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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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**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.**

*Caroline M Moore^{1,2}, Nicola L Robertson^{1,2}, Fatima Jichi³, Adebisi Damola^{1,2},
Gareth Ambler³, Francesco Giganti⁴, Ashley J Ridout^{1,2}, Simon RJ Bott⁵,
Mathias Winkler⁶, Hashim U Ahmed^{1,2}, Manjit Arya^{1,2}, Anita V Mitra⁷, Neil
McCartan², Alex Freeman⁸, Charles Jameson⁸, Ramiro Castro⁹, Giulio
Gambarota^{10,11}, Brandon J Whitcher^{12,13}, Clare Allen⁴, Alex Kirkham⁴, Mark
Emberton^{1,2}.*

¹Division of Surgery & Interventional Science, University College London, UK

²Department of Urology, University College London Hospitals NHS Foundation
Trust, London, UK

³ Biostatistics Group, University College London Hospitals/University College
London Research Support Centre, University College London, UK

⁴ Department of Radiology, University College London Hospital Trust, London,
UK

⁵Department of Urology, Frimley Park Hospital, Surrey, UK

⁶Department of Urology, Charing Cross Hospital, Imperial College NHS Trust,
London, UK

⁷ Department of Clinical Oncology, University College Hospital London, London,
UK

⁸Department of Pathology, University College London Hospital Trust, London, UK

⁹ GlaxoSmithKline Research and Development. Philadelphia. USA

¹⁰INSERM, U1099, Rennes, F-35000, France

¹¹Université de Rennes 1, LTSI, Rennes, F-35000, France

¹² Klarismo, London, UK

¹³ Department of Mathematics, Imperial College London, UK

Corresponding author:

Caroline M Moore

caroline.moore@ucl.ac.uk

Division of Surgical & Interventional Sciences

4th Floor, 74 Huntley Street

London, UK

WC1E 6AU

Running head (max 50 characters):

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 ≥ 0.2 ml 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.

1 Introduction

2 Dutasteride is licensed for men with lower urinary tract symptoms (LUTS)
3 associated with benign prostatic enlargement¹. When assessed in placebo
4 controlled prostate cancer studies, dutasteride reduced the proportion of men
5 diagnosed with prostate cancer by 22.8% over 4 years², and was associated
6 with lower rates of disease progression over 3 years in men on active
7 surveillance³. Magnetic resonance imaging (MRI) of the prostate allows
8 assessment of prostate cancer volume over time^{4,5}. We report the use of MRI to
9 assess the effect of dutasteride on prostate cancer volume in men on active
10 surveillance.

11

12

13

1 **Materials and methods**

2 This investigator led study, sponsored by University College London, was
3 approved by the Hammersmith & Queen Charlotte's & Chelsea Research Ethics
4 Committee (UK) (09/H0707/84), the Medicines & Health Regulatory Agency
5 and registered on the European Clinical Trials register (EudraCT 2009-102405-
6 18).

8 *Primary and secondary objectives*

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

12
13 Secondary objectives included percentage reduction in tumour volume at 3
14 months, and on functional MR sequences, namely dynamic contrast enhanced
15 (DCE) imaging and diffusion weighted imaging (DWI). Prostate cancer typically
16 shows rapid wash-in and wash-out on DCE imaging due to the increased
17 vascularity of its' highly permeable neo-vessels. DWI of prostate cancer typically
18 shows restricted diffusion due to disorganized tissue structure, seen as high
19 signal (bright areas) on high b-value imaging ⁶.

21 *Patient population*

22
23 The full study protocol has been published⁷. Eligible men met the UK NICE 2008
24 active surveillance criteria⁸ (up to Gleason 3+4 disease, PSA up to 15 ng/ml),
25 based on biopsy within the preceeding two years. In addition, men were
26 required to have a ≥ 0.2 ml lesion on the standard of care T2-weighted MRI.

1

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

8

9 An exit biopsy was offered to all men, with 10 standard cores and additional
10 cores targeted to the MRI lesion using visual registration⁹. Men were not re-
11 biopsied for discordant histology at baseline, in order to avoid post biopsy
12 artefact on the study MRI scans. The concordance between baseline histology,
13 lesion on MRI and exit histology was assessed.

14

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

17

18 *Randomization and masking*

19

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

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

3

4 *Outcomes and statistical analysis*

5 The primary outcome was percentage reduction in tumor volume between
6 baseline and 6 months on T2-weighted imaging. This was calculated using
7 $(\text{baseline volume} - 6\text{-month volume}) / \text{baseline volume} \times 100\%$, where baseline
8 volume and 6 months volume were the average of the measurements from the
9 two raters. This percentage reduction was compared between the dutasteride
10 and placebo groups using a t-test, with statistical significance set at a p-value of
11 0.05.

12

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

17

1 Results

2 Fifty six men consented to the study after meeting eligibility criteria based on
3 standard of care MRI, histology and blood tests. Seven men were excluded as
4 the study PSA or renal function did not meet the eligibility criteria. Forty-nine
5 men had a study MRI scan. Seven of these men were excluded on MRI criteria.
6 Forty-two men were randomized between June 2010 and January 2012
7 (CONSORT¹⁰ diagram, figure 1).

8

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

14

15 When the baseline scans were formally reported, it was noted that a total of
16 11/42 randomized men had lesions which measured as less than 0.2ml on T2-
17 weighted images by one (n = 5) or both (n=6) study radiologists. All of these
18 men had lesions volume of 0.2ml on other sequences (DCE and diffusion
19 weighted imaging) by at least one of the radiologists. One of the men was
20 deemed to have a visible lesion by one radiologist but not by the other. Eight
21 men had a mean lesion volume of <0.2ml for the lesion on T2 weighted imaging.

22

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

1

2 **Primary outcome**

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

4 In the dutasteride group, the average volumes at baseline and 6 months were
5 0.55ml and 0.38ml respectively, and the average percentage reduction was
6 36%. In the placebo group, the average volumes at baseline and 6 months were
7 0.65ml and 0.76ml respectively, and the average percentage reduction was -
8 12% 9ie 12% growth). The difference in percentage reductions between groups
9 was 48% (95% CI 27.4 – 68.3, $p < 0.0001$) (figure 2).

10

11 Fifteen of twenty men (75%) randomized to dutasteride had a reduction in tumor
12 volume; 5/20 (25%) had stability (defined as $< 20\%$ volume change). No man
13 randomized to dutasteride had an increase in tumor volume. In contrast, 2 men
14 (10%) in the placebo group had a reduction in volume, 13 (65%) were stable
15 and 5 (25%) exhibited an increase of $> 20\%$ (figure 3).

16

17 **Secondary outcomes**

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

19 On DCE imaging, men randomized to dutasteride had a 42.3% reduction in
20 tumor volume at 6 months compared to 4.2% reduction in men men randomized
21 to placebo (38% mean difference between groups, 95% CI: 16.59- 59.64, $p =$
22 0.001).

23

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

1 randomized to placebo, conferring a mean difference between groups of 40%
2 (95% CI 21.31 - 59.63, $p = 0.0001$).

3

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

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

8

9 *Change in prostate volume*

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

13

14 *Agreement between raters*

15

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

19

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

26

1 *Histological data (Supplementary table 2)*

2 All men were offered an end of study biopsy, although 12 of 40 men declined.

3 Histological upgrading to Gleason $\geq 4+3$ was seen in 3/15 (20%) in the
4 dutasteride group, and in 6/13 (46%) in the placebo group.

5

6 *Concordance of MRI lesions and histology (supplementary table 3)*

7

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

12

13 *PSA changes (supplementary table 4)*

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

17

18 *Medication compliance*

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

21

22 *Adverse events*

23 No serious adverse events occurred, and no subject discontinued study
24 medication due to adverse events. Deterioration of sexual function (at least a 4
25 point reduction in IIEF-15¹¹) occurred in 8 of 40 men (5/20 (25%) on dutasteride
26 and 3/19 (16%) on placebo.

1 Discussion

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

5

6 This volume change was associated with less histological upgrading at targeted
7 biopsy on study exit when randomized to dutasteride than to placebo (20%
8 versus 46%). However, the lack of targeted biopsies at baseline to match to
9 targeted exit biopsies and the small sample size limit the ability to definitively
10 ascribe this to the effect of dutasteride. The rate of upgrading in the placebo
11 group was high compared to that seen in men undergoing scheduled repeat
12 standard 10-12 core systematic biopsy on active surveillance protocols¹².

13 However, this was expected due to the use of image-guided targeting as well as
14 standard biopsy exit, compared to standard biopsy alone at entry, in the
15 majority¹³.

16

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

21

22 There have been concerns that dutasteride may act selectively on low grade
23 tumors, and may be associated with a greater likelihood of developing high-
24 grade cancers¹⁴, although radical prostatectomy data from randomized studies
25 have not confirmed this¹⁵.

26

1 In this study, two men randomized to dutasteride had 1mm and 2mm
2 respectively of Gleason 4 + 4 on targeted biopsy at exit, with an overall Gleason
3 grade of 3 + 4. At entry, the first had 9mm Gleason 3 + 3 on standard transrectal
4 biopsy, with a lesion volume of 0.97ml, which reduced to 0.64ml at 6 months.
5 The second had 4mm 3+ 4 on targeted biopsy at entry, with a lesion volume of
6 0.20ml, which reduced to 0.13ml at 6 months. This grade increase on targeted
7 biopsy at exit would be compatible with the grade shift seen with a targeted
8 biopsy approach¹⁶.

9

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

16

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

21

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

25

1 The study is limited in both its sample size and duration. The 20% threshold for
2 a reduction in tumor volume change was chosen, as it was the least change that
3 might be considered both clinically meaningful and assessable by our
4 independent observers. Sufficient men were recruited to achieve a power of
5 80% to detect a 20% volume change. A six-month interval of assessment is
6 common in many active surveillance protocols¹², and is known to show
7 response to dutasteride in studies of men with LUTS. The fact that a study of
8 this size and duration could meet its primary endpoint is promising for future
9 exploratory studies of this type.

10

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

19

20 Men with lesions seen exclusively on functional imaging were excluded. We do
21 not know whether radiological phenotype predicts prognosis or responsiveness,
22 although men with no visible lesion on MRI are at lower risk of progression than
23 men with a visible lesion¹⁷.

24

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

1 Four men had tumor volumes >1 ml, 3 of whom were randomized to placebo.
2 We repeated the analysis with these men removed and found very similar
3 results. In addition, a formal analysis that adjusted for baseline volume was
4 performed with little change in the outcome.
5 Our findings may have important clinical implications. First, if MRI reliably
6 detects prostate cancer volume change then it could be useful for reassessment
7 during surveillance¹⁸. Further work is needed to determine the imaging
8 parameters (rate of change or an absolute threshold) at which transition to
9 active treatment should be initiated, as recommended in the recent PRECISE
10 guidelines¹⁹
11
12 Second, this novel design might be useful in assessing well tolerated agents
13 that might modify the natural history of prostate cancer (e.g. aspirin, vitamin D,
14 and dietary modifications including cruciferous vegetables²⁰⁻²²). To date, large
15 and expensive epidemiological studies of long duration ²⁰ using repeat random
16 biopsies in men on active surveillance ²¹ have been used. Our novel study
17 design could allow initial screening of potential agents for further study.

19 **Conclusions**

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

2499/2500 words

ACCEPTED MANUSCRIPT

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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References

1. Roehrborn CG, Boyle P, Nickel JC, et al. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology*. 2002;60(3):434-4.
2. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010;362(13):1192-1202.
3. Fleshner NE, Lucia MS, Egerdie B, et al. Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;379:1103-1111.
4. Kirkham APS, Emberton M, Allen C. How good is MRI at detecting and characterising cancer within the prostate? *Eur Urol*. 2006; 50(6):1163-1174; discussion 1175.
5. Villers A, Puech P, Mouton D, et al. Dynamic contrast enhanced, pelvic phased array magnetic resonance imaging of localized prostate cancer for predicting tumor volume: correlation with radical prostatectomy findings. *J Urol*. 2006;176(6):2432-2437.
6. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur Radiol*. 2012;22(4):746-757.
7. Robertson NL, Moore CM, Ambler G, et al. MAPPED study design: A 6month randomised controlled study to evaluate the effect of dutasteride on prostate cancer volume using magnetic resonance imaging. *Contemp Clin Trials*. 2012;34(1):80-89.
8. National Institute for Health and Clinical Excellence. Prostate cancer: diagnosis and treatment (February 2008). Accessed via <http://www.nice.org.uk/nicemedia/pdf/CG58NICEGuideline>.

9. Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of Reporting for MRI-targeted Biopsy Studies (START) of the Prostate: Recommendations From An International Working Group. *Eur Urol.* 2013;64(4):544-552.
10. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA.* 1996;276(8):637-639
11. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A Multidimensional Scale for Assessment of Erectile Dysfunction. *Urology.* 1997;49(6):822-830.
12. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active Surveillance for Early-stage Prostate Cancer: Review of the Current Literature. *Cancer.* 2008;112(8):1650-1659.
13. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. "Comparison of MR/ultrasound Fusion-guided Biopsy with Ultrasound-guided Biopsy for the Diagnosis of Prostate Cancer. *JAMA* 2015;313(4):390-397.
14. Andriole GL, Bostwick DG, Gomella LG, et al. Modeling and analysis of Gleason score 8-10 prostate cancers in the REDUCE study. *Urology.* 2014;84(2):393-399.
15. Iczkowski KA, Qiu J, Qian J, et al. The dual 5-alpha-reductase inhibitor dutasteride induces atrophic changes and decreases relative cancer volume in human prostate. *Urology.* 2005;65(1):76-82.
16. Robertson NL, Hu Y, Ahmed HU, et al. Prostate Cancer Risk Inflation as a Consequence of Image-targeted Biopsy of the Prostate: A Computer Simulation Study. *Eur Urol.* 2014;65(3):628-634

17. Park, BH, Jeon HG, Choo SH, et al. Role of Multiparametric 3.0 Tesla Magnetic Resonance Imaging in Prostate Cancer Patients Eligible for Active Surveillance. *BJU Int* 2014;113(6):864-870
18. Graham J, Kirkbride P, Cann K, et al. Prostate cancer: a summary of updated NICE guidance , *BMJ*. 2014;348 :f7524.
19. Moore CM, Giganti F, Albertsen P et al. Reporting MRI in men on active surveillance for prostate cancer. The PRECISE recommendations: A report of a European School of Oncology Task Force. *Eur Urol* 2016 doi: 10.1016/j.eururo.2016.06.011
20. Veitonmäki T, Tammela TLJ, Auvinen A, et al. Use of Aspirin, but Not Other Non-steroidal Anti-inflammatory Drugs Is Associated with Decreased Prostate Cancer Risk at the Population Level. *Eur J Cancer*. 2013;49(4):938-945.
21. Marshall DT, Savage SJ, Garrett-Mayer E, et al., Vitamin D3 supplementation at 4000 international units per day for one year results in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate cancer under active surveillance. *J Clin Endocrinol Metab*. 2012;97(7):2315-2324.
22. Liu B, Mao Q, Cao M, Xie L. Cruciferous vegetables intake and risk of prostate cancer: a meta-analysis. *Int J Urol*, 2012;9(2):134-141.

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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 months (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 (%).

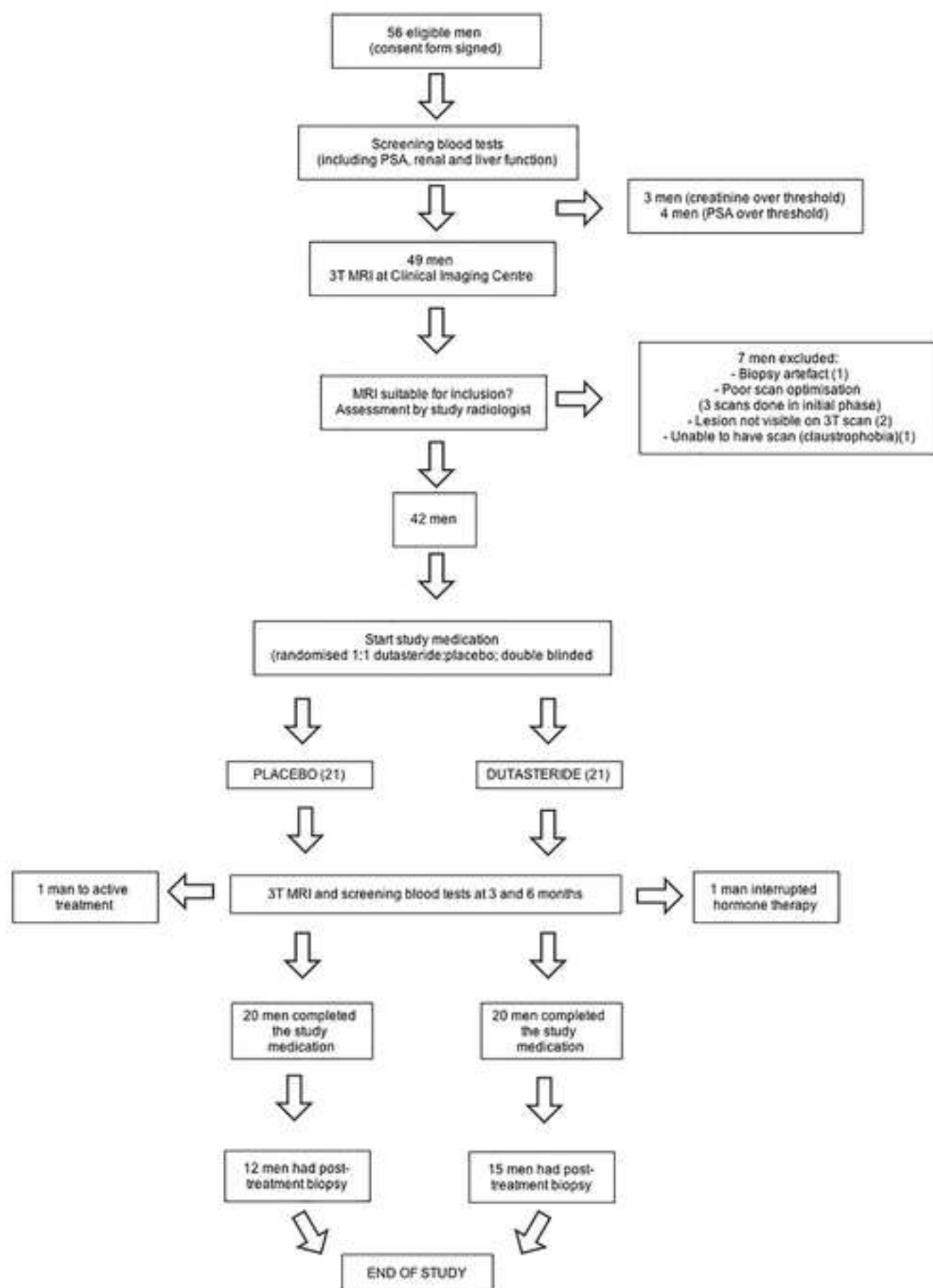
	Dutasteride (n = 21)	Placebo (n = 21)
Age (yrs)	63.9 (7.3, 49.0 to 79.2)	64.2 (7.5, 39.5 to 76.0)
Total PSA (ng/ml)	6.94 (3.0, 1.8 to 13.4)	6.01 (2.3, 1.3 to 9.7)
Prostate volume (ml)	47.02 (20.7, 20.7 to 98.8)	52.97 (22.1, 16.7 to 104.3)
PSA density (ng/ml/ml)	0.16 (0.06, 0.07 to 0.28)	0.12 (0.05, 0.05 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)

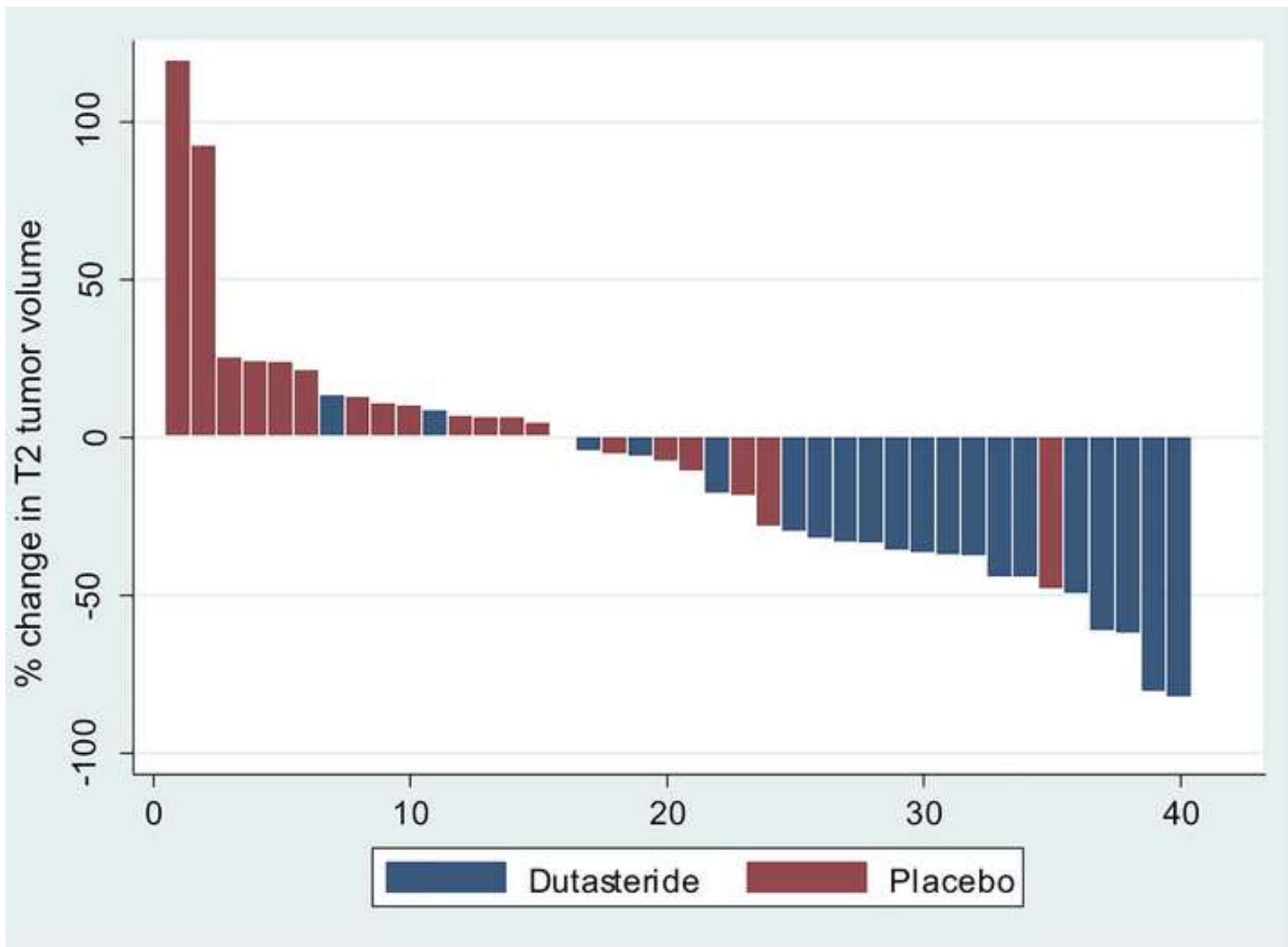
Total number of positive cores	4.62 (2.8, 1 to 12)	4.95 (3.6, 1 to 12)
Percentage of positive cores	29.5 (21.9, 2 to 75)	29.2 (18.4, 5 to 75)
Maximum cancer core length (mm)	5.05 (2.3, 1 to 9)	4.57 (2.2, 1 to 9)
Tumor volume (ml) : T2WI	0.55 (0.49, 0.12 to 0.36)	0.65 (0.8, 0 to 3.27)
Tumor volume (ml) : 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)

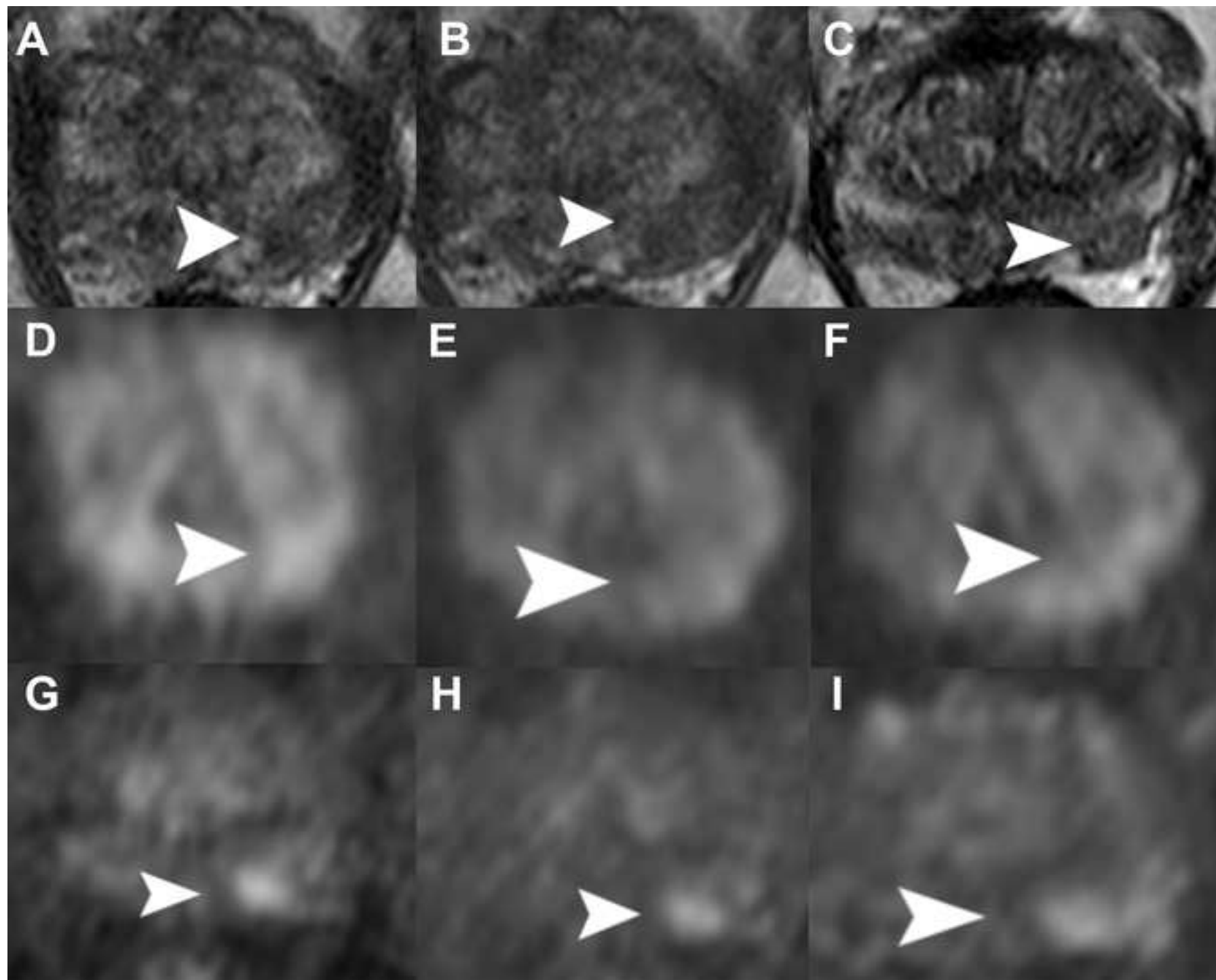
Table 2: Change in total tumor volume between baseline and six months on**T2-weighted imaging, dynamic contrast enhancement and diffusion weighted imaging**

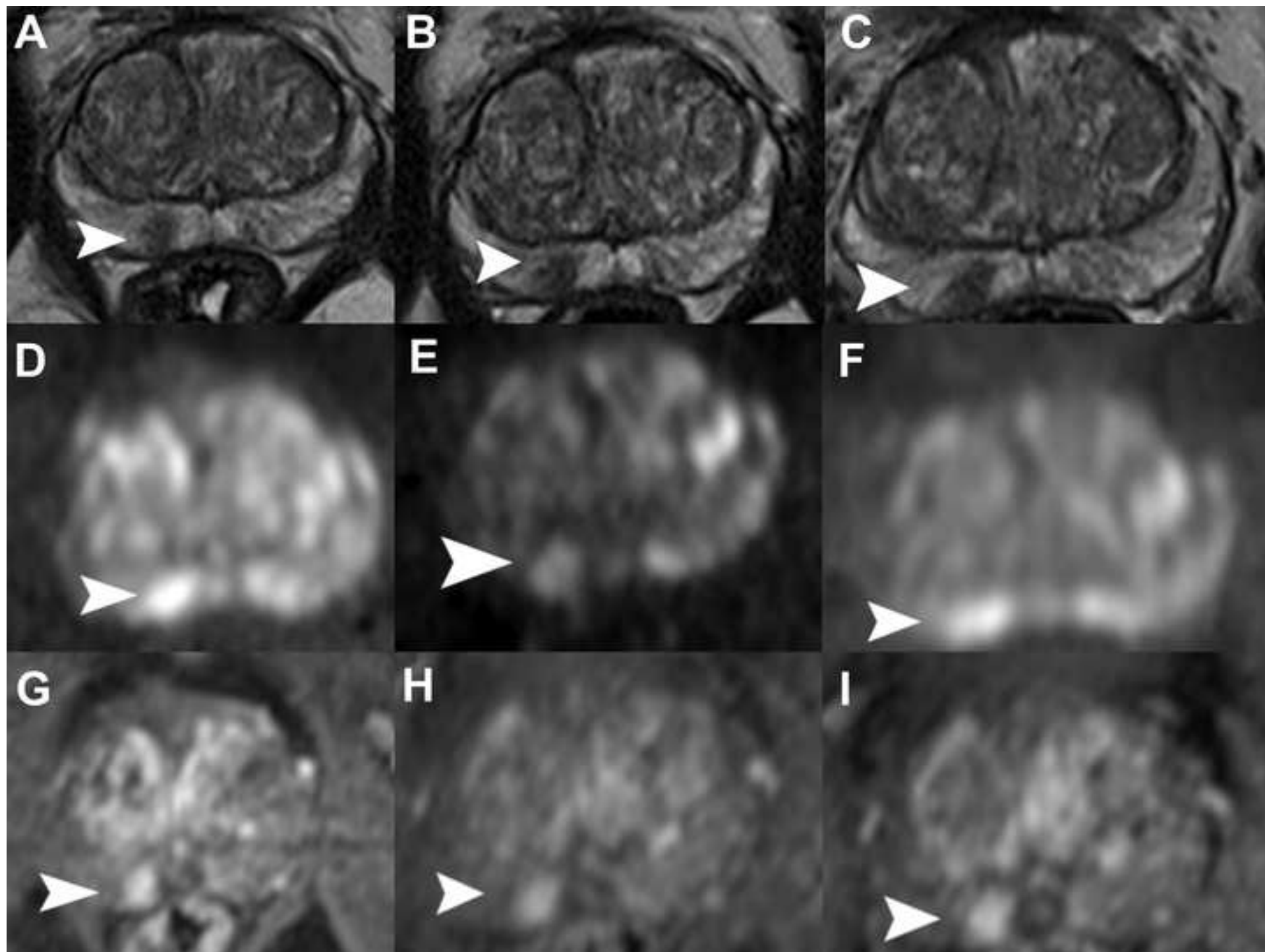
	Dutasteride (20) Mean (sd, range)	Placebo (20) Mean (sd, range)	Mean difference (95% CI) p- value
Total tumor volume (ml) at baseline (T2)	0.55 (0.5, 0.12 to 2.36)	0.65 (0.8, 0 to 3.27)	
Total tumor volume (ml) at 6 months (T2)	0.38 (0.4, 0.02 to 1.59)	0.76 (0.9, 0.09 to 3.96)	
% change in total tumor 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=0.0 001
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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	<i>Targeted bx</i> – left base 2 mm 3+4	Concordant at baseline and exit
R003	P	1 mm 3+3 right apex	Right apex	<i>Targeted bx</i> – right apex 4 mm 4+3	Concordant at baseline and exit
R004	D	9 mm, 3mm, 2mm 3+3 left	Left mid and apex	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – right lateral mid 4 mm 3+3	Concordant baseline and exit
R009	D	8mm, 1 mm 3+3 right	Right mid	<i>Targeted bx</i> –	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	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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)	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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	<i>Targeted bx</i> –	Concordant at

		3 mm 3+4 left	lateral Right mid- base anterior	right mid 6 mm 3+4 <i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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 I 2 mm 3+3 para-posterior apex I 1 mm 3+3 para-posterior apex I 1 mm 3+3 right para- posterior apex	Left mid	<i>Targeted bx</i> – left mid 4 mm, 3mm, 1mm 3+4	Concordant at exit

		4 mm 3+4 I			
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	<i>Targeted bx</i> – right posterior 5 mm 4+3 <i>Targeted bx</i> – 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	<i>Targeted bx</i> – left 5 mm 3+4 <i>Targeted bx</i> – 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	<i>Targeted bx</i> – 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 men 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 ($\geq 20\%$)	- 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 ($\geq 20\%$)	- 2.3
Dutasteride	5	Stable lesion (20% reduction to increase of 20%)	- 3.35
Dutasteride	0	Significant increase ($> 20\%$)	n/a

