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The effect of dutasteride on MRI-defined prostate cancer lesions: MAPPED (Magnetic resonance imaging in Primary Prostate Cancer after Exposure to Dutasteride) - a randomized placebo-controlled, double-blind clinical trial.

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MAPPED: Effect of dutasteride on prostate cancer

Key words (1 to 5)

Prostate cancer; active surveillance; MRI; targeted biopsy; dutasteride

Abstract (249/250)

Purpose

Dutasteride is licensed for symptomatic benign prostatic hyperplasia, and has been associated with a lower progression rate in low-risk prostate cancer. We have evaluated the effect of dutasteride on prostate cancer volume as assessed by T2-weighted Magnetic Resonance Imaging (MRI).

Materials and methods

In this randomized, double-blind, placebo-controlled trial, men with biopsy-proven low-intermediate risk prostate cancer (up to Gleason 3+4 and PSA up to 15 ng/ml) who had an MR visible lesion of >/= 0.2ml on T2-weighted sequences were randomized to daily dutasteride 0.5mg or placebo for 6 months. Lesion volume was assessed at baseline, 3 and 6 months, with an image-guided biopsy to the lesion at study exit. The primary endpoint was percentage reduction in lesion volume over 6 months. This trial was registered with the European Clinical Trials register (EudraCT 2009-102405-18).

Results

Forty-two men were recruited between June 2010 and January 2012. In the dutasteride group, the average volumes at baseline and 6 months were 0.55ml and 0.38ml respectively, and the average percentage reduction was 36%. In the placebo group, the average volumes at baseline and 6 months were 0.65ml and 0.76ml respectively, and the average percentage reduction was -12%. The difference in percentage reductions between groups was 48% (95% CI 27.4-68.3%. p< 0.0001). The most common adverse event was deterioration in

erectile function (25% in men randomized to dutasteride, 16% in men randomized to placebo).

Conclusions

Dutasteride was associated with a significant reduction in prostate cancer volume on T2 weighted MRI images compared to placebo.

Introduction

Dutasteride is licensed for men with lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement[1]. When assessed in placebo controlled prostate cancer studies, dutasteride reduced the proportion of men diagnosed with prostate cancer by 22.8% over 4 years[2,] and was associated with lower rates of disease progression over 3 years in men on active surveillance[3]. Magnetic resonance imaging (MRI) of the prostate allows assessment of prostate cancer volume over time[4,5]. We report the use of MRI to assess the effect of dutasteride on prostate cancer volume in men on active surveillance.

Materials and methods

This investigator led study, sponsored by University College London, was approved by the Hammersmith & Queen Charlotte's & Chelsea Research Ethics Committee (UK) (09/H0707/84), the Medicines & Health Regulatory Agency and registered on the European Clinical Trials register (EudraCT 2009-102405-18).

Primary and secondary objectives

The primary objective was to evaluate the percentage reduction in tumour volume, assessed by T2-weighted MRI (T2W-MRI), following exposure to dutasteride 0.5 mg daily for six months, compared to placebo.

Secondary objectives included percentage reduction in tumour volume at 3 months, and on functional MR sequences, namely dynamic contrast enhanced (DCE) imaging and diffusion weighted imaging (DWI). Prostate cancer typically shows rapid wash-in and wash-out on DCE imaging due to the increased vascularity of its' highly permeable neo-vessels. DWI of prostate cancer typically shows restricted diffusion due to disorganized tissue structure, seen as high signal (bright areas) on high b-value imaging [6].

Patient population

The full study protocol has been published[7]. Eligible men met the UK NICE 2008 active surveillance criteria[8] (up to Gleason 3+4 disease, PSA up to 15 ng/ml), based on biopsy within the preceeding two years. In addition, men were required to have a $\geq$0.2 ml lesion on the standard of care T2-weighted MRI.

All eligible consented men had a study specific standardized multi-parametric 3 Tesla MRI. The images were reviewed by one study radiologist (CA, AK) to assess for the presence of a T2W lesion ≥0.2 ml. When confirmed, the man was randomized to placebo or dutasteride 0.5mg daily for 6 months. MRI was repeated at 3 and 6 months. Each MRI scan was reported separately by each of the study radiologists, who were blinded to treatment allocation.

An exit biopsy was offered to all men, with 10 standard cores and additional cores targeted to the MRI lesion using visual registration[9]. Men were not re-biopsied for discordant histology at baseline, in order to avoid post biopsy artefact on the study MRI scans. The concordance between baseline histology, lesion on MRI and exit histology was assessed.

PSA, renal and liver function and adverse events were assessed at baseline, 3 and 6 months.

Randomization and masking

Seventeen patients were required to complete each arm to detect a 20% reduction in tumor volume, assuming a common standard deviation of 20.5%, power of 80% and 5% statistical significance. To account for failure to complete, we aimed to recruit 21 men per arm. Men were individually randomized using block randomization with varying block sizes. The statistical team at University College London (UCL) supplied UCLH pharmacy with a randomization list to allocate study medication. The patients, study doctors, radiologists and

histopathologists were blind to treatment allocation. The radiologists and histopathologists were also blind to PSA results.

Outcomes and statistical analysis

The primary outcome was percentage reduction in tumor volume between baseline and 6 months on T2-weighted imaging. This was calculated using (baseline volume – 6-month volume)/baseline volume $\times$100%, where baseline volume and 6 months volume were the average of the measurements from the two raters. This percentage reduction was compared between the dutasteride and placebo groups using a t-test, with statistical significance set at a p-value of 0.05.

The secondary outcomes of percentage reduction in tumor volume as measured by DCE and DWI at six months, were compared between the dutasteride and placebo groups using a t-test. Each analysis was repeated for percentage reduction in tumour volume at three months.

Results

Fifty six men consented to the study after meeting eligibility criteria based on standard of care MRI, histology and blood tests. Seven men were excluded as the study PSA or renal function did not meet the eligibility criteria. Forty-nine men had a study MRI scan. Seven of these men were excluded on MRI criteria. Forty-two men were randomized between June 2010 and January 2012 (CONSORT[10] diagram, figure 1).

Twenty-one men were randomized to each group (Table 1). One man exited the dutasteride group prior to taking any study medication as he wished to conceive a child. Another man exited the placebo group to have active treatment in response to upgrading from Gleason 3 + 3 to Gleason 3 + 4 at UCLH pathology review. The primary endpoint was derived in 20 men within each group.

When the baseline scans were formally reported, it was noted that a total of 11/42 randomized men had lesions which measured as less than 0.2ml on T2-weighted images by one (n = 5) or both (n=6) study radiologists. All of these men had lesions volume of 0.2ml on other sequences (DCE and diffusion weighted imaging) by at least one of the radiologists. One of the men was deemed to have a visible lesion by one radiologist but not by the other. Eight men had a mean lesion volume of <0.2ml for the lesion on T2 weighted imaging.

These men were included in the analysis, as they had met the original inclusion criteria (one study radiologist assessing the MRI scan as showing a 0.2ml lesion on MRI). The agreement in volume assessment between the 2 raters was formally assessed.

Primary outcome

Change in total tumor volume on T2W-MRI over 6 months (Table 2)

In the dutasteride group, the average volumes at baseline and 6 months were 0.55ml and 0.38ml respectively, and the average percentage reduction was 36%. In the placebo group, the average volumes at baseline and 6 months were 0.65ml and 0.76ml respectively, and the average percentage reduction was -12% 9ie 12% growth). The difference in percentage reductions between groups was 48% (95% CI 27.4 – 68.3, p <0.0001) (figure 2).

Fifteen of twenty men (75%) randomized to dutasteride had a reduction in tumor volume; 5/20 (25%) had stability (defined as < 20% volume change). No man randomized to dutasteride had an increase in tumor volume. In contrast, 2 men (10%) in the placebo group had a reduction in volume, 13 (65%) were stable and 5 (25%) exhibited an increase of > 20% (figure 3).

Secondary outcomes

Change in tumor volume on functional imaging over 6 months (Table 2)

On DCE imaging, men randomized to dutasteride had a 42.3% reduction in tumor volume at 6 months compared to 4.2% reduction in men men randomized to placebo (38% mean difference between groups, 95% CI: 16.59- 59.64, p= 0.001).

On diffusion weighted imaging, men randomized to dutasteride had a 33% reduction in tumor volume at 6 months compared to a 7% increase in the men

randomized to placebo, conferring a mean difference between groups of 40% (95% CI 21.31 - 59.63, p = 0.0001).

Change in tumor volume over 3 months (T2-weighted imaging)

At 3 months there was a 34% reduction in tumor volume in the dutasteride group compared to 0.21% in the placebo group (mean difference between groups 34% (95% CI 21 – 47%, p = < 0.0001).

Change in prostate volume

The average percentage reduction in prostate volume at 6 months was 15% in the dutasteride group, compared to an increase of 3.3% in the placebo group (mean difference between groups 18.8% (95% CI 14.9 – 22.8%, p<0.0001).

Agreement between raters

The agreement between the raters was investigated using a Bland-Altman plot based on the percentage reduction in tumor volume calculated separately for each individual rater (supplementary figure 1).

In addition, the analysis of the primary outcome was repeated for each rater separately (supplementary table 1). One patient was deemed by one rater to have an increase in volume and the other rater to have a reduction in volume, and this had a significant effect on the results of rater 1. The table shows the analysis with and without this outlier. The results are consistent across the raters although rater 1 has recorded a larger volume reduction than rater 2.

Histological data (Supplementary table 2)

All men were offered an end of study biopsy, although 12 of 40 men declined. Histological upgrading to Gleason $\geq$ 4+ 3 was seen in 3/15 (20%) in the dutasteride group, and in 6/13 (46%) in the placebo group.

Concordance of MRI lesions and histology (supplementary table 3)

Thirty seven men of forty men had histological confirmation of the MRI lesion at baseline or exit. The remaining three men had discordant baseline histology, of whom one had a negative exit biopsy (placebo group) and two declined the exit biopsy (one placebo, one dutasteride).

PSA changes (supplementary table 4)

In men on placebo, the direction of change of PSA mirrored the direction of change in tumour volume. All men on dutasteride showed a PSA reduction, with no clear correlation between the change in lesion volume and PSA.

Medication compliance

All men were compliant with medication according to the returned tablet count at the end of each 3 month prescription period.

Adverse events

No serious adverse events occurred, and no subject discontinued study medication due to adverse events. Deterioration of sexual function (at least a 4 point reduction in IIEF-15[11]) occurred in 8 of 40 men (5/20 (25%) on dutasteride and 3/19 (16%) on placebo.

Discussion

Dutasteride 0.5mg daily was associated with an average reduction in prostate cancer volume of 36%, compared to an average increase of 12% in men on placebo, as assessed by T2W-MRI over six months.

This volume change was associated with less histological upgrading at targeted biopsy on study exit when randomized to dutasteride than to placebo (20% versus 46%). However, the lack of targeted biopsies at baseline to match to targeted exit biopsies and the small sample size limit the ability to definitively ascribe this to the effect of dutasteride. The rate of upgrading in the placebo group was high compared to that seen in men undergoing scheduled repeat standard 10-12 core systematic biopsy on active surveillance protocols[12]. However, this was expected due to the use of image-guided targeting as well as standard biopsy exit, compared to standard biopsy alone at entry, in the majority[13].

In 3 of 40 men there was a lack of concordance between biopsy and entry histology, not resolved on targeted biopsy at exit, which may represent a false positive MRI lesion, although 2 of the men declined the exit biopsy, and so this could not be confirmed.

There have been concerns that dutasteride may act selectively on low grade tumors, and may be associated with a greater likelihood of developing high-grade cancers[14], although radical prostatectomy data from randomized studies have not confirmed this[15].

In this study, two men randomized to dutasteride had 1mm and 2mm respectively of Gleason 4 + 4 on targeted biopsy at exit, with an overall Gleason grade of 3 + 4. At entry, the first had 9mm Gleason 3 + 3 on standard transrectal biopsy, with a lesion volume of 0.97ml, which reduced to 0.64ml at 6 months. The second had 4mm 3+ 4 on targeted biopsy at entry, with a lesion volume of 0.20ml, which reduced to 0.13ml at 6 months. This grade increase on targeted biopsy at exit would be compatible with the grade shift seen with a targeted biopsy approach[16].

Dutasteride-associated reduction in prostate cancer volume was seen at 3 months, with marginal additional reduction by 6 months, with a similar timescale to prostate volume reduction in LUTS studies. We noted greater proportional reduction in tumor volume compared to whole prostate volume which suggests that prostate cancer may be more sensitive to androgen depletion than non-cancerous prostate tissue.

The functional MRI sequences (DCE and DWI) assess perfusion and cell density, respectively. The percentage volume reduction in functional sequences was similar to that on T2Wi, although DWI tumor volumes were lower than on other sequences.

The adverse event profile was compatible with the known side effects of dutasteride, with significantly more men taking dutasteride (25% vs 16%) showing deterioration in sexual function.

The study is limited in both its sample size and duration. The 20% threshold for a reduction in tumor volume change was chosen, as it was the least change that might be considered both clinically meaningful and assessable by our independent observers. Sufficient men were recruited to achieve a power of 80% to detect a 20% volume change. A six-month interval of assessment is common in many active surveillance protocols[12], and is known to show response to dutasteride in studies of men with LUTS. The fact that a study of this size and duration could meet its primary endpoint is promising for future exploratory studies of this type.

Another limitation of the study relates to the external validity of the study population. The eligibility criteria consisted of the UK NICE 2008 criteria for active surveillance in men with low or intermediate risk disease (Gleason sum 7 or less, PSA $\leq$ 15ng/ml), clinical T2b disease). Of note, these criteria do not include any estimation of burden of disease such as the number of cores positive, maximum cancer core length or percentage cancer core involvement. In addition to the UK NICE criteria, men were required to have a lesion visible on T2W-MRI.

Men with lesions seen exclusively on functional imaging were excluded. We do not know whether radiological phenotype predicts prognosis or responsiveness, although men with no visible lesion on MRI are at lower risk of progression than men with a visible lesion[17].

We assessed for an imbalance of tumor size in each group which might lead to a spurious result, if larger tumors are assumed to have a greater growth rate.

Four men had tumor volumes >1 ml, 3 of whom were randomized to placebo. We repeated the analysis with these men removed and found very similar results. In addition, a formal analysis that adjusted for baseline volume was performed with little change in the outcome.

Our findings may have important clinical implications. First, if MRI reliably detects prostate cancer volume change then it could be useful for reassessment during surveillance[18]. Further work is needed to determine the imaging parameters (rate of change or an absolute threshold) at which transition to active treatment should be initiated, as recommended in the recent PRECISE guidelines[19]

Second, this novel design might be useful in assessing well tolerated agents that might modify the natural history of prostate cancer (e.g. aspirin, vitamin D, and dietary modifications including cruciferous vegetables[20-22]). To date, large and expensive epidemiological studies of long duration [20] using repeat random biopsies in men on active surveillance [21] have been used. Our novel study design could allow initial screening of potential agents for further study.

Conclusions

Dutasteride is associated with a reduction in prostate cancer volume as assessed by T2W-MRI in men with biopsy proven low or intermediate risk prostate cancer suitable for active surveillance, over a six-month period. This novel imaged based study design may be of use in assessing response to other well tolerated interventions in men on active surveillance.

2499/2500 words

Disclosures

The study was investigator-led and sponsored by University College London. The study was supported financially by GSK who also provided supplies of both drug and placebo. GSK had no input into the design, conduct and analysis of the study. The manuscript has been reviewed by GSK but final editorial control rests with the principal investigator (ME), who serves as guarantor of the study.

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Figure 1 CONSORT diagram showing men in study

Figure 2 The percentage change in total tumor volume for all 40 patients between baseline and six months as measured on T2-weighted imaging

Figure 3A: A 68 year-old man with a lesion in the left peripheral zone (arrow). The lesion is seen as low signal on T2-weighted imaging at baseline (A), and to have reduced in size at 3 months (B) and further at 6 months (C) after 6 months of daily dutasteride 0.5mg.

On diffusion weighted imaging, the baseline scan (D) shows high signal lesion of smaller volume than the T2-weighted lesion. At 3 months (E) and 6 months (F) this has decreased in size, although to a lesser extent than the reduction evident on the T2-weighted and diffusion weighted imaging.

Dynamic contrast enhanced images at baseline (G) show an enhancing lesion in the left peripheral zone. This reduces in volume at 3 moths (H) and 6 months (I).

Figure 3B: A 71 year-old man from the placebo group with a right peripheral zone lesion at baseline on T2-weighted imaging (A). This is stable at 3 months (B) and 6 months (C).

The lesion is seen as high signal on diffusion weighted imaging at baseline (D), and stable at 3 months (E) and 6 months (F).

The lesion shows enhancement on dynamic contrast enhanced images at baseline (G), and whilst less conspicuous at 3 months (H) these are stable at 6 months (I).

Figure S1

Bland Altman plot showing the relationship between the percentage reduction in tumor volume between raters.

Table 1: Baseline characteristics in each group. Continuous variables summarized as mean (sd, range) and categorical variables summarized as n (%).

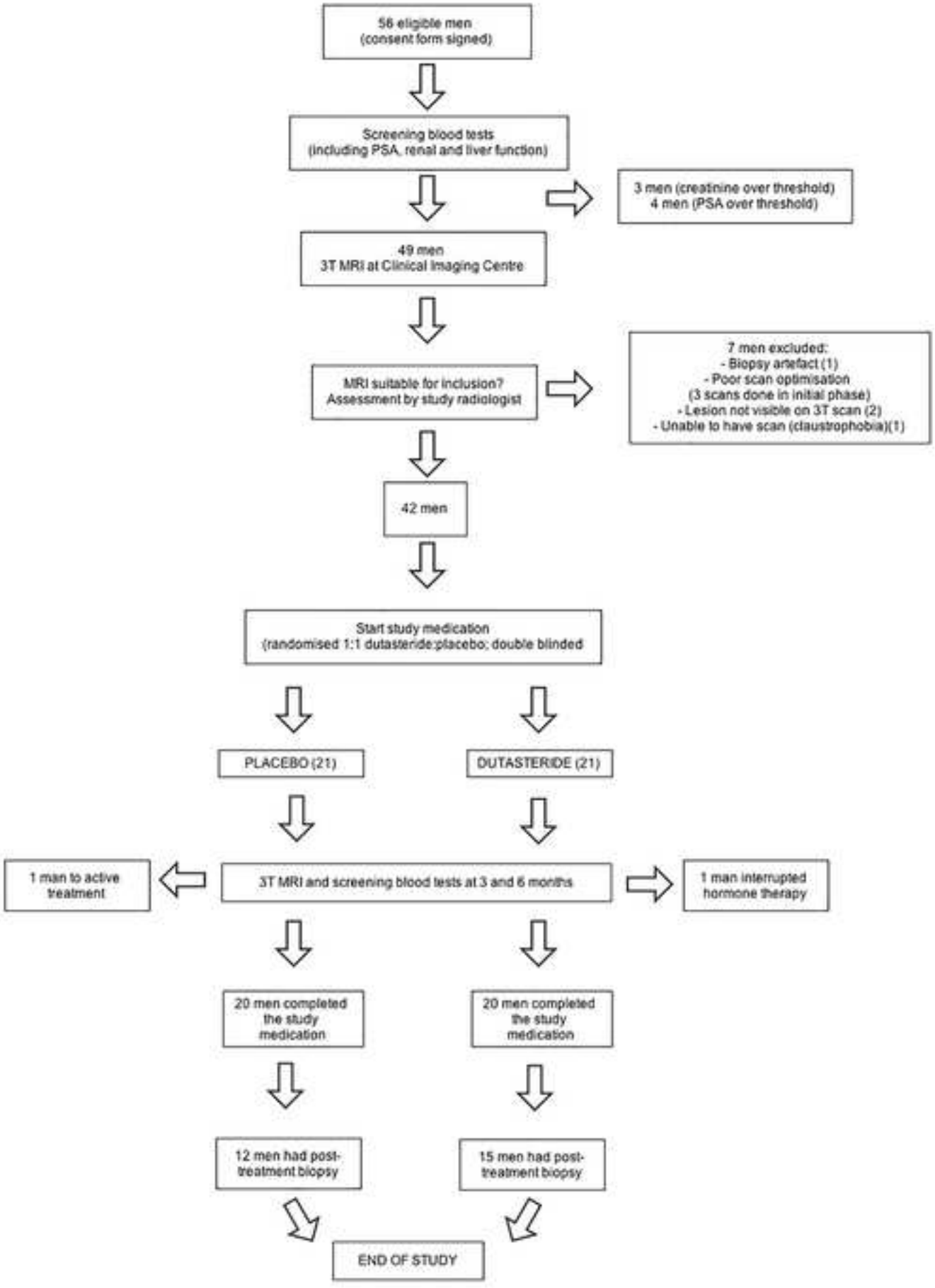
	Dutasteride (n = 21)	Placebo (n = 21)
Age (yrs)	63. 9 (7.3, 49.0 to 79.2)	64.2 (7.5, 39.5 to 76.0)
Total PSA (ng/ml)	6.94 (3.0, 1.8 to 13.4)	6.01 (2.3, 1.3 to 9.7)
Prostate volume (ml)	47.02 (20.7, 20.7 to 98.8)	52.97 (22.1, 16.7 to 104.3)
PSA density (ng/ml/ml)	0.16 (0.06, 0.07 to 0.28)	0.12 (0.05, 0.05 to 0.23)
Targeted transrectal biopsy	3 (14.3)	4 (19.1)
Targeted template biopsy	3 (14.3)	3 (14.3)
Template guided transperineal biopsy	5 (23.8)	2 (9.52)
Transrectal biopsy	10 (47.6)	12 (57.1)
UCL biopsy	12 (57.1)	14 (66.7)
Biopsy at local referral center	9 (42.9)	7 (33.3)
Maximum Gleason 3 + 3	11 (52.4)	12 (57.1)
Maximum Gleason 3 + 4	10 (47.6)	9 (42.9)
Total no. of cores (median, range)	12 (8 to 95)	14 (8 to 64)

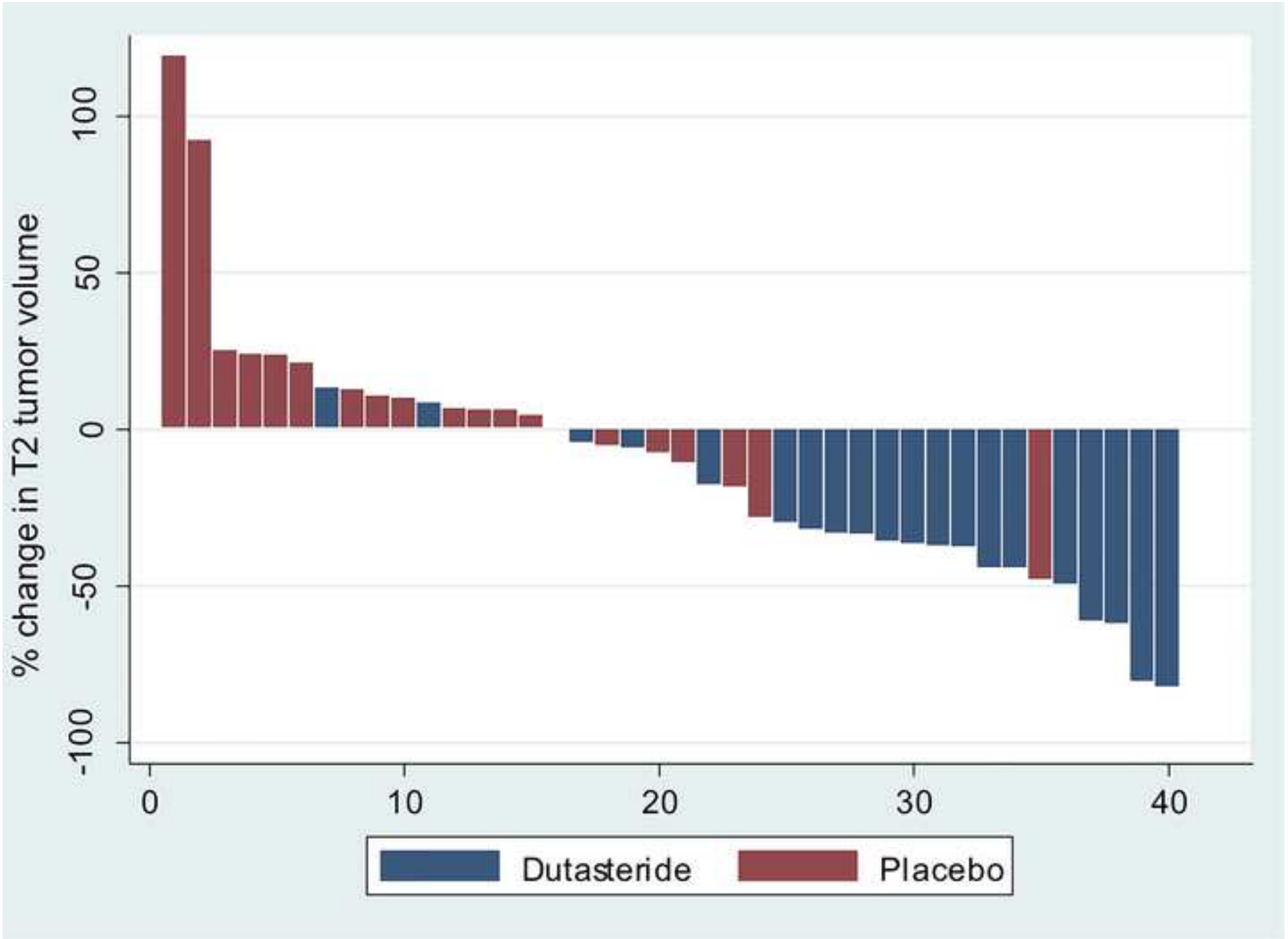
Total number of positive cores	4.62 (2.8, 1 to 12)	4.95 (3.6, 1 to 12)
Percentage of positive cores	29.5 (21.9, 2 to 75)	29.2 (18.4, 5 to 75)
Maximum cancer core length (mm)	5.05 (2.3, 1 to 9)	4.57 (2.2, 1 to 9)
Tumor volume (ml) : T2WI	0.55 (0.49, 0.12 to 0.36)	0.65 (0.8, 0 to 3.27)
Tumor volume (ml) : DCE	0.58 (0.5, 0.06 to 2.34)	0.67 (0.8, 0.09 to 3.72)
Tumor volume (ml) :DWI	0.48 (0.6, 0.07 to 2.70)	0.42 (0.3, 0 to 1.18)
Total index tumor volume (ml) on		
T2 weighted imaging	0.50 (0.34, 0.12 to 1.44)	0.59 (0.6, 0 to 2.21)
DCE	0.52 (0.3, 0.06 to 1.41)	0.63 (0.7, 0.09 to 3.25)
Diffusion	0.42 (0.3, 0.07 to 1.59)	0.37 (0.3, 0 to 1.18)

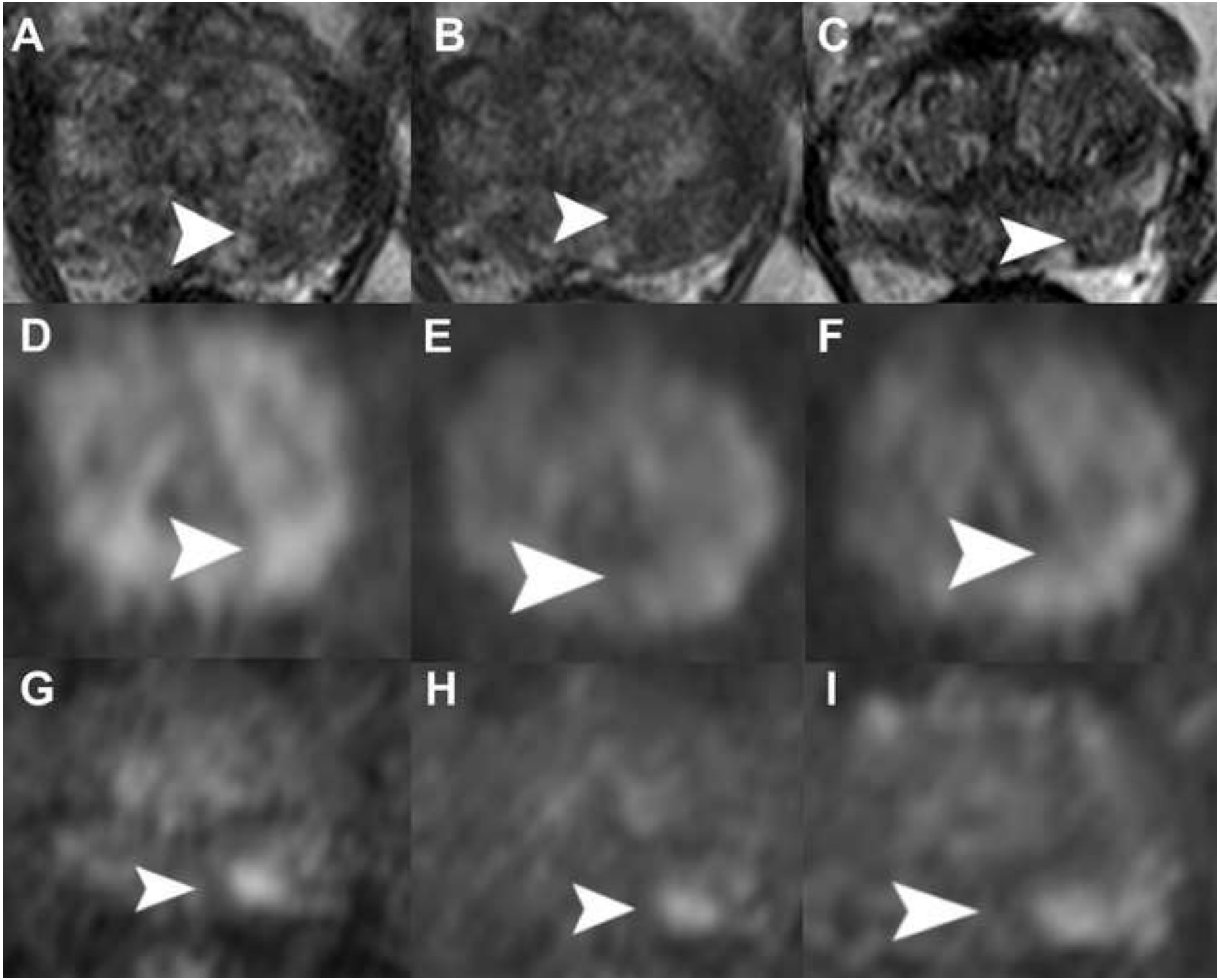
Table 2: Change in total tumor volume between baseline and six months on T2-weighted imaging, dynamic contrast enhancement and diffusion weighted imaging

	Dutasteride (20) Mean (sd, range)	Placebo (20) Mean (sd, range)	Mean difference (95% CI) p-value
Total tumor volume (ml) at baseline (T2)	0.55 (0.5, 0.12 to 2.36)	0.65 (0.8, 0 to 3.27)	
Total tumor volume (ml) at 6 months (T2)	0.38 (0.4, 0.02 to 1.59)	0.76 (0.9, 0.09 to 3.96)	
% change in total tumor volume from 0-6 months (T2)	-35.73 (25.7, -82.61 to 13.21)	12.15 (37.2, -48.48 to 119.16)	47.88 (27.42, 68.34), p <0.0001
Total tumor volume at baseline (gadolinium/DCE)	0.58 (0.5, 0.055 to 2.342)	0.67 (0.8, 0.09 to 3.72)	
Total tumor volume at 6 months (gadolinium/DCE)	0.35 (0.3, 0.025 to 1.328)	0.66 (0.8, 0.045 to 3.68)	
% change in total tumor volume from 0-6 months (gadolinium/DCE)	-42.32 (25.6, -88.37 to 3.76)	-4.20 (38.5, -64.41 to 102.22)	38.11 (16.59, 59.64) p=0.0010
Total tumor volume at baseline (diffusion)	0.48 (0.6, 0.07 to 2.695)	0.42(0.3, 0 to 1.18)	
Total tumor volume at 6 months (diffusion)	0.30 (0.3, 0.05 to 1.284)	0.45 (0.4, 0 to 1.165)	
% change in total tumor	-33.46 (21.8,	7.01 (35.9,	40.47

volume from 0-6 months (diffusion)	-70.49 to 20.24)	-24.73 to 95.49)	(21.31, 59.63)p=0.0001


56 eligible men
(consent form signed)
Screening blood tests
(including PSA, renal and liver function)
3 men (creatnine over threshold)
4 men (PSA over threshold)
49 men
3T MRI at Clinical Imaging Centre
MRI suitable for inclusion?
Assessment by study radiologist
7 men excluded:
- Biopsy artefact (1)
- Poor scan optimisation
(3 scans done in initial phase)
- Lesion not visible on 3T scan (2)
- Unable to have scan (claustrophobia)(1)
42 men
Start study medication
(randomised 1:1 dutasteride:placebo; double blinded
PLACEBO (21)
DUTASTERIDE (21)
1 man to active treatment
3T MRI and screening blood tests at 3 and 6 months
1 man interrupted hormone therapy
20 men completed the study medication
20 men completed the study medication
12 men had post-treatment biopsy
15 men had post-treatment biopsy
END OF STUDY


% change in T2 tumor volume
100
50
0
-50
-100
0
10
20
30
40
Dutasteride
Placebo


A
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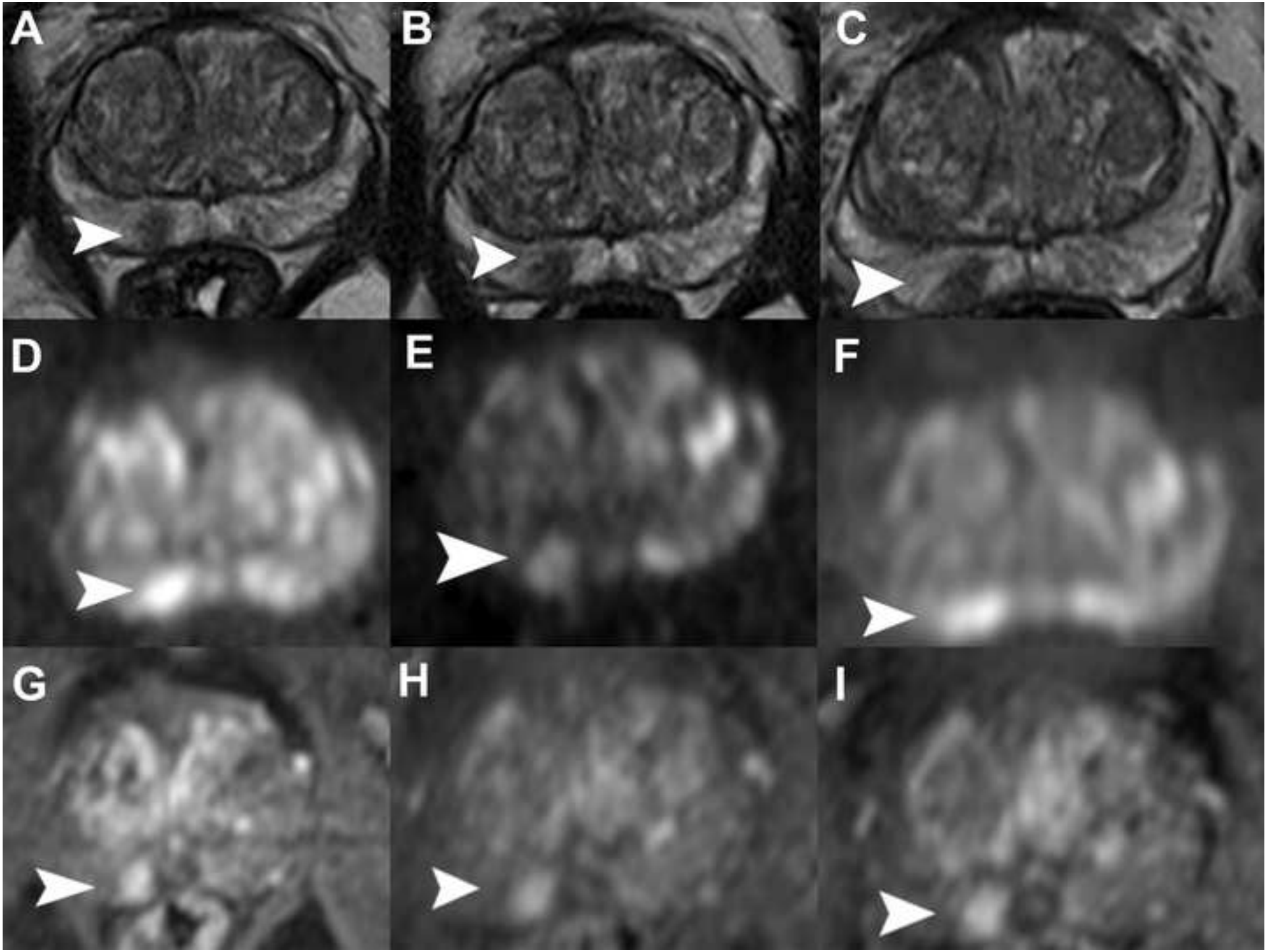
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List of abbreviations

DHT = dihydrotestosterone

LUTS = lower urinary tract symptoms

MRI = magnetic resonance imaging

T2W-MRI = T2-weighted MRI

DCE = dynamic contrast enhanced

DWI = diffusion weighted imaging

UCLH = University College London Hospital

UCL = University College London

BPH = benign prostatic hyperplasia

Supplementary table 1 : Agreement between radiological raters

Analysis Subset	**Dutasteride (n = 20) Mean (SD)**	**Placebo (n = 20) Mean (SD)**	**Mean difference (95% CI) P-value**
Rater 1: Percentage reduction in total tumour volume from 0-6 months (T2)	41.4 (29.2)	-27.3 (121.9)	68.7 11.9 to 125.4 P = 0.019
(as above with outlier omitted)	41.4 (29.2)	-0.7 (26.8)	42.0 23.8 to 60.2 P < 0.0001
Rater 2: Percentage reduction in total tumour volume from 0-6 months (T2)	24.0 (31.9)	-1.3 (31.5)	25.2 (5.0 to 45.5) P = 0.016
Both (average): Percentage reduction in total tumour volume from 0-6 months (T2)	35.7 (25.7)	-5.8 (27.6)	41.5 (24.5 to 58.6)

Supplementary table 2: Maximum cancer core length and maximum Gleason score at exit

a) Men in the dutasteride group (n=15)

Maximum core length	Maximum Gleason score					Total
	3+3	3+4	4+3	4+4	Too small	
2	1	1	0	0	0	**2**
3	0	1	1	1	0	**3**
4	0	0	0	1	0	**1**
5	0	1	0	0	0	**1**
6	1	1	0	0	0	**2**
8	0	4	0	0	0	**4**
9	1	0	0	0	0	**1**
10	0	1	0	0	0	**1**
Total	**3**	**9**	**1**	**2**	**0**	**15**

b) Men in the placebo group (n=13)

Maximum core length	Maximum Gleason score					Total
	3+3	3+4	4+3	4+4	Too small	
1	0	0	1	0	1	**2**
4	0	0	1	0	0	**1**
5	0	1	1	0	0	**2**
7	0	2	0	0	0	**2**
8	0	1	2	0	0	**3**
9	0	1	1	0	0	**2**
11	0	1	0	0	0	**1**
Total	**0**	**6**	**6**	**0**	**1**	**13**

Supplementary table 3: Concordance of histology and MRI findings

Randomization number	Dutasteride (D) or Placebo (P)	Initial histology	Location of lesion on mpMRI	Histology at exit	Concordance
R001	P	1 mm 3+3 left anterior horn 1 mm 3+3 left lateral mid, left para mid, left para base	Right base-mid	No report	Not concordant at baseline; no exit histology. Post study biopsy showed focal HGPIN only.
R002	D	4 mm 3+3 left lateral base 5 mm 3+3 left para base 1 mm 3+3 left para base 3 mm 3+3 left para mid	Left base	*Targeted bx* – left base 2 mm 3+4	Concordant at baseline and exit
R003	P	1 mm 3+3 right apex	Right apex	*Targeted bx* – right apex 4 mm 4+3	Concordant at baseline and exit
R004	D	9 mm, 3mm, 2mm 3+3 left	Left mid and apex	*Targeted bx* – left lateral mid 2 mm 3+4	Concordant at baseline and exit
R005	D	1 mm 3+3 left para-anterior apex 1 mm 3+3 right para-anterior apex 2 mm 3+3 right para-anterior apex 1 mm 3+3 left medial anterior apex	Right mid-base and apex	Right para-mid 1 mm 3+4 Right lateral mid 3 mm 3+3 Right apex 1 mm 3+3 Right lateral base 1 mm 3+3	Concordant at baseline and exit

		1 mm 3+3 left medial anterior apex 4 mm 3+3 left medial anterior apex 1 mm 3+3 left lateral 1 mm 3+3 left lateral 1 mm 3+3 right para-posterior base 3 mm 3+3 left medial posterior apex 1 mm 3+3 right medial posterior base			
R006	P	1 mm 3+3 right post medial apex 3 mm 3+3 post medial apex 3 mm 3+3 right posterior para-apex	Right base	Right para-base 11 mm 3+4 Right para-mid 1 mm 4+3	Concordant at baseline and exit
R007	P	4 mm 3+4 right base pz 5 mm 3+3 right base pz 1 mm 3+3 right para-base 5 mm 3+3 left mid pz 5 mm 3+4 left apex pz 2 mm 3+3 apex pz 5 mm 3+3 para-apex	Left base-mid-apex	*Targeted bx* – left 2 mm 3+4	Concordant at baseline and exit
R008	D	4mm, 4mm, 4 mm 3+3 left 8, 6, 5, 2 mm 3+4 right	Right mid Left mid-base	*Targeted bx* – right lateral mid 4 mm 3+3	Concordant baseline and exit
R009	D	8mm, 1 mm 3+3 right	Right mid	*Targeted bx* –	Concordant at

				right mid 4 mm 3+4	baseline and exit
R010	P	2 mm 3+3 left para-anterior apex 3 mm 3+3 left para-anterior base 2 mm 3+3 left para-anterior apex 3 mm 3+3 right para-anterior base 8 mm 3+3 right para-anterior base 3 mm 3+3 right medial-anterior base 4 mm 3+3 right medial-anterior base 6 mm 3+3 right medial-anterior base 1 mm 3+3 right medial-anterior apex 1 mm 3+3 right medial-anterior apex 2 mm 3+3 right medial-anterior apex	Left mid-base Right mid-base	No tumor at biopsy exit	Concordant at baseline; negative at exit. Went on to have focal ablation based on initial template biopsy.
R011	P	4mm, 2mm, 1 mm 3+4 right	Right mid-base	*Targeted bx* – right mid-base 8 mm 3+4	Concordant at baseline and exit
R012	P	3 mm, 3mm 3+4 right NK 1 mm 3+3 left	Right mid-apex	*Targeted bx* – right mid-lateral 8	Concordant at baseline and exit

				mm, 6mm 3+4	
R013	D	1 mm, 0.5mm 3+3 right	Mid-base (anterior)	*Targeted bx* – anterior 2 mm 3+4	Concordant at baseline and exit
R014	D	1 mm 3+3 left lateral base 2 mm 3+3 left central lateral 1 mm 3+3 right base lateral 1 mm 3+3 right central lateral 2 mm 3+3 right apex	Right mid-base	*Targeted bx* – right mid – 6mm, 3 mm 3+4	Concordant at baseline and exit
R015	P	2 mm 3+3 left anterior	Right mid	No tumor at biopsy exit	Discordant at entry; negative biopsy at exit. Remains on active surveillance.
R016	D	1 mm 3+3 right lateral 1 mm 3+3 left para-anterior apex	Right apical	*Targeted bx* – right apex-mid 3 mm 3+4	Concordant at biopsy and exit
R017	D	5mm,2mm,1mm, 1mm, 1 mm 3+4 right apex 6mm,4mm, 2 mm 3+4 right base 4 mm 3+3 left apex 3 mm 3+4 left base 1 mm 3+3 left base	Right mid-lateral Left mid-lateral	Right mid-lateral – 5 mm 3+4 Left mid-lateral – 2 mm 3+3	Concordant at baseline and exit
R018	D	3mm, 2mm,1 mm 3+4 right	Right mid-base	*Targeted bx* –	Concordant at

		3 mm 3+4 left	lateral Right mid- base anterior	right mid 6 mm 3+4 *Targeted bx* – right base ant. 3 mm 3+3	baseline and exit
R019	D	5mm, 4mm, 3mm, 2mm, 2 mm 3+4 right 1 mm, 1mm 3+3 left	Left mid-apex	Left para-posterior apex - 4 mm 3+4 Left medial posterior base – 8 mm 3+4	Concordant at baseline and exit
R020	P	2 mm 3+3 right 5mm, 3mm, 1mm, 1mm 1 mm 3+3 left	Left mid	*Targeted bx* – left mid-apex 9mm, 8 mm, 1.5mm 3+3	Concordant at baseline and exit
R021	P	5mm,1mm, 1 mm 3+4 left 1 mm 3+4 right	Left mid	*Targeted bx* – left mid 8mm, 6mm, 4mm, 4mm, 3mm 3+4	Concordant at baseline and exit
R022	P	1 mm 3+3 NK 8 mm 3+4 NK 3 mm 3+4 right lateral base 1 mm 3+3 left para-apex 1 mm 3+3 left para-base 4 mm 3+3 right para-apex 2 mm 3+4 right para-base 2 mm 3+3 right lateral apex	Right base	No biopsy at exit	Concordant at baseline ; no exit biopsy. No further biopsies.

R023	D	6 mm 3+4 right lateral mid 4 mm 3+3 right para-mid 1 mm 3+3 right para-apex 5 mm 3+4 right mid-peripheral zone	Right mid-base	*Targeted bx* – right mid-base 8, 2mm 3+4	Concordant at baseline and exit
R024	P	4mm,3mm,1 mm 3+3 left lateral base	Left mid-base	No tumor at biopsy exit	Concordant at baseline; no biopsy at exit
R025	D	4 mm, 3mm 3+4 left lateral base	Left base	*Targeted bx* – left base 2 mm 3+3	Concordant at baseline and exit
R026	P	2 mm 3+3 mid-apex 6 mm 3+3 right medial anterior apex 1 mm 3+3 right mid anterior base 5 mm 3+3 right mid anterior base 1 mm 3+3 right medial posterior apex 1 mm 3+3 right medial posterior base 1 mm 3+3 right 3 mm 3+3 right 1 mm 3+3 targeted right anterior horn 1 mm 3+3 targeted right anterior horn 2 mm 3+3 targeted right	Right mid-base	No biopsy at exit	Concordant at baseline; no biopsy at exit

		anterior horn 5 mm 3+3 targeted right anterior horn			
R027	D	3mm, 1 mm 3+3 right 5mm, 4 mm 3+3 left	Right base	*Targeted bx* – right base 6mm, 5 mm 3+3	Concordant at biopsy and exit
R028	P	1 mm,1mm,1mm 3+3 6mm, 3mm, 3mm, 1mm, 1 mm 3+3 right	Right mid-base	No biopsy at exit	Concordant at baseline; no biopsy at exit
R029	P	1 mm 3+3 right base medial 1 mm 3+4 right lateral base	Right mid-base Left mid-base	No biopsy at exit	Concordant at baseline; no biopsy at exit
R030	D	6 mm 3+4 right lateral base 6 mm 3+4 right mid-lateral base	Right mid	*Targeted bx* – right mid 7 mm, 7mm 3+4	Concordant at biopsy and exit
R031	D	3.5 mm 3+3 right NK 6 mm 3+3 right NK 0.5 mm 3+3 right NK	Left mid	No biopsy at exit	Discordant at baseline; no biopsy at exit.
R032	D	3 mm 3+3 mid anterior apex l 2 mm 3+3 para-posterior apex l 1 mm 3+3 para-posterior apex l 1 mm 3+3 right para-posterior apex	Left mid	*Targeted bx* – left mid 4 mm, 3mm, 1mm 3+4	Concordant at exit

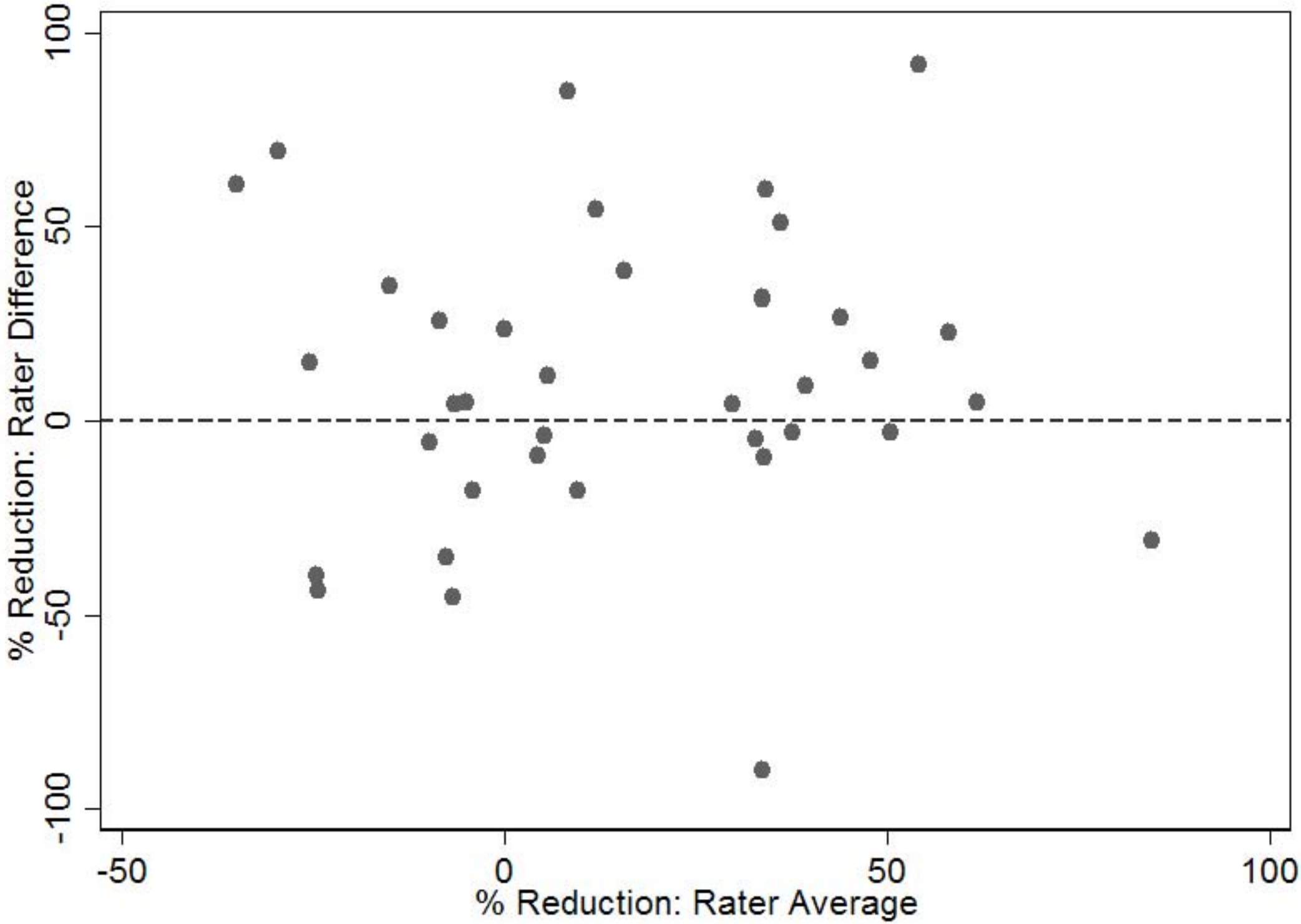
		4 mm 3+4 l			
R033	P	1 mm 3+3 right lateral apex 2 mm 3+3 right mid 7 mm 3+3 right apex	Right mid-base Mid apex	Mid-base: 4 mm 3+3	Concordant at baseline and exit
R034	D	1 mm 3+3 left para-anterior apex 4 mm 3+4 mid-apex 1 mm 3+3 left medial anterior apex 1 mm 3+3 left medial anterior base 1 mm 3+3 left medial anterior apex 1 mm 3+3 right medial anterior apex 1 mm 3+4 left lateral 1 mm 3+4 right medial posterior apex 6 mm 3+3 right targeted	Left mid-base	No biopsy at exit	Concordant at baseline; no biopsy at exit. Exited study before taking medication as wanted to conceive.
R035	P	1 mm 3+3 left NK 1 mm 3+3 left NK 1 mm 3+3 right NK 1 mm 3+3 right NK	Right mid-apex	*Targeted bx* – right posterior 5 mm 4+3 *Targeted bx* – right posterior 1 mm 4+3	Concordant at baseline and exit
R036	P	1.5 mm 3+3 mid-base 4 mm 3+3 right para-posterior apex	Right mid	No biopsy at exit	Concordant at baseline. Exited study before taking

		5 mm 3+3 right para-posterior base 5 mm 3+3 right para-posterior base 1 mm 3+3 right para-posterior base 12 mm 3+3 right medial-posterior apex 3 mm 3+3 right medial-posterior base 1 mm 3+3 right apex 4 mm 3+3 right apex 6 mm 3+3 right apex			study medication o have radical prostatectomy due to upgrade of external histology on UCLH pathology. Radical prostatectomy showed Gleason 3 + 4 (maximal 4 + 3).
R037	P	4mm, 3mm, 3mm, 2 mm 3+4 right	Right mid Left mid	*Targeted bx* – left 5 mm 3+4 *Targeted bx* – right 4 mm 3+4	Concordant at baseline and exit
R038	P	8mm, 1 mm 3+4 right anterior 3 mm 3+3 right medial	Right mid-apex	*Targeted bx* – right anterior 9mm, 7mm, 3.5 mm 3+4	Concordant at baseline and exit
R039	D	3 mm 3+3 left lateral 8 mm 3+3 right lateral 5 mm 3+3 right lateral 4 mm 3+3 right lateral 1 mm 3+3 left medial posterior apex	Right mid	No biopsy at exit	Concordant at baseline, no biopsy at exit
R040	D	2 mm 3+3 right para-	Right mid-base	No biopsy at exit	Concordant at

		anterior apex 1 mm 3+3 right mid-anterior apex 6 mm 3+3 right medial posterior apex 3 mm 3+3 right medial posterior base 3 mm 3+4 right peripheral zone			baseline, no biopsy at exit
R041	D	0.3 mm 3+3 left posterior 3 mm 3+3 left posterior 3 mm 3+3 left posterior 3 mm 3+3 left mid 1 mm 3+3 left mid 1 mm 3+3 left anterior 0.3 mm 3+3 left anterior	Left mid	No biopsy at exit	Concordant at baseline, no biopsy at exit
R042	P	1 mm 3+3 right lateral base 3 mm 3+4 right lateral mid 5 mm 3+3 right para mid 2 mm 3+3 right para apex 1 mm 3+3 left lateral mid 4 mm 3+4 left lateral apex 3 mm 3+4 left para mid 4 mm 3+4 left para apex 4 mm 3+4 left apex	Left apex	Left apex – 1 mm 3+3	Concordant at baseline and exit

Supplementary table 4 : PSA changes in man allocated to placebo and dutasteride

Treatment	Number of men in group	Change in Lesion Volume	Median change in absolute PSA at 6 months
Placebo	2	Significant reduction (≥ 20%)	- 0.72
Placebo	12	Stable lesion (20% reduction to increase of 20%)	+ 0.75
Placebo	6	Significant increase (> 20%)	+ 1.07
Dutasteride	15	Significant reduction (≥ 20%)	- 2.3
Dutasteride	5	Stable lesion (20% reduction to increase of 20%)	- 3.35
Dutasteride	0	Significant increase (> 20%)	n/a


% Reduction: Rater Difference
100
50
0
-50
-100
-50
0
50
100
% Reduction: Rater Average