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Prostate cancer detection using quantitative T2 and T2-weighted imaging: the effects of 5-alpha-reductase inhibitors in men on active surveillance

Running title: Quantitative T2 and dutasteride in PCa

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ABSTRACT

Background: T2-weighted imaging (T2-WI) information has been used in a qualitative manner in the assessment of prostate cancer. Quantitative derivatives (T2 relaxation time) can be generated from T2-WI. These outputs may be useful in helping to discriminate clinically significant prostate cancer from background signal.

Purpose/Hypothesis: To investigate changes in quantitative T2 parameters in lesions and non-cancerous tissue of men on active surveillance for prostate cancer taking dutasteride 0.5 mg or placebo daily for six months.

Study type: Retrospective

Population/Subjects: Forty men randomized to 6 months of daily dutasteride (n=20) or placebo (n=20).

Field strength/Sequence: Multiparametric 3T MRI at baseline and 6 months. This included a multi-echo MR sequence for quantification of the T2 relaxation times, in three regions of interest [index lesion, non-cancerous peripheral (PZ) and transitional (TZ) zones]. A synthetic signal contrast (T2Q contrast) between lesion and non-cancerous tissue was assessed using quantitative T2 values. Signal contrast was calculated using the T2-weighted sequence (T2W contrast).

Assessment: Two radiologists reviewed the scans in consensus according to Prostate Imaging Reporting and Data System (PI-RADS v.2) guidelines.

Statistical tests: Wilcoxon and Mann-Whitney U tests, Spearman's correlation.

Results: When compared to non-cancerous tissue, shorter T2 values were observed within lesions at baseline (83.5 and 80.5 ms) and 6 months (81.5 and 81.9 ms) in the placebo and dutasteride arm, respectively. No significant differences for T2W *contrast* at baseline and after 6 months were observed, both in the placebo [0.40 (0.29-0.49) vs 0.43 (0.25-0.49); p=0.881] and dutasteride arm [0.35 (0.24-0.47) vs 0.37 (0.22-0.44); p = 0.668]. There was a significant, positive correlation between the T2Q contrast and the T2W contrast values ($r=0.786$; $p<0.001$).

Data conclusion: The exposure to antiandrogen therapy did not significantly influence the T2 contrast or the T2 relaxation values in men on active surveillance for prostate cancer.

Keywords: Prostatic neoplasms; Active surveillance; Magnetic Resonance Imaging; Quantitative T2; Dutasteride; Placebo.

INTRODUCTION

Multiparametric magnetic resonance imaging (mpMRI) combines high-resolution T2-weighted imaging (T2-WI) sequences with dynamic contrast-enhanced - DCE - and diffusion-weighted imaging - DWI -, and/or spectroscopy (1). Today mpMRI plays a pivotal role in the diagnosis and risk stratification of men with prostate cancer (2). The key sequences that drive this process are T2-WI and DWI with DCE providing useful input in select cases (3-4).

T2-WI generates a high signal-to-noise ratio and confers high spatial resolution. These attributes permit the depiction of subglandular structures and for the differentiation of the zonal anatomy of the prostate (e.g. peripheral/transitional zone, seminal vesicles, neurovascular bundles and urethra) (5-6).

The peripheral zone is characterized by high signal intensity on T2-WI, due to its higher water content, and cancer is frequently seen as an area of lower signal intensity. However, other conditions such as prostatitis, fibrosis, scar tissue, post-biopsy hemorrhage may also cause low T2 signal intensity, and result in false positive diagnoses (7). The degree of intensity decrease on T2-WI in the peripheral zone has been correlated with Gleason score, with higher Gleason scores having lower signal intensities (8).

T2-WI is also considered the most important sequence for the detection of cancer in the transitional zone according to recent guidelines (9-10), even though the heterogeneous appearance of benign prostate hyperplasia nodules in the transitional zone makes assessment for cancer challenging in this area (11).

Historically, T2-WI information has been used by radiologists in a qualitative manner and imputed into risk models such as Prostate Imaging Reporting and Data System (PI-RADS) (9). However, quantitative derivatives (T2 relaxation time) can also be generated from the T2-WI. These outputs may be useful in helping to discriminate clinically significant cancer from the background signal. Roebuck and colleagues evaluated T2 values on a pixel-by-pixel base using Carr-Purcell-Meiboom-Gill (CPMG) quantitative imaging, and found that prostate cancer shows a significantly shorter T2 value when compared to healthy tissue (12).

It is known that dutasteride inhibits the enzyme 5 alpha-reductase, which converts testosterone to dihydrotestosterone, and is widely used for the treatment of lower urinary tract symptoms associated with an enlarged prostate (13). Dutasteride is

associated with a reduction of prostate volume, and there is evidence that dutasteride may delay the rate of progression in men on active surveillance for prostate cancer (14). However, it is not known what effect dutasteride may have on the appearance of prostate cancer on T2-WI, and this is a clinically important information since mpMRI is gaining popularity as one of the assessment tools in patients on active surveillance.

In order to further evaluate the role of quantitative T2 outputs we undertook specific analyses on the T2-WI and multi-echo CPMG sequences from men recruited into MAPPED – a randomized study of dutasteride versus placebo in men with low risk prostate cancer on active surveillance, using mpMRI as an endpoint (15).

Our aim was to measure the T2 relaxation time, a biomarker of tissue pathology, in cancerous and non-cancerous tissue, and to examine the effect of dutasteride on those parameters.

MATERIALS AND METHODS

This study is a retrospective analysis from a phase II, randomized, double blind, prospective clinical trial approved by the Hammersmith & Queen Charlotte's & Chelsea Research Ethics Committee (UK) (09/H0707/84), and the Medicines & Health Regulatory Agency and registered on the European Clinical Trials register (EudraCT 2009-102405-18) (15). The study was sponsored by University College London and GlaxoSmithKline (GSK) funded it through an unrestricted grant.

Eligibility criteria and study design

All men gave their consent to participate in this study and the full protocol has been published (15). Between June 2010 and January 2012, 42 men were recruited, and 40 completed the study. Eligible men had biopsy-proven low-intermediate risk prostate cancer and an MR visible lesion ≥ 0.2 ml on T2-weighted sequences, based on biopsy within the preceding two years. All eligible men met the National Institute for Health and Clinical Excellence (NICE 2008) active surveillance criteria for low-intermediate risk prostate cancer (up to Gleason 3+4, PSA up to 20 ng/ml and/or clinical stage up to T2c) (16).

All men included in this study did not have any prostate cancer treatment (hormone manipulation, prostatic surgery, and treatment with any 5-alpha reductase inhibitor) in the previous 12 months. A 3T MR scan including T1- and T2-weighted and DW imaging was performed and after review by a study radiologist confirming suitability, men were individually randomized (1:1) to daily placebo or dutasteride using block randomization with varying block sizes. MpMRI was repeated at 6 months.

MR imaging

All patients underwent MR imaging on a 3T system (Magnetom Verio, Syngo MR B 17; Siemens Healthcare, Erlangen, Germany) and a pelvic phased-array coil. All examinations included unenhanced axial, sagittal and coronal turbo spin-echo T2 weighted imaging, axial DWI (b values of 0, 100, 800 and 1400 s/mm^2) with reconstruction of the apparent diffusion coefficient (ADC) map and axial T1-weighted imaging during intravenous injection of 0.1 mmol/kg of body weight of gadoterate meglumine (Dotarem®, Guerbet, Roissy, France) at a rate of 2 mL/s. The protocol was in line with standard guidelines (17).

Quantitative T2 imaging was performed with a multi-echo approach based on the CPMG imaging sequence (12). The vendor-supplied CPMG sequence consisted of optimized 180° sinc refocusing pulses, with spoiler gradients of constant amplitude applied around each refocusing pulse along the frequency-encoding direction (18). The multi-echo CPMG protocol was optimized to ensure a good compromise between several parameters; these

included the in-plane spatial resolution, the sampling of the T2 relaxation decay, the signal-to-noise ratio and the scan time. Protocol optimization was carried out on 3 healthy volunteers; the CPMG sequence parameters chosen for the quantitative T2 imaging of the current study are shown in Table 1.

Image analysis

All mpMRI data were anonymized. Two board-certified radiologists (AK and FG, with 11 and 4 years of experience in prostate cancer mpMRI interpretation, respectively) reviewed the scans in consensus according to PI-RADS v.2 guidelines (9), using commercial image viewing software (Osirix ® v. 4.1.2; Geneva, Switzerland). Both readers were unaware of treatment allocation and were privy only to the date of the scan. To ensure consistency, all scans were reported in chronological order (i.e. first baseline, and then 6-month scan).

All lesions were visible on T2-WI (used as the reference standard) at baseline and after 6 months, and image quality was adequate in all patients.

First, the two readers manually traced three regions of interest (ROIs) on the T2-weighted high-resolution images. The largest lesion (index tumor) was chosen, if multiple foci were detected in the same patient. The ROI was copied and pasted in the non-cancerous peripheral (PZ) and transitional (TZ) zone, in mirror position to the lesion (Fig. 1) on the same slice. The signal values from this sequence were defined as T2-weighted (T2W).

The three ROIs were then copied and pasted on the multi-echo CPMG sequence. Quantitative T2 data analysis of each ROI started with visual inspection of the T2 relaxation decays. The signal of the first echo was observed to be lower than expected - at times even lower than the second echo. This is in line with previous observations on CPMG data (12, 19). Thus, the signal of the first echo was omitted from the data analysis. T2 values were estimated by fitting the signal S_n obtained at the echo times TE_n ($n = 2, 3, \dots, 8$) to the mono-exponential decay function $S_n = S_0 e^{-TE_n/T2}$ where S_0 is a parameter proportional to the tissue proton density and external experimental factors. T2 data fitting was performed using MATLAB (MathWorks, Natick, MA, USA). The T2 values of the lesion, PZ and TZ were determined both at baseline and after 6 months.

For each patient, we also measured the signal intensity of the lesion (S_L) and compared it to the signal intensity of presumed non-cancer tissue in mirror position, i.e. (S_{PZ}) for (S_L) in the PZ and (S_{TZ}) for (S_L) in the TZ on T2-WI. For example, we calculated the T2W contrast between a lesion in the PZ and the non-cancerous tissue using the equation: T2W contrast = $(S_{PZ} - S_L)/S_{PZ}$. Furthermore, to investigate whether there was a correlation between the T2-weighted and the quantitative T2 imaging data, we calculated

a 'synthetic' contrast using the T2 values obtained from the CPMG data fitting. The calculation was as follows: first, we calculated the signal intensity that the lesion (with a T2 obtained from quantitative T2 imaging) would yield in the T2-weighted image. This was achieved by using the equation $S_L^s = S_0 e^{-TE/T2}$, where TE is the echo time (103 milliseconds) of the T2W image and S^s stands for synthetic. We performed the same calculation for the signal of the PZ, S_{PZ}^s . The last step consisted in calculating the 'synthetic' contrast, $T2Q\ contrast = (S_{PZ}^s - S_L^s) / S_{PZ}^s$, which was obtained by using the quantitative T2 data.

Statistical methods

Clinical and demographic data are reported using descriptive statistics. Continuous variables were summarized by their median values and interquartile range (IQR, 1st quartile to 3rd quartile); categorical variables were summarized by means of frequencies and percentages.

We carried out the Wilcoxon signed-rank test to compare baseline and 6-month values (T2 values and contrast), first in the placebo and then in the dutasteride group. The Mann-Whitney U test was applied to investigate the differences between the two groups (placebo vs dutasteride). The relationship between T2W and T2Q *contrast* was assessed by means of the Spearman's correlation coefficient.

P values less than 0.05 were considered to indicate a significant difference. All statistical analyses were performed by using SPSS (version 20.0; SPSS, Chicago, Illinois, USA).

RESULTS

A total of 40 men (median age 65.15 years; range 49-79 years) were eligible for the present study. Lesion locations were as follows: 35/40 (87 %) in the PZ [14/35 (40 %) left, 1/35 (3 %) midline and 20/35 (57 %) right] and 5/40 (13 %) in the TZ.

All men had a positive biopsy at entry; specifically, 22/40 (55%) men had Gleason score 3+3 and 18/40 (45%) had Gleason 3+4. Of note, thirty-seven men of forty men (93%) had histological confirmation of the mpMRI lesion contained cancer either at baseline or exit. Three men had discordant histology at baseline, one of whom had a negative exit biopsy (placebo group) and two who declined the exit biopsy (one placebo, one dutasteride).

There was no difference in PSA values between the placebo and the dutasteride group at baseline [6.2 (5.3–7.8) vs 6.4 (5.1-8.8) ng/mL, $p = 0.482$], respectively. There was a significant difference in PSA values between the two arms after 6 months [6.6 (5.6-8) vs 3.9 (2.2-5.6) ng/mL, $p < 0.001$].

Table 2 compares median ROI measurements at baseline and after 6 months. There was a significant difference between baseline and 6-month ROI areas in the dutasteride arm [0.38 (0.27-0.61) vs 0.27 (0.20-0.53) cm²; $p = 0.005$]. Table 3 reports the comparison between T2 values of lesions and non-cancerous tissues (for PZ and TZ) at baseline and after 6 months. There was a significant difference ($p < 0.001$) between lesions and PZ for each arm, both at baseline and after 6 months (Fig. 2). Table 4 reports the comparison for T2 values from all ROIs for each of the two arms, at baseline and after 6 months. There were no significant differences both for lesions and non-cancerous tissues (PZ and TZ). It should be noted that the median values in the PZ for the placebo arm at baseline were virtually the same as those after 6 months. The same finding was observed in the dutasteride arm.

No significant differences for T2W *contrast* at baseline and after 6 months were observed, both in the placebo [0.40 (0.29-0.49) vs 0.43 (0.25-0.49); $p=0.881$] and dutasteride arm [0.35 (0.24-0.47) vs 0.37 (0.22-0.44); $p = 0.668$] (Fig. 3). Additionally, there were no significant differences in T2W *contrast* between the placebo and the dutasteride arm at baseline [0.40 (0.29-0.49) vs 0.35 (0.24-0.47); $p = 0.409$] and after 6 months [0.43 (0.25-0.49) vs 0.37 (0.22-0.44); $p=0.372$].

There was a significant, positive correlation between T2W and T2Q *contrast* values ($r=0.786$; $p < 0.001$), as shown in Fig. 4.

DISCUSSION

Our previous paper (20) showed a reduction in tumor volume on T2-WI in men on dutasteride for 6 months compared to men on placebo. A further paper analyzing the DWI (21) has shown a reduction in conspicuity of prostate cancer in men on dutasteride for 6 months compared to placebo.

In this paper, we report the analysis of dedicated research sequences, namely quantitative T2 imaging, at the same time as the anatomical T2-WI, but not previously analyzed. In contrast to the effect on DWI, the T2Q contrast values (quantitative) and the T2W contrast (qualitative) appear to be unaffected by exposure to dutasteride.

Quantitative T2 imaging allows for measuring the T2 relaxation time, a biomarker sensitive to tissue microenvironment. However, during a standard mpMRI of the prostate, only qualitative T2 imaging (with a high signal-to-noise ratio and spatial resolution) is performed, to differentiate the zonal anatomy of the gland and the possible presence of cancer (9). Cancerous tissue consists of highly compacted cells, and this results in a decrease in T2 signal (22).

Although several recent studies have also evaluated the utility of quantitative T2 imaging in prostate cancer (12, 23-29), quantitative in vivo T2 mapping is still a challenge due to the long scan duration, and therefore this approach is not routinely performed during a standard prostate mpMRI scan.

Our retrospective study aimed to fill this gap by analyzing a cohort of men on active surveillance exposed to dutasteride as part of the initial trial, who underwent a dedicated multi-echo T2 sequence in addition to the standard mpMRI (15). The data acquisition protocol was optimized to yield the full volume coverage of the prostate, a good in-plane spatial resolution and a detailed sampling of the T2 relaxation decay in order to obtain an accurate measurement of the T2 relaxation time. The data analysis was performed on the ROIs, and data fitting was carried out offline with MATLAB.

It is known that antiandrogen therapy affects prostatic tissues, which inevitably affects the interpretation of mpMRI studies. The quantitative T2 values are closely related to tissue properties and in our study, they were not influenced by dutasteride.

The correlation between the T2W and T2Q contrast provides insight into the results obtained from the qualitative and quantitative T2 imaging data. Considerable variability

of the contrast in the T2-WI was observed; same consideration applies to quantitative T2 measurements, where different T2 values were measured in different patients. Does this variability in T2-WI contrast and quantitative T2 values originate from measurement error, or reflect true inter-individual differences? The correlation found between the contrast measured on the T2-weighted images and the “synthetic” contrast calculated from the quantitative T2 measurement indicates that the variability could be partly explained by inter-individual differences. In other words, in patients with a high lesion contrast in the PZ (measured on T2-WI), the T2 values measured by T2Q would have yielded T2-weighted images with a high contrast. Similarly, in patients with a low lesion contrast in the PZ, the T2 values would have yielded T2-weighted images with a low contrast.

Starobinets and colleagues (29) reported no significant differences in contrast on T2-WI between untreated and treated men. Similarly, we did not find any difference between the two arms, both at baseline and after 6 months of exposure to dutasteride. Following our definition of contrast, we could consider this parameter as a surrogate of the conspicuity of the lesion on T2-WI. It follows that the use of dutasteride does not seem to influence lesion conspicuity on T2-WI (i.e. the lesion is still detectable after treatment). This finding is also supported by the significant difference in T2 values from quantitative T2 measurements between the lesion and non-cancerous PZ for each arm, before and after treatment.

It is known that visible lesions on mpMRI have an increased overall risk of cancer progression, so that identifying these lesions is of clinical importance (30).

Our results confirm that mpMRI can be used for reassessment during active surveillance in patients treated with 5-alpha-reductase inhibitors, as these medications do not affect signal intensity on quantitative and qualitative T2 imaging, although our previous publication (20) suggests that 5-alpha-reductase inhibitors do result in a decrease in MRI-visible tumor volume. We agree with the PRECISE (Prostate Cancer Radiological Estimation of Change in Sequential Evaluation) recommendations (31) for reporting MRI in active surveillance that further studies are necessary to investigate exactly which imaging parameters (e.g. tumor volume measurements on T2-WI) would be most appropriate to initiate repeat biopsy or indeed treatment.

A number of methodological limitations in our study should be mentioned. First amongst these is the relatively small cohort of men. In mitigation, the men were all included in a prospective randomized controlled trial and therefore we subject to standardized mpMRI and assessment. The study was of relatively short duration for a prostate cancer study

and therefore does not reflect the natural history of the condition. Secondly, some may regard the absence of tissue verification by means of radical prostatectomy step section pathological processing as a limitation. In this relatively low risk population who had elected to enroll in an active surveillance study few would choose to have surgery and therefore we would have to deal with missing data. The use of targeted biopsy - the reference test used in this study that could be applied to all men – has been shown to be as accurate as 5mm template biopsy (32). It is acknowledged that PZ and TZ tumors are scored differently according to PI-RADS v. 2 guidelines (9), and our cohort was composed of 35 PZ and 5 TZ tumors. There is some likelihood that dissimilar evaluations would have arisen if the number of TZ lesions (more heterogeneous from a histological point of view) had been higher.

In conclusion, after this retrospective analysis, we found that T2 relaxation times and T2-WI were not significantly influenced by the exposure to dutasteride in men on active surveillance for prostate cancer. This suggests that the drug may not impair our ability to measure tumor volume in active surveillance and longitudinal studies.

Table 1. MRI parameters of the Carr-Purcell-Meiboom-Gill (CPMG) sequence for quantitative T2 imaging.

	CPMG
TR (ms)	3000
Number of Echoes	8
TE values (ms)	15, 30, 45, 60, 75, 90, 105, 120,
Number of Slices	14
Slice thickness (mm)	4
In plane resolution (mm)	1.1 x 1.1
Interslice Gap (mm)	1
BW (Hz/px)	352
Orientation	Axial
FOV (mm)	165 x 220
Scan Time (mins:secs)	7:52
Number of Averages	1

Note – TR = repetition time; ms = milliseconds; TE = echo time; mm=millimeters; Hz = Hertz; px = pixel; BW = band-with; FOV: field of view; mins = minutes; secs=seconds

Table 2. ROI areas (cm²) for each of the two arms at baseline and after 6 months.

	Placebo			Dutasteride		
	Baseline	6 months	<i>p</i>	Baseline	6 months	<i>p</i>
ROI (cm ²)	0.46 (0.33-0.62)	0.45 (0.33-0.64)	0.881	0.38 (0.27-0.61)	0.27 (0.20-0.53)	0.005

Note - Data are medians with interquartile ranges in parentheses. ROI: region of interest.

Table 3. T2 values (in milliseconds) for lesions (L) and non-cancerous tissues (PZ and TZ) at baseline and after 6 months for each of the two arms. The p-values (Wilcoxon signed-rank test) for T2 comparison between L–PZ and L-TZ are also displayed.

Placebo					
	Lesion	Non-cancerous PZ	p (L-PZ)	Non-cancerous TZ	p (L-TZ)
Baseline	83.5 (70.1-95.8)	133.7 (99.6-152.4)	< 0.001	97.7 (84.4-106.0)	0.117
6 months	81.5 (72.4-100.5)	133.7 (109.5-157.2)	< 0.001	96.2 (88.4-103.6)	0.108
Dutasteride					
	Lesion	Non-cancerous PZ	p (L-PZ)	Non-cancerous TZ	p (L-TZ)
Baseline	80.5 (74.2-89.5)	107.2 (97.1-126.6)	<0.001	88.1 (75.4-94.6)	0.113
6 months	81.9 (72.4-85.8)	107.9 (95.9-129.5)	<0.001	83.2 (76.5-90.2)	0.351

Note - Data are medians with interquartile ranges in parentheses PZ: peripheral zone; TZ: transition zone.

Table 4. T2 values (in milliseconds) for each of the two arms included in the study at baseline and after 6 months. The p-values (Wilcoxon signed-rank test) for T2 comparison between baseline and 6-month mpMRI are also displayed.

	Placebo			Dutasteride		
	Baseline	6 months	<i>p</i>	Baseline	6 months	<i>p</i>
Lesion	83.5 (70.1-95.8)	81.5 (72.4-100.5)	0.179	80.5 (74.2-89.5)	81.9 (72.4-85.8)	0.681
Non-cancerous PZ	133.7 (99.6-152.4)	133.7 (109.5-157.2)	0.654	107.2 (97.1-126.6)	107.9 (95.9-129.5)	0.794
Non-cancerous TZ	97.7 (84.4-106.0)	96.2 (88.4-103.6)	0.332	88.1 (75.4-94.6)	83.2 (76.5-90.2)	0.502

Note - Data are medians with interquartile ranges in parentheses. PZ: peripheral zone; TZ: transition zone

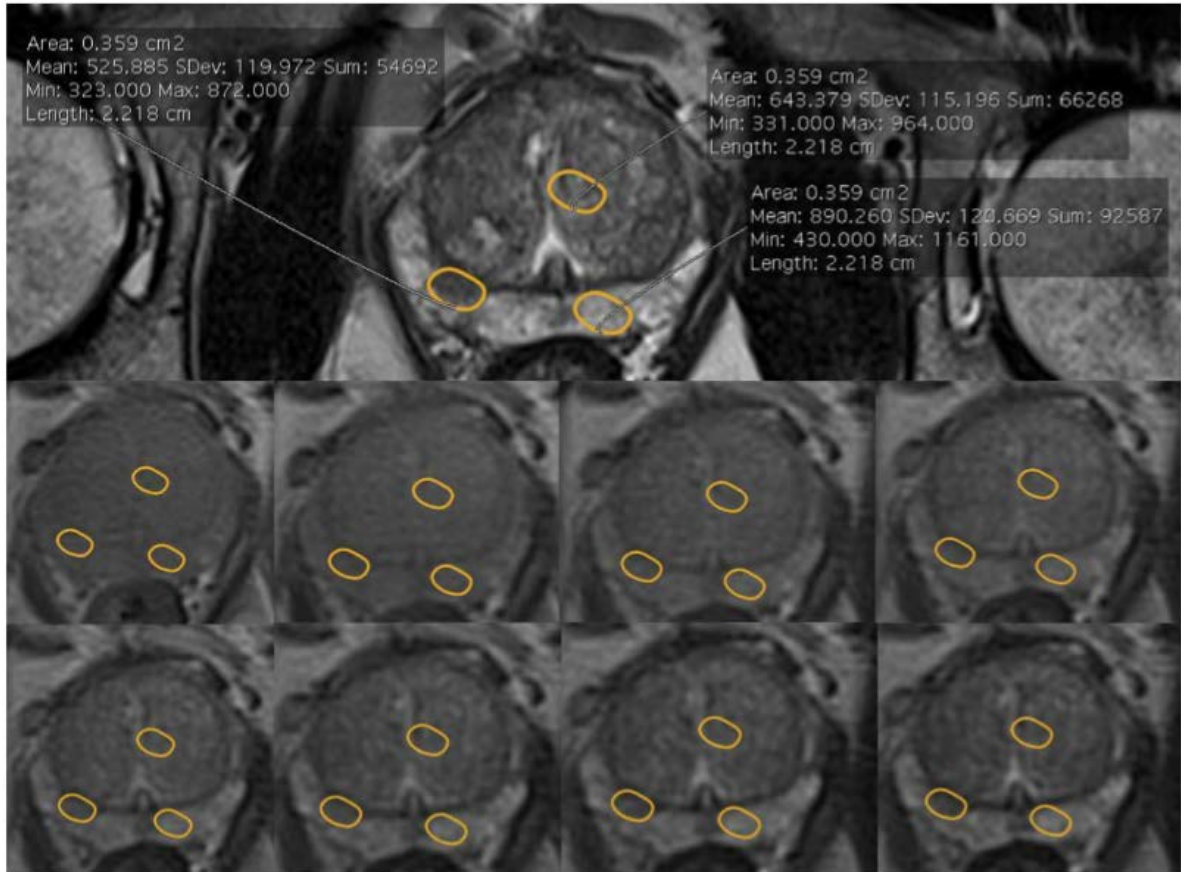


Figure 1

MR images of the prostate of a 69-year-old man with a PSA of 5.83 ng/ml and a Gleason 3+4 tumor in the mid-right peripheral zone at entry biopsy. The region of interest (ROI) for quantitative T2 analysis is here illustrated. Three ROIs (lesion, non-cancerous peripheral and transitional zones) were drawn on the high-resolution T2 image. These ROIs were then copied and pasted on the multi-echo images.

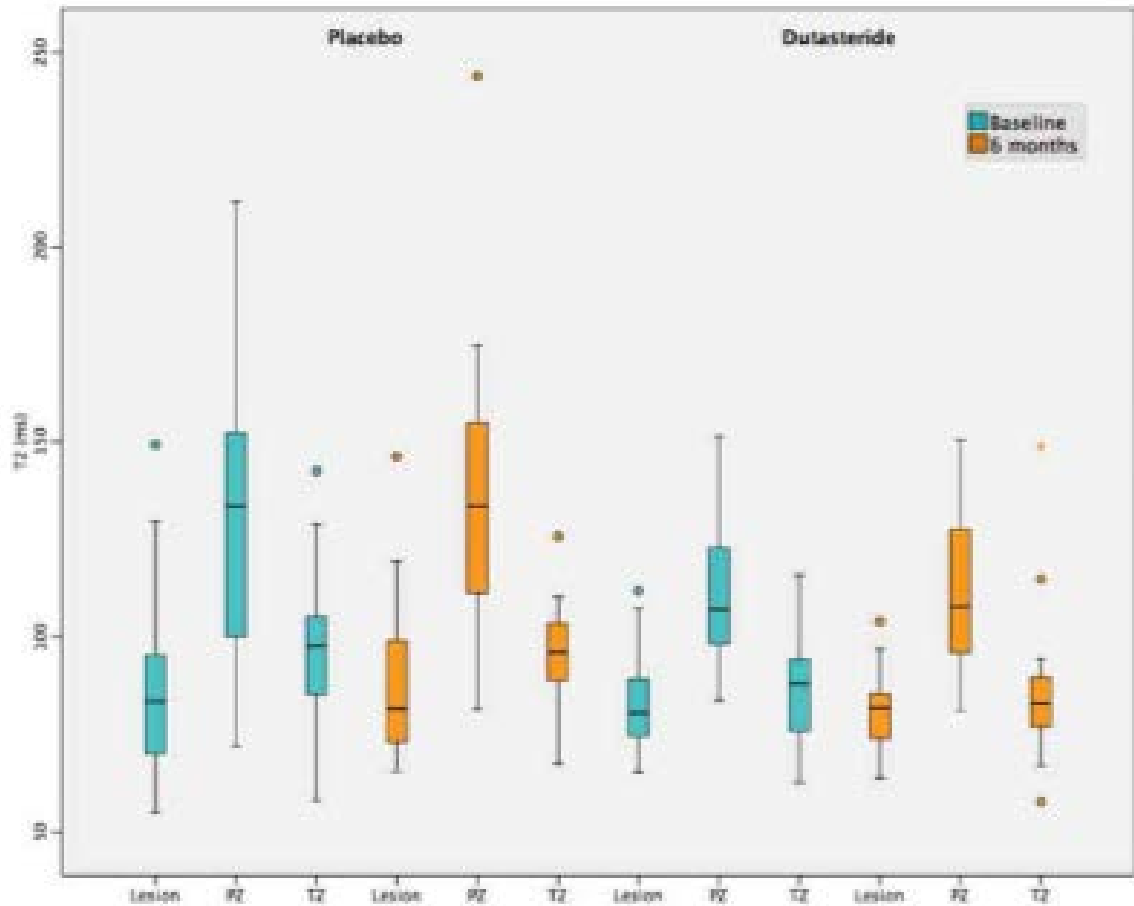


Figure 2

Box and whisker plots showing T2 values from the three ROIs for each arm, both at baseline and after 6 months. [Bottom of box = 25th percentile, center line = median, top of box = 75th percentile, whiskers = 10th and 90th percentiles, ° = outliers (between 1.5 and 3 interquartile ranges), * = extreme outliers (more than 3 three interquartile ranges)]. PZ: peripheral zone; TZ: transition zone

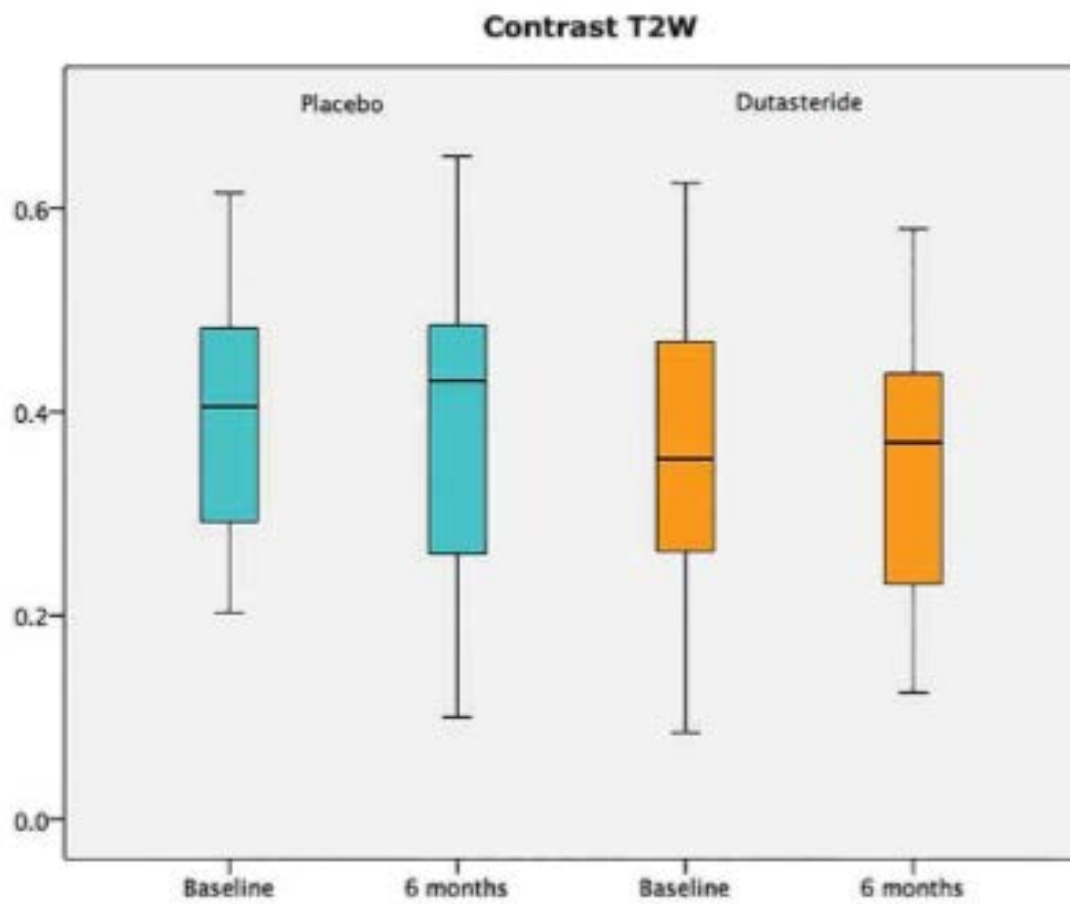


Figure 3
Box and whisker plots showing T2-weighted contrast values for each arm, both at baseline and after 6 months. [Bottom of box = 25th percentile, center line = median, top of box = 75th percentile, whiskers = 10th and 90th percentiles].

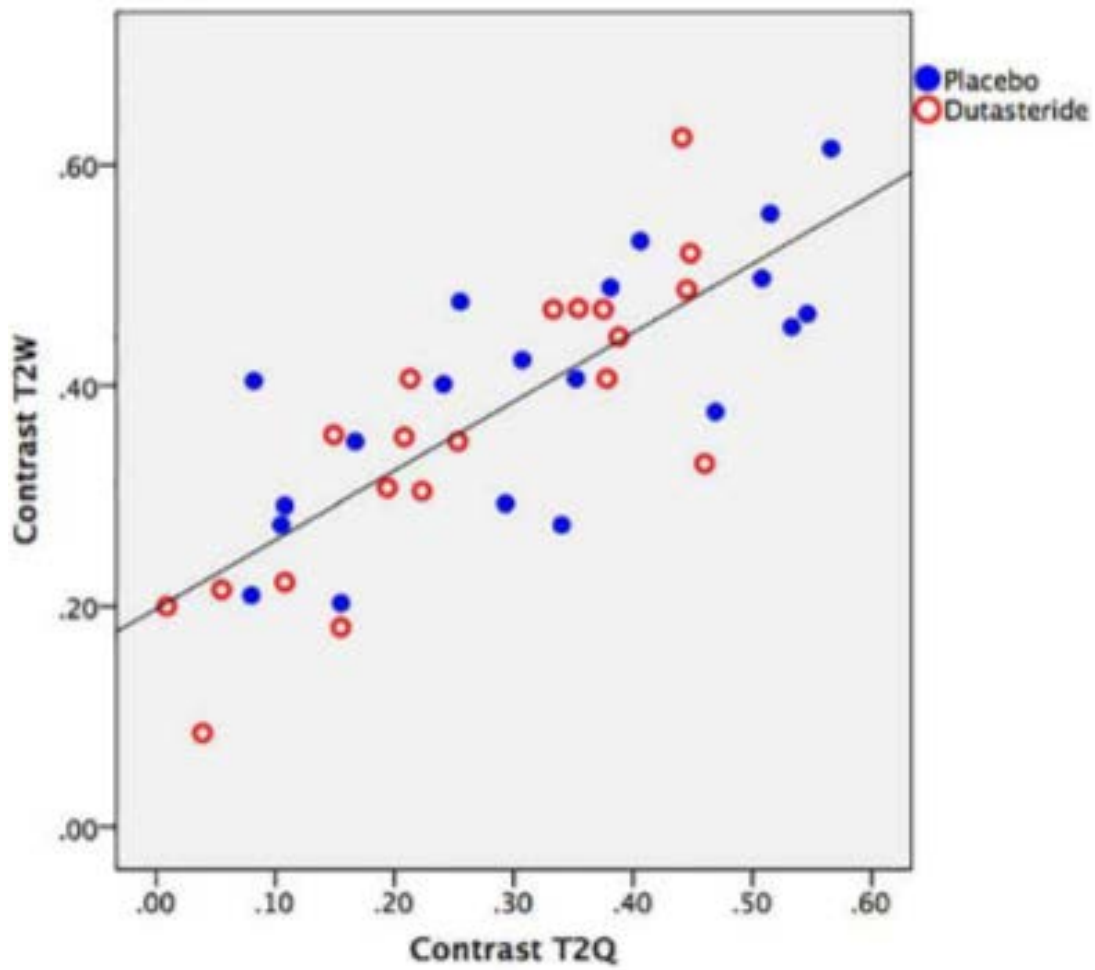


Figure 4
Scatter plot of contrast from high-resolution T2-weighted (T2W) and quantitative T2 (T2Q) imaging, showing a positive correlation ($r=0.786$; $p < 0.001$).

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