

Visually-estimated and image-fusion MRI-targeted prostate biopsy

Accuracy of transperineal targeted prostate biopsies, both visual-estimation and image-fusion for men needing a repeat biopsy in the PICTURE trial

Lucy A. M. Simmons^{1,2} MD(Res)

Abi Kanthabalan^{1,2} MBBS

Manit Arya² FRCS(Urol)

Tim Briggs^{2, 3} FRCS(Urol)

Dean Barratt⁴ PhD

Susan C. Charman^{5,6} MSc

Alex Freeman⁷ FRCPath

James Gelister³ FRCS(Urol)

David Hawkes⁴ PhD

Yipeng Hu⁴ PhD

Charles Jameson⁷ FRCPath

Neil McCartan^{1,2}

Caroline M. Moore^{1,2} FRCS(Uol)

Shonit Punwani⁸ FRCR

Jan van der Muelen^{5,7} PhD

Mark Emberton^{1,2}§ FRCS (Urol)

Hashim U. Ahmed^{1,9, 10}§ FRCS(Urol)

§ Joint senior authors

Visually-estimated and image-fusion MRI-targeted prostate biopsy

1. Division of Surgery and Interventional Science, Faculty of Medical Sciences,
University College London, London, United Kingdom
2. Department of Urology, UCLH NHS Foundation Trust, London, UK
3. Department of Urology, The Royal Free London NHS Foundation Trust, London, UK
4. Centre for Medical Imaging and Computing, Department of Computer Science,
University College London, London, UK
5. Clinical Effectiveness Unit, The Royal College of Surgeons of England, London, UK
6. Department of Health Services Research and Policy, London School of Hygiene and
Tropical Medicine, London, UK
7. Department of Pathology, UCLH NHS Foundation Trust, London, UK
8. Department of Radiology, UCLH NHS Foundation Trust, London, UK
9. Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine,
Imperial College London, London, UK
10. Imperial Urology, Charing Cross Hospital, Imperial College Healthcare NHS Trust,
London, UK

Corresponding Author

Hashim U. Ahmed

Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial
College London, London, UK

Email: hashim.ahmed@imperial.ac.uk

Visually-estimated and image-fusion MRI-targeted prostate biopsy

Manuscript word count: 2448

Abstract word count: 250

Abbreviations

mpMRI- Multiparametric Magnetic Resonance Imaging

PHS- Prostate HistoScanning

TRUS biopsy- Transrectal ultrasound guided biopsy

TTPM- Transperineal Template Mapping biopsy

PSA- Prostate specific antigen

NPV- Negative predictive value

PPV- Positive predictive value

Abstract

Purpose: To evaluate detection of clinically significant prostate cancer (csPCa) using MRI-targeted biopsies, and compare visual-estimation to image-fusion targeting, in patients requiring repeat prostate biopsies.

Materials and Methods: Prospective, ethics-committee approved, registered PICTURE trial enrolling 249 consecutive patients (11th/January/2012-29th/January/2014). Men underwent an mpMRI and were blinded to its results. All underwent transperineal template prostate mapping (TTPM) biopsies. In 200 with a lesion, this was preceded by visual-estimation and image-fusion targeted biopsies. For the primary endpoint, csPCa was defined as Gleason $\geq 4+3$ and/or any grade of cancer length ≥ 6 mm. Other definitions of csPCa were also evaluated.

Results: Mean (SD) age was 62.6 (7) years, median (IQR) PSA 7.17ng/ml (5.25, 10.09), mean primary lesion size 0.37cc (SD1.52), with mean 4.3 (SD2.3) targeted cores per lesion (visual-estimation and image-fusion combined) and mean 48.7 (SD12.3) TTPM-biopsy cores. TTPM-biopsies detected 97 (48.5%) cases of csPCa and 85 (42.5%) insignificant cancers. Overall, mpMRI-targeted biopsies detected 81 (40.5%) csPCa and 63 (31.5%) insignificant cancers. Eighteen (9%) with csPCa on MRI-targeted biopsies were benign or clinically insignificant on TTPM-biopsy. Thirty-four (17%) had csPCa detected on TTPM-biopsy but not on MRI-targeted biopsies; approximately half of these were present in non-targeted areas. csPCa was found with visual-estimation and image-fusion in 53/169 (31.3%) and 48/169 (28.4%)

Visually-estimated and image-fusion MRI-targeted prostate biopsy

(McNemar's test, $p=0.5322$). Visual-estimation missed 23 (13.6%) csPCa detected by image-fusion; image-fusion missed 18 (10.8%) csPCa that visual-estimation detected.

Conclusions: MRI-targeted biopsies are accurate at detection of csPCa and reducing over-diagnosis of insignificant cancers. To maximise detection both visual-estimation and image-fusion targeted biopsies are required.

Trial Registration: The PICTURE trial was registered with ClinicalTrials.gov Identifier: NCT01492270 (URL <https://clinicaltrials.gov/ct2/show/NCT01492270>)

Funding: PICTURE received funding from the US National Institute of Health (primary award 1R01CA135089; sub-award via Riverside Research Institute NYO.G00351P.011741.12) and an unrestricted research grant from Advanced Medical Diagnostics SA.

Introduction

The diagnosis of prostate cancer remains a challenge due to the inaccuracy of transrectal ultrasound-guided (TRUS) biopsy, the diagnostic test that is most frequently used in men who have an elevated serum prostate specific antigen (PSA). TRUS-biopsy deploys 10 to 12 needles into the prostate blind to possible location of the suspected cancer. It has been estimated to miss-classify disease in approximately 30-50% (1)(2).

Multi-parametric MRI (mp-MRI) permits targeted biopsies to areas of suspicion within the prostate and has been shown to improve the detection of clinically significant prostate cancer (csPCa) and reduce the over-diagnosis of clinically insignificant prostate cancer (3-6).

The PICTURE trial was designed to overcome methodological issues inherent to studies that evaluated the properties of new approaches to diagnose prostate cancer using TRUS-biopsy or radical prostatectomy as the reference standard (7). The former being inaccurate and the latter incorporating selection biases because men had to test positive for cancer on a TRUS-biopsy and then chose surgical treatment. PICTURE aimed to assess the role of imaging in the risk stratification of prostate cancer in men who had already undergone TRUS-biopsy, but where there was still a suspicion of csPCa following a negative biopsy, or assessed for suitability for active surveillance or focal therapy. We recently reported on the sensitivity and specificity of mpMRI against transperineal template prostate mapping (TTPM)

Visually-estimated and image-fusion MRI-targeted prostate biopsy

biopsies from the PICTURE study (8). Here, we report on the agreement between mpMRI-targeted biopsies with TTPM-biopsies and compare visual-estimation targeting and image-fusion targeting.

Methods

The PICTURE trial is a single-centre prospective cohort study reporting diagnostic validity results compliant with Standards of Reporting Diagnostic (STARD) (9) (10) and Standards of reporting for MRI-targeted biopsy (START) studies (11). The full details of our protocol have been published (7). Ethics-committee approval for the study was granted by London City Road and Hampstead National Research Ethics Committee (reference 11/LO/1657) and the trial was registered with ClinicalTrials.gov (NCT01492270) on 6th/December/2011 prior to recruitment occurring 11th/January/2012 to 29th/January/2014. A prototype SmartTarget[®] non-rigid image-fusion system was used (12).

When we compared MRI-targeted biopsies with TTPM-biopsies, we also assessed whether the missed csPCa by targeted biopsies were errors of targeting or errors in mpMRI reporting. We did this by assessing whether the missed csPCa were within the targeted region on TTPM-biopsies or areas that were not targeted.

Eligibility: Men who had undergone prior TRUS-biopsy were eligible for the study if clinical suspicion remained that either csPCa had been missed or they had been

Visually-estimated and image-fusion MRI-targeted prostate biopsy

incorrectly classified, or if they were recommended for further TTPM-biopsy for assessment of suitability for focal therapy or active surveillance.

mpMRI: All eligible men underwent mpMRI using a 3T scanner with a pelvic-phased array coil. MRI sequences included T1-weighted, T2-weighted, dynamic contrast enhancement with gadolinium (DCE), diffusion-weighting (DWI) with high b-value (b=2000) sequence and apparent diffusion coefficient (ADC) map using multiple b-values (b=0,150,500,1000) (13). MRIs were prospectively scored by a single expert uro-radiologist with 5 years' experience in the interpretation of prostate mpMRI, using a 5-point Likert scale for likelihood of the presence of csPCa (14). This scoring system was based on the outputs of a consensus meeting that was convened prior to the publishing of the PIRADS versions 1 and 2 mpMRI consensus (15,16) and has been shown to have validity when compared to PIRADS (17). Men remained blinded to their MRI results to prevent attrition bias.

Biopsy: The biopsy procedure was carried out under general or spinal anaesthesia with antibiotic prophylaxis and patients in the lithotomy position. All biopsies were performed transperineally. Prior to TTPM-biopsies, targeted biopsies were taken in men who had an area with mpMRI score ≥ 3 . The most suspicious area scoring ≥ 3 was targeted; in case of two lesions of the same score ≥ 3 the largest was sampled. In addition, to test the performance of image-fusion biopsies compared to visual-estimation, we carried out image-fusion targeted biopsies using our in-house, academically-developed, prototype software (SmartTarget[®]). This uses deformable, non-rigid, MRI-ultrasound image registration to demonstrate the likely anatomical

Visually-estimated and image-fusion MRI-targeted prostate biopsy

location of a lesion within the gland live at the time of biopsy (12,18,19).

(Supplementary-Figure-a). Image-fusion biopsies were followed by visual-estimation targeted biopsies in which the urologist taking the biopsies determines needle deployment independent of any software. In order to minimise incorporation bias, the operator declared which template grid coordinates would be used for visual-estimation biopsies prior to the image-fusion software being deployed. Once the image-fusion biopsies were taken, biopsy cores from these pre-declared locations were then taken. Where the grid coordinates were overlapping between the two types of targeting, the information from these biopsies was used for both strategies in the analysis. Each targeted core was individually identified by its specific grid location. Up to four targeted cores per targeting strategy were permitted.

All men then underwent TTPM-biopsies, which was performed according to a set standardised protocol by trained urologists regardless of the imaging findings.

A urethral catheter was inserted in order to visualize and avoid traversing the urethral lumen with biopsy needles. 5mm sampling was obtained using 17G biopsy core needles inserted via a brachytherapy grid fixed on a stepper. In most prostates, two biopsies at each grid point were required in order to sample the full cranio-caudal length of the gland. All biopsies were reported by two expert uro-pathologists with more than 20 years' experience each. All negative biopsies were double-reported for quality control (20). The cancer involvement per core was reported as the actual amount of cancer seen in each core in millimetres without counting the intervening areas of benign glands (21).

Visually-estimated and image-fusion MRI-targeted prostate biopsy

Target condition: Disease significance was defined by criteria we previously developed, validated and used with TPPM-biopsies (22). Our primary outcome was based on detecting any grade (Gleason $\geq 3+3=6$ or more) of cancer core length involvement ≥ 6 mm AND/OR the presence of Gleason $\geq 4+3=7$ (UCL/Ahmed Definition 1). In addition, we evaluated our endpoints with other target conditions in mind. These were, a) any grade of cancer core length ≥ 4 mm AND/OR any length of cancer Gleason score $\geq 3+4=7$ (UCL/Ahmed Definition 2), and b) any Gleason $\geq 3+4=7$. The overall aggregate Gleason score from all targeted cores was used.

Statistics: Patient and tumour characteristics and biopsy features are summarised using mean (standard deviation [SD]), median (interquartile range [IQR]) or frequency (%) as appropriate. We compiled 3-by-3 contingency tables for the overall MRI-targeted biopsies (incorporating both visual-estimation and image-fusion) compared to TPPM-biopsy. We also assessed the agreement between visual-estimation and image-fusion targeted biopsies, reporting the proportion exact agreement with 95%CI. McNemar's test for paired proportions (two-tailed) was used to compare two types of biopsy tests (targeted versus TPM; visual estimation versus image-fusion) for each definition of cancer. STATA version 13.0 software was used for all analyses.

The sample size calculation was based on the PICTURE study's primary objectives (i.e., to assess the clinical validity of mpMRI and Prostate-HistoScanning) (23-25). As a consequence, there was no *a priori* sample size calculation for the assessment of agreement between different biopsy strategies.

Results

Patient Demographics: Three-hundred and thirty were enrolled with 81 withdrawals (Figure-1). Patient demographics for men eligible for biopsy were mean age 62 years (SD7), median PSA 6.8ng/ml (IQR4.8-9.8) and median number of previous biopsies 1 (IQR1-2) and gland size 37ml (26.8-50.0) (Table-1). 121 (48.6%) had Gleason 6 disease on TRUS-biopsy whilst 52 (21.1%) had low volume Gleason 7 disease; 76 (30.5%) had no prior cancer.

Of these, 249 had paired datasets of mpMRI and biopsy; 49 (19.6%) did not have an mpMRI lesion scoring ≥ 3 , and thus did not have a MRI-targeted biopsy. Therefore, 200 had targeted biopsies with mean size of primary lesion 0.37cc (SD1.52) and maximum diameter of the main mpMRI lesion 11.7mm (SD6.7), with mean 4.3 (SD2.4) targeted cores per lesion overall (fusion and visual estimation combined), mean 2.3 cores fusion and mean 2.4 cores for visually estimation cores and a mean 48.7 (SD12.3) TTPM cores. Mean number of cores positive for cancer on targeting was 1.9 (SD1.03) (Supplementary-Table-a).

Primary outcome:

Overall, TTPM-biopsies detected 97 (48.5%) definition 1 csPCa and 85 (42.5%) insignificant cancers, 18 (9%) men were benign at TTPM. MRI-targeted biopsy detected 81 (40.5%) csPCa and 63 (31.5%) insignificant cancers with 56 (28%) men benign at MRI targeted biopsy. Eighteen (9%) of those with csPCa on MRI-targeted

Visually-estimated and image-fusion MRI-targeted prostate biopsy

biopsies had been designated benign or clinically insignificant by TTPM-biopsies (Table-2). Thirty-four (17%) had csPCa detected on TTPM-biopsy but were designated benign or clinically insignificant by MRI-targeted biopsy ($p=0.0375$) (Table-2 and Supplementary-Table-c).

Secondary Outcomes:

Using definition 2 csPCa as the threshold for significance, TTPM-biopsies detected 168 (84%) csPCa and 41 (20.5%) clinically insignificant cancers. MRI-targeted biopsies detected 122 (61%) csPCa and 22 (11%) insignificant cancers. Nine (4.5%) of those with definition 2 csPCa on MRI-targeted biopsies had been designated benign or clinically insignificant by TTPM-biopsies. Forty (20%) had definition 2 csPCa detected on TTPM-biopsy but designated benign or clinically insignificant by MRI-targeted biopsy ($p=0.0001$) (Table-3). Table-4 shows the differences for any Gleason 7 disease ($p=0.0003$).

Second, Gleason 3+3=6 was detected in 38 (19%) and Gleason $\geq 3+4=7$ in 106 (53%) on MRI-targeted biopsies (Table-5). Eleven (5.5%) of those with Gleason $\geq 3+4=7$ on MRI-targeted biopsies had been designated benign or clinically insignificant by TTPM-biopsies. Thirty-seven (18.5%) had Gleason $\geq 3+4=7$ detected on TTPM-biopsy but designated benign or clinically insignificant by MRI-targeted biopsy (Table-5).

Third, 3 (1.5%) patients with Gleason $\geq 4+4=8$ on TTPM-biopsies were not identified by MRI-targeted biopsy. Four (2%) classified as insignificant or benign by

Visually-estimated and image-fusion MRI-targeted prostate biopsy

TTPM-biopsies were found to have Gleason $\geq 4+4=8$ disease by MRI-targeted biopsy (Table-5).

Fourth, we evaluated reasons for targeted biopsies miss-classifying cancer as no cancer. Forty men had cancer detected at TTPM-biopsy but no cancer on MRI-targeting; 22/40 (55%) were within the targeted area and therefore the targeting strategy had failed. Of men not detected by targeted biopsy, only 3/40 (7.5%) had csPCa by definition 1. 18/40 (45%) had disease in areas that were not targeted i.e., scored negative on mpMRI and therefore an mpMRI detection error; of these missed cancers only 2/40 (5%) were csPCa (Supplementary-Table-b).

Fifth, we compared agreement between visual-estimation targeted biopsies with image-fusion targeted biopsies. For the 169 men with available data from both types of targeting there was exact agreement for the presence or absence of any cancer between the two targeting modalities in 137 (81% [95%CI 74-87%]) (Supplementary-Table-d) and agreement for presence or absence of definition 1 csPCa in 128 (76% [95%CI 69-82%]) (Table-6). Overall, definition 1 csPCa was found with visual-estimation targeting in 48/169 (28.4%) and image-fusion targeting in 53/169 (31.3%). Visual-estimation missed 23/169 (13.6%) definition 1 csPCa detected by image-fusion. Image-fusion missed 18/169 (10.8%) definition 1 csPCa that visual-estimation detected ($p=0.5322$). Supplementary Tables e, f, g and h summarise agreement between visual-estimation targeting and image-fusion targeting for other thresholds of clinical significance.

Discussion

In summary, our PICTURE trial shows that MRI-targeted biopsies, based on the Likert reporting system for mpMRI, have a good detection rate of csPCa and agreement with TTPM-biopsies in 81% of cases (137/169) on disease classification, whilst reducing by 40% (43/106) the unnecessary diagnosis of clinically insignificant disease when compared to TTPM-biopsy. Although TTPM-biopsies detected more csPCa than MRI-targeted biopsies, they did so with 44 more biopsies per patient on average and found 43 more clinically insignificant cancers overall. Our results also showed that both visual-estimation and image-fusion biopsies are required to achieve optimal results.

Our results also demonstrated that in some cases visual- estimation detected csPCa that fusion- targeting did not. No fusion software can pick-up when it is miss-registered, but an expert operator can adjust cognitively according to visual cues. Visual is not passive whereas until fusion builds in landmark detection on images to feedback loop into the registration/fusion system, there may be occasional technical errors.

Limitations to our MRI-targeted biopsy protocol were the inclusion of only the largest lesion on mpMRI for specific targeting and also a limit on the number of targeted samples per lesion. One could argue that all mpMRI-detected lesions should have been sampled. This is especially pertinent since our primary definition of csPCa is based on cancer core length involvement and therefore exclusion of smaller

Visually-estimated and image-fusion MRI-targeted prostate biopsy

lesions may have biased our outcomes. However, our rationale for these two steps was to minimise the burden of extra biopsy cores on the patient, who also underwent TTPM-biopsy; in many respects, this may have under-estimated the performance of targeted biopsy in our study. Second, the deformable MRI-US image-fusion device used in the study was a prototype and this may have limited the performance of image-fusion biopsies. Third, whilst we attempted to eliminate incorporation bias by declaring coordinates for visual-estimation targeting before the start of image-fusion, carrying out image-fusion biopsies might have either led to poorer outcomes from visual-estimation due to biopsy-related swelling or better outcomes by the operator being helped by the needle tracks from the previous biopsy.

A number of recent systematic reviews have assessed the role of MRI-targeted biopsy. These have shown that a biopsy of the prostate using mpMRI to inform sampling resulted in detection rates of csPCa of about 42% (5). Our results from a prospective study that blinded patients to the imaging results showed that targeted biopsies had a detection rate of between 41% and 61% depending on the definition of csPCa used.

When evaluating the results from targeted biopsy studies it is important to identify the areas for possible error. By incorporating both visual-estimation and image-fusion we aimed to reduce any miss-registration errors that may have occurred by the use of one strategy alone. We have shown that about half of the cases in which targeted biopsies were benign when TTPM-biopsy showed cancer were due to

Visually-estimated and image-fusion MRI-targeted prostate biopsy

mpMRI detection errors with the other half being targeting errors that might be improved, either by increasing the number of cores taken and/or with further refinements to fusion software.

Nonetheless, it is worth noting that all diagnostic tests and strategies have advantages and disadvantages. The large burden of TPPM-biopsies make this strategy untenable in any healthcare system due to requirement for general anaesthetic, high burden and morbidity for the patient and high resource use and cost for the institution. Whilst targeted biopsies were carried out under the same general anaesthetic as the TPPM-biopsies in PICTURE through necessity to minimise burden and also minimise withdrawals between biopsy strategies were they to be performed on separate days, we have recently demonstrated the feasibility of doing transperineal targeted biopsies under local anaesthetic (26).

Conclusion

MRI-targeted biopsies have good accuracy at detecting clinically significant prostate cancer compared to an intensive biopsy sampling strategy. Targeting identified most significant cancers when present with almost ten-fold fewer biopsies and reduced unnecessary diagnosis of clinically insignificant disease. For optimal detection both visual-estimation and image-fusion targeted biopsies were required. However, some clinically significant cancers were missed, suggesting that some systemic sampling alongside targeting might aid in minimising this.

Acknowledgements

Visually-estimated and image-fusion MRI-targeted prostate biopsy

We would like to thank the men who participated in this study.

Other sources of funding and potential conflicts of interest

Hashim Ahmed receives funding from the Wellcome Trust. Hashim Ahmed is supported by infrastructure support provided by the NIHR Imperial Biomedical Research Centre. Mark Emberton's research is supported by core funding from the NIHR UCH/UCL Biomedical Research Centre. He was awarded an NIHR Senior Investigator.

Hashim Ahmed receives funding from Sonacare Medical, Sophiris Inc. and Trod Medical for other trials and personal consultancy fees for trial activity from Sophiris Inc. Funding for travel and lectures as well as proctoring fees are provided by Sonacare Inc. and BTG Medical (previously Galil).

Mark Emberton has stock interest in Nuada Medical Ltd. He is also a consultant to Steba Biotech and GSK. He receives travel funding from Sanofi Aventis, Astellas, GSK and Sonacare. He previously received trial funding or resources from GSK, Steba Biotech and Angiodynamics and currently receives funding for trials from Sonacare Inc, Sophiris Inc and Trod Medical.

Alex Freeman has stock interest in Nuada Medical Ltd.

All others have no conflicts of interest.

Authorship

Visually-estimated and image-fusion MRI-targeted prostate biopsy

Study concept and initial design: Simmons, Moore, Emberton, Ahmed.

Study design and statistical analysis: Ahmed, Moore, Emberton, Simmons,
Charman, van der Meulen

Acquisition of data and Data analysis and interpretation: Arya, Ahmed, Briggs,
Charman, Emberton, Freeman, Gelister, Jameson, Kanthabalan, McCartan, Moore,
Simmons, van der Meulen,

Guarantor of data: Ahmed

Tables and Figure Legends:

- Figure 1: Study flow diagram
- Table 1: Patient demographics
- Table 2. MRI targeted biopsies versus TTPM-biopsies in men with a target of UCL/Ahmed definition 1 csPCa in 200 men with a target
- Table 3. MRI targeted biopsies versus TTPM-biopsies in men with a target of UCL/Ahmed definition 2 csPCa in 200 men with a target
- Table 4. MRI targeted biopsies versus TTPM-biopsies in men using any Gleason 7 in 200 men with a target
- Table 5: Targeted biopsies (combination of visual-estimated and image-fusion) versus TTPM-biopsies (Gleason grade alone)
- Table 6: Agreement between two types of MRI-targeted biopsies (visual-estimated versus image-fusion targeted biopsies) for UCL/Ahmed definition 1 clinically significant cancer

Supplementary tables legends (see attached separate file:

- Supplementary Figure a) An example of a targeted biopsy using the SmartTarget® image-fusion software
- Supplementary Table a) Gleason grade distribution of Targeted patients
- Supplementary Table b) MRI Targeted evaluation data: reasons for targeted biopsies miss-classifying cancer on TTPM-biopsies as no cancer
- Supplementary Table c) Targeted biopsies (combination of visual-estimated and image-fusion) versus TTPM-biopsies (Definitions 1 and 2)
- Supplementary Table d) Agreement between visual-estimated and image-fusion targeted biopsies for any cancer

Visually-estimated and image-fusion MRI-targeted prostate biopsy

- Supplementary Table e) Agreement between visual-estimated and image-fusion targeted biopsies for various definitions
- Supplementary Table f) Agreement between visual-estimated and image-fusion targeted biopsies for UCL/Ahmed definition 2 clinically significant cancer
- Supplementary Table g) Agreement between visual-estimated and image-fusion targeted biopsies for any Gleason 7
- Supplementary Table h) Agreement between visual-estimated and image-fusion targeted biopsies for various Gleason scores

Tables and Figures:

Figure 1: Study flow diagram

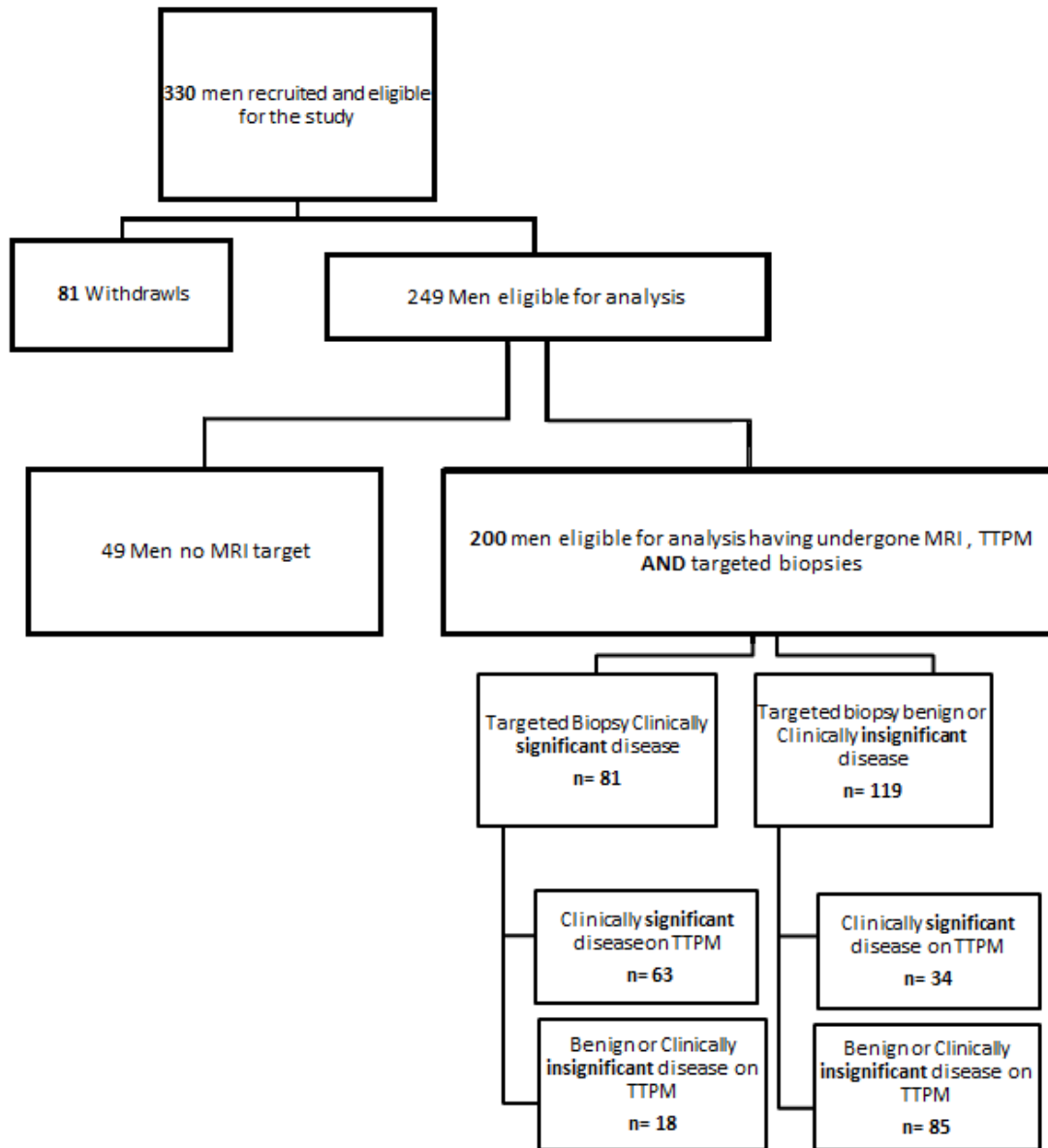


Table 1: Patient demographics

	Men enrolled n=330	Eligible men following withdrawals n=249
Characteristic	Median (IQR)	Median (mean, SD, range)
Age, years	63 (42-83)	62 (62.0, 7.16, 42-83)
PSA concentration at consent, ng/ml	7.4 (0.7-58.05)	6.8 (7.81, 4.26, 0.7-30.3)
	Mean (SD)	Mean (SD)
Number of previous biopsies	1.49 (0.79)	1.41 (0.69)
MRI Prostate volume, cc	46.48 (26.53)	37.1 (15.5)

)

Table 2. MRI targeted biopsies versus TTPM-biopsies in men with a target of UCL/Ahmed definition 1 csPCa in 200 men with a target

Visually-estimated and image-fusion MRI-targeted prostate biopsy

		Transperineal Template Mapping Biopsies		
		Benign	UCL/Ahmed Definition 1	Totals
MRI targeted biopsies (combined visual-estimation and image-fusion)	Benign	85	34	119
	UCL/Ahmed Definition 1	18	63	81
	Totals	103	97	200

McNemar's test for paired proportions (two-tailed) when csPCa (UCL/Ahmed defn 1) and no csPCa (no UCL/Ahmed defn 1) used to dichotomise outcomes to derive paired proportions: $p=0.0375$

Table 3. MRI targeted biopsies versus TPM-biopsies in men with a target of UCL/Ahmed definition 2 csPCa in 200 men with a target

Visually-estimated and image-fusion MRI-targeted prostate biopsy

		Transperineal Template Mapping Biopsies		
		Benign	UCL/Ahmed Definition 2	Totals
MRI targeted biopsies (combined visual-estimation and image-fusion)	Benign	38	40	78
	UCL/Ahmed Definition 2	9	113	122
	Totals	47	153	200

McNemar's test for paired proportions (two-tailed) when csPCa (UCL/Ahmed defn 2) and no csPCa (no UCL/Ahmed defn 2) used to dichotomise outcomes to derive paired proportions: $p=0.0001$

Table 4. MRI targeted biopsies versus TTPM biopsies in men using any Gleason 7 in 200 men with a target

Visually-estimated and image-fusion MRI-targeted prostate biopsy

		Transperineal Template Mapping Biopsies		
		Benign	Any Gleason 7	Totals
MRI targeted biopsies (combined visual-estimation and image-fusion)	Benign	57	37	94
	Any Gleason 7	11	95	106
	Totals	68	132	200

McNemar's test for paired proportions (two-tailed) when any Gleason 7 used to dichotomise outcomes to derive paired proportions: p=0.0003

Table 5: Targeted biopsies (combination of visual-estimated and image-fusion) versus TTPM-biopsies (Gleason grade alone)

Transperineal Template Mapping biopsies
--

Visually-estimated and image-fusion MRI-targeted prostate biopsy

		Benign	Gleason 3+3	Gleason 3+4 or 4+3	Gleason >/=4+4	Totals
MRI targeted biopsies (combined visual-estimation and image-fusion)	No MRI target	22	16	11	0	49
	Benign	15	25	15	1	56
	Gleason 3+3	0	17	21	0	38*
	GI 3+4 or 4+3	1	7	91	2	101
	Gleason >/=4+4	2	1	1	1	5
	Totals	40	66	139	4	249
Key to shading						
No MRI target						
Significant disease missed by TTPM-biopsies						
Significant disease missed by targeting						

Table 6: Agreement between two types of MRI-targeted biopsies (visual-estimated versus image-fusion targeted biopsies) for UCL/Ahmed definition 1 clinically significant cancer

Image-fusion targeted biopsy

Visually-estimated and image-fusion MRI-targeted prostate biopsy

		Benign	UCL/Ahmed Definition 1	Totals
Visual-estimation targeted biopsies	Benign	98	23	121
	UCL/Ahmed Definition 1	18	30	48
	Totals	116	53	169

*McNemar's test for paired proportions (two-tailed) for UCL/Ahmed 1 csPCa:
p=0.5322*

References

Visually-estimated and image-fusion MRI-targeted prostate biopsy

1. Shaw GL, Thomas BC, Dawson SN, Srivastava G, Vowler SL, Gnanapragasam VJ, et al. Identification of pathologically insignificant prostate cancer is not accurate in unscreened men. *Br J Cancer*. 2014;110(10):2405-11.
2. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet*. 2017;389(10071):815-22.
3. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA*. 2015;313(4):390-7.
4. Valerio M, Donaldson I, Emberton M, Ehdai B, Hadaschik BA, Marks LS, et al. Detection of Clinically Significant Prostate Cancer Using Magnetic Resonance Imaging-Ultrasound Fusion Targeted Biopsy: A Systematic Review. *Eur Urol*. 2015;68(1):8-19.
5. Moore CM, Robertson NL, Arsanious N, Middleton T, Villers A, Klotz L, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. *Eur Urol*. 2013;63(1):125-40.
6. Wegelin O, van Melick HH, Hooft L, Bosch JL, Reitsma HB, Barentsz JO, et al. Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique? *Eur Urol*. 2017;71(4):517-31.
7. Simmons LA, Ahmed HU, Moore CM, Punwani S, Freeman A, Hu Y, et al. The PICTURE study - Prostate Imaging (multi-parametric MRI and Prostate HistoScanning)

Visually-estimated and image-fusion MRI-targeted prostate biopsy

Compared to Transperineal Ultrasound guided biopsy for significant prostate cancer Risk Evaluation. *Contemp Clin Trials*. 2014;37(1):69-83.

8. Simmons LAM, Kanthabalan A, Arya M, Briggs T, Barratt D, Charman SC, et al. The PICTURE study: diagnostic accuracy of multiparametric MRI in men requiring a repeat prostate biopsy. *Br J Cancer*. 2017;116(9):1159-65.

9. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Clin Biochem*. 2003;36(1):2-7.

10. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. *Ann Intern Med*. 2003;138(1):40-4.

11. Moore CM, Kasivisvanathan V, Eggener S, Emberton M, Futterer JJ, Gill IS, 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):544-52.

12. Hu Y, Ahmed HU, Taylor Z, Allen C, Emberton M, Hawkes D, et al. MR to ultrasound registration for image-guided prostate interventions. *Med Image Anal*. 2012;16(3):687-703.

13. Simmons LA, Ahmed HU, Moore CM, Punwani S, Freeman A, Hu Y, et al. The PICTURE study - Prostate Imaging (multi-parametric MRI and Prostate HistoScanning) Compared to Transperineal Ultrasound guided biopsy for significant prostate cancer Risk Evaluation. *Contemp Clin Trials*. 2013;37(1):69-83.

14. Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of

Visually-estimated and image-fusion MRI-targeted prostate biopsy

prostate cancer: recommendations from a European consensus meeting. *Eur Urol.* 2011;59(4):477-94.

15. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. *Eur Radiol.* 2012;22(4):746-57.

16. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. *Eur Urol.* 2016;69(1):16-40.

17. Vache T, Bratan F, Mege-Lechevallier F, Roche S, Rabilloud M, Rouviere O. Characterization of prostate lesions as benign or malignant at multiparametric MR imaging: comparison of three scoring systems in patients treated with radical prostatectomy. *Radiology.* 2014;272(2):446-55.

18. Hu Y, Carter TJ, Ahmed HU, Emberton M, Allen C, Hawkes DJ, et al. Modelling prostate motion for data fusion during image-guided interventions. *IEEE Trans Med Imaging.* 2011;30(11):1887-900.

19. Hu Y, Ahmed HU, Allen C, Pendse D, Sahu M, Emberton M, et al. MR to ultrasound image registration for guiding prostate biopsy and interventions. *Med Image Comput Comput Assist Interv.* 2009;12(Pt 1):787-94.

20. Epstein JI, Allsbrook WC, Amin MB, Egevad LL. The 2005 international society of urological pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol.* 2005;29(9):1228-42.

21. Karram S, Trock BJ, Netto GJ, Epstein JI. Should intervening benign tissue be included in the measurement of discontinuous foci of cancer on prostate needle biopsy? Correlation with radical prostatectomy findings. *Am J Surg Pathol.* 2011;35(9):1351-5.

Visually-estimated and image-fusion MRI-targeted prostate biopsy

22. Ahmed HU, Hu Y, Carter T, Arumainayagam N, Lecornet E, Freeman A, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. *J Urol*. 2011;186(2):458-64.
23. Flahault A, Cadilhac M, Thomas G. Sample size calculation should be performed for design accuracy in diagnostic test studies. *J Clin Epidemiol*. 2005;58(8):859-62.
24. Salmi LR, Michel P. Sample size for diagnostic accuracy studies. *J Clin Epidemiol*. 2004;57(8):869-70; author reply 71-2.
25. Knottnerus JA, Muris JW. Assessment of the accuracy of diagnostic tests: the cross-sectional study. *J Clin Epidemiol*. 2003;56(11):1118-28.
26. Bass E, Donaldson I, Freeman A, Jameson C, Punwani S, Moore C, Arya M, Emberton M, Ahmed HU. Magnetic Resonance Imaging Targeted Transperineal Prostate Biopsy: A Local Anaesthetic Approach. Accepted by *Prostate Cancer Prostate Diseases*. February 2017.