Personalized Medicine and Imaging

Prostate MRI: Evaluating Tumor Volume and Apparent Diffusion Coefficient as Surrogate Biomarkers for Predicting Tumor Gleason Score

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Abstract

**Purpose:** To investigate whether tumor volume derived from apparent diffusion coefficient (ADC) maps (Volume_{ADC}) and tumor mean ADC value (ADC_{mean}) are independent predictors of prostate tumor Gleason score (GS).

**Experimental Design:** Tumor volume and GS were recorded from whole-mount histopathology for 131 men (median age, 60 years) who underwent endorectal diffusion-weighted MRI for local staging of prostate cancer before prostatectomy. Volume_{ADC} and ADC_{mean} were derived from ADC maps and correlated with histopathologic tumor volume and GS. Univariate and multivariate analyses were performed to evaluate prediction of tumor aggressiveness. Areas under receiver-operating characteristics curves (AUC) were calculated to evaluate the performance of Volume_{ADC} and ADC_{mean} in discriminating tumors of GS 6 and GS ≥7.

**Results:** Histopathology identified 116 tumor foci >0.5 mL. Volume_{ADC} correlated significantly with histopathologic tumor volume (r = 0.683). The correlation increased with increasing GS (r = 0.453 for GS 6 tumors; r = 0.643 for GS 7 tumors; r = 0.980 for GS ≥8 tumors). Both Volume_{ADC} (p = 0.286) and ADC_{mean} (p = -0.309) correlated with GS. At univariate analysis, both Volume_{ADC} (P = 0.0325) and ADC_{mean} (P = 0.0033) could differentiate GS = 6 from GS ≥7 tumor foci. However, at multivariate analysis, only ADC_{mean} (P = 0.0156) was a significant predictor of tumor aggressiveness (i.e., GS 6 vs. GS ≥7). For differentiating GS 6 from GS ≥7 tumors, AUCs were 0.644 and 0.704 for Volume_{ADC} and ADC_{mean}, respectively, and 0.749 for both parameters combined.

**Conclusion:** In patients with prostate cancer, ADC_{mean} is an independent predictor of tumor aggressiveness, but Volume_{ADC} is not. The latter parameter adds little to the ADC_{mean} in predicting tumor GS. Clin Cancer Res; 20(14); 1–7. ©2014 AACR.

**Introduction**

It was estimated that 30% to 50% of the approximately 238,590 American men diagnosed with prostate cancer in 2013 would have an indolent form of the disease unlikely to become life-threatening. These men could potentially take advantage of an increasing spectrum of patient-tailored disease management options—including active surveillance and various forms of focal ablation—that are designed to minimize adverse treatment-related effects (1–3). However, to ensure that patients are indeed suited for such conservative management approaches, it is essential not only to detect and localize prostate cancer, but also to assess its aggressive potential—a task that remains challenging. Clinical, biochemical and pathologic features are typically used to triage patients according to the likelihood of rapid disease progression (4–8).

Recently, diffusion-weighted MRI (DWI) has garnered interest for its potential to noninvasively characterize prostate cancer aggressiveness. DWI probes variations in free water movement within tissues, which tends to be more restricted in the presence of tumor due to changes in cell number, size, and architecture. On DWI images, variations in water diffusion manifest as changes in signal intensity, and degrees of diffusion restriction can be assessed quantitatively by means of the apparent diffusion coefficient (ADC). A relatively simple metric, the ADC can be calculated on a pixel-by-pixel basis with clinical MRI platforms.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Many prostate cancers diagnosed today are likely indolent, but better means of assessing prostate cancer prognosis are needed to identify the appropriate, patient-specific treatment option. Distinguishing tumors of Gleason score (GS) 6 from tumors of GS ≥7 is especially critical for assessing eligibility for active surveillance. In patients who underwent diffusion-weighted MRI before radical prostatectomy, we assessed the value of the mean tumor apparent diffusion coefficient (ADCmean) and the tumor volume measured from ADC maps (VolumeADC) for predicting two important prognostic factors: tumor volume and tumor GS on histopathology. VolumeADC correlated well with histopathologic tumor volume, and the strength of the correlation increased with the tumor GS. Both VolumeADC and ADCmean correlated with tumor GS, but on multivariate analysis only ADCmean independently distinguished tumors of GS 6 from tumors of GS ≥7. Our findings indicate that independent of the tumor volume, ADCmean could serve as a biomarker to predict prostate cancer aggressiveness.

A number of studies have shown an inverse correlation between ADC values on DWI and prostate cancer Gleason scores (GS; refs. 9–14). However, the ADC values of prostate cancer foci with different GS overlap, and no method has been developed to determine the GS unequivocally based on ADC analysis alone (9–14).

Pathology studies have shown that higher tumor volumes are associated with higher GSs and worse outcomes (15, 16). Tumor volume measured on DWI correlates well with the histopathologic tumor volume (17, 18). However, the relationship between ADC and prostate tumor volume and the potential synergy of these two parameters in evaluating prostate cancer aggressiveness have not been explicitly explored. Thus, the purpose of our study was to investigate whether tumor mean ADC value (ADCmean) and tumor volume derived from ADC maps (VolumeADC) are independent predictors of tumor GS and can be used to distinguish tumors with GSs of 6 from those with GSs of 7 or above.

Materials and Methods

The IRB approved our retrospective study and waived the informed consent requirement. Our study was compliant with the Health Insurance Portability and Accountability Act.

Patients

Patients who underwent MRI of the prostate including DWI between July 2008 and April 2010 and for whom whole-mount step-section pathologic tumor maps were available were identified (n = 377). Patients who met the following inclusion criteria were selected: (i) 1.5-Tesla MRI of the prostate, including a DWI sequence with b = 0, 1,000 seconds/mm² and (ii) radical prostatectomy performed at our institution within 6 months after MRI. Patients were excluded if (i) they had undergone prior prostate cancer treatment, including hormone therapy or radiation; (ii) acquisition was incomplete or imaging artifacts rendering the examination nondiagnostic were present; or (iii) MRI was performed without an endorectal coil. Our final study population consisted of 131 consecutive patients who were previously included in a study analyzing histogram-derived ADC parameters (19). Patients’ characteristics are summarized in Supplementary Table S1.

MRI acquisition

All images were acquired on a 1.5-Tesla MRI system (GE Healthcare Technologies). A body coil was used for excitation; a pelvic four-channel phased-array coil and an endorectal coil (Medrad) were used for signal reception. T1- and T2-weighted, and DWI sequences were acquired but only DWI sequence was used for analysis in this study. DWI was performed using a single-shot spin-echo echoplanar imaging sequence with b = 0, 1,000 seconds/mm² (TR/TE, 1,200–6,800 ms/40–113 ms; section thickness, 3–4 mm; no intersection gap; field of view, 12–16 cm; matrix, 96 × 96–128 × 128). Parametric maps of ADC values were calculated using a designated workstation (Advanced Workstation, GE Medical Systems).

MRI–histopathologic correlation

Histopathologic preparation. After prostatectomy, specimens were submitted to histopathology, where they were sliced from apex to base at 3 to 4 mm intervals. Microslices were placed on glass slides and stained with hematoxylin and eosin after paraffin embedding. For each patient, one of two dedicated genitourinary pathologists at our institution with more than 30 years of combined experience verified and assigned a GS for each tumor outlined on the histology slides.

Measurement of histopathologic tumor volume. Tumor volume on pathology slices was measured in consensus by two of the authors using software (Image, version 1.47a; NIH, Bethesda, MD). If a lesion extended into more than one histopathologic zone, the areas of tumor foci on all slices were summed to obtain an estimate of the histopathologic volume of the whole lesion. Tumors that covered both zones, the transition zone as well as the peripheral zone, were considered to be transition zone tumors if more than 70% of the tumor was in the transition zone (20); all others were considered to be peripheral zone tumors (9).

Correlation of lesions on MRI and histopathology. Working in consensus, three radiologists (with 1, 1, and 9 years of experience in interpreting prostate MRI) correlated MR images with whole-mount pathology maps to establish the locations of tumors on MRI. Using software (Image), version 1.47a; NIH), the radiologists drew a freehand region of interest (ROI) around the discernible tumor tissue on the ADC maps (19). If a tumor was depicted on more than one slice, all traced ROIs corresponding to that...
tumor were included in the estimation of the tumor volume (Volume_{ADC}) and the calculation of the mean ADC value (ADC_{mean}; ref. 19). On each slice containing tumor, the area of the tumor focus was determined on a voxel basis by considering the acquisition matrix, reconstruction matrix as well as the FOV. Volume_{ADC} (mL) was calculated as [sum of all tumor areas on the slices (cm^2) × slice thickness (cm)].

**Statistical analysis**

The correlation between Volume_{ADC} and volume derived from histopathology as well as the correlations of Volume_{ADC} and ADC_{mean} with tumor GS were assessed using Spearman correlation coefficient (ρ). The between-subject correlation coefficient proposed by Bland and Altman (21) was calculated and tested to take into account multiple lesions per patient.

To evaluate whether Volume_{ADC} and ADC_{mean} could differentiate a GS of 6 from a GS ≥7, a generalized linear regression and generalized estimating equations method was used with an independent correlation structure and robust covariance matrix, to take into account multiple lesions per patient. Univariate and multivariate analyses with both Volume_{ADC} and ADC_{mean} as covariates were performed. The OR describing the likelihood of a tumor having GS ≥7, along with the 95% confidence interval (CI), was estimated. Nonparametric ROC curve analysis was performed, and the AUC was estimated to evaluate the performance of Volume_{ADC} and ADC_{mean} in discriminating between GS 6 and GS ≥7. Sensitivity and specificity based on the estimated probabilities from the multivariate model were used to estimate the AUC for the combination of both variables.

All statistical analyses were performed with SAS 9.2 (SAS Institute Inc.) and R version 2.13 (The R Foundation for Statistical Computing). Results with P < 0.05 were considered statistically significant.

**Results**

Forty-six patients presenting only insignificant cancer lesions in terms of volume (<0.5 mL; ref. 22) were excluded from comparative analysis. One hundred and sixteen clinically significant lesions (>0.5 mL) on histopathology were found in 85 patients. Eighty-nine (76.7%) of the 116 lesions originated in the peripheral zone and 27 of 116 (23.3%) originated in the transition zone. Lesion characteristics, including tumor volume and GS, are shown in Supplementary Table S2.

**Correlation of volume_{ADC} and histopathologic tumor volume**

The Spearman correlation coefficient for Volume_{ADC} and histopathologic tumor volume in lesions >0.5 mL was ρ = 0.683 (P < 0.0001; Fig. 1). The correlation coefficient increased as the tumor GS increased, rising from ρ = 0.453 (P = 0.1042) for tumors with a GS of 6 (3+3) to ρ = 0.643 (P < 0.0001) for tumors with a GS of 7 (3+4 or 4+3) and ρ = 0.980 (P < 0.0001) for tumors with a GS ≥8 (Table 1). The correlation between histopathologic tumor volume and Volume_{ADC} was highest for tumors of GS ≥8.

**Correlations of histopathologic tumor volume, volume_{ADC} and ADC_{mean} with GS**

Histopathologic tumor volume and Volume_{ADC} both correlated positively with tumor GS [ρ = 0.336 (P = 0.0017) and ρ = 0.286 (P = 0.0081), respectively], whereas ADC_{mean} correlated negatively with tumor GS [ρ = −0.309 (P = 0.0087)].

**Differentiation of tumor aggressiveness by volume_{ADC} and ADC_{mean}**

In a univariate analysis including all lesions (peripheral zone and transition zone), both Volume_{ADC} and ADC_{mean} could differentiate tumors of GS 6 from those with a GS ≥7 (OR, 1.73 for Volume_{ADC} and 0.64 for ADC_{mean}; P = 0.0325 and 0.0033, respectively; Table 2). In a subanalysis considering only tumors originating in the peripheral zone, ADC_{mean} could differentiate between tumors of GS 6 and those with a GS ≥7 (P = 0.0025), but Volume_{ADC} could not (P = 0.2709; Table 2). The number of lesions originating in the transition zone was too small to permit a subanalysis.

In a multivariate analysis, after adjustments were made for the influence of Volume_{ADC}, ADC_{mean} independently discriminated between tumors of GS 6 and tumors of GS ≥7 (P = 0.0156; Fig. 2). However, after adjustments were made for the influence of ADC_{mean}, Volume_{ADC} could not independently differentiate between these two tumor GS categories (P = 0.0733; Table 2; Fig. 3).

Accuracy in discriminating tumors of GS 6 from those with a GS ≥7 was slightly lower for Volume_{ADC} than for ADC_{mean} (AUC = 0.644 and AUC = 0.704, respectively; P = 0.3262). Combining these variables as covariates in a
multivariate model resulted in a minor increase in AUC (to 0.749; Supplementary Fig. 1).

Discussion

In our study, tumor volume measured on ADC maps correlated with tumor volume on histopathology, and the strength of the correlation increased with the tumor GS. In addition, the ADC\textsubscript{mean}, but not the Volume\textsubscript{ADC}, independently differentiated tumors of GS 6 from those of GS 7 or above. The Volume\textsubscript{ADC} added little to the ADC\textsubscript{mean} in predicting the tumor GS.

The correlation between Volume\textsubscript{ADC} and histopathologic tumor volume in our study (r = 0.68) was very similar to that reported by Isebaert and colleagues (r = 0.75; ref. 17), and it was slightly higher than the correlation between tumor volume on T2-weighted MRI and histopathologic tumor volume reported by Turkbey and colleagues (r = 0.63; ref. 23). The difference between our result and that of Turkbey and colleagues is consistent with an earlier study by Mazaheri and colleagues, which found that prostate cancer tumor volume measurements based on ADC maps correlated better with histopathologic tumor volumes than did measurements based on T2-weighted MRI (17, 18). Furthermore, the correlation between imaging- and histopathology-derived tumor volumes may have been stronger in our study because, unlike Turkbey and colleagues, we used a pixel-based calculation to determine imaging and histopathologic tumor volumes, outlining tumor borders instead of using the ellipsoid formula, which is based on linear measurements and does not take into account the irregular shapes of prostate cancer foci.

In keeping with the existing literature, we demonstrated that ADC-based tumor volume and histopathologic tumor volume correlate better in prostate cancer foci with higher GSs. This may be explained by the fact that tumors with higher GSs are better depicted on ADC maps because they contrast more strongly with benign tissue (10, 13); this makes it easier to trace the borders of the lesions and likely results in more accurate representations of the actual areas of tumor on ADC maps.

The correlation between Volume\textsubscript{ADC} and GS in our study (r = 0.29) was similar to that recently reported by Verma and colleagues (r = 0.35; ref. 24). Likewise, the correlation between ADC\textsubscript{mean} and GS in our patient cohort (r = 0.31) was within the range of such correlations reported in recent studies (r = −0.26 to −0.38; refs. 12, 14, 24). At multivariate analysis, ADC\textsubscript{mean} was the only parameter that independently predicted the category of the tumor GS (GS 6 vs.

Table 1. Correlation between tumor volume on histopathology and tumor volume on ADC maps

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>P</th>
<th>Lesions</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tumors</td>
<td>0.683</td>
<td>&lt;0.0001</td>
<td>116</td>
<td>85</td>
</tr>
<tr>
<td>PZ tumors</td>
<td>0.706</td>
<td>&lt;0.0001</td>
<td>89</td>
<td>73</td>
</tr>
<tr>
<td>TZ tumors</td>
<td>0.677</td>
<td>0.0003</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>GS 6 tumors</td>
<td>0.453</td>
<td>0.1042</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>GS 7 tumors</td>
<td>0.643</td>
<td>&lt;0.0001</td>
<td>92</td>
<td>71</td>
</tr>
<tr>
<td>GS ≥8 tumors</td>
<td>0.980</td>
<td>&lt;0.0001</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

NOTE: 95% CI was estimated using the bootstrapping method of resampling patients.
Abbreviations: PZ, peripheral zone; TZ, transition zone.

Table 2. Results of univariate and multivariate analyses for prediction of tumor GS ≥7 by ADC\textsubscript{mean} and Volume\textsubscript{ADC}

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All lesions &gt;0.5 mL</td>
<td></td>
<td>PZ lesions &gt;0.5 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Univariate analysis</td>
<td></td>
<td>Multivariate analysis</td>
<td></td>
</tr>
<tr>
<td>ADC\textsubscript{mean} (100-unit increment)</td>
<td>0.64 (0.47–0.86)</td>
<td>0.0033</td>
<td>0.50 (0.32–0.78)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Volume\textsubscript{ADC} (0.5 mL increment)</td>
<td>1.73 (1.05–2.87)</td>
<td>0.0325</td>
<td>1.50 (0.73–3.07)</td>
<td>0.2709</td>
</tr>
<tr>
<td>ADC\textsubscript{mean} (100-unit increment)</td>
<td>0.68 (0.50–0.93)</td>
<td>0.0156</td>
<td>0.51 (0.33–0.79)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Volume\textsubscript{ADC} (0.5 mL increment)</td>
<td>1.57 (0.96–2.59)</td>
<td>0.0733</td>
<td>1.14 (0.66–1.98)</td>
<td>0.6359</td>
</tr>
</tbody>
</table>

NOTE: OR interpretation: the tumors are less likely to have a GS of 7 or above as the ADC\textsubscript{mean} increases (OR for 100-unit increase = 0.68, 95% CI, 0.50–0.93), controlling for Volume\textsubscript{ADC}.
Transition zone tumors were not assessed separately due to the small number of lesions in the transition zone.
Abbreviation: PZ, peripheral zone.
It seems that though the predictive value of ADC$_{\text{mean}}$ for tumor aggressiveness is independent of tumor size, when ADC$_{\text{mean}}$ is not clearly predictive, Volume$_{\text{ADC}}$ cannot be used to resolve the ambiguity. These results contrast with those of a recent study by Verma and colleagues, in which both mean ADC value and Volume$_{\text{ADC}}$ were identified as significant predictors of tumor aggressiveness in the peripheral zone at multivariate analysis (24). There are several possible reasons for the discrepancy. First, different statistical methods were used for the multivariate analyses of the two studies. Second, our measurements were based on whole-mount step-section pathology slides instead of recreated histologic maps. Third, the $b$ values used to create the ADC maps in our patient cohort ($b = 0, 1,000$ seconds/mm$^2$) differed from those used in the other study ($b = 0, 600$ seconds/mm$^2$; ref. 24). (ADC values are dependent on the chosen $b$ values; ref. 25, and therefore ADC measurements cannot be compared between protocols using different $b$ values. However, as long as the imaging parameters, including the $b$ value, are kept constant, ADC values measured in the abdomen may be comparable across different scanners and field strengths; ref. 26). Fourth, in the study by Verma and colleagues, only the voxels of the most central slice were used to calculate ADC parameters. Although the results of the multivariate analyses differed, accuracy levels in identifying prostate cancer foci of GS $\geq 7$ by combining ADC$_{\text{mean}}$ and Volume$_{\text{ADC}}$ were similar in the two studies (24).

We acknowledge the following limitations of our study: First, so that we would be able to correlate imaging findings with histopathology, we only included patients who underwent radical prostatectomy, causing a selection bias. Therefore, our results may not apply to a broader population of patients with newly diagnosed prostate cancer, especially because there is a trend for increasing use of active surveillance of low-risk prostate cancer (27). However, this selection bias is inherent to every study that uses whole-mount step-section histopathology specimens as a reference standard for evaluating imaging variables. Second, an endorectal coil was used for acquisition of MRI, potentially deforming the prostate gland and the tumor foci. However, the use of an endorectal coil provides a higher signal-to-noise ratio (28) and may therefore be preferable for quantitative ADC analysis. Third, our approach of retrospectively delineating the prostate cancer foci on ADC maps using the histopathology maps as a guide does not represent the sequence of events in the clinical setting, where histopathology maps would not be available at the time of MRI.

Figure 2. Top row, whole-mount histopathology slice (A) and ADC map ($b = 0, 1,000$ seconds/mm$^2$; B) demonstrating a prostate cancer focus with a GS of 3+3 (arrows), a total tumor volume of 0.65 mL and a mean ADC of $1.165.2 \times 10^{-6}$ mm$^2$/second. The bottom row shows the whole-mount histopathology slice (C) and ADC map ($b = 0, 1,000$ seconds/mm$^2$; D) of a prostate cancer focus with a GS of 3+4 (arrows). Despite having a histopathologic volume (0.68 mL) similar to that of the tumor focus in A, the tumor focus shown in C and D has a lower mean ADC ($964.2 \times 10^{-6}$ mm$^2$/second). Note: Images A and C show only one representative slice out of 12 and eight total histopathology slices, respectively. The tumors in A and C were both present on seven contiguous slices.
Therefore, we are not able to provide information on the accuracy of prostate cancer detection in this study or on the effect that potentially missed lesions might have had on our results. Furthermore, using histopathology slices for identification of tumor foci may have introduced a potential bias in the evaluation of lesion volume on ADC maps as the location of tumors was available to the radiologists encircling the tumor foci. Although, the ROI drawn by the radiologists for the purposes of this study only contained clearly discernible tumor tissue on ADC maps (e.g., voxels that were visually darker than the surrounding healthy tissue), we acknowledge that the correlations reported in this study would be influenced by the diagnostic accuracy of prostate cancer detection in routine clinical practice.

In summary, our results suggest that although Volume_{ADC} is useful to predict true tumor volume, ADC_{mean} is the more useful parameter for distinguishing between GS 6 and higher GS tumors, a distinction that is critical for identifying suitable candidates for active surveillance.

**Disclosure of Potential Conflicts of Interest**
No potential conflicts of interest were disclosed.

**Authors’ Contributions**
Conception and design: O.F. Donati, A. Afaq, H. Hricak, O. Akin
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 Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Afaq, Y. Mazaheri, O. Akin
 Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): O.F. Donati, Y. Mazaheri, H.A. Vargas, J. Zheng, C.S. Moskowitz, O. Akin
 Writing, review, and/or revision of the manuscript: O.F. Donati, A. Afaq, H.A. Vargas, J. Zheng, H. Hricak, O. Akin
 Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): O.F. Donati, A. Afaq, O. Akin
 Study supervision: O. Akin

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