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Monitoring radiotherapy induced tissue changes in localized prostate cancer by multi-parametric magnetic resonance imaging (MP-MRI)

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KEYWORDS
Multi-parametric MRI (MP-MRI);
Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI);
Diffusion-weighted MRI (DW-MRI);
Radiotherapy;
Prostate cancer

Abstract
Purpose: To evaluate the utility of multi-parametric magnetic resonance imaging (MP-MRI), including dynamic contrast-enhanced MRI and diffusion-weighted MRI, for monitoring tumor tissue changes after volumetric-modulated arc radiotherapy in localized prostate cancer (PCa), and to compare the radiotherapy induced tumor tissue changes between conventional, moderate and extreme hypofractionated groups. Furthermore, we aimed to evaluate if follow-up by MRI has an incremental value compared to the standard care by prostate-specific antigen (PSA) serum level measurement.
Materials and methods: Fifty-five men (mean age: 70 ± 5 [SD] years; range: 60—79 years) with biopsy-proven PCa underwent MRI examination before radiotherapy, and at 3 and 12 months after radiotherapy. Pharmacokinetic analysis post-processing platform with dedicated software (Tissue 4D) was used to generate colorized parametric maps of enhancing tumors. The volume transfer constant (K^{trans}), reflux constant (K_{ep}), and initial area under curve (iAUC) were calculated from the tumors. Tumor apparent diffusion coefficient (ADC) value was measured on the ADC map. The patients were allocated into three radiotherapy groups: 17 conventional (39 × 2 Gy), 16 moderate (20 × 3 Gy) and 22 extreme hypofractionated (5 × 7.25 Gy) regimen.
Results: Sixty lesions were detected in the prostates of the 55 patients. Follow-up MRI showed decreases in tumor size and degree of enhancement. K^{trans}, K_{ep}, and iAUC all decreased at 3

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months ($P < 0.001$, respectively) and decreased further at 12 months ($P < 0.001$, respectively). ADC increased at 3 months ($P < 0.001$) and increased further at 12 months ($P < 0.001$). There were no significant differences in the percentage changes of the measured MP-MRI parameters of the tumors from baseline to 12 months between the conventional, moderate and extreme hypofractionated regimen groups.

Conclusion: MP-MRI is a reliable tool for lesion detection and follow-up, providing both qualitative and quantitative data.

Introduction

Approximately 30—50% of patients with prostate cancer (PCa) develop a recurrence within 5 years after external beam radiotherapy, and half of them will present a local recurrence only and mainly at the site of the primary tumor [1,2]. It is essential to monitor the patients and to detect and locate the recurrence. The assessment of PCa response to radiotherapy by serum prostate-specific antigen (PSA) is challenging due to false-positive and false-negative results [3]. Prostate biopsy after radiotherapy is invasive, prone to sampling errors and problems in interpretation because of the indeterminate results [4,5]. Therefore, improved monitoring methods are needed. Magnetic resonance imaging (MRI) potentially offers non-invasive insight into tumor pathophysiology, which may influence tumor development and response to therapy. Tumors have increased vascular microcirculation and permeability owing to neo-angiogenesis, which is essential for tumor growth, proliferation, and metastasis [6]. Quantitative MRI analysis employing tracer kinetic models yields physiological parameters related to tissue perfusion and capillary permeability. Diffusion-weighted MRI (DW-MRI) quantifies the random motion of water molecules in tissue by means of apparent diffusion coefficient (ADC) value measurement [7]. Multi-parametric MRI (MP-MRI), including T2-weighted, DW-MRI and dynamic contrast-enhanced (DCE)-MRI, provides spatial maps of quantitative metrics and has shown a potential role in lesion detection, characterization, and staging of PCa [8]. MP-MRI yields excellent results in the detection of local recurrences after radiotherapy and can be used for guiding targeted biopsy [9,10]. However, to date there is no well-designed prospective study that has investigated the quantitative changes of MP-MRI derived diffusion and perfusion parameters after radiotherapy.

Radiotherapy is an established treatment modality for PCa. However, determining the optimal fractionation scheme remains at issue for radiation oncologists. Currently used conventional fractionated external beam radiotherapy protocol consists of 39 sessions (2 Gy/fraction) over about 8 weeks. Modern moderately hypofractionated radiotherapy is showing favorable response to conventional fractionation with acceptable toxicity to the nearby rectum and bladder [11,12]. However, long-term efficacy and safety data of hypofractionated radiotherapy are not well established, especially for extreme hypofractionated radiotherapy. As a result, methods of treatment, late complications and their possible reduction require further investigation.

The purpose of this study was to evaluate the utility of MP-MRI for monitoring tumor tissue changes after radiotherapy in clinically localized PCa, and to compare the radiotherapy induced tumor tissue changes between conventional, moderate and extreme hypofractionated groups. Furthermore, we aimed to evaluate if follow-up by MRI have an incremental value compared to the standard care by PSA serum level measurement.

Materials and methods

Patients

Seventy-two consecutive men with histologically proven PCa were enrolled in our prospective clinical trial. The study identifier at https://www.ClinicalTrials.gov is NCT02319239. The flow chart shows details of the patients' inclusion and exclusion (Fig. 1). Four patients were excluded because the tumor had spread outside prostate or to lymph nodes. Thirteen patients were excluded from MRI analyses: 7 had no suspicious lesion on MRI; 2 had no DCE images due to allergy to the contrast agent, and 4 others had missing MRI examination during the 12 months follow-up period, leaving a study population of 55 patients. The inclusion and exclusion criteria and clinical examinations have been described in our previous publication [13]. Briefly, newly diagnosed adult patient with one or two of the intermediate-risk features (Gleason score 7, staging T2b—T2c, PSA 10—20 ng/mL) according to the National Comprehensive Cancer Network (NCCN) criteria. The study was approved by the Ethics Committee of Tampere University Hospital (Nr. R14009), and all patients gave written informed consent. Transrectal ultrasound-guided biopsy (12 cores, 6 on each lobe) was performed. Pathology was graded according to the Gleason system. Baseline MRI was performed 6—10 weeks after biopsy.

Radiotherapy

Radiotherapy was performed with TrueBeam STx accelerator (Varian Medical Systems, Palo Alto, CA, USA) using

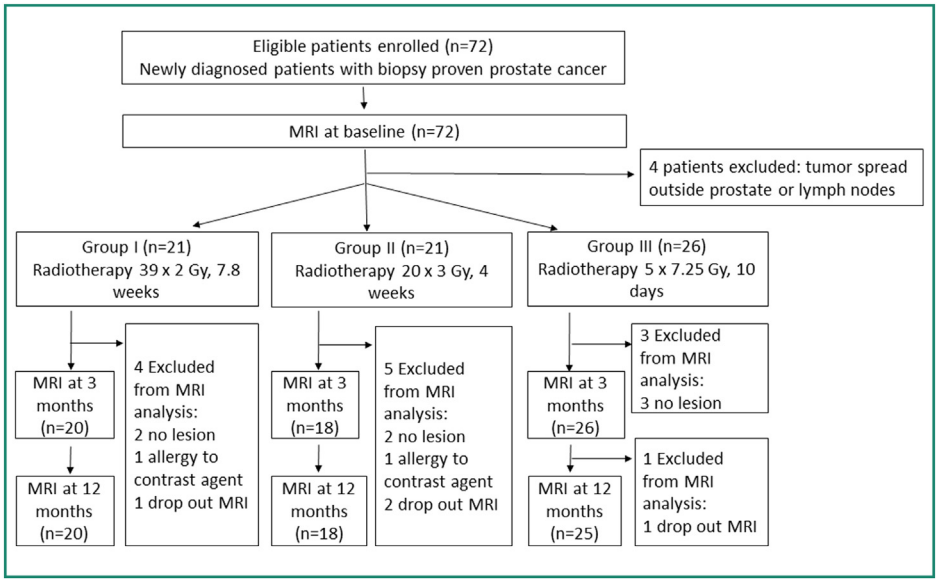

Figure 1. Flow diagram of patients selection for the study. Four patients were excluded due to the tumor had spread outside prostate or to lymph nodes. Thirteen patients were excluded from MRI analyses: 7 had no suspicious lesion on MRI; 2 had no DCE images due to allergy to the contrast agent, and 4 others had missing MRI examination during the 12 months follow-up period, leaving a study population of 55 patients.

volumetric-modulated arc therapy technique and two full arcs of 6 MV flattened beams. The patients were allocated into three groups for radiotherapy. Group I: 17 with conventional regimen, 39 sessions of 2 Gy per fraction (39 × 2 Gy) in 7.8 weeks; Group II: 16 with moderate hypofractionated regimen (20 × 3 Gy) in 4 weeks; Group III: 22 with extreme hypofractionated regimen (5 × 7.25 Gy) in 10 days.

Time points of serial MRI and serum PSA determination

All patients were imaged by the same MRI scanner before radiotherapy, and at 3 and 12 months after radiotherapy completion. Serum PSA was assessed on the day of each MRI scan. In addition, our patients were monitored by PSA immediately after radiotherapy completion, at 6 months, and every 6 months thereafter. The efficacy and side effects of radiotherapy are observed clinically and by questionnaire for at least 5 years.

Multi-parametric MRI acquisition

MP-MRI that covers the entire prostate was acquired using a 3 Tesla MR System (Trio-Tim, Siemens Healthineers) [13]. Tri-planar T2-weighted turbo spin echo images were obtained. DW-MRI was acquired with a single-shot echo-planar sequence on the axial plane using three b values (50, 400, and 800 s/mm^2) [13]. A DCE-MRI series was performed after intravenous administration of gadoterate meglumine (Dotarem®, Guerbet) at a dose of 0.2 ml/kg, with temporal resolution of 8 s; acquisition time 4 min 40 s with axial T1-weighted 3D volumetric interpolated breath-hold examination sequence [14]. DW-MRI was performed with the following parameters: echo time (TE), 77 ms; repetition time (TR), 3800 ms; field of view (FOV), 221 × 260 mm; flip angle (FA), 90○; acquisition matrix, 102 × 160 mm; slice/gap, 3.6/0 mm. DCE-MRI was performed with the following parameters: TE, 1.7 ms; TR, 4.9 ms; FOV, 260 × 260 mm; FA, 12○; acquisition matrix, 138 × 192 mm; slice/gap, 3.6/0 mm. T2-weighted MRI was performed with the following parameters: TE, 100 ms; TR, 4000-5000 ms; FOV, 200 × 200 mm; FA, 90°; acquisition matrix, 288 × 320 mm; slice/gap, 3.0/0.6 mm.

MR image analysis

All MR images were analyzed on a Syngo® Multimodality Workplace with Tissue 4D software (Siemens Healthineers) by two observers (X.W. with 10 years' of experience; T. V. with 20 years of experience). The analysis method has been described in our previous publication [14]. Briefly, motion correction, pre-contrast and morphological image co-registration, region of interest (ROI) selection from the PCa foci in early enhancing region of DCE-MRI, T1 map calculation according to the entered contrast agent. Parametric maps were calculated and K^{trans}, K_{ep}, V_e, and iAUC in the ROI were estimated. ADC value of the identified tumor was measured directly on the parametric ADC maps [13]. Follow-up MRI examinations and quantitative analyses were repeated in the same area of the initial pretreatment tumor.

Statistical analysis

Statistical analysis was performed with SPSS (version 23.0, SPSS Inc., Chicago, Illinois, USA). Quantitative variables were expressed as means ± standard deviations (SD) and ranges. Qualitative variables were expressed as raw numbers, proportions and percentages. One-way analysis of variance (ANOVA) was used to compare age, PSA serum level, tumor size, ADC, K^{trans}, K_{ep}, V_e, or iAUC between the three radiotherapy regimen groups. Paired t test was used to compare the PSA, diffusion, and perfusion parameters

Table 1 Baseline characteristics of 55 patients with prostate cancer in 3 different radiotherapy groups.

	Total ($n = 55$)	Group I ($n = 17$)	Group II ($n = 16$)	Group III ($n = 22$)
Age (year)	70 ± 5 [60—79]	68 ± 4 [60—74]	71 ± 6 [61—79]	71 ± 4 [63—79]
PSA serum level (ng/mL)	9.3 ± 3.7 [3.4—19.1]	9.7 ± 3.4 [3.9—14.7]	8.6 ± 4.0 [3.4—18.4]	9.4 ± 3.8 [4.3—19.1]
Gleason Score				
GS 3 + 3	18	6	6	6
GS 3 + 4	35	11	10	14
GS 4 + 3	2	0	0	2
Clinical stage				
Stage 1c	9	2	2	5
Stage 2a	14	5	4	5
Stage 2b	6	1	2	3
Stage 2c	26	9	8	9

Group I: conventional regimen; Group II: moderate hypofractionated regimen; Group III: extreme hypofractionated regimen. There were no significant differences in age and PSA serum level between the 3 radiotherapy groups; PSA = prostate-specific antigen

Table 2 Baseline serum PSA and MRI diffusion and perfusion parameters of 60 tumors in 55 patients with prostate cancer.

	All lesions ($n = 60$)	Group I ($n = 19$)	Group II ($n = 17$)	Group III ($n = 24$)
Tumor area (cm^2)	0.75 ± 0.49 [0.21—2.48]	0.60 ± 0.33 [0.21—1.58]	0.89 ± 0.61 [0.32—2.48]	0.78 ± 0.50 [0.24—2.43]
ADC ($\times 10^{-3}$ mm^2/s)	0.86 ± 0.15 [0.60—1.34]	0.87 ± 0.16 [0.62—1.11]	0.83 ± 0.10 [0.67—1.00]	0.88 ± 0.18 [0.60—1.34]
K^{trans} (min^{-1})	0.15 ± 0.05 [0.06—0.27]	0.14 ± 0.06 [0.06—0.26]	0.15 ± 0.05 [0.06—0.25]	0.15 ± 0.05 [0.08—0.27]
K_{ep} (min^{-1})	0.57 ± 0.23 [0.17—1.32]	0.58 ± 0.26 [0.17—1.09]	0.54 ± 0.20 [0.17—0.91]	0.58 ± 0.23 [0.24—1.32]
V_e	0.28 ± 0.07 [0.14—0.47]	0.28 ± 0.09 [0.16—0.47]	0.28 ± 0.05 (0.19—0.38]	0.28 ± 0.07 [0.14—0.45]
iAUC (mmoL/L/min)	16.91 ± 5.87 [6.00—32.56]	16.15 ± 6.42 [6.00—29.74]	16.88 ± 4.92 [5.72—25.96]	17.54 ± 6.19 [7.70—32.56]

Numbers are expressed as means ± standard deviations. Numbers in brackets are ranges. PSA = prostate-specific antigen; ADC = apparent diffusion coefficient; K^{trans} = volume transfer constant; K_{ep} = reflux constant; V_e = extravascular extracellular leakage volume fraction; iAUC = initial area under curve. Group I: conventional regimen; Group II: moderate hypofractionated regimen; Group III: extreme hypofractionated regimen. There were no significant differences in the measured parameters between the 3 radiotherapy groups.

before and after radiotherapy. Kruskal-Wallis Test was used to compare the percentage changes of tumor ADC, K^{trans}, K_{ep}, V_e, or iAUC between the three radiotherapy groups after radiotherapy. P values < 0.05 were considered to indicate significant difference.

Results

Patient characteristics

Sixty lesions were detected in the prostates of the 55 men (mean age: 70 ± 5 [SD] years; range: 60—79 years). There were 18 patients with a Gleason score 3 + 3, 35 with a Gleason score 3 + 4, and 2 with a Gleason score 4 + 3 tumor. Nine patients had clinical stage T1c tumors, and 46 had T2 (14 in T2a, 6 in T2b, and 26 in T2c) tumors according to TNM classification. Mean baseline PSA serum level was 9.3 ± 3.7 (SD) ng/mL (range: 3.4—19.1 ng/mL) (Table 1). There were no significant differences in age and PSA serum level between the 3 radiotherapy groups at baseline. Neither were significant differences detected in tumor size, ADC value, K^{trans}, K_{ep}, V_e or iAUC between the 3 radiotherapy groups at baseline (Table 2).

Recurrence

Currently the mean follow-up time is 2.4 ± 0.9 (SD) years (range: 1.0—3.7 years) after radiotherapy. A recurrent prostate cancer was detected in a 60-year-old man at the same location as the original tumor. The patient had a T2c tumor with Gleason score 3 + 4 and baseline PSA

serum level of 4 ng/mL, the PSA decreased gradually to less than 0.2 ng/mL one year after moderate hypofractionated radiotherapy, but it started to increase from 1.5 years (0.4 ng/mL) and increased gradually to 0.8 ng/mL at 2 years, and further to 1.6 ng/mL at 2.5 years. Therefore, an MP-MRI was performed and detected the recurrent tumor and histopathological analysis of biopsy specimens confirmed the relapse 2.5 years after radiotherapy.

PSA serum level

Post-radiotherapy PSA serum levels declined continually. PSA serum levels decreased of 32.6% immediately after radiotherapy (6.1 ± 4.1 [SD] ng/mL; $P < 0.001$). It decreased a further 37.5% at 3 months (2.9 ± 2.4 [SD] ng/mL; $P < 0.001$), 9.6% at 6 months (2.0 ± 1.9 [SD] ng/mL; $P < 0.001$), and 7.0% at 12 months (1.4 ± 2.7 [SD] ng/mL; $P < 0.05$). The total PSA serum level decrease was 86.7% from baseline to 12 months (Fig. 2). However, there were PSA serum level bounces (e.g., a phenomenon in which PSA serum level increases ≥ 0.2 ng/mL temporarily): immediately after radiotherapy ($n = 5$ patients), at 6 months ($n = 1$ patient) and 12 months ($n = 3$ patients). There was one patient who had 2 bounces during the 12 months' follow-up period.

PSA serum level decrease patterns were similar in the 3 radiotherapy groups, and the total decrease from baseline to 12 months for group I, II, and III was 87.0%, 89.8%, and 84.1%, respectively (Fig. 2). There were no significant differences in percentage changes of PSA serum level from baseline to 12 months between the conventional, moderate and extreme hypofractionated groups.

DCE-MRI derived parameters

On perfusion MRI, all 55 patients had at least one enhancing focal tumor in the prostate. All the 60 tumors showed decrease in size and degree of enhancement on follow-up MRI (Fig. 3). There were 50 (50/60; 83.3%) partial resolutions and 10 (10/60; 16.7%) complete resolutions of the 60 enhancing tumors at 3 months. Altogether 13 (13/60; 21.7%) partial resolutions and 47 (47/60; 78.3%) complete resolutions were found at 12 months.

Tumor K^{trans} significantly decreased from baseline (0.15 ± 0.05 [SD] min^{-1}) to 3 months (0.12 ± 0.05 [SD] min^{-1}) ($P < 0.001$) and further decreased at 12 months (0.07 ± 0.04 [SD] min^{-1}) ($P < 0.001$). The total decrease from baseline to 12 months was 53.1% ($P < 0.001$) (Table 3, Fig. 4). The total decrease of tumor K^{trans} from baseline to 12 months was 59.9%, 52.3%, and 48.4% for group I, II, and III ($P < 0.001$ for all) (Fig. 5). There were no significant differences in percentage changes of tumor K^{trans} from baseline to 12 months between the conventional, moderate and extreme hypofractionated groups.

Tumor K_{ep} decreased significantly from baseline (0.57 ± 0.23 [SD] min^{-1}) to 3 months (0.28 ± 0.12 [SD] min^{-1}) ($P < 0.001$) and further decreased at 12 months (0.15 ± 0.13 [SD] min^{-1}) ($P < 0.001$). The total decrease from baseline to 12 months was 68.6% ($P < 0.001$). The total decrease of tumor K_{ep} from baseline to 12 months was 73.5%, 64.2% and 67.9% for group I, II, and III ($P < 0.001$ for all). There was no significant difference in the percentage changes of tumor K_{ep} from baseline to 12 months between the conventional, moderate and extreme hypofractionated groups.

Tumor V_e significantly increased from baseline (0.28 ± 0.07 [SD]) to 3 months (0.45 ± 0.11 [SD]) ($P < 0.001$), and further increased at 12 months (0.53 ± 0.19 [SD]) ($P < 0.05$). The total increase from baseline to 12 months was 110.1% ($P < 0.001$). The total increase of tumor V_e from baseline to 12 months was 110.6%, 95.5% and 120.1% for group I, II, and III ($P < 0.001$ for all). There were no significant differences in the percentage changes of tumor V_e from baseline to 12 months between the

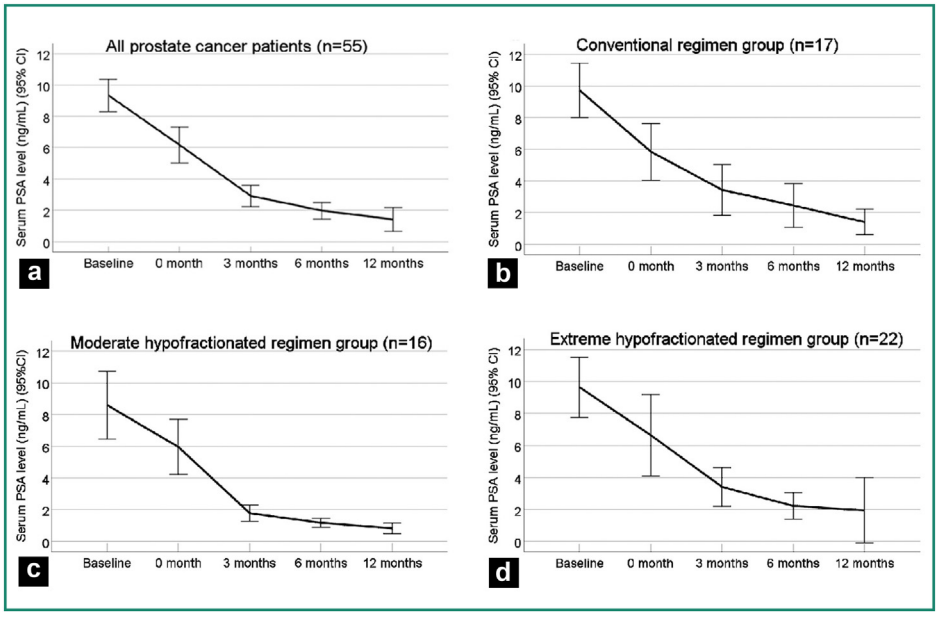

Figure 2. Prostate-specific antigen (PSA) serum level in patients with prostate cancer. (a) PSA decreased continuously after radiotherapy in the 55 patients; similarly in the conventional group (b), and moderate and extreme hypofractionated groups (c) and (d).

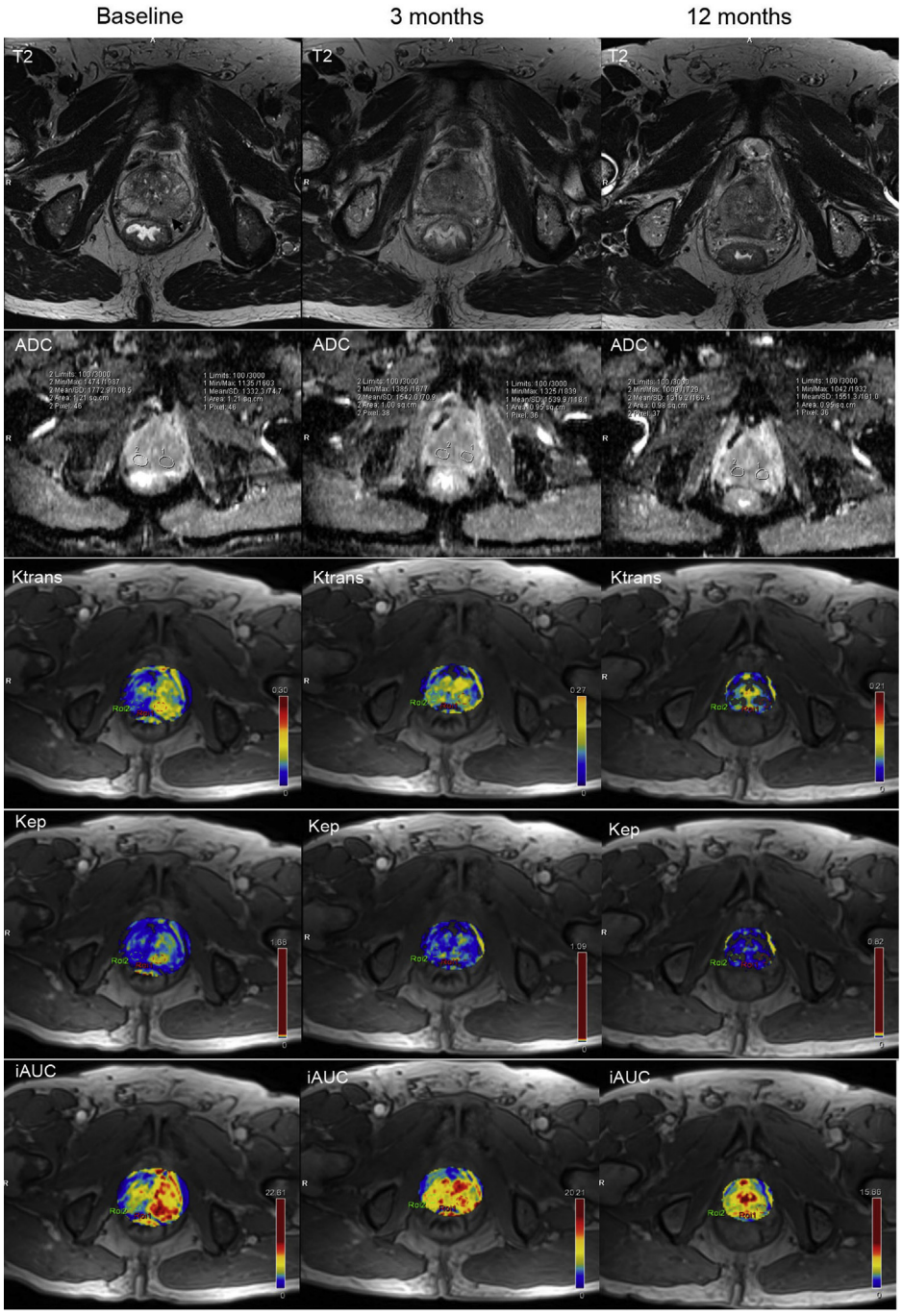

Figure 3. Prostate MRI before and at 3 and 12 months after extreme hypofractionated (5×7.25 Gy) radiotherapy from a 71-year-old man with biopsy-proven prostate cancer. At baseline, there was a diffused hypointensity region in the left peripheral region on T2-weighted image (arrow), and the ADC value was lower in the tumor (ROI1: 0.13×10^{-3} mm^2/s) than the control region (ROI2: 0.18×10^{-3} mm^2/s). The lesion was enhanced on dynamic contrast-enhanced (DCE) images. K^{trans} (min^{-1}), K_{ep} (min^{-1}), and iAUC (mmoL/L/min) were 0.17, 0.68 and 21.87 in ROI1; and 0.06, 0.27, and 7.84 in ROI2; respectively. At 3 months, tumor disappeared on T2-weighted image and ADC map, smaller and less enhanced on DCE-MRI, with K^{trans}, K_{ep}, and iAUC 0.11, 0.27, and 14.53 in ROI1; and 0.09, 0.24, 11.40 in ROI2; respectively. At 12 months, the tumor disappeared on T2-weighted image and ADC map, not enhanced any more on DCE-MRI.

conventional, moderate and extreme hypofractionated regimen groups.

Tumor iAUC decreased significantly from baseline to 3 months (16.91 ± 5.87 vs. 13.91 ± 5.26 mmoL/L/min; $P < 0.001$), and it decreased further at 12 months (7.71 ± 4.44 mmoL/L/min; $P < 0.001$). The total decrease was 52.0% ($P < 0.001$) from baseline to 12 months. The total decrease was 61.2%, 49.0%, and 47.0% for group I, II, and III ($P < 0.001$ for all). There was no significant difference in the percentage changes of tumor iAUC from baseline to 12

Table 3 Comparison of serum PSA and tumor ADC value, K^{trans}, K_{ep}, V_e, and iAUC before, and at 3 and 12 months after radiotherapy in the 60 lesions of the 55 men with localized prostate cancer.

	Baseline	3 Months	12 Months
	Mean ± SD	Mean ± SD	Mean ± SD
PSA serum level (ng/mL)	9.3 ± 3.7	2.9 ± 2.4 (70.1%) *	1.4 ± 2.7 (16.6%) ***
ADC ($\times 10^{-3}$ mm^2/s)	0.86 ± 0.15	1.19 ± 0.16 (40.5%) *	1.30 ± 0.16 (13.2%) ***
K^{trans} (min^{-1})	0.15 ± 0.05	0.12 ± 0.05 (15.1%) *	0.07 ± 0.04 (38.0%) ***
K_{ep} (min^{-1})	0.57 ± 0.23	0.28 ± 0.12 (43.5%) *	0.15 ± 0.13 (25.1%) ***
V_e	0.28 ± 0.07	0.45 ± 0.11 (69.5%) *	0.53 ± 0.19 (40.6%) **
iAUC (mmoL/L/min)	16.91 ± 5.87	13.91 ± 5.26 (11.5%) *	7.71 ± 4.44 (40.5%) ***

PSA = prostate-specific antigen; ADC = apparent diffusion coefficient; K^{trans} = volume transfer constant; K_{ep} = reflux constant; V_e = extravascular extracellular leakage volume fraction; iAUC = initial area under curve.
* $P < 0.001$ compared with baseline, in parentheses is the corresponding percentage change.
** $P < 0.05$.
*** $P < 0.001$ compared with 3 months, in parentheses is the corresponding percentage change.

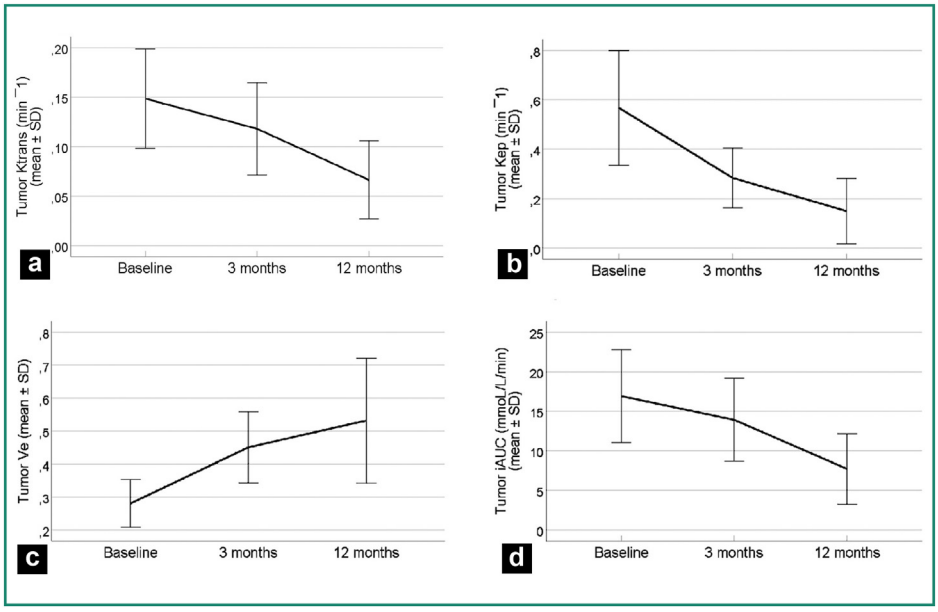

Figure 4. Diagram shows tumor K^{trans}, K_{ep}, V_e, and iAUC changes after radiotherapy of 60 lesions in 55 patients with prostate cancer. (a) K^{trans}, (b) K_{ep}, and (d) iAUC decreased continuously; and (c) V_e increased continuously during the first year after radiotherapy.

months between the conventional, moderate and extreme hypofractionated groups.

DW-MRI ADC value

Tumor ADC increased significantly from baseline (0.86 ± 0.15 [SD] × 10^{-3} mm^2/s) to 3 months (1.19 ± 0.16 [SD] × 10^{-3} mm^2/s) ($P < 0.001$), and further increased at 12 months (1.30 ± 0.16 [SD] × 10^{-3} mm^2/s) ($P < 0.001$). The total increase was 53.7% ($P < 0.001$) from baseline to 12 months (Fig. 6). The total increase was 50.1%, 59.1%, and 52.7% for group I, II, and III ($P < 0.001$for all). Neither were significant differences detected in the percentage changes of tumor ADC from baseline to 12 months between the conventional, moderate and extreme hypofractionated groups.

Discussion

DCE-MRI allows to measure properties of tissue microcirculation resulting from tumor neovascularization [15]. The DCE-MRI parameter K^{trans} represents the rate at which the contrast agent transfers from blood to the interstitial space and indicates the tissue microcirculation and surface infiltration area. The reflux constant (K_{ep}) reflects the contrast agent transfer rate from the extravascular extracellular space back to blood. The extravascular extracellular leakage volume fraction ($V_e = K^{trans}/K_{ep}$) reflects the percentage of contrast agent in the extravascular extracellular space. The semi-quantitative parameter initial area under curve (iAUC) represents the overall perfusion and tumor interstitial space index [16]. We identified 60 enhancing tumors in 55 patients with PCa by MP-MRI. Follow-up MRI showed decreases in both tumor size and degree of enhancement.

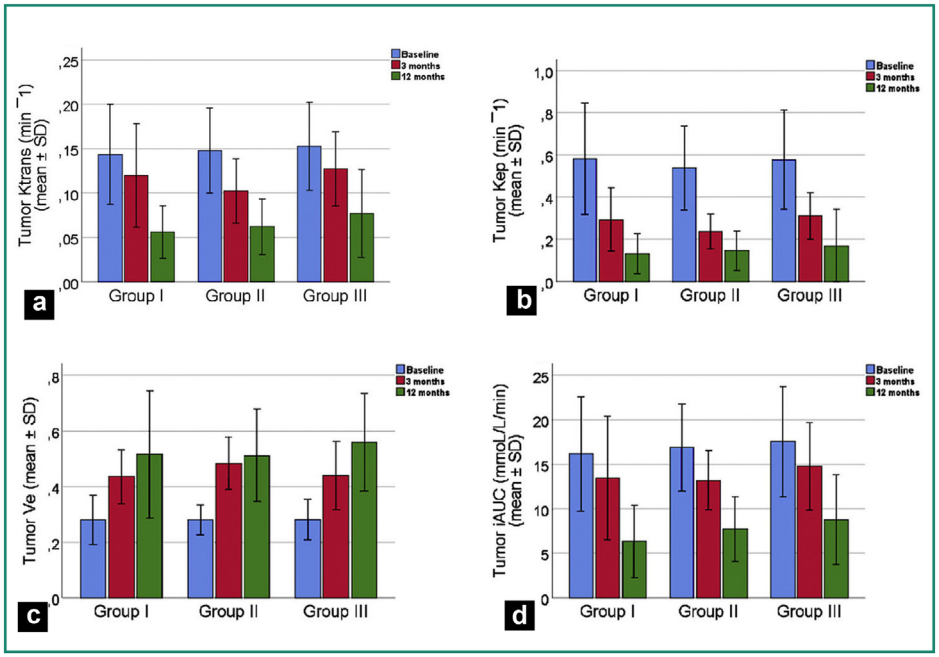

Figure 5. Diagram shows tumor K^{trans}, K_{ep}, V_e, and iAUC changes after radiotherapy in group I (conventional, $n = 19$ lesions), II (moderate, $n = 17$ lesions) and III (extreme hypofractionated, $n = 24$ lesions); (a) K^{trans}, (b) K_{ep}, and (d) iAUC decreased continuously; and (c) V_e increased continuously in all the 3 groups during the first 12 months after radiotherapy.

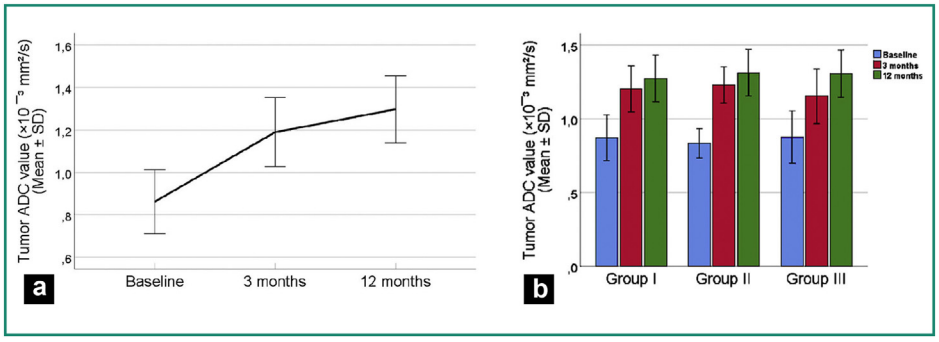

Figure 6. Diagram shows tumor ADC value before and after radiotherapy patients with prostate cancer. (a) During the first year after radiotherapy ADC value increased continuously in 60 lesions of the 55 patients; with no significant differences between the 3 groups (b): group I (conventional, $n = 19$ lesions), II (moderate, $n = 17$ lesions) and III (extreme hypofractionated, $n = 24$ lesions).

Three months after radiotherapy, the DCE-MRI derived perfusion and permeability parameters including K^{trans}, K_{ep}, and iAUC all decreased significantly, and decreased further at 12 months. It means that there was a decrease in tumor microcirculation after effective radiotherapy, and the status could be monitored by DCE-MRI quantitatively. Our study confirms the results of a pilot study that involved only 6 patients, which showed that DCE-MRI derived perfusion parameters were suitable for monitoring response to radiotherapy in PCa [17]. Our results are consistent with an retrospective study, which showed K^{trans} continuously decreasing during two years follow-up after radiotherapy [18].

Successful treatment leads to necrosis, loss of cell membrane integrity and altered water homeostasis, decreased tumor cell density and increased extracellular space, and, therefore, an increase in water diffusion, which is indicated by increased ADC value [19]. We detected that the tumor ADC value increased significantly 3 months after radiotherapy and increased further at 12 months, and at the same time PSA and DCE-MRI derived perfusion parameters decreased, which was indicating a response to radiotherapy. A previous study showed that radiotherapy induced cellular changes could be detected by DW-MRI as early as week 2 after radiotherapy initiation [20]. Therefore, DW-MRI is a potential, early non-invasive MRI biomarker for radiotherapy response evaluation of PCa.

Previous studies that compared the utility of DW-MRI in combination with T2-weighted MR images to T2-weighted MR images alone showed great promise for DW-MRI in post-radiotherapy imaging [21]. DCE-MRI has an important role in post-radiotherapy evaluation, and it is more powerful if it can be correlated with abnormalities seen on T2-weighted or DW-MRI [22]. The MP-MRI technique presented here might also enable earlier detection of recurrent tumor after radiotherapy, if the patients are followed by MP-MRI regularly for the first 5 years.

We detected a recurrent prostate cancer by MP-MRI, which was confirmed by biopsy, in a patient with biochemical failure. Although the PSA serum level decreased continuously after radiotherapy, we detected 8 patients (8/55; 14.5%) who had at least one PSA bounce within the first year after radiotherapy. A noninvasive MP-MRI allows monitoring the outcome of radiotherapy, and it also has the potential to provide earlier reassurance information concerning the response to therapy in patients with a PSA bounce [9]. A recent study confirmed that MP-MRI can distinguish recurrent tumor from benign tissue [23]. Thus, MP-MRI may play a role in conjunction with PSA for localizing biopsy sites and guiding targeted biopsy of suspicious areas and confirming the recurrences.

Although MP-MRI has excellent sensitivity in lesion detection and follow-up of PCa after radiotherapy, we have to keep in mind that negative MP-MRI findings must be regarded with care in high-risk patients [24]. There were 7 biopsy-proven PCa patients who had no visible lesions on MP-MRI in our study (7/72, 9.7%). In addition, the absolute values of the quantitative DCE-MRI parameters should be used with caution, since MR imager, image analysis software and techniques can have a significant impact on them [25].

We did not find significant differences in the measured quantitative MP-MRI parameters between the conventional, moderate and extreme hypofractionated radiotherapy groups over the 12 months follow-up. The α/β ratio is a way of expressing the fractionation sensitivity of tumors and surrounding normal tissues. Most cancers (with α/β ratio around 10 Gy) are more sensitive to total radiation dose than dose per fraction. The surrounding normal tissues (with α/β ratio around 3 Gy) have a higher sensitivity to fraction dose. Previous studies suggest that the α/β ratio for PCa may be as low as 1.5 Gy [26], which has prompted investigators to explore hypofractionated radiotherapy. In addition to the therapeutic rationale, hypofractionated regimens save resources and ameliorate inconvenience for the patients. However, this is a short-term observation, and long-term efficacy and side-effects need to be investigated further.

Our study has limitations. First, all patients underwent needle biopsies before MRI examination, hemorrhagic changes caused by this procedure might have affected the MRI findings. However, we excluded visible bleeding on pre-contrast T1-weighted images. Secondly, this study had the potential error of MRI measurements in tumors because of volume shrinkage after radiotherapy, although the MP-MRI parameters were performed carefully. Thirdly, high b values were not used in our study, although this will not affect the follow-up observations.

In conclusion, MP-MRI is a reliable tool for lesion detection and follow-up of PCa after radiotherapy, providing both qualitative and quantitative data. No significant difference was detected by quantitative MP-MRI parameters of the tumors between the conventional, moderate and extreme hypofractionated radiotherapy groups in this short-term observation period.

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Disclosure of interest

The authors declare that they have no competing interest.

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