was scored for the presence of PCA on the five-point scale.¹² Lesions with PI-RADS 1 and 2 were classified for the purpose of statistical analysis as "not malignant". Lesions with PI-RADS 3–5 were classified as malignant. If one lesion in a patient was classified as malignant, the patient was considered for the purpose of statistical analysis as "malignant".

The TRUS-guided random core biopsies were obtained with an 18-gauge biopsy cut needle by two urologists and included five samples per lobe (lateral, apex, middle, base and TZ). In patients in whom the suspicious area based on mp-MRI might have been outside the routine TRUS-guided random core biopsy, additional targeted core biopsies of the suspicious area were performed.

Histopathology of all obtained samples was correlated site-by-site with MRI results by the two radiologists. The Gleason grading system was used to classify PCA as low grade (Gleason score of ≤ 6) and high grade (Gleason score ≥ 7).

Statistical analyses

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

The Kruskal–Wallis test was used to compare PSA value and histopathological results. The Mann–Whitney U test was applied for the estimation of differences for lesion size and their histological results and for the estimation of differences in volume of the prostate in patients with and without PCA. The Fisher's exact test was used for the estimation of differences of PI-RADS categories and the histopathological results. For independent variables, a multivariate regression model was performed. Stepwise logistic regression was applied to select the best predictors of benign lesions. The coefficient of determination R^2 was obtained.

RESULTS

Patients

The median time interval between MRI and TRUS-guided biopsy was 21 days (range: 2–48 days). TRUS-guided core biopsy revealed PCA in 43 of 94 (46%) patients, prostatitis in 30 of 94 (32%) patients, normal prostate tissue in 19 of 94 (20%) patients and prostatic intraepithelial neoplasia (PIN) or atypical hyperplasia in 2 of 94 (2%) patients.

In 32 of 43 (74.4%) patients, PCA was localized in PZ; in 11 of 43 (25.6%) patients, PCA was localized in TZ.

In the TRUS-guided random core biopsy, a mean of 11 tissue samples (range: 10–13 tissue samples) was obtained. In 38 of 94 (40.4%) patients, additional targeted core biopsies were performed. In 56 of 94 (59.6%) patients, only TRUS-guided random core biopsies were performed.

Additional targeted core biopsies were obtained in 17 of 43 (40%) patients with PCA. 11 of 17 targeted core biopsies contained PCA. 5 of 11 PCAs were diagnosed only by the additional targeted core biopsies and not by the TRUS-guided random core biopsies.

Prostate

The average PSA value was 9 ng ml^{-1} (range: $3\text{--}31 \text{ ng ml}^{-1}$). The mean volume of the prostate was 51 cm^3 (range: $17\text{--}140 \text{ cm}^3$). We diagnosed benign prostate hyperplasia (BPH) in TZ in 84 of 94 (89%) patients. 17 of 84 (20.2%) patients showed compression of PZ due to BPH.

Lesion characteristics

In 94 patients, we evaluated 207 lesions. The mean diameter of lesions was 14.3 mm (range: 2–36 mm). 174 of 207 (84%) lesions were found in PZ; 33 of 207 (16%) lesions were found in TZ.

Lesion configuration in PZ was a diffuse area of low SI in 72 of 174 (41%) lesions, a focal nodular mass in 64 of 174 (37%) lesions and a segmental low SI area in 38 of 174 (22%) lesions. In TZ, all lesions showed “erased charcoal sign”.

2 of 207 (1%) lesions were categorized in PI-RADS 1, 66 of 207 (32%) lesions were categorized in PI-RADS 2, 3 of 207 (2%) lesions in PI-RADS 3, 129 of 207 (62%) lesions in PI-RADS 4 and 7 of 207 (3%) lesions in PI-RADS 5.

TRUS-guided core biopsy revealed PCA in 68 of 207 (32.9%) lesions, prostatitis in 69 of 207 (33.3%) lesions, normal prostate tissue in 63 of 207 (30.4%) lesions and PIN and atypical hyperplasia in 7 of 207 (3.4%) lesions.

In 49 of 68 (72%) malignant lesions, the Gleason score was seven; in 19 of 68 (28%), the Gleason score was six.

Patient-based MRI results

2 of 94 (2%) patients with atypical hyperplasia and PIN were categorized as not malignant. The sensitivity of mp-MRI was 97.7% [42 of 43; 95% confidence interval (CI): 87.7–99.9%], and the specificity was 11.8% (6 of 51; 95% CI: 4.4–23.9%). The positive-predictive value (PPV) was 48.3% (42 of 87; 95% CI: 37.4–59.3%), and the negative-predictive value (NPV) was 85.7% (6 of 7; 95% CI: 42.1–99.6%).

mp-MRI was false negative in 1 of 43 (2.3%) patients with malignant histology and false positive in 45 of 51 (88.2%) patients with benign histology.

Figures 1 and 2 show patients with true-positive MRI results.

Figures 3 and 4 show patients with false-positive MRI results. Histopathology revealed prostatitis.

Figure 1. Prostate in a 77-year-old patient (prostate-specific antigen 14.3 ng ml^{-1}) with true-positive MRI result classified as prostate imaging reporting and data system 5. Histopathology revealed prostate cancer in the right peripheral zone (PZ) of the prostate (Gleason 7). (a) Axial T_2 weighted image (T2WI) shows a focal lesion with low signal intensity in the right PZ of the prostate (arrow). (b) Axial apparent diffusion coefficient (ADC) map shows a low ADC value (mean: $828 \text{ mm}^2 \text{ s}^{-1}$) in the corresponding area (arrow). (c) Parametric map from dynamic contrast-enhanced MRI shows contrast enhancement kinetics with washout characteristics within the lesion, coded as red by the software (arrow). A persistent increase is coded as blue pixels and a plateau as green pixels. (d) MR spectroscopy reveals a ratio $[\text{choline (Cho)} + \text{creatine (Cr)}]/\text{citrate (Ci)} = 1.23$ (arrow). Avg, average; Min, minimum; SD, standard deviation. For colour images see online.

Figure 2. Prostate in a 70-year-old patient (prostate-specific antigen 11.5 ng ml^{-1}) with a true-positive MRI result classified as prostate imaging reporting and data system 5. Histopathology revealed prostate cancer in the right anterior transitional zone (TZ) of the prostate (Gleason 6). (a) Axial T_2 weighted image (T2WI) shows a focal lesion with “erased charcoal sign” in the right TZ of the prostate (arrow). (b) Apparent diffusion coefficient (ADC) map shows a low ADC value (mean: $407 \text{ mm}^2 \text{ s}^{-1}$) in the corresponding area (arrow). (c) Parametric map from dynamic contrast-enhanced MRI shows contrast enhancement kinetics with washout characteristics within the lesion, coded as red by the software (arrow). A persistent increase is coded as blue pixels and a plateau as green pixels. (d) MR spectroscopy reveals a ratio [choline (Cho) + creatine (Cr)]/citrate (Ci) = 3.02 (arrow). Avg, average; Min, minimum; SD, standard deviation. For colour images see online.

The volume of the prostate in patients without malignant histology was significantly higher (average: 56 cm^3 , range: $21\text{--}129 \text{ cm}^3$) than in patients with PCA (average: 45 cm^3 , range: $17\text{--}139.5 \text{ cm}^3$) ($p = 0.002$).

Lesion-based MRI results

The sensitivity of mp-MRI based on 200 lesions (7 lesions with PIN and atypical hyperplasia were excluded) was 80.9% (55 of 68; 95% CI: 69.5–89.4%), and the specificity was 44.7% (59 of 132; 95% CI: 36.0–53.6%). PPV was 43% (55 of 128; 95% CI: 34.3–52.0%), and NPV was 81.9% (59 of 72; 95% CI: 71.1–90.0%).

MRI was false negative in 13 of 68 (19.1%) lesions with malignant histology. MRI was false positive in 73 of 132 (55.3%) lesions with benign histology.

The sensitivity of mp-MRI based on 169 lesions in PZ (5 lesions in PZ with PIN and atypical hyperplasia were excluded) was 75.9% (41 of 54; 95% CI: 62.4–86.5%), and the specificity was

51.3% (59 of 115; 95% CI: 41.8–60.7%). PPV was 42.3% (41 of 97; 95% CI: 32.3–52.7%), and NPV was 81.9% (59 of 72; 95% CI: 71.1–90.8%).

MRI was false negative in 13 of 68 (19.1%) lesions with malignant histology. MRI was false positive in 56 of 115 (48.7%) lesions with benign histology.

All 33 lesions in TZ were considered as malignant lesions in MRI. 2 of 33 (6%) lesions in TZ with PIN and atypical hyperplasia in histology were excluded from the analysis. In 14 of 31 (45.3%) lesions in TZ, histology was malignant, in 11 of 31 (35%) lesions, histology showed prostatitis and 6 of 31 (19.4%) lesions showed normal tissue. Therefore, 17 of 31 (54.8%) were false positive in MRI.

The PI-RADS categories were significantly different in all lesion groups (normal vs malignant vs prostatitis) ($p < 0.001$). Lesions with normal tissue and malignant lesions showed statistical differences

Figure 3. Prostate in a 56-year-old patient (prostate-specific antigen 18.6 ng ml^{-1}) with false-positive MRI result classified as prostate imaging reporting and data system 4. Histopathology revealed atrophic tissue and prostatitis. (a) Axial T_2 weighted image (T2WI) shows a focal lesion with low signal intensity in the left peripheral zone of the prostate (arrow). (b) Apparent diffusion coefficient (ADC) map shows a low ADC value (mean: $530 \text{ mm}^2 \text{ s}^{-1}$) in the corresponding area. (c) Parametric map from dynamic contrast-enhanced MRI shows contrast enhancement kinetics with washout characteristics within the lesion, coded as red by the software (arrow). A persistent increase is coded as blue pixels and a plateau as green pixels. MR spectroscopy reveals no suspicious ratio [choline (Cho) + creatine (Cr)]/citrate (Ci). Avg, average; SD, standard deviation. For colour image see online.

regarding PI-RADS categories ($p > 0.002$). Lesions with normal tissue and prostatitis showed also statistical differences regarding PI-RADS categories ($p = 0.026$). In malignant lesions and lesions with prostatitis, there were no significant differences regarding PI-RADS categories. Table 2 shows the characteristics of lesions in MRI.

Lesions size was not statistically different in malignant and benign histology. Malignant lesions showed more focal nodular mass than lesions with prostatitis and normal tissue. The mean ADC value of malignant lesions was lower than in lesions with prostatitis and normal tissue. The MR spectroscopy ratio was higher in malignant lesions than in lesions with prostatitis and normal tissue. Malignant lesions showed more washout, coded as red pixels, than lesions with prostatitis and normal tissue. Table 3 shows the results of bivariate analysis of the functional MRI modalities in lesions.

Normal tissue showed a significantly different ADC value than malignant lesions ($p > 0.001$). Malignant lesions showed a significantly different ADC value than lesions with prostatitis ($p = 0.009$). In lesions with normal prostate tissue and prostatitis, the differences

in ADC value were not significant. DCE MRI showed no significant differences in all lesions.

Normal tissue showed a significantly different MR spectroscopy ratio than did malignant lesions ($p = 0.001$) and in lesions with prostatitis ($p = 0.003$). MR spectroscopy ratio was not significantly different in malignant lesions and lesions with prostatitis ($p = 0.662$). Table 4 shows the classification based on logistic regression model for all lesions.

The regression model was based on the reference categories ADC ≥ 1000 , DCE MRI with blue pixels and MR spectroscopy ratio < 1 . In this model, ADC value was the only significant parameter to differentiate malignant and benign lesions ($p = 0.042$). Lesions with ADC value $< 1000 \text{ mm}^2 \text{ s}^{-1}$ showed 2.298 more risk of malignancy than lesions $\geq 1000 \text{ mm}^2 \text{ s}^{-1}$. Regression coefficient R^2 was 0.085. Table 5 shows the classification based on logistic regression model for lesions in PZ of the prostate.

In this model, ADC value was a marginal insignificant parameter for differentiation of malignant and benign lesions in PZ

Figure 4. Prostate in a 66-year-old patient (prostate-specific antigen 5.1 ng ml^{-1}) with false-positive MRI result classified as prostate imaging reporting and data system 4. Histopathology revealed prostatitis. (a) Axial T_2 weighted image (T2WI) shows a focal lesion with low signal intensity in the left anterior transitional zone of the prostate (arrow). (b) Apparent diffusion coefficient (ADC) map shows a low ADC value (mean: $615 \text{ mm}^2 \text{ s}^{-1}$) in the corresponding area. (c) MR spectroscopy reveals a ratio [choline (Cho) + creatine (Cr)]/citrate (Ci) = 1.11 (arrow). Parametric map from dynamic contrast-enhanced MRI reveals no suspicious contrast kinetics. Avg, average; SD, standard deviation.

Table 2. Characteristics of lesions in MRI ($n = 200$)

Variables and values	Malignant lesions ($n = 68$)	Prostatitis ($n = 69$)	Normal tissue ($n = 63$)
Lesion size, mean $\pm$ SD	13.6 $\pm$ 7.518	13.9 $\pm$ 8.454	15.9 $\pm$ 8.635
Lesion configuration, n (%)			
Focal nodular mass	34 (50.0)	21 (30.4)	14 (22.2)
Segmental hypointense SI	10 (14.7)	24 (34.8)	14 (22.2)
Diffuse hypointense SI	24 (35.3)	24 (34.8)	35 (55.6)
Apparent diffusion coefficient value, mean $\pm$ SD	904.2 $\pm$ 288.95	1031.6 $\pm$ 280.44	1075.0 $\pm$ 194.62
MR spectroscopy, n (%)			
Ratio (choline + creatine)/citrate ≥ 1	54 (80)	16 (23)	4 (6)
Ratio (choline + creatine)/citrate < 1	14 (20)	53 (77)	59 (94)
MR spectroscopy, mean $\pm$ SD			
Ratio (choline + creatine)/citrate	0.98 $\pm$ 0.875	0.78 $\pm$ 0.592	0.49 $\pm$ 0.319
Dynamic contrast-enhanced MRI, n (%)			
Blue pixels	20 (29.4)	32 (46)	30 (48)
Green pixels	5 (7.4)	9 (13)	6 (9)
Red pixels	43 (63.2)	28 (41)	27 (43)

SD, standard deviation; SI, signal intensity.

($p = 0.053$). Lesions with ADC value $< 1000 \text{ mm}^3 \text{ s}^{-1}$ show 2.461 more risk of malignancy than lesions $\geq 1000 \text{ mm}^3 \text{ s}^{-1}$. Regression coefficient R^2 was 0.072.

The bivariate analysis of all functional MRI techniques of the lesions in TZ of the prostate did not show any significant differences in lesions with PCA, prostatitis and normal tissue.

DISCUSSION

Our patient-based mp-MRI results reached a sensitivity of 97.7% with a specificity of 11.8%. mp-MRI imaging was false negative in only one patient. Our lesion-based mp-MRI results showed a lower sensitivity of 80.9% with a better specificity of 44.7%.

Tanimoto et al⁵ evaluated T2WI, DWI and DCE MRI for diagnosis of PCA in patients with elevated PSA levels. With a 1.5-T scanner and an eight-channel phased-array body coil, they found a sensitivity of 95% with a specificity of 74%.

We reached similar sensitivities in diagnosis of PCA using 1.5-T scanner with a 16-channel phased-array body coil using T2WI and 3 functional techniques for mp-MRI.

In our study, the histology revealed prostatitis in 30 of 94 (32%) patients and in 69 of 207 (33.3%) lesions. That seems to be a contributing factor for the low specificity of diagnostic PCA in our study.

Table 3. Bivariate analysis of the functional MRI modalities in lesions ($n = 200$)

Variables	Values	Malignant lesions ($n = 68$), n (%)	Prostatitis ($n = 69$), n (%)	Normal tissue ($n = 63$), n (%)
ADC	≥ 1000	21 (30.9)	36 (52.2)	43 (68)
	< 1000	47 (69.1)	33 (47.8)	20 (32)
DCE MRI	Blue pixels	20 (29)	32 (46.4)	30 (48)
	Green pixels/ red pixels	48 (71)	37 (53.6)	33 (52)
MR spectroscopy	Ratio < 1	54 (80)	53 (77)	59 (94)
	Ratio ≥ 1	14 (20)	16 (23)	4 (6)

ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced.

ADC: normal tissue vs malignant vs prostatitis, $p < 0.001$; normal tissue vs malignant, $p < 0.001$; normal tissue vs prostatitis, $p = 0.148$; malignant vs prostatitis, $p = 0.009$. DCE MRI: normal tissue vs malignant vs prostatitis, $p = 0.058$; normal tissue vs malignant, $p = 0.065$; normal tissue vs prostatitis, $p = 1$; malignant vs prostatitis, $p = 0.035$. MR spectroscopy: normal tissue vs malignant vs prostatitis, $p = 0.001$; normal tissue vs malignant, $p = 0.001$; normal tissue vs prostatitis, $p = 0.003$; malignant vs prostatitis, $p = 0.662$.

Table 4. Classification based on logistic regression model for apparent diffusion coefficient (ADC), dynamic contrast-enhanced (DCE) MRI and MR spectroscopy parameters of lesions ($n = 200$)

Independent variables	Reference category	Standard failure	<i>p</i> -value	Odds ratio	95% confidence interval	
					Upper range	Lower range
Intercept		0.364	<0.001			
ADC	≥ 1000	0.4082	0.042	2.298	1.032	5.114
DCE MRI	Blue pixels	0.4044	0.816	1.099	0.497	2.427
MR spectroscopy	Ratio <1	0.4399	0.174	1.819	0.768	4.308

Watanabe *et al*¹³ observed chronic prostatitis to be the second most cause of false-positive findings when performing targeted biopsy of regions of low ADC. In studies with MRI-guided prostate biopsies in which no cancer was detected, the histology showed chronic prostatitis.

In our study, 31 lesions in TZ were considered in MRI as malignant. In only 14 of these 31 (45.3%) lesions, histology revealed PCA. We observed 54.8% of false-positive lesions on MRI in TZ, which was even higher than in PZ.

A 3.0-T MRI study of Hoeks *et al*¹⁴ found that DWI using ADC maps and DCE MRI may not improve TZ cancer detection as compared with T2WI. Therefore, T2WI warrants the strongest weighting in the TZ.

We observed significantly different ADC values in malignant tissue compared with normal tissue and prostatitis. In the logistic regression model, the ADC value was the best parameter to differentiate malignant *vs* benign lesions of the prostate in the PZ. In other studies,^{3,15} DWI has also been observed as the best functional technique in diagnosis of PCA in the PZ.

Lim *et al*¹⁶ reported about a sensitivity of 78–88% and a specificity of 88–89% in detection of PCA when ADC map was combined with T2WI, as opposed to T2WI alone, with a sensitivity of 67–74% and a specificity of 77–79%.

The advantages of DWI such as short acquisition time, high-contrast resolution and the development of using parallel imaging with DWI that reduces motion artefacts and chemical-shift

artefacts are important advantages that make it easy to use this functional modality as an adjunct to improve detection and localization of PCA. Therefore, we recommend the use of DWI with ADC maps routinely for mp-MRI of the prostate.

Our MR spectroscopy ratio was not significantly different in malignant lesions and lesions with prostatitis. We observed overlap between these histological results. In our logistic regression analysis, MR spectroscopy ratio was not significant in differentiating malignant *vs* benign lesions of the prostate.

A study by Wetter *et al*¹¹ combined MRI and MR spectroscopy of the prostate using an endorectal coil. They could find no diagnostic advantage in staging of PCA over MRI alone.

False-negative results are reported in a study of Lee *et al*.¹⁷ They observed a patient with PCA and a normal MR spectroscopy. They concluded that false-negative MR spectroscopy may lead to a false-negative diagnosis if MRI is not suspicious.

We found that MR spectroscopy should be a part of mp-MRI of the prostate to improve diagnosis of PCA, but the role of MR spectroscopy should not be overestimated; rather, it should be seen in the context with the other techniques of MRI. New software techniques allow analysis of MR spectroscopy data easier and faster when MR spectroscopy ratio is overlaid on the T2WI axial images as colour metabolic maps. Therefore, visualization of the prostatic and periprostatic anatomy is possible and might be useful for orientation, whether a certain MR spectroscopy ratio refers to the prostate gland or not.

Table 5. Classification based on logistic regression model for apparent diffusion coefficient (ADC), dynamic contrast-enhanced (DCE) MRI and MR spectroscopy parameters for lesions in peripheral zone of prostate ($n = 169$)

Independent variables	Reference category	Standard failure	<i>p</i> -value	Odds ratio	95% confidence interval	
					Upper range	Lower range
Intercept		0.3866	<0.001			
ADC	≥ 1000	0.4655	0.053	2.461	0.988	6.128
DCE MRI	Blue pixels	0.4565	0.741	1.163	0.475	2.845
MR spectroscopy	Ratio <1	0.5660	0.569	1.381	0.455	4.187

The current available studies do not provide a clear conclusion regarding the role of DCE MRI in detection of PCA. Watanabe et al¹³ were able to show an improvement of DCE MRI in combination with MRI. In the study of Hara et al,¹⁸ DCE MRI was shown to have a sensitivity of 93% and specificity of 96% in patients with elevated PSA before TRUS-guided biopsy.

We found that DCE MRI might be useful in diagnosis of PCA, especially in PZ, and should therefore be a part of functional technique in mp-MRI. In TZ, the use of DCE MRI is problematic because BPH can enhance and washout like PCA.

We used a software package (iCAD Inc., Nashua, NH) that automatically and reliably converts contrast kinetic information of the entire prostate pixel-based into colour-coded images. It allows time-consuming manual ROI placements.

There has been no study with regard to which technique is the best in diagnosis of PCA. Each technique has one or more advantages and limitations. In our study, logistic regression analysis of all three functional techniques resulted in a regression coefficient R^2 of 0.085. Therefore, there must be other factors not examined in this study that explain the outcome parameters. We recommend the use of all three functional techniques in mp-MRI.

We performed additional targeted biopsies in 17 of 43 (39.5%) patients with PCA. 11 of 17 targeted core biopsies contained PCA. Five of them were diagnosed only by the additional targeted core biopsies. Three of these five PCA were localized in TZ.

Haffner et al⁷ observed sensitivity, specificity and accuracy of targeted biopsies of 95%, 100% and 98% compared with 95%, 83% and 88% for systematic TRUS-guided biopsies, respectively. The detection accuracy of significant PCA by targeted biopsies was higher than that of systematic TRUS-guided biopsies.

The TZ of the prostate, especially the anterior part of TZ, is undersampled by TRUS-guided biopsy, possibly leading to false-negative biopsy results. This is problematic because the increasing evidence of these tumours indicates that PCA in these areas may have clinically significant PCA.¹⁹ In patients who underwent MR-guided biopsy after negative TRUS-guided biopsy, PCAs were found in the anterior part of the prostate in 47–57%.²⁰ Therefore, MRI may be used to investigate the possibility of PCA in TZ, especially in the anterior TZ.

There are some limitations of our study. We did not provide data on the quality of spectra. Another limitation of this study was that definitive pathology from radical prostatectomy in patients with operated PCA was not available. Our reference standard was TRUS-guided core biopsies. A limitation was the choice for TRUS-guided biopsies, to validate lesions that were identified on MRI. We did not use software co-registration of ultrasound and MRI. The urologist aims the biopsy needle at the prostate area where the reviewed prior MRI demonstrates the suspicious lesion. Therefore, sample errors cannot be excluded, especially in small lesions. In patients with benign results, no follow-up was available in our study.

CONCLUSION

mp-MRI in patients with PSA elevation should be performed before initial TRUS-guided biopsy to allow additional targeted biopsies from areas rendered suspect by MRI. This could reduce false-negative results of random TRUS-guided biopsies.

We recommend that mp-MRI should be performed with morphological T2WI in combination with all three functional techniques (DWI, DCE MRI and MR spectroscopy).

DWI with ADC value is the most reliable technique to differentiate malignant vs benign lesions of the prostate and should be used in every mp-MRI of the prostate.

REFERENCES

1. Hoeks CM, Barentsz JO, Hambrock T, Yakar D, Somford DM, Heijmink SW, et al. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. *Radiology* 2011; **261**: 46–66. doi: [10.1148/radiol.11091822](https://doi.org/10.1148/radiol.11091822)
2. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012; **22**: 746–57. doi: [10.1007/s00330-011-2377-y](https://doi.org/10.1007/s00330-011-2377-y)
3. Portalez D, Rollin G, Leandri P, Elman B, Mouly P, Jonca F, et al. Prospective comparison of T2w-MRI and dynamic-contrast-enhanced MRI, 3D-MR spectroscopic imaging or diffusion-weighted MRI in repeat TRUS-guided biopsies. *Eur Radiol* 2010; **20**: 2781–90. doi: [10.1007/s00330-010-1868-6](https://doi.org/10.1007/s00330-010-1868-6)
4. Durmus T, Stephan C, Grigoryev M, Diederichs G, Saleh M, Slowinski T, et al. Detection of prostate cancer by real-time MR/ultrasound fusion-guided biopsy: 3T MRI and state of the art sonography. [In German.] *Rofo* 2013; **185**: 428–33.
5. Tanimoto A, Nakashima J, Kohno H, Shinmoto H, Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. *J Magn Reson Imaging* 2007; **25**: 146–52. doi: [10.1002/jmri.20793](https://doi.org/10.1002/jmri.20793)
6. Franiel T, Vargas HA, Mazaheri Y, Böhmer S, Hricak H, Akin O, et al. Role of endorectal prostate MRI in patients with initial suspicion of prostate cancer. *Rofo* 2013; **184**: 967–74. doi: [10.1055/s-0033-1350415](https://doi.org/10.1055/s-0033-1350415)
7. Haffner J, Lemaitre L, Puech P, Haber GP, Leroy X, Jones JS, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. *BJU Int* 2011; **108**: E171–8. doi: [10.1111/j.1464-410X.2011.10112.x](https://doi.org/10.1111/j.1464-410X.2011.10112.x)
8. Scheenen TW, Heijmink SW, Roell SA, Hulsbergen-Van de Kaa CA, Knipscheer BC, Witjes JA, et al. Three-dimensional proton MR spectroscopy of human prostate at 3 T without endorectal coil: feasibility. *Radiology* 2007; **245**: 507–16.
9. Hauth EA, Jaeger HJ, Maderwald S, Muehler A, Kimmig R, Forsting M. Quantitative 2- and 3-dimensional analysis of pharmacokinetic model-derived variables for breast

- lesions in dynamic, contrast-enhanced MR mammography. *Eur J Radiol* 2008; **66**: 300–8. doi: [10.1016/j.ejrad.2007.05.026](https://doi.org/10.1016/j.ejrad.2007.05.026)
10. Shukla-Dave A, Hricak H, Eberhardt SC, Olgac S, Muruganandham M, Scardino PT, et al. Chronic prostatitis: MR imaging and ¹H MR spectroscopic imaging findings—initial observations. *Radiology* 2004; **231**: 717–24. doi: [10.1148/radiol.2313031391](https://doi.org/10.1148/radiol.2313031391)
 11. Wetter A, Engl TA, Nadjmabadi D, Fliessbach K, Lehnert T, Gurung J, et al. Combined MRI and MR spectroscopy of the prostate before radical prostatectomy. *AJR Am J Roentgenol* 2006; **187**: 724–30. doi: [10.2214/AJR.05.0642](https://doi.org/10.2214/AJR.05.0642)
 12. Westphalen AC, Rosenkrantz AB. Prostate imaging reporting and data system (PI-RADS): reflections on early experience with a standardized interpretation scheme for multiparametric prostate MRI. *AJR Am J Roentgenol* 2014; **202**: 121–3. doi: [10.2214/AJR.13.10889](https://doi.org/10.2214/AJR.13.10889)
 13. Watanabe Y, Nagayama M, Araki T, Terai A, Okumura A, Amoh Y, et al. Targeted biopsy based on ADC map in the detection and localization of prostate cancer: a feasibility study. *J Magn Reson Imaging* 2013; **37**: 1168–77. doi: [10.1002/jmri.23908](https://doi.org/10.1002/jmri.23908)
 14. Hoeks CM, Hambrock T, Yakar D, Hulsbergen-van de Kaa CA, Feuth T, Witjes JA, et al. Transition zone prostate cancer: detection and localization with 3-T multiparametric MR imaging. *Radiology* 2013; **266**: 207–17. doi: [10.1148/radiol.12120281](https://doi.org/10.1148/radiol.12120281)
 15. Shimofusa R, Fujimoto H, Akamata H, Motoori K, Yamamoto S, Ueda T, et al. Diffusion-weighted imaging of prostate cancer. *J Comput Assist Tomogr* 2005; **29**: 149–53. doi: [10.1097/01.rct.0000156396.13522.f2](https://doi.org/10.1097/01.rct.0000156396.13522.f2)
 16. Lim HK, Kim JK, Kim KA, Cho KS. Prostate cancer: apparent diffusion coefficient map with T2-weighted images for detection—a multireader study. *Radiology* 2009; **250**: 145–51. doi: [10.1148/radiol.2501080207](https://doi.org/10.1148/radiol.2501080207)
 17. Lee J, Yamaguchi T, Abe A, Shizukuishi K, Uemura H, Miyagi E, et al. Clinical evaluation of choline measurement by proton MR spectroscopy in patients with malignant tumors. *Radiat Med* 2004; **22**: 148–54.
 18. Hara N, Okuizumi M, Koike H, Kawaguchi M, Bilim V. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a useful modality for the precise detection and staging of early prostate cancer. *Prostate* 2004; **62**: 140–7. doi: [10.1002/pros.20124](https://doi.org/10.1002/pros.20124)
 19. Yacoub JH, Verma S, Moulton JS, Eggener S, Aytakin O. Imaging-guided prostate biopsy: conventional and emerging techniques. *Radiographics* 2012; **32**: 819–37. doi: [10.1148/rg.323115053](https://doi.org/10.1148/rg.323115053)
 20. Hambrock T, Somford DM, Hoeks C, Bouwense SA, Huisman H, Yakar D, et al. Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen. *J Urol* 2010; **183**: 520–7. doi: [10.1016/j.juro.2009.10.022](https://doi.org/10.1016/j.juro.2009.10.022)