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Clinical Significance of the Apparent Diffusion Coefficient Ratio in Prostate Cancer Treatment with Intensity-modulated Radiotherapy

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Abstract. *Aim: We aimed to investigate the correlation between biochemical recurrence (BCR) and the pretreatment apparent diffusion coefficient (ADC) ratio of tumor to normal prostate tissue in patients with prostate cancer who underwent intensity-modulated radiotherapy (IMRT). Patients and Methods: Retrospective analyses were performed for 101 patients diagnosed with localized prostate cancer who underwent IMRT at a dose of 70-78 Gy to the prostate gland and medial part of the seminal vesicles. Before treatment, all patients underwent magnetic resonance imaging including diffusion-weighted imaging of the prostate. BCR was defined as a rising prostate-specific antigen level (the Phoenix criterion). Results: The median follow-up for all patients was 29 months, and BCR occurred in 10 patients (9.9%). ADC ratios and Gleason scores were significant independent prognostic factors of BCR by multivariate analysis. Conclusion: The pretreatment ADC ratio was an independent prognostic factor for BCR in patients with prostate cancer who underwent IMRT.*

Cancer statistics show that prostate cancer is the second most frequently diagnosed cancer among men worldwide (1). Clinically localized prostate cancer is typically managed by established therapies such as radical prostatectomy, external-beam radiotherapy, and brachytherapy. For external-beam radiotherapy, three-dimensional conformal radiotherapy (3D-CRT) is the gold standard; however, intensity-modulated radiotherapy (IMRT) is becoming more widely used for image-guided radiotherapy. In patients with intermediate- and high-risk prostate cancer, dose escalation from 76 to 81 Gy in combination with external irradiation and androgen deprivation therapy (ADT) has also been shown to significantly improve outcomes (2).

Magnetic resonance imaging (MRI) has proven to be effective in the detection and staging of prostate cancer and is thought to be crucial to pretreatment evaluation in prostate cancer (2-5). Diffusion-weighted (DW) MRI, in addition to morphology, can measure quantitative parameters (2, 6), including the pretreatment apparent diffusion coefficient (ADC) ratio of tumor to normal tissue. Moreover, several studies have shown that the diffusion-weighted imaging can serve as a prognostic factor in different types of cancers, including localized prostate cancer treated with radical prostatectomy (7-9, 15). However, it remains unclear whether the pretreatment ADC ratio in prostate cancer can be used to predict outcomes after IMRT.

The aim of this study was to evaluate the usefulness of the pretreatment ADC ratio of prostate cancer for predicting biochemical recurrence (BCR) after IMRT.

Patients and Methods

Patient selection. Our Institute's Ethical Committee approved this retrospective study (approval number: 15336). We identified patients with clinically localized prostate cancer who underwent IMRT at our Institution between June 2008 and October 2014. Patients who met the following criteria were then included: (a) biopsy-proven prostate adenocarcinoma; (b) had not received hormonal, radiation, or surgical treatment for prostate cancer before MRI; and (c) had undergone prostate MRI, including DW imaging, before IMRT. All participants provided their written informed consent. Clinical data were also collected, including the patient's age, Gleason score, initial serum prostate-specific antigen (PSA) level, clinical tumor stage, risk group derived from The National

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Comprehensive Cancer Network guideline (10), percentage of positive cores among all biopsy cores, tumor location, ADT duration, and total delivered RT dose.

Treatment. All patients underwent step-and-shoot IMRT at our institution, with 49 patients using Oncor Impression PLUS (Siemens Medical Systems, Concord, CA, USA) and the remaining 52 patients using Siemens Artiste linac (Siemens Medical Systems, Concord, CA, USA). Patients were asked to empty their rectums and bladders 30 min before treatment. During treatment, patients were immobilized in the supine position using Vac-Lok Cushions (CIVCO Medical Solutions, Orange City, IA, USA), and contouring was performed by an experienced radiation oncologist. The clinical target volume was defined as the prostate and medial part of seminal vesicles plus a 3 mm margin in all directions, and the planning target volume was defined as the clinical target volume plus a 5 mm margin in all directions. For the patients who were treated using Oncor Impression PLUS (n=52), the prescription dose was as follows: 74 Gy/37 fractions for patients in the high- (T3-T4, GS >7, or PSA >20 ng/ml) ,or intermediate- (T2b-T2c, GS 7, or PSA 10–20 ng/ml) risk group, and 70 Gy/35 fractions for patients in the low-risk (T1c-T2a, GS <7 and PSA ≤10 ng/ml) group. For the patients who were treated using Siemens Artiste linac (n=49), the prescription dose was as follows: 78 Gy/39 fractions for patients in the high- (T3-T4, GS >7, or PSA >20 ng/ml) ,or intermediate- (T2b-T2c, GS 7, or PSA 10–20 ng/ml) risk group, and 74 Gy/37 fractions for patients in the low-risk (T1c-T2a, GS <7 and PSA ≤10 ng/ml) group. Dose–volume constraints for risk organs were set as follows: rectum V45 Gy <35%, V65 Gy <17%; bladder V40 Gy <50%, V65 Gy <25%, femoral head maximum dose <50 Gy, and small intestine maximum dose <60 Gy. In the 46 patients who received 74 Gy and the six patients who received 70 Gy, the dose was normalized to cover 95% of the planning target volume with the prescribed dose. In the remaining 49 patients, the dose was normalized to cover 50% of the planning target volume with the prescribed dose.

Imaging technique. MRI studies were performed by 1.5- or 3-Tesla (T) MRI scanners. The entire prostate gland and seminal vesicles were imaged in axial and sagittal slices for each patient, using a T2-weighted turbo spin-echo sequence. The imaging parameters were as follows: repetition time=3,167–8,000 ms; echo time=86-140 ms; slice thickness=4-5 mm; field of view=200-310 mm; and matrix=256-520×256-520. Axial DW images were obtained by single-shot echo-planner imaging with b values of 0 and 800 s/mm^2, 0 and 1000 s/mm^2, 0 and 1200 s/mm^2, or 0 and 2000 s/mm^2. The imaging parameters were as follows: repetition time=4255-7000 ms; echo time=70-130 ms; field of view=220-360 mm; and matrix=140-256×108-256.

Image analysis. Post-processing was performed automatically on each scanner or workstation, with the ADC values calculated from the DW images. The ADC value of each pixel was calculated according to the following formula: $SIb=SIb0 \times \exp(-b \times ADC)$, where *SIb* and *SIb0* correspond to the signal intensities of specific *b* value and *b0* images, respectively. One of the following four combinations of *b* values were used: 0 and 800 s/mm^2, 0 and 1,000 s/mm^2, 0 and 1,200 s/mm^2, or 0 and 2,000 s/mm^2. All suspicious tumor foci were evaluated by the same radiologist (20 years' experience in prostate MRI interpretation) and the same radio-oncologist (3 years' experience in prostate MRI interpretation) who were blinded to clinical stage, number of positive specimens, percentage of tumor tissue per specimen, lesion site, and histopathological biopsy results. The lesion was determined to be a visible tumor if it was recognized as being markedly hypointense on ADC or markedly hyperintense on DW imaging or having definite extraprostatic extension/invasive behavior; or as being lenticular or non-circumscribed, homogenous on DW imaging, and moderately hypointense on T2-weighted imaging; or having definite extraprostatic extension/invasive behavior in T2-weighted image. The anatomical locations of all lesions considered to be visible tumors, as well as the biopsy-proven tumor site, were recorded. Each visible tumor site was checked for consistency with the biopsy-positive cores.

Mean ADC values for individual tumors were obtained by manually drawing a region of interest within the largest area of the tumor on each ADC map, avoiding tumor margins, the prostate capsule, and the urethra. If multiple tumors were present in the peripheral zone or transitional zone, ADC values were determined for the largest tumor. The regions of interest were also drawn for the biopsy-proven benign tissue in the same anatomical zone in the prostate. For all tumor foci, the ADC ratio was calculated as the mean ADC value of biopsy-proven cancer divided by the mean ADC value of biopsy-proven benign tissue.

Follow-up. All patients underwent laboratory tests after prostate IMRT. The PSA level was checked every 3 months in the first and second years, every 6 months up to the fifth year, and annually thereafter. The median follow-up interval was recorded in months.

Outcome. Biochemical recurrence-free survival (BFS) was chosen as the clinical outcome of interest. BCR was defined according to the Phoenix criterion, as follows: PSA nadir + 2 ng/ml (11). The BFS was then defined as the time from the initiation of IMRT to the date of BCR.

Analysis. Receiver operating characteristic (ROC) curve analyses were performed to determine the cut-off value of the ADC ratio. Statistical differences between the two groups (those above and those below the cutoff value) were analyzed by the Kaplan–Meier method with the log-rank test. The relationship between BCR and the ADC ratio, as well as other clinical factors, was explored by univariate Cox proportional hazards regression analysis. The other clinical factors of interest were the pretreatment ADC ratio, Gleason score, clinical tumor stage (cT), initial serum PSA level, patient age, percentage of positive cores in all biopsy cores, duration of ADT, delivered IMRT dose, and magnetic field strength during MRI. Multivariate analyses were performed by Cox proportional hazard modeling in which we only included variables that were statistically significant in the univariate analysis. For all statistical analyses, a *p*-value of less than 0.05 was considered significant. The independent sample Student *t*-test was used to assess differences in the ADC ratio between the following groups based on the Gleason score: (i) High Gleason score group: the group with a Gleason score of 8, 9, or 10; and (ii) Low Gleason score group: the group with a Gleason score of 6 or 7. All analyses were performed with JMP pro 12 (SAS Institute Inc., Cary, NC, USA).

Results

Participants. During the study period, 231 patients underwent IMRT for clinically localized prostate cancer at our Institution. Of these, 84 were excluded because they had started hormonal therapy before undergoing MRI, and 46 were excluded because they had not undergone DW imaging to allow the measurement of ADC. The remaining 101

patients were included, and the characteristics of these patients and their tumors are summarized in Table I. The median Gleason score was 7 (range=6-10).

Therapy and ADC results. Before treatment, 50 patients underwent MRI with 1.5-T devices and the remaining 51 underwent MRI with 3-T devices. Tumors were visible on ADC maps in 86 patients, thus the ADC ratios were calculated for these patients. In the other 15 cases, the ADC ratios were defined as 1 because the tumors were invisible. Visible tumors tended to be located in the peripheral zone (n=64) followed by the transitional zone (n=22). The mean ADC ratios for patients scanned with 1.5-T and 3-T devices were 0.614 and 0.612, respectively, with no significant differences in values between the groups (p=0.947).

The prescription dose for IMRT was 74 Gy/37 fractions for the 52 low-, intermediate-, or high-risk patients, 78 Gy/39 fractions for the 43 high-risk patients, and 70 Gy/35 fractions for the 6 low-risk patients depending on the system used for administration. Three high-risk patients also received simultaneous integrated boost RT to the pelvic lymph node area, whole prostate gland, and medial seminal vesicles. Each visible tumor site was consistent with those of the biopsy-positive cores.

Follow-up and outcomes. The median follow-up interval was 29±16.0 (range=11-83) months. The median duration of ADT was 10±11.4 (range=0-52) months.

The BFS rate at 3 years was 90.5%, with BCR occurring in 10 patients during the observation period. All patients with BCR underwent hormonal therapy after disease recurrence. These were no cases of acute or late complication of grade 3 or more.

Independent predictors of BCR. We used ROC curve analyses to evaluate whether the pretreatment ADC ratio predicted BCR. ROC curve analyses showed an optimal ADC ratio of 0.59 (n=101) with an area under the ROC curve of 0.71. Patients were then divided into a high ADC ratio group if their ADC ratios were more than 0.59, and a low ADC ratio group if their ADC ratios were less than 0.59. Representative cases with low and high ADC ratios are shown in Figures 1 and 2. Patients were also divided by their Gleason scores into high or low Gleason score groups, as defined in the Patients and Methods section.

Figure 3 shows that patients in the low ADC ratio and high Gleason score groups had shorter BFS compared to patients in the high ADC ratio and low Gleason score groups (p=0.0381 and p=0.0180, respectively), and these factors were included in the multivariate analysis. However, no statistically significant correlations were found between BFS and patient age, initial serum PSA value, clinical tumor stage, percentage of positive cores in all biopsy cores, or receipt of neoadjuvant, concomitant, and adjuvant hormonal therapies.

Table I. *Patient and tumor characteristics*.

Characteristic	Value
Median age at treatment (range), years	71 (57-85)
Median initial serum PSA (range), ng/ml	9.24 (1.2-171.3)
Gleason score	
6	25
7	40
8	23
9	12
10	1
T Classification	
T1c	15
T2a	38
T2b	12
T2c	9
T3a	16
T3b	10
T4	1
Risk group	
Low	11
Intermediate	41
High	49
Total prescription dose at IMRT	
70 Gy	6
74 Gy	52
78 Gy	43
Androgen deprivation therapy	
Yes	77
No	24
Mean positive cores of all biopsy cores(range), %	34 (5-100)
Tumor location	
Peripheral zone	64
Transitional zone	22
Not identified	15

IMRT, Intensity-modulated radiotherapy; PSA, prostate-specific antigen.

In the multivariate analysis, an ADC ratio <0.59 [hazard ratio (HR)=5.850, 95% confidence interval (CI)=1.092-108.09, p=0.0374) and a Gleason score ≥8 (HR=3.977, 95% CI=1.098-18.54, p=0.0353) were independent prognostic factors for BCR. Detailed results of the multivariate analyses are shown in Table II. The ADC ratio was significantly lower in the high Gleason score group than in the low Gleason score group.

Discussion

Previous studies have shown that ADC values correlate negatively with the aggressiveness of a tumor (12, 13), and that lower pretreatment tumor ADC values are associated with treatment response in cervical, head and neck squamous cell, and pancreatic cancer (8, 9, 14). For localized prostate cancer treated by radical prostatectomy, pretreatment tumor ADC values have also been reported to be associated with the rate of BCR (15). It is thought that the ADC reflects the

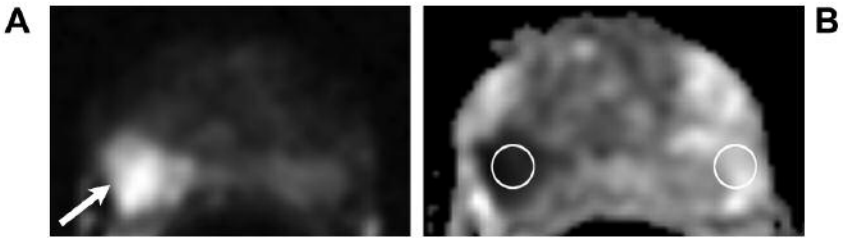

Figure 1. *Representative case with a low apparent diffusion coefficient (ADC) ratio. A 68-year-old man with prostate cancer and the following characteristics: Prostate-specific antigen level, 8.4 ng/ml; biopsy Gleason score, 4+4 (8); and cT2a without extracapsular extension or seminal vesicle invasion. A: Axial diffusion-weighted image (b=1200 s/mm^2) shows an area of markedly rounded hyperintensity (arrow) at the site of biopsy-proven cancer. B: The axial ADC map with regions of interest (circles) placed at the center of the tumor, which shows markedly lower ADC value than the surrounding tissue, and at a biopsy-proven benign site yielded an ADC ratio of 0.26.*

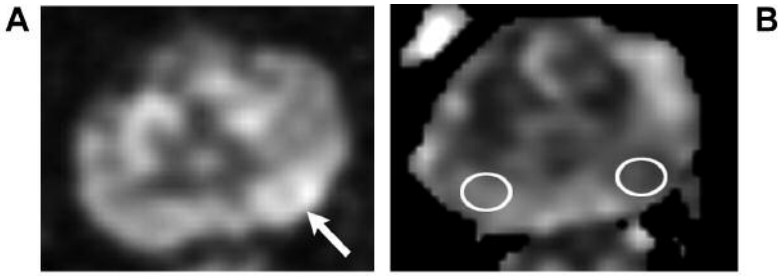

Figure 2. *Representative case with a high apparent diffusion coefficient (ADC) ratio. A 69-year-old man with prostate cancer and the following characteristics: Prostate-specific antigen level, 8.8 ng/ml; biopsy Gleason score, 3+4 (7); and cT2c without extracapsular extension or seminal vesicle invasion. A: Axial diffusion-weighted image (b=1,200 s/mm^2) shows an area of rounded hyperintensity (arrow) at the biopsy-proven cancer site. B: Axial ADC map with regions of interest (circles) placed at the center of the tumor, which shows slightly lower ADC value than the surrounding tissue, and at a biopsy-proven benign site yielded an ADC ratio of 0.77.*

cell density in the tissue of interest, with the ADC of tumor tissue reported to be lower than those of normal tissue (12, 16-22). Generally, cell density is increased in tumor tissue, with the diffusion of cell water restricted by barrier structures such as cell membranes that result in decreased ADC values (23).

In localized prostate cancer, the Gleason score, pretreatment PSA, and clinical tumor stage have been reported to be predictive of BCR after radical prostatectomy (15). In cases where patients undergo definitive external beam RT, several factors have been shown to correlate with BCR, including initial PSA (>20 ng/ml), Gleason score (8-10), high-risk group (T2c-T3, GS >7, or PSA >20 ng/ml), TNM stage (≥T2cN0M0), radiotherapy (dose <70 Gy, or with a two-dimensional technique), and hormonal therapy (patients at high risk) (24). The Gleason scoring system is the most commonly accepted and widely used system for evaluating the biological aggressiveness of prostate cancer (25, 26), and it has been established as a prognostic factor (27). In addition, previous studies have shown that both ADC ratios and values in prostate cancer negatively correlate with the Gleason score (12, 28-30).

To our knowledge, this is the first study to evaluate the prognostic value of ADC obtained from pretreatment DW imaging for prostate cancer treated by definitive external-beam RT. By multivariate analysis, we showed that a lower ADC ratio was associated with a significantly higher rate of BCR. This suggests that tumors with lower ADC values at pretreatment DW imaging might be associated with a higher risk of BCR after IMRT. Multivariate analysis also revealed that the Gleason score was a significant prognostic factor. Although the combination of IMRT and ADT is generally thought to improve treatment outcomes, ADT had no significant effect on the outcome in our analyses. Therefore, when used to calculate ADC values, our results suggest that DW imaging predicts the treatment outcomes of patients with prostate cancer who undergo IMRT. Unlike the Gleason score which requires an invasive procedure, ADC ratios obtained from DW imaging may be useful as a non-invasive prognostic marker.

There are several limitations to this study. Firstly, the relatively short 29-month follow-up period and the relatively small number of patients precluded, among other things, evaluation of prostate cancer-specific mortality and

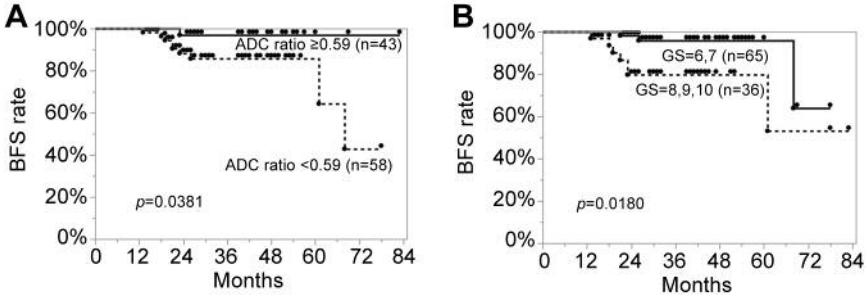

Figure 3. *Kaplan–Meier curve for the biochemical recurrence-free survival (BFS) rates according to apparent diffusion coefficient (ADC) (A) and Gleason score (B). The cut-off value was 0.59. The p-value was calculated using the log-rank test.*

Table II. *Results of univariate and multivariate Cox regression analyses for biochemical recurrence-free survival.*

		Univariate analysis		Multivariate analysis	
Variable	Category	HR (95% CI)	*p*-Value	HR (95%CI)	*p*-Value
ADC ratio	<0.59 *vs.* ≥0.59	6.618 (1.241-122.091)	0.0236	5.850 (1.092-108.09)	0.0374
Gleason score	8, 9, 10 *vs.* 6, 7	4.472 (1.233-20.851)	0.0223	3.977 (1.098-18.50)	0.0353
cT	cT3a-4 *vs.* cT1c-2c	1.474 (0.362-5.346)	0.567	–	–
Initial serum PSA level	<20 *vs.* ≥20 ng/ml	1.762 (0.258-7.656)	0.51	–	–
Age	<70 *vs.* ≥70 years	2.176 (0.604-8.670)	0.232	–	–
Percentage of positive cores in all biopsy cores	≥50% *vs.* <50%	1.595 (0.406-5.611)	0.48	–	–
Androgen deprivation therapy	No *vs.* yes	1.197(0.256-4.353)	0.8	–	–
Delivered dose in IMRT	70 Gy, 74 Gy *vs.* 78 Gy	3.563 (0.627-66.84)	0.17	–	–
Magnetic field strength	1.5 T *vs.* 3 T	1.340 (0.329-6.541)	0.688	–	–

ADC: Apparent diffusion coefficient; cT: clinical tumor stage; PSA: prostate-specific antigen; IMRT: intensity-modulated radiotherapy; HR: hazard ratio; CI: confidence interval.

disease-free survival. Secondly, MRI was performed at multiple institutions under different magnetic field strengths (1.5 and 3.0 T) with four different combinations of *b* values. Theoretically, however, the ADC does not depend on magnetic field strength (13, 31), and even if it did, we found no significant difference in the ADC ratio between the 1.5-T and 3.0-T groups. In contrast, ADC does vary depending on the combination of *b* values, hence it is impossible to compare the absolute ADC values obtained by different MRI sequences. However, it was recently shown that using the simple ratio of prostate cancer ADC to normal tissue ADC may be a more robust means of assessing restricted diffusion in the prostate than using absolute ADC values (32).

In conclusion, we found that the ADC ratio is a predictive factor for BCR of localized prostate cancer following IMRT. However, further studies with a longer follow-up period and a larger sample are needed to verify our results.

Conflicts of Interest

None.

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