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Assessment of Prostate Cancer Aggressiveness by Use of the Combination of Quantitative DWI and Dynamic Contrast-Enhanced MRI

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Abstract

OBJECTIVE—The objective of this study was to investigate whether the apparent diffusion coefficient (ADC) value from DWI and the forward volume transfer constant (K^{trans}) value from dynamic contrast-enhanced MRI independently predict prostate cancer aggressiveness, and to determine whether the combination of both parameters performs better than either parameter alone in assessing tumor aggressiveness before treatment.

MATERIALS AND METHODS—This retrospective study included 158 men with histopathologically confirmed prostate cancer who underwent 3-T MRI before undergoing prostatectomy in 2011. Whole-mount step-section pathologic maps identified 195 prostate cancer foci that were 0.5 mL or larger; these foci were then volumetrically assessed to calculate the per-tumor ADC and K^{trans} values. Associations between MRI and histopathologic parameters were assessed using Spearman correlation coefficients, univariate and multivariable logistic regression, and AUCs.

RESULTS—The median ADC and K^{trans} values showed moderate correlation only for tumors for which the Gleason score (GS) was 4 + 4 or higher ($\rho = 0.547$; $p = 0.042$). The tumor ADC value was statistically significantly associated with all dichotomized GSs ($p < 0.005$), including a GS of 3 + 3 versus a GS of 3 + 4 or higher (AUC, 0.693; $p = 0.001$). The tumor K^{trans} value differed statistically significantly only between tumors with a GS of 3 + 3 and those with a primary

Gleason grade of 4 ($p = 0.015$), and it made a statistically significant in differentiating tumors with a GS of 4 + 3 or higher (AUC, 0.711; $p < 0.001$) and those with a GS of 4 + 4 or higher (AUC, 0.788; $p < 0.001$) from lower-grade tumors. Combining ADC and K^{trans} values improved diagnostic performance in characterizing tumors with a GS of 4 + 3 or higher and those with a GS of 4 + 4 or higher (AUC, 0.739 and 0.856, respectively; $p < 0.01$).

CONCLUSION—Although the ADC value helped to differentiate between all GSs, the K^{trans} value was only a benefit in characterizing more aggressive tumors. Combining these parameters improves their performance in identifying patients with aggressive tumors who may require radical treatment.

Keywords

DWI; MRI; prostate cancer

For patients with aggressive prostate cancers, radical treatment approaches, such as prostatectomy or radiation therapy, are However, because the adverse effects of radical treatments can be severe, more conservative treatment options, including active surveillance and focal ablation [1], are increasingly being considered for men with relatively indolent tumors. As a result, correct assessment of the aggressiveness of a lesion is becoming increasingly necessary to avoid the possibility of undertreatment.

Standard methods for risk stratification, which are based on clinical assessment, measurement of prostate-specific antigen levels, and pathologic parameters [2, 3], leave considerable room for improvement. Multiparametric MRI already plays an important role in the detection, localization, and staging of prostate cancer [4, 5], and researchers have also recently been investigating the potential of various MRI techniques for noninvasive assessment of prostate cancer aggressiveness (i.e., determination of the Gleason score [GS]). Although several studies have shown an inverse relationship between apparent diffusion coefficient (ADC) values from DWI and GSs [6–14], the ranges of ADC values for different GSs overlapped considerably [6, 7, 10, 14], hindering their use in clinical decision making. Other studies have evaluated dynamic contrast-enhanced MRI (DCE-MRI) for the assessment of tumor aggressiveness in small patient cohorts; the preliminary results have been variable [12, 15–17], and although some studies showed significant differences in pharmacokinetic parameters (e.g., the volume transfer constant [K^{trans}]) at different levels of aggressiveness, the ranges of parameter values once again overlapped substantially [17, 18].

Both DWI and DCE-MRI are widely available and have already been incorporated into standard prostate cancer reporting guidelines, such as those of the European Society of Urogenital Radiology [19, 20], which focus on the detection of significant prostate cancer. A quantitative assessment with direct histopathologic correlation, as performed in this study, could provide new insights into the tumor microenvironment and thus help in the assessment of tumor aggressiveness.

The purpose of the present study was to investigate whether ADC and K^{trans} values independently predict prostate cancer aggressiveness and to determine whether the

combination of these two quantitative parameters performs better than either parameter alone in assessing tumor aggressiveness.

Materials and Methods

Patients

The institutional review board at the Memorial-Sloan Kettering Cancer Center approved this HIPAA-compliant study and waived the requirement for informed patient consent. Radiology, pathology, and urology department databases for the year 2011 were retrospectively searched to identify patients who met the following criteria: pre-operative multiparametric 3-T endorectalcoil MRI performed at our institution less than 180 days before surgery with the use of a dedicated MRI protocol, radical prostatectomy performed at our institution, pathologic confirmation of prostate cancer with a volume of at least 0.5 mL, and whole-mount step-section pathologic maps available for tumor localization (see Fig. 1A, for example). This initial search identified 166 patients, seven of whom were excluded because they had received treatment (hormonal therapy or radiation) before undergoing MRI examination and one of whom was excluded because pathologic findings revealed severe prostatitis. The mean time between MRI examination and prostatectomy was 23 days (range, 1–131 days).

Up to three lesions per patient were included in the study. The final patient cohort consisted of 158 patients with 195 lesions. Nineteen of these lesions were excluded from DWI analysis because of the presence of artifacts, distortions, or both (with the decision to exclude the lesions rendered before any analysis was performed), and 11 lesions were excluded from DCE-MRI analysis either because the tumor was not fully covered ($n = 4$) or because deviations from the MRI protocol had occurred (e.g., with respect to timing of contrast material injection or temporal resolution) ($n = 7$). Therefore, ADC values were measured for 176 lesions, and perfusion parameters were measured for 184 lesions; both parameters were measured for 167 lesions.

MRI Acquisition and Analysis

All MRI examinations were performed on 3-T MRI systems and involved the use of a pelvic phased-array coil with four channels as well as an endorectal coil. The dedicated MRI protocol included a DWI sequence with b values of 0 and 1000 s/mm² (single-shot spin-echo echo-planar imaging sequence with the following parameters: TR/TE, 3500–5600/70.3–105.6; slice thickness, 3 mm; no interslice gap; FOV, 14 × 14 cm to 24 × 24 cm; and matrix, 128 × 128) and a T1-weighted DCE-MRI sequence (TR/TE, 3.6–4.9/1.3–1.7; slice thickness, 5 mm; no interslice gap; FOV, 24 × 24 cm; matrix, 256 × 128–160; mean temporal resolution, 10 s; total acquisition time, 7 min). Image acquisition was begun after IV injection of 0.1 mmol of gadopentetate dimeglumine (Magnevist, Berlex Laboratories) per kilogram of body weight at a rate of 2 mL/s, with the use of an automatic injector (Spectris Solaris, Medrad).

To allow better tumor localization, T2-weighted sequences in the axial, coronal, and sagittal planes were also obtained for all patients. ADC maps were generated from DW images on a

voxel-wise basis, with the use of a monoexponential model. The K^{trans} value of the Tofts model [21] was calculated using a software platform (Dynamika, version 3.0.4, Image Analysis) and the dynamic contrast-enhanced sequences. A population-based arterial input function and reference standard T1-weighted imaging time for the prostate (1597 ms at 3 T) were used.

Histopathologic Preparation and Analysis

Every prostatectomy specimen was submitted in its entirety to the pathology department, where it was fixed in formalin and its outer surface was inked. Slices were obtained at intervals of 3–5 mm throughout the prostate and were stained with H and E after paraffin embedding. The border of each tumor was outlined on each slice with the use of a marking pen (see Fig. 1A, for an example), and for each tumor focus, GSs and tumor volume were determined by a dedicated genitourinary pathologist with more than 20 years of clinical experience. A cancer focus was considered to be spatially separate if it was 3 mm or more from the closest cancer in any single section. Every slide was then digitized using a digital photo scanner with 300 dpi resolution.

Histopathologic Correlation and Image Analysis

Each tumor was identified with the help of the pathologic map and T2-weighted sequences. Identification was done by a radiologist performing a fellowship in genitourinary MRI who was blinded to the overall GS and the ADC and K^{trans} values for the lesion at time of analysis. To volumetrically assess tumor on the ADC map, the radiologist drew an ROI that encircled the tumor on each slice where it appeared, with the use of an image processing software program (ImageJ, version 1.47m, National Institutes of Health) [22] and with anatomic landmarks such as the urethra, prostatic capsule, and ejaculatory ducts used for reference. The data from these ROIs were then analyzed using in-house software written in a general-purpose programming language (C#, Microsoft), and median ADC values were generated for each tumor. A similar approach was used to analyze dynamic contrast-enhanced MR images: again, an ROI was drawn around each tumor on each slice where it appeared, and median K^{trans} values were estimated volumetrically for each tumor.

Statistical Analysis

Correlations between median ADC and median K^{trans} values were estimated using the between-subject Spearman correlation coefficient, with multiple lesions per patient taken into account [23]. The median pathologic tumor volume, median ADC value, and median K^{trans} value, with corresponding ranges, were summarized by the GS. Generalized estimating equations with a robust covariance matrix and an independent within-patient correlation structure assuming a gaussian family with an identity link function were used to evaluate whether the ADC value and the logarithm-transformed K^{trans} value differed between GS groups. The combination of ADC and K^{trans} values was constructed by including both parameters in generalized estimating equation models that assumed a binomial family with a logit link function, with the use of a dichotomized GS as the outcome. Odds ratios and 95% CIs were estimated with the increment unit set to 0.0001 for the median ADC value, 0.01 for the median K^{trans} value, and 1 for the pathologic tumor volume. Nonparametric ROC curves and AUCs were estimated to assess the ability of each

parameter and the combination of parameters to discriminate between tumors that had a GS of 3 + 3 versus a GS of 3 + 4 or higher, a GS of 3 + 4 or lower versus a GS of 4 + 3 or higher, and a GS of 4 + 3 or lower versus a GS of 4 + 4 or higher. Sensitivities and specificities, along with respective thresholds, were estimated to maximize the Youden index on ROC curves for each parameter separately and for the combination of parameters. CIs for the AUCs, the sensitivities, and the specificities were estimated using the bootstrap method and by resampling patients. Because testing for a difference in the AUCs for the combination of parameters and each parameter separately involves testing for differences in AUCs from nested models, which has been shown to be problematic [24, 25], we followed the advice of recent studies [24, 26] and used the Wald test from the generalized estimating equations model to determine whether the combination of parameters performed better than the individual parameters. In the present study, all analyses were based on complete data.

A test result for which $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed using statistical software packages (SAS, version 9.2, SAS Institute, and R, version 2.13, The R Foundation for Statistical Computing).

Results

Patient and Tumor Characteristics

Of the 158 patients (mean [$\pm$ SD] age, 59 ± 7.43 years; range, 36–75 years) in the present study, 123 had one lesion, 33 had two lesions, and two had three lesions measured; 144 of the 195 lesions were located in the peripheral zone, and 51 were located in the transition zone. Clinical stage at time of prostatectomy was found to be stage I for 30 patients, stage IIA for 72 patients, stage IIB for 31 patients, stage III for 21 patients, and stage IV for four patients. Thirty-four lesions ($\approx 17\%$) had a GS of 3 + 3, whereas 113 lesions ($\approx 58\%$) had a GS of 3 + 4, 30 lesions ($\approx 15\%$) had a GS of 4 + 3, and 18 lesions ($\approx 9\%$) had a GS of 4 + 4 or higher.

Correlation Between Apparent Diffusion Coefficient and Forward Volume Transfer Constant Values

Table 1 summarizes the correlations between the median ADC and median K^{trans} values, as stratified by the GS. No correlation between the two parameters was seen, except in the subgroup of tumors that had a GS of 4 + 4 or higher ($p = 0.547$; $p = 0.042$).

Apparent Diffusion Coefficient and Forward Volume Transfer Constant Values in Gleason Score Assessment

ADC values decreased significantly in association with increasing tumor aggressiveness ($p < 0.001$) (Table 2 and Fig. 2A). Conversely, K^{trans} values increased in association with increasing tumor aggressiveness (Fig. 2B); however, when the K^{trans} values of tumors with a GS of 3 + 3 were compared with those with higher GSs, this trend was statistically significant 4 + 3 or higher and those with a GS of 4 + 4 or higher (Table 2).

The ADC value was the only parameter for which there was a statistically difference between tumors with a GS of 3 + 3 and those with a GS of 3 + 4 or higher in univariate

analysis ($p = 0.001$ [Table 3]; AUC, 0.693 [Fig. 3A]). In addition, in multivariable analysis, the ADC value made a statistically significant contribution to the differentiation of tumors with a GS of 4 + 3 or higher and tumors with a GS of 4 + 4 or higher ($p = 0.001$ and $p = 0.002$, respectively, as shown in Table 3; AUC, 0.662 and 0.701, respectively, as shown in Figs. 3B and 3C) from lower-grade tumors. The tumor K^{trans} value statistically significantly contributed only to the differentiation of tumors with a GS of 4 + 3 or higher ($p < 0.001$, as shown in Table 3; AUC, 0.711, as shown in Fig. 3B) and tumors with a GS of 4 + 4 or higher ($p < 0.001$, as shown in Table 3; AUC, 0.788, as shown in Fig. 3C) from lower-grade tumors.

Pathologic Tumor Volume and Gleason Score

In univariate analysis, pathologic tumor volume made a statistically significant contribution to the differentiation of tumors with a GS of 4 + 3 or lower from tumors with a GS of 4 + 4 or higher; however, it was not found to be an independent predictor of GS in multivariable analysis (Table 3).

Combination of Apparent Diffusion Coefficient and Forward Volume Transfer Constant Values in the Assessment of Prostate Cancer Aggressiveness

Although only the ADC value parameter made a statistically significant contribution to the differentiation of tumors with a GS of 3 + 3 from those with a GS of 3 + 4 or higher (Table 3), the combination of tumor ADC only for tumors with a GS of and K^{trans} values performed better than either parameter alone in characterizing tumors with a GS of 4 + 3 or higher ($p < 0.01$; AUC, 0.739) (Fig. 3B and Tables 3 and 4) and tumors with a GS of 4 + 4 or higher ($p < 0.01$; AUC, 0.856) (Fig. 3C and Tables 3 and 4). Estimated sensitivities and specificities (including 95% CIs) for ADC and K^{trans} values and the combination of both parameters are detailed in Table 5, which shows an increase in sensitivity for the differentiation between tumors with a GS of 3 + 4 or lower versus those with a GS of 4 + 3 or higher and between tumors with a GS of 4 + 3 or lower versus those with a GS of 4 + 4 or higher, when combining ADC and K^{trans} values into one multiparametric approach.

Discussion

Both DWI and DCE-MRI are commonly used to detect prostate cancer [4, 5]. However, the increasing number of newly discovered sometimes indolent tumors found in elderly men and the introduction of more-conservative treatment options as alternatives to the standard of care for prostate cancer have created a need for better characterization of lesion aggressiveness before making decisions about treatment. Because biopsies are both invasive and known to incorrectly classify the GS in approximately 38% of all cases because of sampling error [27], researchers have been investigating the value of multiparametric MRI sequences, in particular DWI and DCE-MRI, as noninvasive tools with which to assess the aggressiveness of prostate cancer. Our study expanded on prior investigations of the noninvasive assessment of cancer aggressiveness with MRI, because it examined the combined value of the two most commonly used parameters from DWI and DCE-MRI in a large patient cohort, and because it used whole-tumor assessment rather than an approach based on a single ROI, which was used in previous studies [12, 16].

We found no statistically significant correlation between tumor ADC and K^{trans} values, except for the group of tumors with a GS of 4 + 4 or higher. Therefore, we hypothesized that these parameters might be of independent value in distinguishing between tumors of differing aggressiveness, because they assess different histopathologic tumor characteristics. We found a statistically significant inverse correlation between ADC values and GSs for lesions, a finding that has been reported in previous studies [6–14] and that is attributed to the higher cellularity known to be present in higher-grade tumors [28]. In addition, we found statistically significantly higher K^{trans} values for tumors with higher GSs; this finding, which is in accordance with results of prior studies [15, 18], may reflect the fact that aggressive tumors induce neovascularization to accommodate their high demand for blood supply [29]. However, not all previous investigators observed a correlation between higher K^{trans} values and higher GSs [12, 16, 17].

The reasons for the discrepant results might lie in differences in the methods used for DCE-MRI or in the composition of the patient cohorts, which typically have included only small numbers of patients whose lesions were assigned to individual GS categories. Furthermore, some previous studies [16, 17] relied on biopsy results as the reference standard, which might have resulted in incorrect classification of some tumors. In contrast, we used whole-mount step-section pathologic maps for exact localization of tumors on MR images, thus ensuring that MRI parameters were measured and correlated only in histopathologically confirmed tumorous tissue for which GSs had been assessed in a reliable way.

When we assessed a combination of parameters from DWI and DCE-MRI for the characterization of tumor aggressiveness, ADC values were significantly associated with all dichotomized GSs, including a GS of 3 + 3 versus a GS of 3 + 4 or higher. These findings are in accordance with the results of studies by Donati et al. [8, 9] and Hambrock et al. [10], which did not evaluate DCE-MRI. In the present study, the K^{trans} value made a statistically significant contribution only to the characterization of tumors with a primary Gleason grade of 4 or greater (a GS of 4 + 3 or higher or a GS of 4 + 4 or higher).

In the present study, as in previous studies, the ranges of both the ADC and the K^{trans} values overlapped greatly between tumors of different GSs, rendering it difficult to make a distinction on the basis of an individual parameter in clinical practice. However, the combination of ADC and K^{trans} values in a quantitative multiparametric MRI approach yielded better diagnostic performance and improved sensitivity in assessing tumors with a GS of 4 + 3 or higher or a GS of 4 + 4 or higher than did the use of either parameter alone. A noninvasive MRI approach for distinguishing aggressive cancers would be of great value in routine clinical practice, because patients with tumors with a GS of 3 + 3 are increasingly undergoing active surveillance rather than radical prostatectomy, and preliminary reports suggest that even patients with tumors with a GS of 3 + 4 may be candidates for active surveillance, if strict criteria can be applied [30].

The present study had a number of limitations. First, we included only patients who underwent radical prostatectomy and for whom step-section whole-mount histopathologic maps were available, causing a selection bias inherent to the design of all studies that use histopathologic standard. The use of histopathologic maps allowed both exact tumor

localization on MR images and reliable assessment of the GS of the lesions; however, because the reader thus was not blinded to the histopathologic findings of a patient, and because whole-mount histopathologic findings are not available in the preoperative setting, our findings should be verified in further studies that use targeted biopsies as the reference standard. Also, the use of an endorectal coil potentially might have deformed the prostate and intraprostatic lesions in some cases, although it allowed an improved signal-to-noise ratio, which may be preferable when performing quantitative assessment of MRI parameters.

In addition, our DCE-MRI protocol lacked a T1 signal mapping sequence, used a population-based approach for modeling of the arterial input function, and had a mean temporal resolution of 10 seconds, which potentially could have influenced the K^{trans} values generated. Finally, although this study explored the value of median ADC and K^{trans} values in the characterization of prostate cancer aggressiveness, the analysis of other metrics from histogram or texture analysis could provide further insight and incentive for future studies, which ideally should also incorporate an assessment of reproducibility to investigate the effect of multiple readers on the results.

In conclusion, the present study showed that volumetrically calculated ADC and K^{trans} values are of independent value in the assessment of prostate cancer aggressiveness. Although the ADC value helped to differentiate between GSs at all cutoff points, including a GS of 3 + 3 versus a GS of 3 + 4 or higher, the K^{trans} value was of benefit only in distinguishing more aggressive tumors with a primary Gleason grade of 4 or greater. The combination of both parameters in a quantitative multiparametric MRI approach provided the best diagnostic performance in distinguishing these aggressive tumors. This approach could allow more-precise as well as noninvasive identification of patients for whom radical treatment may be needed.

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References

1. Ahmed HU, Akin O, Coleman JA, et al. Transatlantic Consensus Group on active surveillance and focal therapy for prostate cancer. *BJU Int.* 2012; 109:1636–1647. [PubMed: 22077593]
2. Wolters T, Roobol MJ, van Leeuwen PJ, et al. A critical analysis of the tumor volume threshold for clinically insignificant prostate cancer using a data set of a randomized screening trial. *J Urol.* 2011; 185:121–125. [PubMed: 21074212]
3. Lawrentschuk N, Klotz L. Active surveillance for low-risk prostate cancer: an update. *Nat Rev Urol.* 2011; 8:312–320. [PubMed: 21519351]
4. Haghighi M, Shah S, Taneja SS, Rosenkrantz AB. Prostate cancer: diffusion-weighted imaging versus dynamic-contrast enhanced imaging for tumor localization—a meta-analysis. *J Comput Assist Tomogr.* 2013; 37:980–988. [PubMed: 24270122]
5. Arumainayagam N, Ahmed HU, Moore CM, et al. Multiparametric MR imaging for detection of clinically significant prostate cancer: a validation cohort study with transperineal template prostate mapping as the reference standard. *Radiology.* 2013; 268:761–769. [PubMed: 23564713]

6. Bittencourt LK, Barentsz JO, de Miranda LC, Gasparetto EL. Prostate MRI: diffusion-weighted imaging at 1.5T correlates better with prostatectomy Gleason grades than TRUS-guided biopsies in peripheral zone tumours. *Eur Radiol.* 2012; 22:468–475. [PubMed: 21913058]
7. Jung SI, Donati OF, Vargas HA, Goldman D, Hricak H, Akin O. Transition zone prostate cancer: incremental value of diffusion-weighted endorectal MR imaging in tumor detection and assessment of aggressiveness. *Radiology.* 2013; 269:493–503. [PubMed: 23878284]
8. Donati OF, Afaq A, Vargas HA, et al. Prostate MRI: evaluating tumor volume and apparent diffusion coefficient as surrogate biomarkers for predicting tumor Gleason score. *Clin Cancer Res.* 2014; 20:3705–3711. [PubMed: 24850842]
9. Donati OF, Mazaheri Y, Afaq A, et al. Prostate cancer aggressiveness: assessment with whole-lesion histogram analysis of the apparent diffusion coefficient. *Radiology.* 2014; 271:143–152. [PubMed: 24475824]
10. Hambrock T, Somford DM, Huisman HJ, et al. Relationship between apparent diffusion coefficients 3.0-T MR imaging and Gleason grade in peripheral zone prostate cancer. *Radiology.* 2011; 259:453–461. [PubMed: 21502392]
11. Itou Y, Nakanishi K, Narumi Y, Nishizawa Y, Tsukuma H. Clinical utility of apparent diffusion coefficient (ADC) values in patients with prostate cancer: can ADC values contribute to assess the aggressiveness of prostate cancer? *J Magn Reson Imaging.* 2011; 33:167–172. [PubMed: 21182135]
12. Oto A, Yang C, Kayhan A, et al. Diffusion-weighted and dynamic contrast-enhanced MRI of prostate cancer: correlation of quantitative MR parameters with Gleason score and tumor angiogenesis. *AJR.* 2011; 197:1382–1390. [PubMed: 22109293]
13. Vargas HA, Akin O, Franiel T, et al. Diffusion-weighted endorectal MR imaging at 3 T for prostate cancer: tumor detection and assessment of aggressiveness. *Radiology.* 2011; 259:775–784. [PubMed: 21436085]
14. Verma S, Rajesh A, Morales H, et al. Assessment of aggressiveness of prostate cancer: correlation of apparent diffusion coefficient with histologic grade after radical prostatectomy. *AJR.* 2011; 196:374–381. [PubMed: 21257890]
15. Peng Y, Jiang Y, Yang C, et al. Quantitative analysis of multiparametric prostate MR images: differentiation between prostate cancer and normal tissue and correlation with Gleason score—a computer-aided diagnosis development study. *Radiology.* 2013; 267:787–796. [PubMed: 23392430]
16. Padhani AR, Gapinski CJ, Macvicar DA, et al. Dynamic contrast enhanced MRI of prostate cancer: correlation with morphology and tumour stage, histological grade and PSA. *Clin Radiol.* 2000; 55:99–109. [PubMed: 10657154]
17. Chen YJ, Chu WC, Pu YS, Chueh SC, Shun CT, Tseng WY. Washout gradient in dynamic contrast-enhanced MRI is associated with tumor aggressiveness of prostate cancer. *J Magn Reson Imaging.* 2012; 36:912–919. [PubMed: 22711415]
18. Vos EK, Litjens GJ, Kobus T, et al. Assessment of prostate cancer aggressiveness using dynamic contrast-enhanced magnetic resonance imaging at 3 T. *Eur Urol.* 2013; 64:448–455. [PubMed: 23751135]
19. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur Radiol.* 2012; 22:746–757. [PubMed: 22322308]
20. American College of Radiology. [Accessed December 12, 2015] MR prostate imaging reporting and data system version 2.0. American College of Radiology website. www.acr.org/Quality-Safety/Resources/PIRADS/
21. Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T₁-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging.* 1999; 10:223–232. [PubMed: 10508281]
22. Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods.* 2012; 9:671–675. [PubMed: 22930834]
23. Bland JM, Altman DG. Calculating correlation coefficients with repeated observations. Part 2. Correlation between subjects. *BMJ.* 1995; 310:633. [PubMed: 7703752]

24. Seshan VE, Gönen M, Begg CB. Comparing ROC curves derived from regression models. *Stat Med.* 2013; 32:1483–1493. [PubMed: 23034816]
25. Demler OV, Pencina MJ, D'Agostino RB Sr. Misuse of DeLong test to compare AUCs for nested models. *Stat Med.* 2012; 31:2577–2587. [PubMed: 22415937]
26. Pepe MS, Kerr KF, Longton G, Wang Z. Testing for improvement in prediction model performance. *Stat Med.* 2013; 32:1467–1482. [PubMed: 23296397]
27. Freedland SJ, Kane CJ, Amling CL, Aronson WJ, Terris MK, Presti JC. Upgrading and downgrading of prostate needle biopsy specimens: risk factors and clinical implications. *Urology.* 2007; 69:495–499. [PubMed: 17382152]
28. Gibbs P, Liney GP, Pickles MD, Zelhof B, Rodrigues G, Turnbull LW. Correlation of ADC and T2 measurements with cell density in prostate cancer at 3.0 Tesla. *Invest Radiol.* 2009; 44:572–576. [PubMed: 19692841]
29. Russo G, Mischi M, Scheepens W, De la Rosette JJ, Wijkstra H. Angiogenesis in prostate cancer: onset, progression and imaging. *BJU Int.* 2012; 110:E794–E808. [PubMed: 22958524]
30. Ploussard G, Isbarn H, Briganti A, et al. Can we expand active surveillance criteria to include biopsy Gleason 3+4 prostate cancer? A multi-institutional study of 2,323 patients. *Urol Oncol.* 2015; 33:71e1–71.e9.

Fig. 1. 56-year-old man with histopathologically confirmed prostate cancer (Gleason score, 4 + 4) in right transition zone

A, Whole-mount pathologic map shows tumor (*outlined area*).

B, Corresponding T2-weighted axial MR image also shows tumor.

C and D, Apparent diffusion coefficient map (**C**) (b values, 0 and 1000 s/mm²) and T1-weighted dynamic contrast-enhanced axial image (**D**). White dashed line indicates exemplary ROI for this slice (tumors were assessed volumetrically).

Fig. 2. Measured apparent diffusion coefficient (ADC) value and volume transfer constant (K^{trans}) value (expressed in min⁻¹) value, as stratified by Gleason score

A and B, Graphs show that ADC values (**A**) decreased as Gleason score increased, whereas K^{trans} values (**B**) were found to be higher for more aggressive tumors (when primary Gleason grade was 4). Dashed line indicates trend, line in box represents median value, height of box represents interquartile range, whiskers are lowest and highest data points still within 1.5 interquartile range, circles denote outliers, and asterisks represent extreme outliers (more than three times interquartile range).

Fig. 3. ROC curves and corresponding AUCs for MRI parameters in differentiating tumors with various Gleason scores

A–C. Graphs show data for MRI parameters for tumors with Gleason scores of 3 + 3 versus 3 + 4 or higher (**A**), 3 + 4 or lower versus 4 + 3 or higher (**B**), and 4 + 3 or lower versus 4 + 4 or higher (**C**). In panel **A**, data are not provided for combination of apparent diffusion coefficient (ADC) value and volume transfer constant (K^{trans}) value, because only ADC was found to be of statistical significance on univariate analysis.

TABLE 1

Between-Subject Spearman Correlation Coefficient for the Correlation Between the Apparent Diffusion Coefficient and the Volume Transfer Constant, as Stratified by Gleason Score

Gleason Score	No. of Lesions	ρ	p
3 + 3	30	0.083	0.682
3 + 4	96	0.018	0.872
4 + 3	27	0.223	0.266
4 + 4 or higher	14	0.547	0.042
All	167	0.010	0.905

TABLE 2

Summary of Pathologic Tumor Volume, Apparent Diffusion Coefficient (ADC) Value From DWI, and Volume Transfer Constant (K^{trans}) Value From Dynamic Contrast-Enhanced MRI, as Stratified by Gleason Score (GS)

GS	Tumor Volume (mL)			ADC Value ($\times 10^{-3} \text{ mm}^2/\text{s}$)			K^{trans} Value (min^{-1})		
	No. of Patients	Median (Range)	<i>p</i>	No. of Patients	Median (Range)	<i>p</i>	No. of Patients	Median (Range)	<i>p</i>
3 + 3	34	0.88 (0.50–5.68)	Reference	30	0.98 (0.70–1.23)	Reference	34	0.21 (0.03–0.54)	Reference
3 + 4	113	1.54 (0.50–29.56)	0.021	101	0.88 (0.54–1.47)	0.003	107	0.21 (0.03–0.62)	0.778
4 + 3	30	3.07 (0.50–17.59)	< 0.001	28	0.84 (0.64–1.17)	< 0.001	28	0.25 (0.13–0.56)	0.015
4 + 4 or higher	18	2.70 (0.71–30.87)	< 0.001	17	0.77 (0.55–0.97)	< 0.001	15	0.31 (0.19–0.90)	< 0.001
All	195	1.60 (0.50–30.87)	< 0.001	176	0.89 (0.54–1.47)	< 0.001	184	0.22 (0.03–0.90)	0.001

Note—Statistical significance of the differences between the GS groups is denoted by *p* values. ADC values for tumors with a GS of 3 + 3 differed significantly from those of tumors with GSs in all other categories; however, K^{trans} values of tumors with a GS of 3 + 3 differed significantly only from those of tumors with a primary Gleason grade of 4.

TABLE 3

Results of Univariate and Multivariable Analysis for the Differentiation of Tumors Grouped by Gleason Score (GS)

Variable	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Tumors with a GS of 3 + 3 vs those with a GS of 3 + 4 or higher				
Tumor volume	1.41 (0.91–2.17)	0.123		
Median ADC value	0.69 (0.56–0.86)	0.001		
Median K ^{trans} value	1.02 (0.98–1.07)	0.300		
Tumors with a GS of 3 + 3 or 3 + 4 vs those with a GS of 4 + 3 or higher				
Tumor volume	1.30 (1.00–1.68)	0.052		
Median ADC value	0.71 (0.58–0.87)	0.001	0.63 (0.49–0.82)	0.001
Median K ^{trans} value	1.06 (1.02–1.09)	< 0.001	1.07 (1.04–1.10)	< 0.001
Tumors with a GS of 3 + 3, 3 + 4, or 4 + 3 vs those with a GS of 4 + 4 or higher				
Tumor volume	1.12 (1.04–1.20)	0.002		
Median ADC value	0.66 (0.49–0.88)	0.004	0.46 (0.28–0.76)	0.002
Median K ^{trans} value	1.07 (1.04–1.10)	< 0.001	1.11 (1.07–1.17)	< 0.001

Note—ADC = apparent diffusion coefficient, K^{trans} = volume transfer constant.

TABLE 4

Estimated AUC (95% CI) for Apparent Diffusion Coefficient (ADC) Value, Volume Transfer Constant (K^{trans}) Value, and the Combination of Both Parameters in Differentiating Between Lesions With Different Gleason Scores (GSs)

Variable	AUC (95% CI)		
	GS of 3 + 3 vs GS of 3 + 4 or Higher	GS of 3 + 4 or Lower vs GS of 4 + 3 or Higher	GS of 4 + 3 or Lower vs GS of 4 + 4 or Higher
Median ADC value	0.693 (0.619–0.771)	0.662 (0.595–0.732)	0.701 (0.585–0.801)
Median K^{trans} value	0.619 (0.525–0.717)	0.711 (0.646–0.776)	0.788 (0.699–0.873)
Both		0.739 (0.673–0.802)	0.856 (0.784–0.932)

TABLE 5

Estimated Sensitivities and Specificities (Including 95% CIs and Thresholds) for Apparent Diffusion Coefficient (ADC) Value, Forward Volume Transfer Constant (K^{trans}) Value, and the Combination of Both Parameters in Differentiating Between Different Gleason Scores (GSs)

GS, Variable	Sensitivity (95% CI)	Specificity (95% CI)	Threshold
3 + 3 vs 3 + 4 or higher			
Median ADC value	0.547 (0.329–0.841)	0.800 (0.500–0.956)	$0.888 \times 10^{-3} \text{ mm}^2/\text{s}$
Median K^{trans} value	0.445 (0.382–0.864)	0.800 (0.364–0.907)	0.248 min^{-1}
3 + 4 or lower vs 4 + 3 or higher			
Median ADC value	0.488 (0.406–0.960)	0.778 (0.331–0.874)	$0.792 \times 10^{-3} \text{ mm}^2/\text{s}$
Median K^{trans} value	0.780 (0.652–0.920)	0.627 (0.548–0.723)	0.229 min^{-1}
Both	0.902 (0.500–0.963)	0.492 (0.442–0.890)	$4591.90 \times \text{ADC} - 6.76 \times K^{\text{trans}} = 2.70$
4 + 3 or lower vs 4 + 4 or higher			
Median ADC value	0.714 (0.546–1.000)	0.634 (0.298–0.852)	$0.84 \times 10^{-3} \text{ mm}^2/\text{s}$
Median K^{trans} value	0.857 (0.613–1.000)	0.660 (0.526–0.913)	0.252 min^{-1}
Both	0.929 (0.667–1.000)	0.647 (0.598–0.957)	$7703.71 \times \text{ADC} - 10.45 \times K^{\text{trans}} = 3.70$