Ability of Combined DTI and DCE MRI to predict pathologic Gleason score

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Introduction

Prostate cancer remains the most common noncutaneous malignancy in North American males and second leading cause of cancer related deaths in men. The pathological grade of the prostate tumor (Gleason score) remains the strongest predictor of its biology and has significant impact on patient management. Various MRI and MRSI techniques have been applied to estimate Gleason score non-invasively with mixed results. We have previously shown that a combination of diffusion and DCE MRI provides better sensitivity of detecting prostate cancer than either of these techniques alone [1,2]. In the current study we tested whether this combination of MRI techniques can be applied to non-invasive prostate tumor grading.

Methods

Thirty seven men with a high clinical suspicion for prostate adenocarcinoma due to an elevated PSA and/or palpable prostatic nodule with no prior treatment were recruited to the study. Subjects underwent MRI examination prior to TRUS guided biopsies. From 8 to 12 needle biopsies were collected depending on the size of the prostate. The radical prostatectomy specimens, obtained from patients with biopsy-proven carcinoma, were all dissected and examined histopathologically.

All MRI exams were carried out on a 3T Philips Achieva MRI scanner. Twelve axial slices (4 mm, no gap) across the prostate gland were acquired for both Diffusion Tensor Imaging (DTI) and DCE MRI data with FOV of 24 cm. DTI MRI data were acquired using a single shot EPI sequence (128x115, 6 directions, b-value=600). DCE MRI was performed using a 3D T_1-weighted spoiled gradient echo sequence: 256x163, TR/TE=3.4/1.06 ms (T1W) or 50/0.95 ms (PD), flip angle = 15^0 (T1W) or 4^0 (PD), and the time resolution of 10.6 sec per 12 slices. 75 time points were acquired following a bolus injection of Gd-DTPA (Magnevist, Berlex Canada, 0.1 mmol/kg within 10 s followed by a 20 ml flush of saline).

The DTI data were processed off-line. Diffusion weighted images were registered to the non-weighted b=0 image with a mutual information algorithm prior to calculating the eigenvalues of the diffusion tensor and generating maps of the average diffusivity <D> (i.e. trace of the diffusion tensor) and fractional anisotropy (FA) with the proprietary DTI processing toolbox PRIDE (Philips Healthcare, Best, the Netherlands). DCE MRI data were processed off-line with software procedures developed in house using Matlab (Mathworks, Natick, MA, USA) and Igor Pro (WaveMetrics, Portland, OR, USA). Prior to further processing, T1W and PD images were registered to one another using PRIDE. Arterial Input Functions (AIFs) were extracted from voxels in the external iliac or femoral arteries in the central slice for each patient [3]. Pharmacokinetic parameters (K^{trans}, extra-vascular extra-cellular space – v_e, plasma volume – v_p) were calculated by fitting the Gd concentration vs. time curves to the extended Kety model [4]. To correlate MRI results with the Gleason score, the average values of MRI parameters were calculated from the Regions of Interest (ROIs) manually drawn around the hypo-intense areas in <D> maps and hyper-intense areas in K^{trans} maps located within the regions deemed cancerous based on the biopsy results. The Gleason score assigned for each ROI was based on biopsy and/or prostatectomy results. Statistical analyses were carried out using MedCalc 11.0 (MedCalc Software, Mariakerke, Belgium) and JMP 4.0 (SAS Institute Inc., Cary, NC). Correlation between MRI parameters and the Gleason score was determined with the Spearman's rho rank correlation test. Two-tailed independent samples t-test was used to assess the statistical significance of the differences in MRI parameters between different Gleason scores. In addition, ordinal logistic regression modeling was carried out to investigate a potential dependence between the MRI parameters and the Gleason score.

Results

Complete data sets were available from 27 patients. Thirteen of these patients had biopsies positive for carcinoma with 29 positive biopsies in total. Eight biopsies had Gleason score 3+3, 11 had score 3+4, scores 4+3 and 4+4 were identified in one biopsy each, 7 biopsies had score 4+5, and the Gleason score was not assigned to one core. Seven patients with biopsy confirmed cancer underwent radical prostatectomy. For 5 of these patients, the Gleason scores assigned on prostatectomy specimens differed from the biopsy Gleason score. In total, 15 lesions were assigned different scores, and the final distribution of the scores was: 7 lesions with 3+3 score, 13 with 3+4 score, 6 with 4+3 score, and 3 lesions with the score of 4+5. Table 1 shows the mean values and standard deviations of the MRI parameters for different Gleason scores. Spearman's rho rank correlation test showed statistically significant correlation between Gleason score and the average diffusivity <D> (rho = -0.661, p = 0.0005), fractional anisotropy FA (rho = - 0.551, p = 0.0036) and the fractional blood plasma volume v_p (rho = -0.423, p = 0.0251). K^{trans} and v_e did not show statistically significant correlation with the Gleason score (rho = -0.126, p = 0.5055 for K^{trans}, and rho = -0.363, p = 0.0549 for v_e). Ordinal logistic regression modeling showed statistically significant dependence between the Gleason score and the MRI parameters ($p < 0.0001$ for the model), however only <D> and FA significantly contributed to the model ($p = 0.018$ for <D> and $p = 0.009$ for FA).

Table 1. Average values (mean ± SD) of DTI and DCE MRI parameters

Gleason score	<D> [$10^{-3}mm^2/sec$]	FA	K^{trans} [min^{-1}]	v_e	v_p
3+3 (n = 7)	$1.30 \pm 0.15^{a,b,c}$	$0.25 \pm 0.04^{e,b,c}$	0.15 ± 0.10	0.21 ± 0.08	0.013 ± 0.010^{g}
3+4 (n = 13)	1.09 ± 0.18	0.19 ± 0.04	0.16 ± 0.07	0.22 ± 0.02^{f}	0.006 ± 0.006^{h}
4+3 (n = 6)	1.05 ± 0.03^{d}	0.20 ± 0.04^{d}	0.12 ± 0.05	0.18 ± 0.04	0.006 ± 0.005
4+5 (n = 3)	0.98 ± 0.04	0.13 ± 0.02	0.14 ± 0.01	0.15 ± 0.01	0.0005 ± 0.0005

a - 3+3 different that 3+4 ($p < 0.05$), b - 3+3 different than 4+3 ($p < 0.01$), c - 3+3 different than 4+5 ($p < 0.01$), d - 4+3 different than 4+5 ($p < 0.05$), e - 3+3 different than 3+4 ($p < 0.01$), f - 3+4 different than 4+5 ($p < 0.001$), g - 3+3 different than 4+5 ($p < 0.05$), h - 3+4 different than 4+5 ($p < 0.01$)

Discussion

Average diffusivity <D> had the strongest correlation with Gleason score of all MRI parameters measured in this study. This result is consistent with previous reports [5,6] that link decrease in <D> values measured in prostate cancers with increased cellular density in the tumor. Correlation between FA and Gleason score observed in this study is likely related to the presence of stroma in prostate gland. Smooth muscle and fibromuscular stroma are likely to be responsible for non-zero FA in normal prostate [7]. Prostate cancers commonly have numerous small, closely packed glands with little stroma between them. Additionally, the normal structural order of the stroma is disrupted by the presence of cancer. Thus one may expect that the increased structural disorder with more advanced tumors will be reflected in lower FA values for higher Gleason scores, which was indeed the case in this study. Lack of consistent correlation between DCE MRI parameters and Gleason score observed in this study is also consistent with previous reports.

In conclusion, both average diffusivity <D> and fractional anisotropy FA correlate strongly with Gleason score. These results strongly suggest that DTI MRI is capable of non-invasively grading prostate tumours.

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