In vivo 3T and ex vivo 7T Diffusion Tensor Imaging of prostate cancer: correlation with histology

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Abstract

The purpose of this work was to test whether Fractional Anisotropy (FA) can contribute to the diagnosis and grading of prostate cancer.

Turbo spin echo T2-weighted (T2W) and single shot Echo Planar Imaging Diffusion Tensor Imaging (EPI DTI) data were collected from 13 subjects with biopsy proven prostate cancer prior to surgical removal of the gland. Rapid Acquisition with Relaxation Enhancement (RARE) T2W and spin-echo DTI data were acquired ex-vivo from the fixed prostatectomy specimens. Digitized whole mount histology sections, examined and annotated by a pathologist, were registered to the in-vivo and ex-vivo DTI data, and the average values of Apparent Diffusion Coefficient (ADC) and FA were calculated from ROIs encompassing normal and cancerous Peripheral Zone (PZ). In addition, Monte Carlo simulations were carried out to assess the dependence of the apparent FA on the ADC values for different signal to noise ratios (SNRs). ADC values were significantly lower in tumors than in normal PZ both in-vivo and ex-vivo, while the difference in FA values between tumors and normal PZ was significant only in-vivo. Paired t-test showed significant difference between in-vivo and ex-vivo FA values in tumors, but not in the normal PZ. The simulations showed that lower SNR results in an increasing overestimation of the FA values with decreasing ADC. These results suggest that the in-vivo increase in FA values in tumors is due to low SNR, rather than the presence of cancer.

The results of this study suggest that FA does not contribute significantly to the diagnostic capabilities of DTI in prostate cancer.

Keywords

apparent diffusion coefficient; prostate cancer; fractional anisotropy; Gleason Score

Introduction

According to the global burden of disease published by the World Health Organization (http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/), prostatic adenocarcinoma (PCa) is among the most common causes of cancer related mortality in men, second only to lung cancer, in the Americas (north, central, and south).

In clinical practice, the ability to non-invasively localize and grade PCa remains challenging. Systematic Transrectal Ultrasound (TRUS) guided biopsy, which is the standard method for PCa diagnosis, misses between 20 to 30% of tumors [1]. Several research groups have used diffusion techniques, including Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) values in different regions of the tissue to provide diagnostic, and perhaps even prognostic, information. MRI is used in some centers prior to surgery as a staging tool that can guide the surgical approach, when there is suspicion of extra capsular spread, seminal vesicle invasion, neuro-vascular bundle involvement, and possible lymph node metastases [2]. The use of a combination of an endorectal coil and a pelvic phased-array has been shown to improve the accuracy of prostate MRI in tumor identification [3]. Local staging has been studied by acquiring combined high resolution T2-weighted (T2W) images, MR Spectroscopy and Dynamic Contrast Enhanced (DCE MRI) data [4, 5]. However, T2W images have low sensitivity and specificity for prostate cancer: e.g. prostatitis and cancer infiltration both present signal decrease on this type of images [2]. More recent reports demonstrated that the addition of Diffusion Tensor Imaging (DTI) to standard T2W MRI improves the accuracy of tumor detection [6]. Miao and his group demonstrated that Diffusion Weighted Imaging (DWI) was much better in detecting PCa than standard T2W images [7, 8]. DTI, which reflects the microscopic organization of tissue, was initially applied to brain studies. However, it recently has been gaining importance in other applications, such as prostate imaging, especially since Sinha et al. carried out a preliminary prostate study on 6 healthy volunteers. The authors concluded that the prostate gland has an architectural anisotropy, and DTI can identify its structural changes at an early stage [9].

Although many previous studies have established that the ADC has a lower value in tumors, compared to healthy prostatic tissue, FA values in prostatic carcinoma in the peripheral zone (PZ) have been reported to be higher [2], lower [5], or unchanged [1] when compared to normal prostate. A study involving the different prostatic zones and comparing cancerous to non-cancerous tissue, suggested higher FA for cancerous foci compared to non-cancerous one [10], however, this study did not use ex vivo examination for the histopathological correlation. The objective of this study was to perform DTI measurements in prostate glands both in vivo and ex vivo in patients following radical prostatectomy and, by comparing to whole mount histology, to determine the usefulness of FA in the diagnosis of the disease.

Materials and methods

Patients

Thirteen patients with biopsy proven carcinoma were recruited to this prospective study. The mean age of these patients was 64 years and ranged between 56–73 years. The prostate glands of all the patients were examined in-vivo preoperatively and ex-vivo after resection.

In-vivo

The in-vivo examination was performed using a 3T Philips Achieva MR scanner (Philips Healthcare, Best, Netherlands) with a combined cardiac phased array/endorectal coil, and involved the acquisition of T2W and DTI data. Axial T2W images were acquired with a turbo spin echo (TSE) pulse sequence (matrix size of 284×225 , repetition time (TR) of 1851.19 ms, field of view (FOV) of 140 cm, and a slice thickness of 4 mm with no gaps).

The diffusion weighted images were obtained using a single shot Echo Planar Imaging (EPI) diffusion sequence. Six non-collinear directions of the diffusion sensitizing gradients were used with a matrix size of 128×115 , TR of 2100 ms, echo time (TE) of 36.4 ms, FOV of 24 cm, slice thickness of 4 mm with no gaps, and b-values of 0 and 600 s/mm^2 .

Ex-vivo

Following the robotic radical prostatectomy, the excised glands were fixed with 10% buffered formalin for at least 24 hours. A 1.8mm diameter plastic rod was inserted through the urethra to facilitate the alignment of the MRI slices with histology sections. The specimens were placed on a small plastic platform and covered with a cotton towel immersed in formalin. The specimens were then positioned inside a volume RF coil and data was collected using a 7T Bruker Biospin 30 cm bore MRI scanner (Bruker, Ettlingen, Germany). T2W images were acquired using a Rapid Acquisition with Relaxation Enhancement (RARE) sequence with a 256×256 matrix, TR of 5000 ms, effective echo time (TE_{eff}) of 46.98 ms, 6 cm FOV, and slice thickness of 4 mm with no gaps. DTI data was obtained using a spin-echo sequence with diffusion sensitizing gradients applied in six non-collinear directions, a matrix of 128×128 , TR of 1500 ms, TE of 22.3 ms, FOV of 6 cm, slice thickness of 4 mm with no gaps, and b-values of 0 and 750 s/mm^2 . Six directions used for the diffusion sensitizing gradients were the same as for the in-vivo procedure.

The lack of signal in the urethra, produced by the presence of the plastic rod, allowed the selection of the slice orientation very close to the one in which the specimens were subsequently sectioned, as is described in the next section. The number of slices was set to encompass the entire specimen. A total time of approximately 1.5 hours was required for the DTI scan.

Histology

After the ex-vivo scans, the specimens were sectioned into 4 mm thick slices with a device designed and built in house [11]. The seminal vesicles, bladder neck, and a small part of the apex were removed by the pathologist prior to sectioning the specimens. Whole Mount

Sections (WMS) were prepared using a Leica RM2245 microtome (Leica, Germany), mounted on oversized glass slides, and stained with hematoxylin and eosin stain.

Tumor areas were manually outlined and graded by the pathologist with the use of a microscope, and digital images were generated from the annotated glass slides using a flatbed scanner. The tumors were graded following the Gleason grading scale.

Histology and MRI co-registration

The registration of histology sections to MR images was performed using the ITK libraries, available with elastix [12], implemented into in-house software developed in Matlab (Mathworks, Natick, MA, USA). The registration for in-vivo and ex-vivo data was performed in a slightly different way. Higher deformations in the in-vivo case required the software to account for it, while in the ex-vivo case the registration was closer to a rigid one. In all cases, the segmentations were done manually using Matlab by delineating the contour of the prostate gland on histology and MRI images.

Ex-vivo to WMS

The ADC and FA maps obtained from the ex-vivo DTI data were calculated using Bruker software, Paravision 3.0.2 (Biospec R system). The diffusion parametric maps and the T2W images were considered registered to each other since the specimen was not moved during data acquisitions. Since anatomical details are better visible in T2W images, the histology sections were selected as moving images and the T2W images as the fixed targets. Corresponding slices were paired based on anatomical details, and the prostate was manually segmented in each of the pairs. An initial affine transformation, which involved a 2D, multi-resolution algorithm with a b-spline interpolator, created an initial alignment of the images. A second non-rigid b-spline transformation was subsequently applied to account for possible deformation. The advanced mutual information metric from elastix [12] was used as the similarity measure for the registration. Once the WMS were registered to the T2W images, the pathologist's highlighted ROIs were used to select tumor tissue and calculate the average values of the diffusion parameters inside these ROIs.

In-vivo to WMS

The in-vivo ADC and FA maps were calculated with software procedures developed in Matlab. Due to the low resolution of the ADC and FA maps, the WMS were registered to the T2W images. The registration followed the same procedure as in the ex-vivo case described above; however, the parameters set in elastix were adjusted to account for tissue deformation by the endorectal coil. The registration of DTI to T2W followed a similar procedure. The inverse of this transformation was subsequently applied to the WMS registered in the first step using the method proposed and evaluated by Metz et. al. [13]. Such approach ensured the proper registration between the tumor ROIs outlined on the WMS and the DTI data, at the same time allowing calculations of the ROI average DTI parameters from the non-deformed parametric maps. Figure 1 shows the procedure followed in the in-vivo registration case.

Validation

The quality of the registration was assessed with the Dice Similarity Coefficient (DSC). DSC is a number between 0 and 1 representing the amount of overlap between two objects, with 1 meaning perfect alignment and 0 meaning no overlap [14]. Although DSC is a straightforward and useful metric, it is not always ideal when deformable registration is used. Thus, the accuracy of registration was also validated using anatomical landmarks as fiducial markers. Corresponding landmarks were selected on T2W images and the registered histology sections, and the distance between them was calculated from the respective coordinate values by taking into account the pixel size in mm. The landmarks used in validation included identifiable anatomical details, e.g. urethra, differently shaped enlarge glands or cysts, and areas of stromal tissue in BPH, visible on corresponding MRI images and histology sections. These landmarks were visible on corresponding MRI images and histology sections, and were identified with the help of the pathologist.

Statistical Analysis

Statistical analyses were carried out using MedCalc 11.0 (MedCalc Software, Mariakerke, Belgium). Two-tail Student t-test was used to assess statistical significance of differences in DTI parameters. The normality of the parameter values distributions was confirmed with the Kolmogorov-Smirnov test. Three groups of the tested ROIs corresponded to the normal peripheral zone (PZ), and tumors with the Gleason score of 3+3 and larger than 3+3. Paired t-test was used to assess differences between FA values obtained in vivo and ex vivo from the same gland. Correlation between DTI parameters and the Gleason Score (GS) was determined with the Spearman's rho rank correlation test.

Simulations

Simulations were performed in order to assess the behavior of FA as a function of ADC for different noise levels in the DTI data.

Ideal, axially symmetrical diffusion tensors were chosen such that values of ADC varied from 0.5 to $0.2 \times 10^{-3} \text{mm}^2/\text{s}$. with true FA = 0, 0.1, 0.2, and 0.3, defined as the value of FA in the limit of infinite SNR. The FA was calculated as usually defined from the eigenvalues λ_1 , λ_2 , and λ_3 of the diffusion tensor as:

$$FA = \sqrt{\frac{1}{2} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_1 - \lambda_3)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}}$$

The ideal, noise-free diffusion weighted signal (S_{dw}^{ideal}) is obtained from a fixed S_0 and the diffusion tensor as stated above using $S_{dw}^{ideal} = S_0 e^{-Db}$. The b-value was varied such that $b=0$ and 600. Noise in S_{dw} was modelled by a Gaussian distribution with mean value given by the ideal diffusion equation and a standard deviation dictated by the chosen noise level:

$$S_{dw}(b) = N(S_0 e^{-Db}, \frac{S_0}{SNR})$$

This simulated, noisy diffusion-weighted signal was used to calculate the eigenvalues. The signal was sampled 1×10^6 times. The FA was calculated for each simulation realization of the diffusion experiment using the FA equation stated above. These FA values were averaged for the million samples for each of the different values of ADC in the mentioned range.

SNR from the obtained images was calculated from the non-diffusion weighted S_0 ($b=0$) images, and the background noise was estimated from areas of no signal (i.e. areas outside the body). The SNR values were estimated at 10 – 50 and around 200 for the in-vivo and ex-vivo cases respectively.

Results

Validation of the Registration Software

Thirty-four slices from the four data sets (ex-vivo T2W, ex-vivo DTI, in-vivo T2W, and in-vivo DTI) were used for the evaluation of the registration software. Figure 2 shows an example of a registered slice in the ex-vivo case. The bottom of the image shows the overlay with a varying level of transparency in order to evaluate the registration method qualitatively. An example of histology section with the outlined regions of interest is shown in Figure 3. A mean DSC values of 0.97 ± 0.01 , 0.95 ± 0.04 , and 0.94 ± 0.05 for ex-vivo DTI to WMS, WMS to in-vivo T2W, and in-vivo DTI to T2W were obtained respectively for the 34 slices. Five slices showed a poor match of the fine anatomical details in the overlay and were not included in the subsequent analyses.

For the anatomical landmark based validation, 65 and 50 landmarks were selected from the in-vivo and ex-vivo data respectively. Registration of the ex-vivo data resulted in the median landmark distance of 0.66 mm (range 0.23 to 2.90 mm), while the distance for the in-vivo data was 1.55 mm (range 0.3 to 3.1 mm) (see Figure 4).

Values of the Diffusion Parameters

A total of 86 slices were analyzed to determine the ADC and FA values in the tumors and normal PZ. Central gland tumors were not analyzed, as most PCa occurs in the peripheral zone [15]. In addition, most of the central gland tumors identified in this study were small, with their sizes being comparable to the inaccuracy of the registration software. Tumors with GS = 3+3 were identified in 9 patients, whereas 7 patients had tumors with GS > 3+3. The average values of the DTI parameters are presented in Table 1. As expected, tumor ADC values were significantly different than those in the normal PZ both in-vivo and ex-vivo. Significant difference in FA values between PCa and normal PZ was found only in-vivo.

Paired t-test was used to assess differences between FA values obtained in vivo and ex vivo from the same glands. The results showed that the FA values were not different between ex-vivo and in-vivo measurements in the normal PZ ($p = 0.88$). However, the difference in PCa was statistically significant ($p = 0.04$). Since it is expected that the fixation process, as well as the difference in the sample temperature, will have an effect on ADC, but not on the FA values [16], this result suggests that the significant difference in the FA between normal PZ and PCa, found in-vivo, is not necessarily related to the presence of the tumor.

ADC correlated significantly with GS both ex-vivo ($\rho = -0.70$, $p < 0.0001$) and in-vivo ($\rho = -0.77$, $p < 0.0001$), while FA correlated significantly only in-vivo, albeit with a very low value of the correlation coefficient ($\rho = 0.31$, $p = 0.0009$), but not ex-vivo ($\rho = 0.05$, $p = 0.60$). The in-vivo correlation may be related to the noise effect on FA, rather than the actual increase in FA due to the presence of higher grade tumors.

Simulations

Figure 5 shows plots of the apparent FA as a function of ADC for the SNR values of 10 and 250, and the true FA values of 0, 0.1, 0.2 and 0.3. As can be seen, the apparent FA for SNR = 10 is significantly higher than the true value, especially for the low values of ADC. Figure 6 shows similar plots for the SNR values of 10, 20, 30, 40, and 50, and the true FA value of 0.17 (the average FA value measured ex-vivo in this study). The overestimation of FA becomes less apparent with the increased SNR. Since the SNR of the in-vivo DTI data in this study was within the 10 – 50 range, and around 200 for the ex-vivo data, these results strongly suggest that the tumor FA values in-vivo were overestimated as a result of the relatively low SNR.

Discussion

Multi-parametric MRI [8, 17] has become a common approach to diagnosing prostate cancer. While different protocols are typically used, vast majority of them involves diffusion MRI. Many previous studies have established that the ADC has a lower value in tumors, compared to healthy prostatic tissue [18–20]; however FA values in prostatic carcinoma in the peripheral zone (PZ) have been reported to be higher [2], lower [5], or unchanged [1] when compared to the normal PZ. In this study, we acquired in-vivo and ex-vivo DTI data from the same glands and used whole-mount histology to identify the location of the tumors. Since the ex-vivo data are typically of higher quality, they are expected to provide the FA closer to its true value. To ensure proper tumor identification, MRI data were co-registered with the whole-mount histology. In addition, we carried out simulations to assess the effect of SNR on the accuracy of calculating FA – it has been shown that low SNR may result in overestimating the FA for the low ADC values [21]. This does not imply that low ADC values have low SNR, but rather that the effect the noise has in the apparent increase of FA is larger for situations of low ADC.

Our results showed that, although as expected the ADC values were significantly lower in tumors than in normal PZ both in-vivo and ex-vivo, the FA values were significantly higher in PCa, but only in-vivo. The results of paired t-test showed that the FA values measured in the same glands in-vivo and ex-vivo were not different in normal PZ. This is to be expected, as the tissue fixation and the sample temperature will affect the ADC values, but not the measure of anisotropy [16]. However, the paired t-test showed that the FA values in tumors were significantly different between in-vivo and ex-vivo data. This suggests that the increases in the tumor FA in-vivo are not necessarily related to the presence of PCa. This was further confirmed by the results of the simulations, which showed that, for the SNR values obtained in this study, the FA values are overestimated for the ADC values similar to the ones measured in tumors in our study. It is well established that SNR is a critical

parameter in the measurement of FA. For example, Farrel et al. [22] have shown, both in simulations and in vivo brain data, that decreased SNR results in overestimation of FA with no significant effect on the ADC values. This effect is now readily acknowledged in studies of diffusion in brain and recommendations lay out that any study reporting FA values should also quote the observed SNR [23]. However, in the case of prostate diffusion MRI, one rarely finds the same reporting standards, which probably contributes to the large variation in the reported values of FA.

Another factor that may adversely affect measurements of diffusion anisotropy is the partial volume effect, which will result in the decrease of the FA values. Most likely, both low SNR and partial volume effects influenced the accuracy of measuring FA in-vivo in our study. The low SNR resulted in the overestimation of FA, which was somewhat mitigated by the partial volume effects. This is in agreement with the a similar work by Xu et al. [1], who concluded that the technical limits make the accurate FA measurements in prostate gland in-vivo challenging.

Non-zero FA in normal PZ has been reported before [1, 2, 5]. The human prostate gland is composed of a mix of fibromuscular (stromal) tissue with glandular and ductal (epithelial) components. It has been shown that the anisotropy is higher in stromal tissue in comparison with the epithelium [24], leading to the hypothesis that at this scale, the stromal tissue is causing the observed anisotropy. This effect is more pronounced in the central gland, where the FA values were reported to be as high as 0.6 [1], due to higher content of stromal component, as compared to normal PZ. The ex-vivo FA value of 0.17 measured in our study compares favorably to those previously reported [1].

We used a 2D image registration in this study. Volume to volume registration was not possible due to the fact that for each 4 mm-thick MRI slice there was only one 20 microns-thick histology section. A 3D surface registration, which has been done before for prostate US images and histology sections [25], was a possibility. However, the main benefit of this approach would be an easier assignment of corresponding slices/sections, with negligible impact on the accuracy of the MRI to histology registration. The selection of the corresponding MRI and histology slices in this study was carried out manually and was based on the general location (i.e. MRI slice number vs. histology section number) and anatomical details identified in both MRI and histology. Due to large difference in thickness between MRI slices and histology sections, the accurate location of the corresponding images was not critical, as long as the slice orientation was the same for both, and the histology section was located within the 4 mm thickness of the corresponding MRI slice. The use of the multi-blade cutting device developed in our laboratory assured that both of these conditions were satisfied.

The size of the prostate gland can change between the in vivo and ex vivo situation due to fixation; however for the reasons outlined above, it did not affect the accuracy of the in vivo MRI to histology registration. Also, no in vivo to ex vivo MRI registration was carried out, but rather each in vivo and ex vivo MRI images were registered to histology separately.

Evaluation of the registration software suggests that there is an accurate alignment between the diffusion parametric maps and the corresponding whole-mount sections. The very high DSC values (0.94 – 0.97) demonstrate a very good alignment of the prostate glands in the fixed and deformed images. Since the DSC is not always ideal when deformable registration is used, we also validated the accuracy of registration using anatomical landmarks. The low median values of the distances between corresponding landmarks indicate that the accuracy of our registration procedure is less than 1 mm ex-vivo and 2 mm in-vivo. Considering that all tumors identified in this study were larger and all analyses were carried out on average values within ROIs, we can safely assume that the accuracy of the registration procedure was adequate.

One limitation of this study is the relatively small sample size, which prevented us from studying central gland tumors. However, PCa occurs predominantly in the epithelial tissue, and since the FA in the normal epithelial central gland tissue is very similar to that of normal PZ [1], it is unlikely that FA may contribute to identifying tumors in the central gland.

In conclusion, this study is consistent with previously published work showing a correlation between lower ADC values and increasing Gleason Score in PCa. Although reported FA values have been inconclusive until now, our results suggest that they do not differentiate between tumors and healthy tissue. Effects of SNR on apparently changing FA values were studied and, together with the partial volume effects, appear to provide a possible explanation for these variable effects observed by others. Finally, this study suggests that FA is not likely to contribute significantly to the DTI capacity of identifying prostate cancer in the peripheral zone.

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Figure 1.

Registration of in-vivo DTI data to histology. Both histology (left) and in-vivo DTI (right) are registered to an in-vivo T2W image (top). The inverse of the transformation found for DTI registration is applied to histology and resized in order to match the original ADC and FA maps obtained from the DTI data.

Figure 2.

Registration of ex-vivo (a) and in vivo (b) DTI data (left) with histology (middle) shows large contour overlap measured with the Dice Similarity Coefficient (right); red and green contours represent the fixed and registered images respectively. Below, an overlay of the original fixed image with the overlaid histology image are shown. The level of transparency is changed in steps of 0.2 from 0 (DTI $b = 0$ left image) to 1 (registered histology section right image).

Figure 3.
An example histology section with the outlined regions of interest.

Figure 4. Box and whisker plot showing the median values of distance between corresponding landmarks in the registered and fixed images for both ex-vivo and in-vivo.

Figure 5. Simulated plots of the behavior of FA as a function of ADC values for different realistic values of FA and SNR.

Figure 6. Simulated plots of the behavior of FA as a function of ADC for the SNR values of 10, 20, 30, 40, and 50, and the true FA value of 0.17 (the average FA value measured ex-vivo in this study).

Table 1

Average values of the DTI parameters.

	ADC [10^{-3} mm ² /sec]		FA	
	<i>ex vivo</i>	<i>in vivo</i>	<i>ex vivo</i>	<i>in vivo</i>
PZ (n = 72)	1.11 ± 0.23	2.07 ± 0.25	0.17 ± 0.08	0.16 ± 0.07
3+3 PCa (n = 17)	0.81 ± 0.15^a	1.59 ± 0.21^a	0.19 ± 0.09	0.20 ± 0.07^c
> 3+3 PCa (n = 19)	0.74 ± 0.09^a	1.41 ± 0.20^{a, b}	0.18 ± 0.05	0.21 ± 0.06^d

^a – significantly different than PZ (p < 0.0001)^b – significantly different than 3+3 PCa (p = 0.012)^c – significantly different than PZ (p = 0.037)^d – significantly different than PZ (p = 0.005)