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FULL PAPER

Effect of androgen deprivation and radiation therapy on MRI fiber tractography in prostate cancer: can we assess treatment response on imaging?

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Objective: To evaluate quantitative changes in Diffusion Tensor Magnetic Resonance Tractography in prostate cancer following androgen deprivation and radiation therapy.

Methods: 22 patients with elevated PSA and biopsy proven prostate carcinoma who underwent MRI of the prostate at 1.5 T with an endorectal coil were included. Group A) was the study group ($n = 11$), participants who underwent androgen deprivation and/or radiation therapy and group B) were Gleason-matched control group ($n = 11$) participants who did not undergo such therapy. Diffusion weighted images were used to generate three-dimensional (3D) map of fiber tracts from DTI. 3D regions of interest (ROI) were drawn over the tumor and healthy prostatic parenchyma in both groups to record tract number and tract density. Tumor region and normal parenchymal tract densities within each group were compared.

Results: Mean tract density in the tumor region and normal parenchyma was 2.3 and 3.3 in study group (tract numbers: 116.6 and 170.2 respectively) and 1.6 and 2.7 in the control group respectively (tract numbers: 252.5 and 346.3 respectively). The difference between these values was statistically significant for the control group ($p = 0.0018$) but not for the study group ($p = 0.11$). The difference between the tract numbers of tumor and normal parenchyma appears to narrow following therapy.

Conclusion: The study demonstrated utility in using tractography as a biomarker in prostate cancer patients post treatment.

Advances in knowledge: Quantitative DTI fiber tractography is a promising imaging biomarker to quantitatively assess treatment response in the setting of post-androgen deprivation and radiation therapy for prostate cancer.

INTRODUCTION

The treatment options for localized prostate cancer are evolving with addition of newer treatment strategies such as radiation, hormone and immunotherapy.^{1–5} These treatment options are continuously being improved to achieve maximum therapeutic benefit while minimizing the risks including systemic injuries as well as local damage to surrounding tissues. A potential challenge faced by imagers is assessing the treatment response in such patients on post-treatment imaging.⁶ Though multiparametric MRI has evolved as an imaging tool for detection, characterization, and staging of prostate cancer, its performance is limited in the setting of post-androgen deprivation and radiation therapies as there is a uniform decrease in the signal of the gland, which poses challenges in lesion

characterization. There have been some studies on spectroscopy, dynamic contrast enhanced MRI (DCE-MRI) and Diffusion Weighted Imaging (DWI), attempting to quantify the therapy induced changes and provide a biomarker in this regard.^{7–12} However, the aptitude of MRI for further interrogation of the prostate cancer treated by post-radiation and androgen deprivation therapy is yet to be fully explored.^{9,13–15}

DWI relies on microscopic molecular motion. Extensions of DWI are diffusion tensor imaging (DTI) and magnetic resonance tractography (fiber tractography), both of which are used to visualize neuronal fiber maps in the brain. Unlike DWI, DTI recognizes the directional properties of bulk water molecule motion. Application of directional gradients

permits pixel wise acquisition of the nine components of the diffusion tensor. In practice, six components are measured and the other three determined from symmetry of the tensor. DTI becomes important when the bulk motion is anisotropic. The direction of fiber tract is determined by the tensor's main eigenvector.

Clinical applications of DTI for mapping neuronal tracts have been well established,^{16,17} however, the application of this technique outside the nervous system has been limited to a few studies on skeletal muscle, myocardium, tongue, uterus and kidneys.^{18–24} Few researchers have attempted use of DTI for prostate gland with reference to mapping periprostatic fiber tracts.^{25–29} A recent small scale study has demonstrated feasibility of DTI of the prostate and shown that tract density could represent a new biomarker to distinguish tumor from normal tissue.³⁰

Following androgen deprivation and radiation therapy, the prostate gland shrinks in size and undergoes fibrosis. This affects ADC values and DTI indices such as fractional anisotropy (FA) and tract density, suggesting that these parameters could potentially be used as quantitative noninvasive biomarkers for the assessment of treatment response.

With this background, our hypothesis was that the tract densities for tumor and normal parenchyma would differ in treatment and control groups and a difference in the mean tract density between tumor and normal parenchyma was likely and could possibly be applied to identify responders from non-responders.

METHODS AND MATERIALS

Study population

In this retrospective, HIPAA compliant, institutional review board approved study 22 patients with elevated PSA and biopsy proven prostate carcinoma were included. The study population was divided into two groups: (A) study group ($n = 11$), participants who underwent androgen deprivation and/ or radiation therapy with proton beam/ GnRH therapy and (B) Gleason-matched control group ($n = 11$) of participants who did not undergo such therapy and chose either active surveillance or surgery as their treatment option. In the study group, 4 patients had disease confined to the prostate gland, 5 patients had extracapsular extension on MRI and 2 patients had evidence of systemic metastatic disease. In the control group, 3 patients had disease confined to the prostate gland, 7 patients had extracapsular extension on MRI and 1 patient had evidence of systemic metastatic disease.

The study group was further divided into responders vs non-responders based on PSA level at the end of 1-year follow-up. A PSA rise of 2 ng ml^{-1} or more above the nadir PSA was considered to distinguish between responders and non-responders.³¹

MRI acquisition and image analysis

MRIs were performed pre treatment and following treatment. The time between the pre treatment and post treatment MR in the study group ranged from 94 to 589 days with an average time of 280 days.

These patients underwent MRI of prostate using an endorectal coil and a 1.5 T scanner (Signa Excite HD, GE Healthcare Waukesha, WI) equipped with 40 mT m^{-1} maximum strength and 80 and $150 \text{ mT m}^{-1} \text{ s}^{-1}$ slew rate TwinSpeed gradients.

The multiparametric MRI examinations were performed in accordance with the standard institutional imaging protocol consisting of T_1 and T_2 weighted imaging, dynamic contrast enhanced sequences as well as acquisition of diffusion-weighted images with EPI DTI sequence with $TE/TR = 90.5/5000 \text{ ms}$, 8 nex, $bw = 1.95 \text{ kHz}$, 128×128 matrix, slice thickness = 5 mm , $FOV = 22 \times 22 \text{ cm}$, voxel size $1.1 \times 1.1 \text{ mm}$, and b values 0, 600 s mm^{-2} with 6 non-collinear sensitizing gradient directions.

After ascertaining the diagnostic quality of the DWI, the raw data was entered into the open-source Diffusion Toolkit and resulted tracts were visualized by TrackVis software (R. Wang, V. J. Wedeen, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, MA).³² A tensor matrix was derived using each voxel and after the diagonalization of the matrix, eigenvalues were obtained. Tract reconstruction was performed using FACT propagation algorithm, angle threshold 35° , spline-filtered, DWI mask image, FA threshold 0.1.

Two radiologists with 5 and 15 years of experience in reading prostate MRI examinations reviewed the images on a picture archiving and communication system (PACS) viewing workstation (Agfa, version 5.3, Richmond, VA). The tumor was identified only if it fulfilled all the three criteria A) abnormal T_2 hypointense signal B) corresponding restricted diffusion as seen on ADC images and C) biopsy proven prostate carcinoma in the region of signal abnormalities identified as mentioned in A and B.

The readers were given the freedom to change the window level. Multiple 3D regions of interest (3D-ROI) were drawn over the tumor and healthy prostatic parenchyma in both of the groups on the same axial slice (with the maximum tumor size) level to record the mean tract number and derive tract density (as a normalized measure of the number of tracts passing through the 3D-ROI). We introduced mean tract density as a quantitative parameter in our study as the following: mean tract number/ V , where $V = r^3$ is the normalized volume and r is the radius of the ROI sphere. We note that the method as defined above is not limited to spherical ROI and could also be extended to other applicable geometries.

Tumor region and normal parenchymal tract numbers and densities within each group were statistically compared using a two-tailed t test. A p value of < 0.05 was considered statistically significant. Differences between the tract numbers and tract densities for the tumor and normal parenchyma were also calculated for responders and non-responders.

RESULTS

In the treatment group, the study population had mean age of 67.9 years and mean ($\pm$ standard deviation) PSA level of $3.1 \pm 5.3 \text{ ng ml}^{-1}$. The control group population had mean age of 65 years with mean ($\pm$ standard deviation) PSA level of $13.4 \pm 18.4 \text{ ng}$

Figure 1. MRI and Tractography Images of patients with prostate cancer and age matched controls. (A) T_2 weighted axial image in a 65-year-old male (from the control group) with T2 hypointense tumor (arrow) in the right mid peripheral zone. (B) shows restricted diffusion in the tumor (arrow) on the ADC image. (C) 3 D fiber tracts in the tumor (green ROI) and normal parenchyma (yellow ROI) superimposed on the axial ADC image showed tract density of 1.1 in the normal parenchymal region. (D-E) Images from study group patient) shows a Gleason matched example of the study group participant who received radiation therapy for prostate cancer. Follow-up MRI shows T2 hypointense gland (D) with no apparent restricted diffusion focus on the ADC map (E). 3D fiber tractography overlaid on the ADC image (E) revealed tract density of 3.8 in the tumor region (green ROI) and 3.5 in the normal parenchymal region (blue ROI). The participant was deemed a responder based on imaging findings and accompanying PSA nadir on the laboratory evaluation. **Figure 1** shows an example of a 64-year-old male who underwent hormone therapy for prostate carcinoma in left base and mid gland peripheral zone tumor (not shown). At 1-year follow-up, his PSA bounced to 14.7 ng ml^{-1} . Axial T_2 weighted image (G) shows a T2 hypointensity (arrow) with capsular bulge in the left peripheral zone with a focus of restricted diffusion on the ADC image (arrow in H). 3D fiber tractography superimposed on ADC maps showed tract density of 5.7 in the tumor region (yellow ROI) and 9.1 in the normal parenchymal region (green ROI). The tract density and tract number difference between the normal parenchyma and tumor was wider for this patient (3.4 and 39 respectively).

Figure 2. (A) Column bar graph showing the distribution of tract densities across the regions of interest in tumor and normal parenchyma in study and control groups. (B) Column bar graph showing distribution of tract numbers across regions of interest in control and study groups (whiskers represent std. error of the mean).

ml⁻¹. In the study group, 8 patients were responders and 3 were non-responders (Figure 1). The software color-coding display shows right/left (red), anterior/posterior (green), superior/inferior (blue) tracts depending on the eigenvector orientation (Figure 1C,E,I). The mean ($\pm$ standard deviation) tract density in the tumor and normal parenchyma was 2.3 ± 1.6 and 3.3 ± 2.8 in the study group (tract numbers: 116.6 ± 75.3 and 170.2 ± 128.4 respectively) and 1.6 ± 0.6 and 2.7 ± 1.1 in the control group respectively (tract numbers: 252.5 ± 278 and 346.3 ± 354.1 respectively) (Figure 2). The difference between tumor and parenchymal tract number was statistically significant for the control group ($p = 0.008$) but not for the study group ($p = 0.18$). Statistically significant differences were also noted between tumor and parenchymal tract densities in the control group ($p = 0.002$) but not in the study group ($p = 0.11$). The difference between the tract numbers of tumor and normal parenchyma was small in the study group (93.8 in control vs 53.6 in study group). Mean tract density in the responder group for the tumor region and normal parenchyma was 2 ± 1.3 and 2.8 ± 2.2 (tract numbers: 124.6 ± 82.6 and 178 ± 139 respectively). In the non-responder group the mean tract density for the tumor region and normal parenchyma was 3.1 ± 2.5 and 4.8 ± 4.1 (tract numbers: 95 ± 59 and 149.3 ± 117.7 respectively). The mean difference between the tract densities for tumor and normal parenchyma was 0.8 ± 2.3 for responders (vs 1.8 ± 1.7 for non-responders). The mean

difference between the tract numbers for tumor and normal parenchyma was 53.4 for responders and 54.3 for non-responders (Figure 3).

DISCUSSION

DTI indices and fiber tractography have demonstrated promising results in the assessment of treatment response in the field of neurology and neurosurgery.^{33,34} We have demonstrated that tract density can be used as a biomarker to distinguish tumor from normal tissue in prostate cancer.³⁰ To our knowledge, DTI for prostate parenchyma following radiation and androgen deprivation therapy has not been previously explored. Up to 39.3% of patients with prostate cancer elect for either external-beam radiation/ brachytherapy/ androgen deprivation monotherapy.³⁵ The prostate gland undergoes fibrosis leaving behind collagenous stroma, which is hyalinized and sclerosed.³⁶ This results in loss of the T2 signal and zonal differentiation, which poses difficulties in evaluating treatment response and recurrence.^{9,37} The standard treatment response criteria (RECIST) used for solid tumors unfortunately cannot be applied to prostate cancer. PSA levels are less reliable post-radiation secondary to the phenomena of PSA bounce, providing scope for the development of novel imaging biomarkers for the quantitative assessment of treatment response.^{38,39} In our study, the tract densities and tract numbers were higher in the study group compared with the control group.

Figure 3. (A) Column bar graph showing tract number difference in the control and study groups. (B) shows a comparison of tract density difference in responders and non-responders (whiskers represent std. error of the mean).

The sclerosed and shrunken gland is a more tightly woven structure, which affects the diffusion of water paths. The higher tract densities in the treatment group are also in agreement with the trends in higher ADC values as shown in studies by Nemoto and Song et al.^{15,40} The narrow difference between tumor and normal parenchyma post-treatment may serve as a quantitative marker to assess treatment response. The absence of an increase in tract density post-therapy and a persistent or wider difference can signify a poor treatment response.

Further applying this observation to the 8 responders and 3 non-responders in our study, we noted that the difference in the tract densities, between malignant and benign tissue, was lower in responders compared with non-responders. The difference between the tract numbers did not differ greatly; this is relevant and shows that tract density as a normalized measure serves as a better parameter as opposed to tract number to use for distinction between responders and non-responders. In addition, tract density could in principle, be applied to create a map over the whole capsule with resolution exceeding imaging resolution of DWI images.⁴¹ This has been recently explored in neuroradiology for thalamic structures and glioblastoma multiformae.^{42,43}

The clinical implication for our results, assuming that our findings were confirmed by a study with a larger patient cohort,

more detailed subgroup analysis and a longer follow-up period would be the possibility of prospectively identifying prostate cancer responders and non-responders following treatment. Patients that are deemed non-responders could undergo a more intensive follow-up regime than responders. In the era of personalized medicine, DTI could serve as a biomarker to allow a more individualized and effective follow-up and treatment regime.

Our study had several limitations. First, it was a retrospective evaluation and involved a small patient population and small number of responders and non-responders. Second, the participants were imaged at a magnet strength of 1.5 T and with six diffusion encoding directions. Third, we did not evaluate the effect of various antiandrogen and radiation therapy regimens on tractography. Lastly, we followed out study participants for only 1 year. A larger study with study groups categorized by treatment received and longer than 1-year follow-up is required to further this application of tractography.

CONCLUSION

Diffusion Tensor Magnetic Resonance Tractography may function as a novel quantitative tool and marker of treatment response in setting of antiandrogen and radiation therapy for prostate cancers.

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