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EDITORIAL

Updates in advanced diffusion-weighted magnetic resonance imaging techniques in the evaluation of prostate cancer

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Abstract

Diffusion-weighted magnetic resonance imaging (DW-MRI) is considered part of the standard imaging protocol for the evaluation of patients with prostate cancer. It has been proven valuable as a functional tool for qualitative and quantitative analysis of prostate cancer beyond anatomical MRI sequences such as T2-weighted imaging. This review discusses ongoing controversies in DW-MRI acquisition, including the optimal number of b-values to be used for prostate DWI, and summarizes the current literature on the use of advanced DW-MRI techniques. These include intravoxel incoherent motion imaging, which better accounts for the non-mono-exponential behavior of the apparent diffusion coefficient as a function of b-value and the influence of perfusion at low b-values. Another technique is diffusion kurtosis imaging (DKI). Metrics from DKI reflect excess kurtosis of tissues, representing its deviation from Gaussian diffusion behavior. Preliminary results suggest that DKI findings may have more value than findings from conventional DW-MRI for the assessment of prostate cancer.

Key words: Prostate cancer; Diffusion-weighted imaging; Diffusion kurtosis imaging; Magnetic resonance imaging; Include intravoxel incoherent motion

Core tip: Diffusion-weighted magnetic resonance imaging (DW-MRI) is considered part of the standard imaging protocol for the evaluation of patients with prostate cancer. In this review we discuss the ongoing controversies in DW-MRI acquisition, including the optimal number of *b*-values to be used for prostate DWI, and summarize the current literature on the use of advanced DW-MRI techniques such as intravoxel incoherent motion imaging and diffusion kurtosis imaging.

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INTRODUCTION

Diffusion-weighted (DW) techniques have been applied extensively for the evaluation of patients with prostate cancer and are now part of most standard prostate magnetic resonance imaging (MRI) clinical protocols. Multiple studies have demonstrated that DW-MRI contributes incremental value to T2-weighted MRI in the detection and localization of prostate cancer[1]. Straightforward, quantitative metrics from DW-MRI – most commonly apparent diffusion coefficient (ADC) values – have been used to distinguish between benign and malignant prostate tissue and also to evaluate prostate cancer aggressiveness[2]. ADC values have been found to correlate inversely with prostate cancer Gleason score as well as tumor proliferation markers such as Ki-67[2-4]. Nevertheless, ADC values of prostate cancer overlap substantially with those of normal prostate and benign conditions, such as prostatitis and post-biopsy inflammation. Therefore, advanced methods for DW-MRI acquisition, processing and interpretation are now being investigated with the goal of further strengthening the value of DW-MRI for prostate cancer assessment.

SELECTION OF *B*-VALUES FOR PROSTATE DW-MRI

The *b*-value is one of the main factors reflecting the strength of the diffusion effects in DW-MRI, with higher *b*-values representing stronger diffusion effects. There is as yet no consensus regarding the optimal choice of *b*-values for acquiring prostate DW-MRI. Absolute ADC values are highly dependent on the *b*-values selected and must therefore be applied cautiously, especially when attempting to define "cut-offs" for distinguishing particular conditions or disease states[5]. Higher *b*-values offer greater tumor-to-normal-tissue contrast but also decrease the signal-to-noise ratio. Tamada *et al*[6] evaluated 50 patients with prostate cancer undergoing 3T prostate DW-MRI acquired with *b*-values of 0, 1000 and 2000 s/mm^2; they found that lesion conspicuity and tumor-to-normal signal intensity ratio were higher when using *b*-values of 0 and 2000 s/mm^2 compared to those using *b*-values of 0 and 1000 s/mm^2[6]. There was a significant correlation between ADC values of tumor regions and Gleason scores at both *b*-values of 0 and 1000 s/mm^2 (rho = -0.602; $P < 0.001$) and 0 and 2000 s/mm^2 (rho = -0.645; $P < 0.001$)[6]. As an alternative to the acquisition of high-*b*-value images, some investigators have proposed "computing" them through voxelwise fitting from a set of images acquired at lower *b*-values. Using numerical simulations, Tamada *et al*[6] found that noise and the contrast-to-noise ratio were comparable between DW-MRI images that were "calculated" and those that were "acquired" at a *b*-value of 1400 s/mm^2 ($P = 0.395$). In one study, diagnostic performance of DW-MRI in prostate tumor detection was compared for four different combinations of measured and acquired *b*-values[7]. The AUCs for protocol A (T2-weighted images alone), B (T2-weighted images in combination with measured DW images with b 1000), C (T2-weighted images in combination with measured DW images with b 2000) and D (T2-weighted images in combination with computed DW images with b 2000) were 0.67, 0.80, 0.86 and 0.84, respectively[7]. Protocols C and D had significantly higher AUCs when compared to protocol B ($P < 0.05$)[7].

INTRAVOXEL INCOHERENT MOTION IMAGING

The optimal number of *b*-values for prostate DW-MRI also continues to be debated. A minimum of two *b*-values is required for monoexponential calculation of ADC. However, to better account for the non-mono-exponential behavior of the diffusion signal intensity at different *b*-values and the influence of perfusion at low *b*-values, intravoxel incoherent motion (IVIM), a model based on the use of three or more *b*-values, can be applied. The use of multiple *b*-values also reduces the influence of *b*-value selection on ADC measurements[8]. One study evaluated prostate DW-MRI acquired with four *b*-values (0, 50, 500, and 800 s/mm²) in 13 biopsy-proven prostate cancer patients and found that ADC (μm^2/ms), molecular diffusion coefficient (D, μm^2/ms) and perfusion fraction (f, %) were significantly lower ($P < 0.005$) in cancer (1.01 ± 0.22, 0.84 ± 0.19 and 14.27 ± 7.10% for ADC, D and f) than in benign tissue (1.49 ± 0.17, 1.21 ± 0.22 and 21.25% ± 8.32%, for ADC, D and f)[9]. Another study applied monoexponential and biexponential fits to diffusion decay curves obtained from 26 patients with prostate cancer using 10 *b*-values ranging from 10 to 1000 s/mm^2)[10]. In 81% of cases, biexponential functions were found to provide statistically better fits than monoexponential functions[10]. Biexponential IVIM was used to calculate the parameters D, f, and D*. Significantly lower values of ADC, D, and f were found in prostate cancer compared to the values in the normal prostatic peripheral zone (PZ), but similar values for f were reported in both benign hyperplastic changes and prostate cancer[10]. There were no significant differences between the D* values found in prostate cancer, benign hyperplasia, and PZ[10].

Some investigators have questioned whether IVIM truly contributes incremental value as compared to simple monoexponential ADC measurements in prostate cancer[11]. One study compared two different algorithms for generating IVIM metrics in 50 patients (27 known prostate cancer patients and 23 without

Table 1 Clinical studies of intravoxel incoherent motion imaging in prostate cancer

Ref.	No. of patients	Pathologic reference	*b*-values (s/mm^2)	MR parameters	PCa values[1]	Normal prostate values[1]	Significance
Döpfert *et al*[9]	13	TRUS biopsy	0, 50, 500, 800	3.0 T; TR/TE: 2600/66 ms; FOV: 204 mm × 204 mm; Matrix: 136 × 136; slice thickness: 3 mm; 8 averages	ADC: 1.01 ± 0.22 D: 0.84 ± 0.19 D*: 7.52 ± 4.77 f: 14.27 ± 7.10	ADC: 1.49 ± 0.17 D: 1.21 ± 0.22 D*: 6.82 ± 2.78 f: 21.25 ± 8.32	ADC, D, f significantly lower in PCa *vs* healthy prostate tissue Higher variation in maps of D and f compared to ADC
Shinmoto *et al*[10]	26	TRUS biopsy or RP	0, 10, 20, 30, 50, 80, 100, 200, 400, 1000	3.0 T; TR/TE: 5132/40 ms; Matrix: 80 × 80; slice thickness/gap: 3.5/0.1 mm; iPAT factor, 2; NEX = 2	ADC: 0.90 ± 0.16 D: 0.50 ± 0.15 D*: 5.35 ± 6.27 f: 35 ± 13	ADC: 1.76 ± 0.22 D: 0.89 ± 0.24 D*: 3.02 ± 0.86 f: 58 ± 11	ADC, D, f significantly lower in PCa *vs* noncancerous PZ Improved fit in 81% of study subjects for biexponential curve
Kuru *et al*[11]	27	MR-TRUS fusion biopsy	0, 50, 100, 150, 200, 250, 800	3.0 T; TR/TE: 3100/52 ms; FOV: 280 mm × 210 mm; Matrix: 128 × 96; slice thickness: 3 mm; iPAT factor, 2; 5 averages	ADC: 0.88 ± 0.29 D: 1.04 ± 0.23 D*: 31.1 ± 45.0 f: 9.5 ± 5.5	ADC: 1.56 ± 0.23 D: 1.44 ± 0.19 D*: 10.9 ± 4.0 f: 11.1 ± 5.0	Only D and ADC showed high AUC (≥ 0.90) for PCa *vs* normal Limited differentiation of PCa grade using f or D*
Pang *et al*[12]	33	MR-TRUS fusion biopsy	0, 188, 375, 563	3.0 T; TR/TE: 4584/59 ms; FOV:160 × 180 mm; slice thickness: 3.0 mm; iPAT factor, 2; 4+ averages	D: 0.99 ± 0.29 f: 7.2 ± 2.6 K^{trans}: 0.39 ±0.22 V_P: 8.4 ± 6.6	D: 1.76 ± 0.35 f: 3.7 ± 1 .9 K^{trans}: 0.18 ± 0.10 V_P: 3.4 ± 2.6	Significant increase in f for PCa *vs* normal prostate Pearson's correlation coefficient (r) for f and K^{trans} of 0.51

[1]Values are mean ± SD [ADC: Apparent diffusion coefficient (μm^2/ms); D: molecular diffusion coefficient (μm^2/ms); D*: Perfusion-related diffusion coefficient (μm^2/ms); f: Perfusion fraction (%); K^{trans}: Volume transfer constant (min^{-1}); V_P: Plasma fractional volume (%)]. AUC: Area under curve; FOV: Field of view; GS: Gleason score; iPAT: Integrated parallel acquisition techniques; IVIM: Intravoxel incoherent motion; MR: Magnetic resonance; NEX: Number of excitations; PCa: Prostate cancer; PZ: Peripheral zone; RP: Radical prostatectomy; T: Tesla; TE: Time of echo; TR: Time of repetition; TRUS: Transrectal ultrasound.

known cancer) who underwent prostate DWI acquired with 7 *b*-values (0, 50, 100, 150, 200, 250, and 800 s/mm^2)[11]. D was similar with the two algorithms (P = 0.22), but f was significantly different between the 2 (higher with algorithm 1) (P < 0.05). The AUCs for differentiating tumor and normal tissues were ⩾ 0.90 for D (from the 2 algorithms) and ADC (but not f or D*). IVIM-derived parameters are also influenced by the range of *b*-values used. Pang *et al*[12] analyzed prostate DW-MRI acquired with five *b*-values ranging between 188 and 750 s/mm^2) and assessed the influence of the choice of *b*-values on the measured D and f. Both parameters were markedly influenced by the choice of *b*-values. The best correlation with DCE-MRI was achieved when the IVIM parameters were calculated without the highest *b*-value (750 s/mm^2). Using this approach, significantly higher f from IVIM and ktrans and plasma fractional volume from DCE-MRI were found for prostate cancers (7.2%, 0.39/min and 8.4% respectively) compared to normal prostate tissue (3.7%, 0.18/min and 3.4% respectively)[12]. In summary, further research into prostate IVIM is needed, with a focus on selecting the most appropriate patient population and on standardizing image acquisition techniques and approaches to fit the IVIM parameters from the DW-MRI data. A summary of clinical studies of IVIM imaging in prostate cancer is presented in Table 1.

DIFFUSION KURTOSIS IMAGING IN PROSTATE CANCER

Diffusion kurtosis imaging (DKI) is another technique that has been used in attempts to more accurately characterize the multi-exponential behavior of diffusion decay in prostate cancer[13-18]. Metrics from DKI reflect excess kurtosis of the tissue, representing its deviation from Gaussian diffusion behavior[15]. Preliminary results suggest that DKI findings may have more value than findings from conventional DW-MRI for prostate cancer assessment.

In a study of 31 subjects (including healthy volunteers and patients undergoing evaluation for raised PSA levels), Quentin *et al*[14] performed DKI with 4 *b*-values ranging between 0 and 1000 s/mm^2 and with diffusion gradients applied in 20 different spatial directions; they found that there was a better fit to the diffusion weighted signal when using DKI compared to when using the monoexponential ADC[14]. Significantly higher mean (K_{mean}) and axial (K_{ax}) kurtosis were reported in prostate tumors (K_{mean} 1.84 ± 0.43; K_{ax} 1.78 ± 0.39,) compared to the normal PZ (K_{mean} 1.16 ± 0.13; K_{ax} 1.09 ± 0.12, P < 0.001) or the transition/central zone (K_{ax} 1.40 ± 0.12, K_{mean} 1.44 ± 0.17; P = 0.01, respectively)[14].

Another study of 47 patients with prostate cancer who underwent 3T DW-MRI using *b*-values up to 2000 s/mm^2 found that the DKI metric K, which represents non-Gaussian diffusion behavior, was significantly higher in prostate sextants involved by tumor compared to sextants containing non-cancerous prostate tissue (0.96 ± 0.24 *vs* 0.57 ± 0.07, P < 0.001) and was also significantly greater in Gleason score > 6 tumors (1.05 ± 0.26) compared to tumors with Gleason scores ⩽ 6 (0.89 ± 0.20; P < 0.001)[16]. For differentiating prostate sextants involved by cancer from non-cancerous prostate sextants, K showed significantly greater

Table 2 Clinical studies of diffusion kurtosis imaging in prostate cancer

Ref.	No. of patients	Pathologic reference	*b*-values (s/mm^2)	MR parameters	Quantitative parameters[1]	Significance
Quentin *et al*[14]	31	Biopsy	0, 300, 600, 1000	3.0 T; TR/TE: 1700/101 ms; FOV: 204 × 204 mm; Matrix: 136 × 136; slice thickness: 6 mm; iPAT factor, 2; 4 averages	K_{axial}, PCa: 1.78 ± 0.39 K_{axial}, TZ: 1.40 ± 0.12 K_{axial}, PZ: 1.09 ± 0.12	DKI better fit than monoexponential; Difference for K between PCa and normal TZ/PZ is significant
Rosenkrantz *et al*[16]	47	Biopsy	0, 500, 1000, 1500, 2000	3.0 T; TR/TE: 3500/81 ms; FOV: 280 mm × 218 mm; Matrix: 100 × 100; slice thickness: 4 mm; iPAT factor, 2; 6 averages	K, high GS: 1.05 ± 0.26 K, low GS: 0.89 ± 0.20 K, PZ: 0.57 ± 0.07	Significant difference between K in high GS *vs* low GS sextants; K found to have better sensitivity, AUC than ADC or D for PCa
Suo *et al*[17]	19	RP	0, 500, 800, 1200, 1500, 2000	3.0 T; TR/TE: 3940/106 ms; FOV: 280 mm × 280 mm; Matrix: 128 × 128; slice thickness/gap: 3/1 mm; 4 averages	K, PCa: 0.96 ± 0.20 K, PZ: 0.59 ± 0.08	Significant difference for K between PCa and normal PZ; GS correlates significantly with K
Tamura *et al*[18]	20	RP	0, 10, 20, 30, 50, 80, 100, 200, 400, 1000, 1500	3.0 T; TR/TE: 5000/49 ms; FOV: 240 × 240 mm; Matrix: 80 × 80; slice thickness/gap: 3.5/0.1 mm; iPAT factor, 2; NEX = 2	K, PCa: 1.19 ± 0.24 K, BPH: 0.99 ± 0.28 K, PZ: 0.63 ± 0.23	Significant difference for K between PCa and normal PZ but marked overlap for K between PCa and BPH

[1]Values are mean ± SD [K: Kurtosis parameter (unitless); K_{axial}: Axial kurtosis (unitless)]. AUC: Area under curve; BPH: Benign prostatic hyperplasia; DKI: Diffusional kurtosis imaging; FOV: Field of view; GS: Gleason score; iPAT: Integrated parallel acquisition techniques; MR: Magnetic resonance; NEX: Number of excitations; PCa: Prostate cancer; PZ: Peripheral zone; RP: Radical prostatectomy; T: Tesla; TE: Time of echo; TR: Time of repetition; TZ: Transitional zone.

sensitivity (0.93) than ADC (0.79) or the DKI parameter D (0.84; $P < 0.001$), which represents diffusion corrected for non-Gaussianity. There was no significant difference in specificity; $P > 0.99$)[16]. The sensitivity of K (0.69) was significantly greater than that of ADC (0.51) or D (0.49) for differentiating between low- and high-grade cancer sextants but the specificity was lower (0.70, 0.81 and 0.83 for K, ADC and D; $P \leqslant 0.023$)[16]. The AUC for differentiating prostate sextants with Gleason Score $\leqslant$ 6 tumors from those with Gleason Score > 6 tumors was greater for K (0.70) than ADC (0.62) ($P = 0.010$)[16]. Similar findings were reported in a study that evaluated 19 prostate patients undergoing DW-MRI[17]. ADC and D values were significantly lower and K values were significantly higher in cancerous compared to non-cancerous PZ (ADC= 0.79 mum^2/ms ± 0.14 *vs* 1.23 ± 0.19 mum^2/ms; D = 1.56 mum^2/ms ± 0.23 *vs* 2.54 ± 0.24 mum^2/ms; K 0.96 ± 0.20 *vs* 0.59 ± 0.08; $P < 0.001$ for all)[17]. In benign PZ and prostate cancer, D and K values overlapped less often than did ADC values[17]. A significant inverse correlation was observed between prostate cancer D and K values (Pearson correlation coefficient $r = -0.729$; $P < 0.001$)[17]. ADC and K values differed significantly in tumors with different Gleason scores ($P \leqslant 0.001$), however D values were similar across tumors with different Gleason scores ($P = 0.325$)[17]. Gleason score correlated significantly with both the ADC value ($r = -0.828$; $P < 0.001$) and the K ($r = 0.729$; $P < 0.001$).

Li *et al*[13] evaluated the utility of diffusion tensor imaging (DTI) and DCE-MRI for detecting prostate cancer of the PZ in 33 patients undergoing 3T MRI of the prostate before biopsy. DTI does not require the introduction of a diffusional kurtosis tensor in addition to the diffusion tensor used in DTI, and can be obtained with 2 b values. They found significant differences in the ADC, fractional anisotropy (FA), volume transfer constant (Ktrans), and rate constant (kep) values between prostate sextants containing prostate cancer *vs* prostate sextants containing benign PZ tissue ($P < 0.0001$ for all)[13]. For tumor detection, a significantly greater AUC was found for the combined DTI and DCE-MRI findings (0.93) compared to DTI (0.86,) or DCE-MRI (0.84) alone ($P = 0.0017$-0.0034)[13].

Despite the encouraging results obtained in the evaluation of prostate cancer with DKI and DTI, both alone and in combination with other MRI techniques, differentiating benign conditions such as prostatic hyperplasia from prostate cancer remains problematic. Tamura *et al*[18] performed DKI using 11 *b*-values (0-1500 s/mm^2) before radical prostatectomy in 20 patients and found DKI parameter K showed a trend toward higher levels in prostate cancer than in stromal benign prostatic hypertrophy, but there was marked overlap between the values in the 2 conditions (1.19 ± 0.24 *vs* 0.99 ± 0.28, $P = 0.051$)[13]. Further efforts to aid discrimination between benign (*e.g.*, inflammatory or hyperplastic) and malignant prostatic tissue are warranted.

DTI has also been applied in an effort to delineate the location and distribution of the periprostatic nerve fibers prior to prostatectomy, with the aim of improving nerve-sparing approaches. Panebianco *et al*[19] compared 2D and 3D T2-weighted images to DTI obtained with 16 gradient directions and $b = 0$ and 1000 s/mm^2 in 36 prostate cancer patients; reporting a partial ability to depict periprostatic nerve fibers using 2D and 3D T2 morphological sequences; with 3D-DTI allowing visualization in lal directions of the entire plexus of the periprostatic nerve fibers[19]. A summary of the clinical studies of DKI in prostate cancer is presented in Table 2.

CONCLUSION

Preliminary results suggest that IVIM , DKI and DTI may contribute incremental value to conventional DW-MRI for the detection of prostate cancer, the assessment of tumor aggressiveness, and the prediction of adverse final pathologic outcomes. However, IVIM DKI and DTI metrics have been found to overlap substantially between different prostate cancer grades as well as between cancer and benign conditions. While combining these techniques with other multiparametric MR sequences may further increase their usefulness, they are still in the early stages of development, and further research is needed to establish their roles in the evaluation of prostate cancer.

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