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Relationship between kurtosis and bi-exponential characterization of high b-value diffusion-weighted imaging: application to prostate cancer

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Abstract

Background: High b-value diffusion-weighted imaging has application in the detection of cancerous tissue across multiple body sites. Diffusional kurtosis and bi-exponential modeling are two popular model-based techniques, whose performance in relation to each other has yet to be fully explored.

Purpose: To determine the relationship between excess kurtosis and signal fractions derived from bi-exponential modeling in the detection of suspicious prostate lesions.

Material and Methods: This retrospective study analyzed patients with normal prostate tissue ($n = 12$) or suspicious lesions ($n = 13$, one lesion per patient), as determined by a radiologist whose clinical care included a high b-value diffusion series. The observed signal intensity was modeled using a bi-exponential decay, from which the signal fraction of the slow-moving component was derived (SFs). In addition, the excess kurtosis was calculated using the signal fractions and ADCs of the two exponentials ($KCOMP$). As a comparison, the kurtosis was also calculated using the cumulant expansion for the diffusion signal (KCE).

Results: Both K and KCE were found to increase with SFs within the range of SFs commonly found within the prostate. Voxel-wise receiver operating characteristic performance of SFs , KCE , and $KCOMP$ in discriminating between suspicious lesions and normal prostate tissue was 0.86 (95% confidence interval [CI] = 0.85 – 0.87), 0.69 (95% CI = 0.68–0.70), and 0.86 (95% CI = 0.86–0.87), respectively.

Conclusion: In a two-component diffusion environment, $KCOMP$ is a scaled value of SFs and is thus able to discriminate suspicious lesions with equal precision. KCE provides a computationally inexpensive approximation of kurtosis but does not provide the same discriminatory abilities as SFs and $KCOMP$.

Keywords

Diffusion, magnetic resonance imaging, MRI, prostate, neoplasm

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Introduction

High b-value diffusion-weighted imaging (DWI) has found utility in several oncologic applications (1–3). By acquiring data over an extended range of b-values outside of those used in standard-of-care DWI, researchers have been able to characterize microstructural properties of both cancerous and

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normal-appearing tissue. The dependence of signal intensity on b-values can be modeled using linear combinations of exponential decay functions, each representing a diffusion component with a particular apparent diffusion coefficient (ADC). The contributions of these components, particularly those of the slowest with an ADC on the order of $0.1 \text{ } \mu\text{m}^2/\text{ms}$, has shown considerable promise as an imaging biomarker in tumor localization and grading (3–5).

Another example of high b-value DWI is the recent surge in diffusion kurtosis imaging in cancer (6–9). As introduced by Jensen et al. (10), the diffusional excess kurtosis attempts to quantify the deviation of the relationship between the observed signal intensity and b-value from that of a single mono-exponential decay. The deviation from this mono-exponential function can provide insight into the microstructural characteristics of the underlying tissue. Jensen et al. (10) described several formulations for the calculation of kurtosis in their original manuscript, two of which are particularly salient to this work. The first is derived from the cumulant expansion of the diffusion nuclear magnetic resonance (NMR) signal which introduces a squared-b-value dependence on the logarithm of the signal intensity. The coefficient of this dependence contains the resulting cumulant expansion kurtosis parameter. The majority of studies using kurtosis as an imaging biomarker in oncology implement this formulation. The second formulation assumes a diffusion environment whose signal decay dependence can be derived using the signal fractions and ADCs of a multi-exponential signal decay.

While bi-exponential modeling and diffusional kurtosis are viewed as extensions to standard-of-care DWI, their relationship to each other has not yet been fully explored. In this work, we aim to investigate the relationship between slow signal fractions obtained from bi-exponential modeling and diffusional excess kurtosis—herein kurtosis in the context of prostate cancer. We developed models specific to the diffusion environment of the prostate using data from patients with radiographically normal tissue or highly suspicious lesions. In addition, we determined the receiver operating characteristic (ROC) performance of each of the parameters in separating the two types of tissue to assess what clinical information, if any, is shared among the parameters.

Material and Methods

Study population

This retrospective study examined patients who underwent a specialized magnetic resonance imaging (MRI) acquisition protocol of their prostate between August

and December 2016 at our institution. Of these patients, those with prostates that were scored as PI-RADS (Prostate Imaging – Reporting and Data System (11)) 1 ($n=12$) or PI-RADS 5 ($n=13$) as part of the clinical read by a department radiologist were selected for analysis. The PI-RADS 1 group provides “normal” levels of prostate tissue signal whereas the PI-RADS 5 group provides lesions that have a high probability of clinically significant disease. The mean age of the patients in PI-RADS 1 and PI-RADS 5 groups was 59 years (age range = 33–74 years) and 69 years (age range = 51–81 years), respectively. The location of the lesion in the PI-RADS 5 group was described as: peripheral ($n=6$); transitional ($n=2$); or transitional + peripheral ($n=5$). This study was approved by our institutional review board.

MRI and post-processing

The MRI protocol was implemented on a 3-T clinical MRI scanner (Discovery MR750, GE Healthcare, Chicago, IL, USA) and included an axial T2-weighted (T2W) series ($\text{TE}=100 \text{ ms}$, $\text{TR}=6225 \text{ ms}$, in-plane voxel dimensions = $0.4297 \times 0.4297 \text{ mm}$, slice thickness = 3 mm , field of view [FOV] = 512×512) and a multi-shell diffusion series ($\text{TE}=80 \text{ ms}$, $\text{TR}=5000 \text{ ms}$, in-plane voxel dimensions = $1.718 \times 1.718 \text{ mm}$, slice thickness = 3 mm , $\text{FOV}=128 \times 128$). Four non-zero b-values of 200, 1000, 2000, and 3000 s/mm^2 , were each acquired at six unique diffusion gradient directions. In addition, six instances of non-diffusion weighted images ($b=0 \text{ s/mm}^2$) were acquired for a total of 30 frames per slice location. The diffusion data were corrected for distortions arising from B0 inhomogeneity (12). The T2W volume was resampled into diffusion space using an in-house algorithm developed in MATLAB (MathWorks, Natick, MA, USA) with an average B0 volume serving as the target.

Prostate data extraction

For each patient, the prostate was manually contoured, slice-by-slice, on the resampled T2W volume using the segmentation tools in Amira (FEI Visualization group, Mérignac, France). The contours were converted into a binary segmentation volume and used for the extraction of the diffusion data.

Noise correction

In order to account for the presence of the noise floor, a correction procedure based on that proposed by Gudbjartsson et al. (13) was applied to the observed signal intensity. Background voxels were selected using an automated procedure by identifying those

voxels whose mean signal intensity at $b=0 \text{ s/mm}^2$ was less than the values recorded for at least 12 of the 24 non-zero diffusion-weighted acquisitions. The mean background signal intensity, across all background voxels, was then calculated for each frame of each patient. The corrected signal intensity (SI_{corr}) for each frame was calculated from the observed signal intensity (SI_{obs}) and mean background signal intensity (SI_{bkg}) as:

$$SI_{corr} = \begin{cases} \sqrt{SI_{obs}^2 - SI_{bkg}^2} & SI_{obs} > SI_{bkg} \\ 0 & SI_{obs} \leq SI_{bkg} \end{cases} \quad (1)$$

Bi-exponential model of prostate diffusion

The relationship between the corrected signal intensity and b-value is modeled as a linear combination of two exponential decays. The bi-exponential model was chosen due to its extensive usage in the prostate diffusion literature:

$$SI_{corr} = SC_S e^{-b \times ADC_S} + SC_F e^{-b \times ADC_F} \quad (2)$$

where b is the diffusion weighting in $\text{ms}/\mu\text{m}^2$, the subscripts S and F refer to slow and fast components, respectively, and SC is the unit-less voxel-wise signal contribution of each component. Within this framework, the SC values are estimated for each voxel, whereas the ADC values are estimated for the entire population of voxels across patients. Thus, the variation in signal intensity across different voxels of an organ is considered to arise from different combinations of the constituent components that make up the DWI signal of that organ. For simplicity, the diffusion is considered to be isotropic, with no dependence on gradient direction.

The model-fitting routine consists of multiple stages. First, ADC_S and ADC_F are initialized at 0.1 and $3 \mu\text{m}^2/\text{ms}$, respectively. The corresponding voxel-wise signal contributions of the two components are then estimated using the built-in non-negative least squares optimization algorithm in MATLAB ("lsqnonneg"). The cost is then calculated as the squared L2-norm of the difference in model-predicted and observed corrected signal intensity divided by the squared L2-norm of the observed corrected signal intensity. If the current overall cost is less than the minimum (initialized to infinity at initiation), the routine updates the initial parameters (minimum cost, ADC) to their current values and proceeds. With each iteration of the routine, the values of ADC are updated by a random fraction, between -0.2 and 0.2 , of their initial value. This is repeated for 1000 iterations, after which the ADC and SC associated with the minimum cost are recorded and used for all further analysis.

Generation of parameter maps

As previously described, three parameters were chosen for comparison: signal fraction of the slow component (SF_S); component-wise kurtosis (K_{COMP}); and the cumulant-expansion kurtosis (K_{CE}). SF_S and K_{COMP} can be directly estimated using the estimated coefficients of the bi-exponential model described in the previous section, while K_{CE} is a relatively model-free approach that can be calculated using the cumulant expansion of the diffusion NRM signal.

SF_S was calculated as:

$$SF_S = \frac{SC_S}{SC_S + SC_F} \quad (3)$$

K_{COMP} was calculated, using the formulation provided by Jensen et al. (14), as:

$$K_{COMP} = 3 \frac{SF_S(1 - SF_S)(ADC_S - ADC_F)^2}{[SF_S \times ADC_S + SF_F \times ADC_F]^2} \quad (6)$$

K_{CE} was calculated, using the formulation provided by Jensen et al. (14), as:

$$K_{CE} = 12 \frac{D^{(1000)} - D^{(2000)}}{2000(2D^{(1000)} - D^{(2000)})^2} \quad (4)$$

where

$$D^{(x)} = \ln \left[\frac{\overline{SI}^{corr}(b=0)}{\overline{SI}^{corr}(b=X)} \right] / X \quad (5)$$

and corresponds to the estimate of the diffusion coefficient using the $(0, X)$ pair of b-values. In this case, $\overline{SI}^{corr}$ is the mean signal intensity across all gradient directions (for non-zero b-values) or instances (for $b=0 \text{ s/mm}^2$).

Discriminating performance between suspicious and normal tissue

Suspicious lesions in the PI-RADS 5 group were manually contoured on the resampled T2W volumes. For each of the parameters (SF_S , K_{CE} , and K_{COMP}), voxel-level ROC curves, and corresponding area under ROC curve (AUC) were generated to evaluate the ability to discriminate between suspicious lesions and normal prostate tissue in the PI-RADS 1 group. The AUC was used to compare the performance of each parameter in discriminating the voxels from the suspicious lesions of the 13 patients in the PIRADS 5 group against those voxels from the normal-appearing prostate tissue of the 12 patients in the PI-RADS 1 group. 95% confidence intervals for the AUC were generated from 1000 bootstrap samples of the original data.

Results

Sample size

The total number of prostate voxels extracted from the 12 patients in the PI-RADS 1 group and 13 patients in the PI-RADS 5 group were 61,084 and 52,311, respectively. The total number of voxels extracted from the suspicious lesion masks in the PI-RADS 5 group was 3581.

Signal intensity curves

Fig. 1 shows the mean natural logarithm of the signal intensity within the prostate for patients within PI-RADS 1 and PI-RADS 5 groups as a function of b-value. The error bars represent the standard deviation of the distribution. The gray line represents the mean SI_{bkg} for each b-value.

Bi-exponential model of prostate diffusion

The optimal values of ADC_S and ADC_F were estimated as 0.3 and $2.6 \mu\text{m}^2/\text{ms}$, respectively. The mean and standard deviation of SC_S and SC_F of prostate voxels in the PI-RADS 1 group were 97 ± 69 and 567 ± 252 , respectively. The mean values of SC_S and SC_F of prostate voxels in the PI-RADS 5 group were 129 ± 91 and 476 ± 312 , respectively. The mean values of SF_S of prostate voxels in PI-RADS 1 and PI-RADS 5 groups were 0.16 ± 0.13 and 0.24 ± 0.18 , respectively. The mean, 10th, and 90th percentile of SF_S across voxels in both PI-RADS groups were 0.20, 0.03, and 0.42, respectively.

Fig. 1. Signal decay curves. The average logarithm signal intensity within the prostate of PI-RADS 1 and PI-RADS 5 patients is plotted for b-values in the range of 0–3000 s/mm². Error bars represent the standard deviation.

Relationship between slow signal fraction and kurtosis

Fig. 2 shows the relationship between SF_S , K_{CE} , and K_{COMP} . The curves were generated by accumulating voxel values within the prostate from all patients and binning the SF_S to the nearest 0.05. The data points represent the mean value in each bin and the error bars represent the standard deviation. In general, the mean values of K_{CE} and K_{COMP} increase monotonically with increasing values of SF_S , except for extreme values of the slow signal fraction >0.9 . Furthermore, for values of SF_S in the range of 0.03–0.42 (10th and 90th percentile of all prostate voxels), the mean values of K_{CE} and K_{COMP} are within 0.63 units of each other.

Parameter maps

Fig. 3 shows representative slices of T2W and parameter maps (SF_S , K_{CE} , and K_{COMP}) for four examples of patients from the PI-RADS 1 or PI-RADS 5 groups. Solely for visualization within this figure, the parameter maps were resampled into the T2W space. The minimum and maximum color limits of each parameter map were set as the 1st and 99th percentile of the accumulated data across all four patients. The suspicious regions in the T2W images of the PI-RADS 5 group

Fig. 2. Relationship between K_{COMB} , K_{CE} , and SF_S . The curves are generated using voxel values within the prostate from all patients, PI-RADS 1 and PI-RADS 5. The data points represent the mean values of each parameter for values of SF_S in the range of 0–1, rounded to the nearest 0.05. Error bars represent the standard deviation. Within the range of SF_S commonly found within the prostate, K_{COMP} and K_{CE} monotonically increase with restricted signal fraction. SF_S , slow signal fraction; K_{CE} , cumulant expansion kurtosis; K_{COMB} component-wise kurtosis.

Fig. 3. Parameter maps. Representative slices of T2W, SF_s , K_{CE} , and K_{COMP} volumes are shown for two examples of PI-RADS 1 and PI-RADS 5 patients. The color bars for each of the diffusion parameters span the range from the 1st to 99th percentile of the distribution of values found within the prostate of the four patients. SF_s , slow signal fraction; K_{CE} , cumulant expansion kurtosis; K_{COMP} , component-wise kurtosis.

(yellow arrows) appear bright on all three parameter maps when compared to both the signal within the prostate of the PI-RADS 1 group as well as the surrounding normal-appearing tissue of the PI-RADS 5 group. The boundaries of the suspicious regions also appear less distinct and identifiable in the K_{CE} maps, compared to SF_s and K_{COMP} .

Discriminating between suspicious lesions and normal tissue

Fig. 4 shows histograms of the distribution of each of the three parameter maps for normal prostate tissue in the PI-RADS 1 group and suspicious lesions within the PI-RADS 5 group. The histograms are normalized so that the sum of the height of bars is equal to 1 for a given tissue type. AUC values, generated from ROC curves, for SF_s , K_{CE} , and K_{COMP} were calculated to

be 0.86 (95% CI = 0.85–0.87), 0.69 (95% CI = 0.68–0.70), and 0.86 (95% CI = 0.86–0.87), respectively.

Discussion

In this study, we sought to investigate the relationship between slow signal fraction and kurtosis in application to prostate cancer detection. Within the range of SF_s commonly found in the prostate, both K_{CE} and K_{COMP} increased with increasing slow signal fraction. AUC analysis demonstrated that SF_s and K_{COMP} performed comparably at discriminating between suspicious lesions in PI-RADS 5 and normal prostate tissue in PI-RADS 1 patients, and that both parameters outperformed K_{CE} .

The selection of these parameters for investigation arose from the growing popularity of bi-exponential and kurtosis modeling of high b-value diffusion data

Fig. 4. Histograms of SF_S , K_{CE} , and K_{COMP} Distributions of SF_S , K_{CE} , and K_{COMP} voxel values within normal tissue of PI-RADS I patients and suspicious lesions of PI-RADS 5 patients and corresponding AUC are shown. SF_S and K_{COMP} showed similar ability to discriminate between the two types of tissue, as evidenced by similar AUC values. K_{CE} performed slightly worse. SF_S , slow signal fraction; K_{CE} , cumulant expansion kurtosis; K_{COMP} , component-wise kurtosis.

of prostate cancer within the community (4,5,7,8,15). Of the parameters estimated from a bi-exponential characterization of signal decay, the fraction of the slow component (SF_S) is of particular interest as it has been thought to represent the degree of cellularity within the tumor (4,16). The two formulations of kurtosis, K_{COMP} and K_{CE} were selected from the original work by Jensen et al. (14) to represent a parameter (K_{COMP}) that could be computed from the bi-exponential signal characterization and thus directly comparable to SF_S , as well as a parameter (K_{CE}) that was more prevalent in the field, and more easily computed without the need for complex, non-linear optimization algorithms.

Our study demonstrated several important findings in the comparison between the kurtosis and bi-exponential parameters. In a two-component system, with fixed ADCs, K_{COMP} is, for all intents and purposes, a scaled version of SF_S and, as a consequence, provides almost identical information to SF_S . K_{CE} does not perform as well as SF_S and K_{COMP} in terms of ROC performance. However, this degradation in performance must be considered in light of the fact that K_{CE} was generated from a truncated dataset compared to SF_S and K_{COMP} , as it did not make use of the data acquired at b-values of 200 and 3000 s/mm². While the truncated dataset may result in poorer performance, it makes for a much simpler and faster acquisition protocol and modeling procedure. Thus, the selection of choice of model for high b-value diffusion data represents a tradeoff between the longer acquisition protocol, complex model estimation, and improved ROC performance associated with bi-exponential characterization vs. the shorter acquisition protocol, simpler parameter estimation, and poorer ROC performance associated with cumulant expansion kurtosis.

Context for this work can be found in a number of studies (6,7,9,17) examining the utility of diffusion kurtosis imaging in prostate cancer. The most similar to our own was reported by Mazzone et al. (9) when comparing cancerous and healthy peripheral prostate tissue using

kurtosis, diffusion coefficients, and perfusion fractions. Pathologic tissue was found to have both greater signal fraction of the slower component and greater kurtosis compared to healthy prostate tissue. However, cancer tissue was found to have a larger ADC in both slow and fast components when compared to healthy tissue in the range of b-values most similar to our own. While our study has shown that the kurtosis is directly related to the slow signal fraction of a two-component model when the ADCs of the components are fixed, the relationship is more complex when the ADCs are allowed to vary. Mazzone et al. also reported that the discriminatory ability of their calculated kurtosis was greater than that of the bi-exponential parameters. While methodological differences in patient groups, choice of b-values, noise-correction technique, and fitting methods can hamper direct comparisons between the two studies, these results suggest that further investigation into the relative discriminatory performance of signal fraction and kurtosis is warranted.

The results presented here must be considered in light of the limitations of the study. The results are derived from a limited sample of patients from a single institution and acquisition protocol and should therefore be tested for generalizability in a larger setting. The analysis does not account for any diffusion anisotropy within the prostate, as both fast and slow ADCs are assumed to be isotropic and invariant to diffusion gradient direction. However, Bourne et al. (18) demonstrated that anisotropic diffusion behavior might exist within the prostate, particularly in regions with fibromuscular stromal tissue. Furthermore, the effect of lesion location (peripheral vs. transitional zone) on parameters and ROC performance could not be assessed because of the low number of lesions in each category. The noise-correction technique used in this study may not be optimal for images with low signal-to-noise ratios, where a large number of voxels within the prostate are assigned a value of 0 if the observed signal is less than the mean signal within the

background. In addition, the discrimination between normal-appearing and malignant tissue was determined using the PI-RADS 5 scoring and not histopathologic determination of the Gleason grading. Therefore, the analysis can only be used to comment on the ability of SF_S , K_{CE} , and K_{COMP} to detect suspicious lesions as opposed to characterizing the lesions. A natural extension of this work for future studies is to assess the ability of the estimated parameters to discriminate between Gleason grades. Further investigation is also needed to determine the effect of acquisition parameters, such as the range of b-values used (19), on the results described here.

In conclusion, kurtosis and signal fractions derived from bi-exponential modelling are closely associated with each other in a two-component diffusion environment of the prostate. In the range of signal fractions most commonly found within the prostate, K_{COMP} is a scaled value of SF_S and is thus able to discriminate between healthy and suspicious lesions with equal precision. K_{CE} does not provide the same level of discriminatory ability as SF_S and K_{COMP} , but does provide a simple formulation that can be easily computed.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Anders Dale reports that he is a Founder of and holds equity in CorTechs Labs, Inc. and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc. and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc.

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