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Mean diffusivity discriminates between prostate cancer with grade group 1&2 and grade groups equal to or greater than 3

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ABSTRACT

Purpose: To test the potential ability of mean diffusivity (MD) and fractional anisotropy (FA) in discriminating between PCa of grade group (GG) 1&2, and GGs ≥ 3.
Material and methods: Diffusion Tensor Imaging (DTI) experiments at 3T in a cohort of 38 patients with PCa (fifty lesions in total) were performed, by using different diffusion weights (b values) up to 2500 s/mm^2. Gleason score (GS) and GG data were correlated with DTI parameters (MD and FA) estimated in PCa. The relation between DTI measures and GS was tested by the linear correlation analysis (Pearson's coefficient). One-way analysis of variance to check the statistical significance of the difference between GG 1&2 and GGs 3, 4, 5, ≥3 was used. Results were reported for each of the three b-values ranges: 0–800 s/mm^2, 0–1500 s/mm^2, 0–2500 s/mm^2.
Results: A negative correlation was found between MD and GS. The highest linear correlation was observed when the fit was performed with data acquired in the b-values range 0–2500 s/mm^2. MD values were significantly different between GG 1&2 and GG = 3 and between GG 1&2 and GG ≥3. Moreover this difference is better defined when high b values (higher than b = 800 s/mm^2) are used. The specificity, sensitivity and accuracy in the discrimination between GG 1&2 and GG = 3 were: 90%, 66.7% and 82.4%, respectively when MD was estimated in the b-values range 0–2500 s/mm^2 while these values were 85%, 58.3% and 78.4% when MD was estimated in the b-values range 0–800 s/mm^2. Conversely FA did not discriminate between GG 1&2 and GG ≥3, at any investigated b-values range.
Conclusion: This study suggests that MD estimation in PCa, obtained from DTI acquired at high b-values, can contribute to the diagnosis and grading of prostate cancer while FA is not a useful parameter for this purpose.

1. Introduction

Prostatic adenocarcinoma (PCa) is the most frequent cancer among males in Europe [1–4]. As a consequence new diagnostic imaging techniques and reliable diagnostic criteria are highly desirable.

The purpose of the present retrospective study was to test the potential ability of diffusion tensor imaging (DTI) derived parameters in discriminating between PCa with grade group (GG) 1&2 (low risk cancer), and GGs ≥3 (intermediate/high risk cancer).

According to the European Association of Urology (EAU) guidelines on prostate cancer [3], the standard diagnostic procedure to confirm the presence of PCa is based on the transrectal or transperineal ultrasonography (TRUS) biopsy. However, the chance of missing a PCa by sextant biopsy using a computerized biopsy simulation is about 25% [5]. Furthermore, while TRUS biopsy has a good accuracy, it may have discrepancies with prostatectomy specimens [6].

From prostatic biopsy a Gleason score is assigned to evaluate the aggressiveness of PCa. For men who suffer from aggressive

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PCa characterized by a Gleason score (GS) ≥4 + 3 radical prostatectomy or irradiation of the prostate gland are indicated. Conversely, patients suffering from a less aggressive (GS ≤ 3 + 4) cancer can be offered less aggressive and invasive treatment [4–6]. As a consequence, the knowledge of the PCa aggressiveness before invasive surgery, is highly desirable to help plan cancer treatments for ensuring all of the tumors treated sparing as much normal tissue as possible. More importantly, a correct differentiation between low risk and intermediate/high risk cancer is desirable to ensure an appropriate management of patients, which can even include focal therapies or active surveillance [7].

In this regard, Epstein et al. [8] have recently proposed a new grading system for PCa to provide a better classification of cancer aggressiveness and thus a more correct prognosis for the patient [8]. In particular they showed [8] a different biochemical recurrence-free progression rate after radical prostatectomy in each assigned grade group (from 1 to 5 according to the Gleason score, GS), highlighting a large difference between PCa with grade group (GG) 1 and 2 (1&2), characterized by GS = 3 + 3 and 3 + 4, respectively compared to GG 3 (characterized by GS = 4 + 3) and greater than 3 (characterized by GS ≥8). In particular, a significant difference between GG 1&2 and GG 3 in terms of prognosis and recurrence after treatment, has been highlighted.

During the last years, multiparametric MRI has been widely used to detect tumor lesions and assess their aggressiveness [9–13]. Importantly, diffusion weighted imaging (DWI) has been indicated as a "dominant" sequence for PCa detection in the peripheral zone (PZ) and it can be helpful for PCa diagnosis in the transition zone (TZ) [14]. DWI provides information about the behavior of water molecules diffusion in tissue that is influenced by tissue topology and microstructures that impede and hinder water motion within tissues. In prostatic tissue, the branching ductal and the acini structure of the normal prostate compared with the highly restricted intracellular and interstitial spaces encountered in PCa produces a substantial differential in DWI image contrast.

Recently, some authors have shown that high b-value DWI images (e.g. with b-values greater than 800 s/mm^2) allow increased delineation of PCa [15,16]. Some other, underlined that DTI could provide a more accurate investigation of the prostatic tissue than that furnished by DWI [17–25]. From DTI measurements, it is possible to derive the mean diffusivity (MD) of water in tissues and various measures of its diffusion anisotropy, such as the fractional anisotropy (FA). In particular, MD was significantly lower in PCa compared to benign prostate tissue [21–23] and a significant correlation between DTI measurements and GS in PCa was found [24,25].

Aim of the present study was to test MD and FA potential ability in discriminating between PCa with GG 1&2, and GGs equal to or greater than 3. Toward this goal, we performed DTI experiments at 3T with b values up to 2500 s/mm^2 in a cohort of 38 patients with PCa. We correlated the anamnestic and histological patients' data with DTI parameters measured by using monoexponential fits performed with data obtained at different b-values ranges: (a) from 0 to 800 s/mm^2, (b) 0 to 1500 s/mm^2 and (c) 0 to 2500 s/mm^2. MD and FA results obtained in PCa belonging to different GGs were compared by using statistical tests. Finally, the relation between the DTI parameters and the GS was investigated in the three above mentioned b-values ranges.

2. Materials and methods

2.1. Patient cohort

Between February and November 2015, a total of 68 subjects with a possible diagnosis of PCa were scanned prior to their first biopsy. The mean age of the patients was 70.8 (age range: 48–86 years) and the averaged PSA was 10,1 ng/mL (PSA range 3,7–26,2 ng/mL). Informed consent was obtained from each patient prior to the MRI examination. The study was approved by the Local Ethics Committee. The biopsy, performed after the MRI examination, indicated 38 patients with GS equal or higher than 3 + 3 (Table 1) and 30 subjects with benign histopathological findings. Seventy-eight image slices were used to evaluate DTI parameters in PCa areas. Fifty lesions in total (16 lesions in TZ and 34 lesions in PZ) were investigated (Table 1). Prostatic tissue of the 30 subjects with negative biopsies was also analyzed by considering sixty image slices to evaluate DTI parameters in benign prostatic tissue.

2.2. MRI

All the examinations were performed using a 3T clinical MRI system (Intera Achieva, Philips Medical Systems, The Netherlands) equipped with high performance gradients with maximum strength of 80 mT/m and a slew rate of 200 mT/m/ms. For all of the examinations, six-channel phased array SENSE torso coil was used. For each patient, the protocol included high spatial resolution T2-weighted turbo spin echo (TSE) and DTI with echo-planar imaging (EPI). T2-weighted TSE images (repetition time (TR) = 3957, echo time (TE) = 150, turbo factor 21, field of view (FOV) = 150 × 130 mm, slice thickness (STK) = 3 mm, gap = 0, acquisition matrix 256 × 178, reconstruction matrix = 512 × 512, number of averaged scans (NSA) = 6, flip angle = 90°) were obtained for all subjects including the entire gland in the axial plane. DTI protocol was performed with a single-shot EPI sequence (TR = 3000, TE = 67, FOV = 150 × 130 × 70 mm^3, acquisition matrix = 64 × 52, reconstruction matrix 96 × 96, STK = 3 mm gap = 0, NSA = 4), by using 7 b-values (0, 500, 800, 1000, 1500, 2000, 2500 s/mm^2) and 6 non co-planar gradient diffusion directions. Spectral Attenuated Inversion Recovery (SPAIR) fat suppression with 200 Hz frequency offset was used after a B0 homogeneity optimization by using high order shim routine. The duration of the entire protocol was approximately 12 min of which the length of the DTI protocol is about 9 min. T2-weighted images (T2WIs) were used as anatomical and morphological reference to determine biopsy zones and as DTI reference image.

2.3. Biopsy

Biopsies were performed to all the patients in a period of 1 day–2 weeks after the MRI examination by expert urologists. T2WIs were used to contour and record lesion locations (Watson Elementary®). We performed a targeted MR/ultrasound fusion biopsy (BiopSee®, Medcom, Darmstadt, Germany) obtaining from 2 to 4 biopsy cores from the targets, followed in the same session by a 12 cores transperineal biopsy (sextant and laterally directed biopsies at base, mid-gland and apex). The targeted MR/ultrasound fusion biopsy and the standard 12 cores transperineal biopsy were performed by different physicians; the one who performed the 12 cores transperineal biopsy was unaware of the MR findings. Histopathological examination was performed and reviewed for each specimen on the basis of the recommendations arising from the "consensus conference ISUP 2014" [26].