Multicenter randomized trial assessing MRI and image-guided biopsy for suspected prostate cancer

Wei, Cheng; Szewczyk-Bieda, Magdalena; Bates, Anthony S.; Donnan, Peter T.; Rauchhaus, Petra; Gandy, Stephen

Published in:
Radiology

DOI:
10.1148/radiol.221428

Publication date:
2023

Document Version
Peer reviewed version

Abbreviated Title Page

Title: Multicenter randomized trial assessing MRI and image-guided biopsy for suspected prostate cancer: The MULTIPROS study

Manuscript type: original research

Summary statement: In this multicenter randomized controlled trial, US/ MRI fusion targeted biopsy and systematic random biopsy when combined detected more clinically significant prostate cancer lesions than either biopsy type alone.

Key results:

- In a prospective trial of 603 men, where 89 men had histologically-confirmed prostate cancer at radical prostatectomy, multiparametric MRI correctly identified 131 of 182 clinically significant cancers: sensitivity, specificity, PPV and NPV, 72% (131/182), 71% (91/128), 78% (131/168) and 64% (91/142), respectively.
- US/MRI fusion targeted biopsy combined with systematic random prostate biopsy had higher odds of detecting clinically significant lesions, without incurring more procedure-related adverse events, than either biopsy type alone, OR, 1.79, *P* =.01

Data sharing statement: Data generated or analyzed during the study are available from the corresponding author by request.

Abstract

Background: The optimal diagnostic pathway for prostate cancer (PCa) is evolving requiring further evaluation in a randomized controlled trial (RCT).

Purpose: To assess the diagnostic accuracy of prebiopsy multiparametric (mp)MRI for the identification of clinically significant (cs)PCa using radical prostatectomy (RP) specimens as the reference standard, and to test the diagnostic accuracy of combined US/MRI fusion biopsy with systematic biopsies.

Materials and methods: In a prospective RCT including university hospitals, men with suspected prostate cancer were recruited between January 2015 and August 2020 to assess the diagnostic accuracy of prebiopsy mpMRI for detection of csPCa at biopsy and RP histopathology (primary outcome). Men with suspicious (PI-RADS ≥3) lesions on mpMRI were first randomized to either systematic random prostate biopsies alone (control), or US/MRI fusion targeted biopsies with systematic random prostate biopsies (intervention) at a ratio of 1:1, to compare the diagnostic accuracy of systematic random vs combined fusion + systematic random biopsies (secondary outcome). A subset of participants recruited (n=89) underwent RP and histological sectioning.

Results: 582 participants were eligible for mpMRI (mean age, 65 years ± 6 [SD]). In total, 413 had a PI-RADS score ≥3 and were randomized into either the intervention group (207/413, 50%) or control group (206/413, 50%). The csPCa detection rate in the intervention arm was higher, with an adjusted OR of 1.79 (95% CI, 1.14-2.79), *P* = .01. A subgroup of 89 men underwent RP (89/413, 21.5%). mpMRI correctly identified 131/182 csPCa foci in 89 men (sensitivity: 72% (131/182), 95% CI 65%-78%). The specificity, positive predictive value and negative predictive value were 71% (91/128), 78% (131/168) and 64% (91/142), respectively.

Conclusions: Prebiopsy multiparametric MRI is accurate in the detection of clinically significant prostate cancer. Combining US/MRI fusion targeted biopsies with systematic biopsies detected more clinically significant lesions than systematic biopsies alone.

ClinicalTrials.gov (NCT02745496)

Introduction

Prebiopsy multiparametric MRI (mpMRI), using the Prostate Imaging - Reporting and Data System (PI-RADS), in the workup of prostate cancer, has been validated in diagnostic accuracy studies and randomized trials.(1–4) Previously, systematic prostatic biopsies were limited by high numbers of false-negative biopsies (21-23%), undersampling, repeat biopsies, under-grading, and subsequent overdiagnosis and the overtreatment of clinically insignificant disease, i.e., <6mm core, Gleason score 3+3. The established paradigm now consists of prebiopsy mpMRI and MRI-guided targeted biopsies (5,6). Prebiopsy mpMRI increases the detection of clinically significant PCa (csPCa) and reduces unnecessary biopsies and the overdiagnosis of clinically insignificant PCa (1–4).

The value of MRI as a prebiopsy test was demonstrated by PROMIS, a paired confirmatory study that used transperineal template biopsies as a reference standard (1). The PRECISION study provided evidence for targeted biopsies, however recent studies indicate systematic biopsies provide additional diagnostic yield (2,7–11). The sensitivity of MRI varies between 44 and 87%, depending on the choice of reference standard (i.e. TRUS, transperineal template or radical prostatectomy [RP] histology), the MRI probability scoring system used, and the definition of csPCa (12). The choice of reference standard is a significant factor in the heterogeneity of the reported diagnostic accuracy of mpMRI (13). In PI-RADS 3 lesions, detection of csPCa varies between 20-60%, and template biopsy results, when matched with and compared with whole-mount specimens, are downgraded in 30-40% (14–16).

The hypothesis was that fusion and standard biopsies, when combined, provide greater diagnostic accuracy compared to either mode of biopsy alone. The objectives therefore of the MULTIPROS randomized controlled trial were to assess the diagnostic accuracy of prebiopsy mpMRI for the identification of csPCa using RP specimens as the reference standard, and to test the diagnostic accuracy of combined US/MRI fusion biopsy with systematic biopsies

Materials and Methods

Study design and participants

The MULTIPROS study (ClinicalTrials.gov, NCT02745496) was a randomized, prospective, multicenter diagnostic accuracy study of prebiopsy mpMRI with subsequent randomization at a 1:1 ratio of men with MRI findings positive for prostate cancer to the intervention group (systematic biopsy and targeted biopsy) or control group (systematic prostate biopsy only). The design of the trial is shown in Figure S1 and was conducted according to a published, pretrial study protocol with full institutional review board and ethics approval (17).

Men with clinically suspected PCa, between 40 and 75 years of age, with at least 10 years of life expectancy were recruited from university hospitals consecutively between February 2015 to August 2020. Suitability for

radical treatment of prostate cancer was based on age and the comorbidities of patients including the performance status of the individuals included as participants. Eligible men had a prostate-specific antigen (PSA) <20 ng/ml, with digital rectal examination (DRE) findings of ≤pT2b. Men were excluded from recruitment if they were unable to provide written informed consent, had undergone prior prostate biopsy, were diagnosed with acute prostatitis within the last 12 months, or had contraindications to biopsy or MRI. Detailed inclusion and exclusion criteria are provided in the protocol.(17) csPCa was defined on whole-mount pathology as a Gleason score (GS) of either ≥3+4 or lesion size >6 mm. Men with atypical small acinar proliferation or high-grade intraepithelial neoplasia were not included.

MpMRI

All men who considered study participation were offered 3 Tesla mpMRI prior to biopsy. The institutional MRI machines included a Siemens 3T Magnetom Trio-PrismaFIT (NHS Tayside), Philips 3.0T Achieva (NHS Grampian) and a Philips 1.5T Ingenia (Royal Free London).

The imaging protocol was standardized as per European Society of Urogenital Radiology guidelines (18) and comprised T2-weighted imaging and diffusion weighted imaging (DWI), including high B value and dynamic contrast enhanced (DCE) sequences, with an additional 3D T2-weighted turbo-spin-echo sequence acquired for biopsy planning (Table S6).

The mpMRI scans performed at each center were prospectively reviewed by experienced uroradiologists (MSB, SKA, and JS with over 5 years of experience) with a caseload of >200 mpMRI per year. The radiologists were blinded to the clinical details of participants, including but not limited to age, PSA level, DRE findings and family history. All MRI reports were read using PI-RADS v 2.0.(19)

Participants with the presence of at least one lesion with a PI-RADS score ≥3 were considered to have positive MRI findings. To assess interobserver agreement, a priori 160 scans were randomly selected (89 from the subset of men undergoing LRP, and 71 from other recruited men) and reanalyzed retrospectively by a second equally qualified uroradiologist, who was also blinded to the clinical data and to each radiology report.(17) Interobserver agreement statistical analyses were completed during the trial.

Randomization

Randomization was performed for all MRI-positive recipients (PI-RADS ≥3) in a 1:1 ratio to the intervention group or control group. The randomization system was compliant with good clinical practice guidelines and monitored by the local institutional research governance board. Randomization was implemented with random block sizes, and stratified by: center, PI-RADS score (3, 4 or 5), suspicious index lesion size (<6 mm or ≥6 mm in maximal diameter on MRI), age (40-59 or 60-75 years old), and PSA (<10.1 or 10.1-20 ng/ml).

Biopsy

Following MRI and randomization, the biopsy procedure was performed within 1 week of the mpMRI scan. Participants were blinded to their mpMRI report findings and biopsy types, i.e., systematic or combined

systematic and targeted biopsies. If randomized to the intervention group, i.e., US fusion biopsy, the uroradiologist who produced the mpMRI report clinically registered mpMRI (3D or T2WI sequences) to the US machine and marked suspicious lesions for targeting, with a maximum of 2 index lesions (highest PI-RADS score and/or largest size) targeted for each procedure (Software and machine data: Table S6). The targeted biopsy was performed, with a minimum of 2 cores taken; subsequently, a systematic biopsy followed (20).

Surgery and Pathological Evaluation

After tumor board ratification and appropriate counselling, some participants selected to undergo Laparoscopic RP for the treatment of clinically localized prostate cancer. Laparoscopic RP was performed by a standardized approach, with or without lymph node dissection (21). Prostate specimens from the men undergoing RP were sectioned in 3D-printed moulds to ensure correct orientation with pathological specimens and to assist accurate sectioning (22). The whole-mount specimen pathology findings were then compared with the MRI findings. Prostate specimens were analyzed by two uropathologists (JW and SL with over 10 years of experience), who were blinded to the MRI findings.

Safety analysis

Adverse events (AEs) and serious adverse events (SAEs) were recorded and reported as per Health Research Authority recommendations and sponsor requirements Only AEs and SAEs, defined as negative outcomes related to the study procedures, i.e., MRI and the biopsy procedure, occurring up until 30 days post-biopsy were reported. AE reporting was completed during the trial.

Power calculation

As outlined in the pre-published study protocol, it was estimated that out of 600 participants, 480 (80%) would have positive mpMRI findings, and each of the two randomization arms would have approximately n=240.(17) Local audit information suggested that after a positive diagnosis of localized PCa, approximately 25% of would opt for RP as a treatment option. Based on the recruitment of 600 those eligible, the power calculation, assessing 80% sensitivity with precision of +/- 9% , that is, a 95% CI width of 18% suggested that at least n=80 participants with complete datasets from imaging and RP histopathology were needed for the diagnostic accuracy study.

Statistical analysis

The primary outcome was the diagnostic accuracy of mpMRI in the detection of csPCa, using RP histopathology as the gold standard. Odds ratios were calculated to compare intergroup (intervention vs control) findings. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated with 95% confidence intervals. Whole-prostatectomy specimen lesions were also grouped by PI-RADS scores and GS for analysis.

The trial analysis was based on the intention-to-treat principle. A comparison of the trial outcome of cancer detected was analyzed using multiple logistic regression, with participants as a random variable adjusted for

PI-RADS score (3, 4 or 5), suspicious index lesion size (<6 mm or ≥6 mm in maximal axial diameter on MRI), age (40-59 or 60-75 years old), and PSA (<10.1 or 10.1-20 ng/ml) with trial arm parameter, fusion or systematic biopsy added. Accuracy or calibration was assessed by implementing the Hosmer–Lemeshow test. Secondary outcomes for the trial included the number of participants with csPCa diagnosed in each randomized group of biopsy approaches, the number of AEs, and mortality.

To measure the mpMRI interobserver agreement or interrater reliability, the observed agreement rate (p_0 or accuracy), chance agreement rate (p_1) and Cohen's kappa coefficient were calculated (23). SAS software (version 9.4, SAS Institute Inc.) was used for all statistical analyses which were performed by statisticians (PTD and PR with 20 years of experience).

Results

Participants

Among 603 participants recruited from three centers between January 2015 and August 2020 (n=595 from NHS Tayside, n=1 from NHS Grampian and n=7 from The Royal Free London NHS Trust), 582 were eligible for mpMRI, with a mean age of 65 years ±6 [SD]. 413/582 (71%) had positive MRI findings for suspicious prostate cancer and were randomized into either the interventional group (207/413, 50%) or control group (206/413, 50%), (Table 1). All those with negative MRI findings (169/582, 29%) were allocated to systematic biopsy as a diagnostic standard of care (Fig 1). 21 participants were withdrawn prior to MRI, and 36/576 biopsies in participants were omitted for various reasons (Fig. 1). Between groups, there were no evidence of significant differences in baseline characteristics (Table 1).

Primary outcome: csPCa detection by mpMRI

A total of 91/413 men with MRI-positive findings (22%) underwent laparoscopic RP (RP), all in NHS Tayside. Of these, the prostates of n=2 were not sectioned in customized moulds and were excluded from the analysis. In 89 prostate specimens, 182 foci of csPCa were detected, out of which mpMRI correctly identified 131 csPCa (sensitivity: 72% (131/182), 95% CI 65%-78%). The specificity, PPV and NPV were 71.1% (91/128), 78% (131/168) and 64% (91/142), respectively (Table 2).

A total of 168 lesions of PI-RADS 3 or above were identified on the mpMRI of 89 men, consisting of 77 PI-RADS 5, 66 PI-RADS 4 and 25 PI-RADS 3 lesions. PI-RADS 5 lesions had the highest percentage of csPCa (91%), followed by PI-RADS 4 (70%) and PI-RADS 3 (52%) lesions, (Fig 2).

When the GSs of the detected cancer foci were considered, MRI detected 87% of GS>7 cancers (26/30), 54% of GS 7 cancers (112/206) and 4.3% of clinically insignificant GS 6 cancers (2/44) (Fig S2, Table S1). These lesion-level data were obtained using whole-mount pathology. The percentage of men with csPCa diagnosed by systematic biopsy but missed by MRI-guided biopsy in the MULTIPROS study was 8.4% (17/203) (Table S4).

Secondary outcome: **Cancer detection between combined fusion and systematic random biopsies versus systematic random biopsies**

In the intervention group (targeted + systematic biopsy), 151/207 (73%) men had PCa detected versus 124/206 (60%) men in the control group (systematic biopsy). There was a higher probability of PCa detection in the intervention versus control group (*P*<.001) and when adjusted for minimization variables (odds ratio [OR] = 2.16; 95% CI 1.3, 3.4) (Table 3). In the intervention arm, csPCa was found in 130/207 (63%) men, while systematic biopsy alone detected csPCa in 106/206 (51%) men. A greater number of csPCa lesions were detected in the targeted combined with systematic biopsy arm than in the control arm (OR= 1.79 (1.14, 2.79), *P*=.002 (Table 3, Table S7).

In a sub-analysis of men from the intervention group, targeted biopsy detected a greater number of all cancer for PI-RADS 5 lesions on MRI, both in PCa detection (82% vs 76%) and csPCa detection (75% vs 66%) (Fig 3). For men with PI-RADS ≤4 on MRI, targeted biopsy did not perform as well as systematic biopsy in detecting all cancers (40% vs 50%) but detected a higher proportion of csPCa (28% vs 35%). For men with a PI-RADS score of ≤3 on MRI, the csPCa detection rate was low, and targeted biopsy was inferior to systematic biopsy (10% vs 21%). In our study, 51/142 participants, i.e., 35%, had a PI-RADS score <3, and a csPCa biopsy GS of ≥3+4 or lesion size of 6 mm and above.

A total of 169 men had negative MRI findings, i.e., no PI-RADS lesion score was assigned to any prostatic tissue, and 138/169 men from this group underwent systematic biopsy. The csPCa detection rate in this group was 6% (8/138).

Interobserver agreement

There was substantial agreement between the mpMRI reporters (p_0=91%, Cohen's kappa coefficient=0.7 (Table S2).

Safety analysis

Forty-eight and 64 men in the control and intervention groups, respectively (23% vs 31%), experienced AEs (Table 4; Table S5). Men in the control group reported fewer post-biopsy AEs, e.g., hematospermia (4% vs 6%), postprocedural hematuria (17% vs 20%), postprocedural hemorrhage (3% vs 5%) and procedural pain (3% vs 5%), than men in the intervention group (Table S3). Only 1 biopsy-procedure-related SAE was reported in each group (both participants had sepsis), (Table 4). One nonprocedural-related SAE in the intervention arm was an intracranial hemorrhage occurring 22 days after biopsy.

Discussion

The optimal diagnostic pathway for prostate cancer is still evolving. The MULTIPROS randomized trial was designed to test the diagnostic accuracy of prebiopsy mpMRI for the identification of csPCa using RP specimens as the reference standard and to test US/MRI fusion targeted biopsy plus systematic biopsy versus systematic biopsy for cancer detection in a randomized controlled trial. In 89 prostate specimens, 182 foci of csPCa were detected, out of which mpMRI correctly identified 131 csPCa lesions. The sensitivity, specificity, PPV and NPV were 72% (131/182), 71% (91/128), 78% (131/168) and 64% (91/142), respectively. 151/207

(73%) men had PCa detected (targeted + systematic biopsy) versus 124/206 (60%) men in the control group (systematic biopsy). There was a higher probability of PCa detection in the intervention vs control group (*P*=.002) and when adjusted for minimization variables (odds ratio [OR] = 2.16; 95% CI: 1.3, 3.4).

The PROMIS study recorded the sensitivity of mpMRI for csPCa using mapping transperineal template biopsy as a reference standard to be 93% (95% CI: 88%, 96%) with a specificity of 41%.(1) The sensitivity achieved was likely higher than that in our study, as it was assessed at the patient level. An alternative explanation is template biopsies overrepresented the true disease extent (14). Furthermore, this histological bias may have been compounded by simultaneous "overcalling" of PI-RADS scores.

At the lesion level, one study reported 100%, 75% and 18% of PCa detection according to PI-RADS scores of 5, 4, and 3, respectively, including clinically insignificant PCa (24). In our dataset, 91%, 77%, and 48% of all lesions with PI-RADS scores of 5 (n=77), 4 (n=66), and 3 (n=25), respectively, corresponded to csPCa foci at RP histopathology. In the PROMIS study, the MRI-positive group showed csPCa in 81%, 58% and 21%, of all lesions with PI-RADS scores of 5, 4, and 3, respectively. Our results confirm that a higher PI-RADS score corresponds to a higher likelihood of csPCa detection and a higher GS. The relatively higher proportion of csPCa in PI-RADS 3 lesions in the present study are comparable to 2/26 studies in a meta-analysis of PIRADS 3 lesions, these studies were the only others in the meta-analysis to use whole mount specimen data (25). We suggest that PI-RADS 3 classification therefore may under-represent some Gleason scores according to the true gold standard (26).

In the intervention group, 151/207 (73%) men had PCa detected (targeted + systematic biopsy) versus 124/206 (60%) men in the control group (systematic biopsy). There was a higher probability of PCa detection in the intervention vs control group (*P*<.001) and when adjusted for minimization variables (odds ratio [OR] = 2.16; 95% CI: 1.3, 3.4). This contrasts with results from the PRECISION study, in which image fusion targeted biopsies outperformed systematic random biopsies (2). Men randomized to biopsies only in the PRECISION study underwent TRUS-guided biopsy, which potentially introduced measurement bias in the cohort undergoing systematic biopsies.

In the MULTIPROS study, only men with mpMRI findings positive for prostate cancer were randomized, and the control group undergoing systematic random biopsies had a confirmed prebiopsy positive MRI scan, modifying the pretest probability of systematic biopsies and improving their predictive value. Although there is still debate on the optimal biopsy technique in biopsy-naïve men with suspicious MRI lesions (27) combined systematic and targeted biopsies for PI-RADS 4 or 5 scores are superior to targeted or systematic biopsies alone in detecting csPCa (26,28–30).

In both arms of our study, the only procedure-related SAE was one case of sepsis in each arm, a well-recognized complication of transrectal prostate biopsies (31). In our series, the higher number of immediate post-biopsy AEs might be related to the higher number of cores taken at combined biopsy.

Histopathological Gleason grading is susceptible to discrepancy between expert pathologists (32–34). A future retrospective study would verify the consistency among pathological reports in MULTIPROS. A limitation to MULTIPROS is the lack of inter-observer variability among pathologists. PI-RADS v2.0 was used for the assessment of mpMRI during our study, and this was replaced by the updated v2.1 in 2019. For consistency, the version used for assessment of mpMRI during the study (v2.0) remained unchanged, and v2.1 consisted of only minor alterations (35). Differences between v2.0 and 2.1 relate predominantly to classification of indeterminate lesions (P2-3) in transition zone and assessment of indeterminate lesions in both peripheral and transition zone to reduce their number, resulting in increased diagnostic accuracy of the scoring system (36–38). Template biopsies yield higher tissue sampling density than targeted or systematic biopsies(14), sampling areas of higher-grade prostate cancer, overrepresenting the true disease extent and leading to downgrading at final histopathology. If a core sample is only Gleason score 4, reporting will be 4 + 4 (GS-8) (14). However, the surrounding tissue is often positive for Gleason score 3 (39) therefore, at the periphery of high-grade disease, RP pathology then shows 3 + 4 (GS-7) or 4 + 3 (GS-7). A single GS-8 transperineal prostate mapping biopsy core strongly biases results toward overgrading. We suggest that transcriptomic and radiomic data at the lesion level in the future might enable a better understanding of intralesional patterns of disease grade. The majority of the missed CS PCa lesions were smaller than 15mm in size and located in the anterior half of the gland. This observation will be useful for the reporting radiologist to include anterior gland as a focused review area.

In conclusion, prebiopsy MRI categorization using PI-RADS v2.0 was accurate in the detection of clinically significant prostate cancer, with acceptable interobserver agreement. Combined US/MRI fusion targeted biopsies and systematic random biopsies detected more clinically significant lesions than either modality alone. Further work is warranted in explaining why multiparametric MRI does not characterize all prostate cancer which is subsequently detected by biopsy, and RP.

Declaration of interests

We declare no competing interests.

Acknowledgments

Tayside Clinical Trials Unit

References

1. Ahmed HU, Bosaily AES, 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. The Lancet. 2017 Feb 25;389(10071):815–22.

2. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018 May 10;378(19):1767–77.

3. Wegelin O, Exterkate L, van der Leest M, Kummer JA, Vreuls W, de Bruin PC, et al. The FUTURE Trial: A Multicenter Randomised Controlled Trial on Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies. Eur Urol. 2019 Apr;75(4):582–90.

4. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. Eur Urol. 2019 Apr;75(4):570–8.

5. Brizmohun Appayya M, Adshead J, Ahmed HU, Allen C, Bainbridge A, Barrett T, et al. National implementation of multi-parametric magnetic resonance imaging for prostate cancer detection - recommendations from a UK consensus meeting. BJU Int. 2018 Jul;122(1):13–25.

6. Overview | Prostate cancer: diagnosis and management | Guidance | NICE [Internet]. NICE; [cited 2022 Sep 5]. Available from: https://www.nice.org.uk/guidance/ng131

7. Padhani AR, Barentsz J, Villeirs G, Rosenkrantz AB, Margolis DJ, Turkbey B, et al. PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway. Radiology. 2019 Aug;292(2):464–74.

8. Muthigi A, George AK, Sidana A, Kongnyuy M, Simon R, Moreno V, et al. Missing the Mark: Prostate Cancer Upgrading by Systematic Biopsy over Magnetic Resonance Imaging/Transrectal Ultrasound Fusion Biopsy. J Urol. 2017 Feb;197(2):327–34.

9. Bryk DJ, Llukani E, Taneja SS, Rosenkrantz AB, Huang WC, Lepor H. The Role of Ipsilateral and Contralateral Transrectal Ultrasound-guided Systematic Prostate Biopsy in Men With Unilateral Magnetic Resonance Imaging Lesion Undergoing Magnetic Resonance Imaging-ultrasound Fusion-targeted Prostate Biopsy. Urology. 2017 Apr;102:178–82.

10. Stabile A, Giganti F, Emberton M, Moore CM. MRI in prostate cancer diagnosis: do we need to add standard sampling? A review of the last 5 years. Prostate Cancer Prostatic Dis. 2018 Nov;21(4):473–87.

11. Alqahtani S, Zhang X, Wei C, Zhang Y, Szewczyk-Bieda M, Wilson J, et al. Predicting the Performance of Concurrent Systematic Random Biopsies during Image Fusion Targeted Sampling of Multi-Parametric MRI Detected Prostate Cancer. A Prospective Study (PRESET Study). Cancers. 2021 Dec 21;14(1):1.

12. Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, et al. Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature. Eur Urol. 2015 Dec;68(6):1045–53.

13. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Diagnostic Performance of Prostate Imaging Reporting and Data System Version 2 for Detection of Prostate Cancer: A Systematic Review and Diagnostic Meta-analysis. Eur Urol. 2017 Aug;72(2):177–88.

14. Crawford ED, Rove KO, Barqawi AB, Maroni PD, Werahera PN, Baer CA, et al. Clinical-Pathologic Correlation Between Transperineal Mapping Biopsies of the Prostate and Three-Dimensional Reconstruction of Prostatectomy Specimens. The Prostate. 2013;73(7):778–87.

15. Greer MD, Shih JH, Lay N, Barrett T, Kayat Bittencourt L, Borofsky S, et al. Validation of the Dominant Sequence Paradigm and Role of Dynamic Contrast-enhanced Imaging in PI-RADS Version 2. Radiology. 2017 Dec;285(3):859–69.

16. Choi MH, Kim CK, Lee YJ, Jung SE. Prebiopsy Biparametric MRI for Clinically Significant Prostate Cancer Detection With PI-RADS Version 2: A Multicenter Study. Am J Roentgenol. 2019 Apr;212(4):839–46.

17. Szewczyk-Bieda M, Wei C, Coll K, Gandy S, Donnan P, Ragupathy SKA, et al. A multicentre parallel-group randomised trial assessing multiparametric MRI characterisation and image-guided biopsy of prostate in men suspected of having prostate cancer: MULTIPROS study protocol. Trials. 2019 Nov 21;20(1):638.

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

19. Turkbey B, Choyke PL. PIRADS 2.0: what is new? Diagn Interv Radiol. 2015 Sep;21(5):382–4.

20. Chang SD, Ghai S, Kim CK, Oto A, Giganti F, Moore CM. MRI Targeted Prostate Biopsy Techniques: AJR Expert Panel Narrative Review. AJR Am J Roentgenol. 2021 Dec;217(6):1263–81.

21. Stolzenburg JU, Kallidonis P, Minh D, Dietel A, Häfner T, Dimitriou D, et al. Endoscopic Extraperitoneal Radical Prostatectomy: Evolution of the Technique and Experience with 2400 Cases. J Endourol. 2009 Sep;23(9):1467–72.

22. Wei C, Li C, Szewczyk-Bieda M, Upreti D, Lang S, Huang Z, et al. Performance Characteristics of Transrectal Shear Wave Elastography Imaging in the Evaluation of Clinically Localized Prostate Cancer: A Prospective Study. J Urol. 2018 Sep;200(3):549–58.

23. McHugh ML. Interrater reliability: the kappa statistic. Biochem Medica. 2012;22(3):276–82.

24. Auer T, Edlinger M, Bektic J, Nagele U, Herrmann T, Schäfer G, et al. Performance of PI-RADS version 1 versus version 2 regarding the relation with histopathological results. World J Urol. 2017 May;35(5):687–93.

25. Wadera A, Alabousi M, Pozdnyakov A, Kashif Al-Ghita M, Jafri A, McInnes MD, et al. Impact of PI-RADS Category 3 lesions on the diagnostic accuracy of MRI for detecting prostate cancer and the prevalence of prostate cancer within each PI-RADS category: A systematic review and meta-analysis. Br J Radiol. 2021 Feb;94(1118):20191050.

26. Baco E, Rud E, Eri LM, Moen G, Vlatkovic L, Svindland A, et al. A Randomized Controlled Trial To Assess and Compare the Outcomes of Two-core Prostate Biopsy Guided by Fused Magnetic Resonance and Transrectal Ultrasound Images and Traditional 12-core Systematic Biopsy. Eur Urol. 2016 Jan;69(1):149–56.

27. Ippoliti S, Fletcher P, Orecchia L, Miano R, Kastner C, Barrett T. Optimal biopsy approach for detection of clinically significant prostate cancer. Br J Radiol. 2022 Mar 1;95(1131):20210413.

28. Hansen NL, Barrett T, Kesch C, Pepdjonovic L, Bonekamp D, O'Sullivan R, et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer. BJU Int. 2018 Jul;122(1):40–9.

29. 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 Jan 27;313(4):390–7.

30. Panebianco V, Barchetti F, Sciarra A, Ciardi A, Indino EL, Papalia R, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urol Oncol. 2015 Jan;33(1):17.e1-17.e7.

31. Rosario DJ, Lane JA, Metcalfe C, Donovan JL, Doble A, Goodwin L, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ. 2012 Jan 9;344:d7894.

32. Brimo F, Schultz L, Epstein JI. The value of mandatory second opinion pathology review of prostate needle biopsy interpretation before radical prostatectomy. J Urol. 2010 Jul;184(1):126–30.

33. Ozkan TA, Eruyar AT, Cebeci OO, Memik O, Ozcan L, Kuskonmaz I. Interobserver variability in Gleason histological grading of prostate cancer. Scand J Urol. 2016 Dec;50(6):420–4.

34. An audit of inter-observer variability in Gleason grading of prostate cancer biopsies: The experience of central pathology review in the North West of England. Integr Cancer Sci Ther [Internet]. 2015 [cited 2022 Sep 6];2(2). Available from: http://oatext.com/An-audit-of-inter-observer-variability-in-Gleason-grading-of-prostate-cancer-biopsies-The-experience-of-central-pathology-review-in-the-North-West-of-England.php

35. Barrett T, Rajesh A, Rosenkrantz AB, Choyke PL, Turkbey B. PI-RADS version 2.1: one small step for prostate MRI. Clin Radiol. 2019 Nov;74(11):841–52.

36. Bhayana R, O'Shea A, Anderson MA, Bradley WR, Gottumukkala RV, Mojtahed A, et al. PI-RADS Versions 2 and 2.1: Interobserver Agreement and Diagnostic Performance in Peripheral and Transition Zone Lesions Among Six Radiologists. AJR Am J Roentgenol. 2021 Jul;217(1):141–51.

37. Wei CG, Zhang YY, Pan P, Chen T, Yu HC, Dai GC, et al. Diagnostic Accuracy and Interobserver Agreement of PI-RADS Version 2 and Version 2.1 for the Detection of Transition Zone Prostate Cancers. AJR Am J Roentgenol. 2021 May;216(5):1247–56.

38. Hötker AM, Blüthgen C, Rupp NJ, Schneider AF, Eberli D, Donati OF. Comparison of the PI-RADS 2.1 scoring system to PI-RADS 2.0: Impact on diagnostic accuracy and inter-reader agreement. PloS One. 2020;15(10):e0239975.

39. Erickson A, He M, Berglund E, Marklund M, Mirzazadeh R, Schultz N, et al. Spatially resolved clonal copy number alterations in benign and malignant tissue. Nature. 2022 Aug;608(7922):360–7.

Tables

Table 1. Baseline characteristics of the participants

Characteristic	Total (n=603)	Intervention group (n=207)	Control group (n=206)	MRI-negative arm (n=169)	No MRI results (n=21)
Age at referral					
Mean (SD)	64.8 (6.4)	65.4 (6.3)	65.1 (6.2)	63.1 (6.0)	63 (6)
Median (IQR)	65 (47, 75)	66 (49, 75)	66 (47, 75)	65 (50, 74)	65 (50, 74)
PSA (ng/ml) at referral					
Mean (SD)	9.0 (6.5)	9.3 (6.1)	10.2 (8.6)	7.1 (3.1)	8.4 (2.8)
Median (IQR)	7.7 (1.0, 86.0)	8.2 (1.0, 74.0)	8.6 (1.0, 86.0)	6.7 (1.0, 18.0)	8.1 (4.0, 14.0)
Highest Gleason grade, N (%)					
No information	57 (9.5)	3 (1.4)	1 (0.5)	32 (18.9)	21 (100.0)
Negative	247 (41.0)	52 (25.1)	79 (38.3)	116 (68.8)	0 (0)
3+3	54 (9.0)	22 (10.6)	19 (9.2)	13 (7.7)	0 (0)
3+4	88 (14.6)	42 (20.3)	40 (19.4)	6 (3.6)	0 (0)
4+3	61 (10.1)	35 (16.9)	24 (11.7)	2 (1.2)	0 (0)

3+5	2 (0.3)	1 (0.5)	1 (0.5)	0 (0)	0 (0)
4+4	27 (4.5)	19 (9.2)	8 (3.9)	0 (0)	0 (0)
4+5	48 (8.0)	24 (11.6)	24 (11.7)	0 (0)	0 (0)
5+4	19 (3.2)	9 (4.3)	10 (4.9)	0 (0)	0 (0)

PSA, prostate-specific antigen.

Table 2. Clinically significant cancer detection rate for MRI compared with laparoscopic radical prostatectomy.

			Pathology			
			No cancer	Clinically insignificant	Clinically significant	Total
MRI (PI-RADS)	mpMRI negative			91	51	142
	mpMRI positive	3	11	1	13	25
		4	14	4	48	66
		5	3	4	70	77
	total		28	100	182	310
Sensitivity			0.72 (95% CI: 0.65, 0.78)			
Specificity			0.71 (95% CI: 0.62, 0.79)			
PPV			0.78 (95% CI: 0.71, 0.84)			
NPV			0.64 (95% CI: 0.56, 0.72)			

Footnote: Clinically significant prostate cancer in this analysis was a lesion with a Gleason score ≥3+4 (n=44) or >6 mm in size (including Gleason score 6, n=7).

PI-RADS, Prostate Imaging-Reporting and Data System; PPV, positive predictive value; NPV, negative predictive value.

TP: true positives; FP: false positives; FN: false negatives; TN: true negatives (note for TP and FP, breakdown by PIRADS score is provided)

Table 3. Results of logistic regression for (1) the outcome of a clinically significant lesion, (2) the trial outcome of all cancers for the intervention group vs the control group, and (3) the trial outcome of all clinically significant prostate cancers for the intervention group vs the control group

	Unadjusted		**Adjusted***	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
(1) MRI lesion (positive vs negative)	1.87 (1.34, 2.45)	<.001	1.90 (1.35, 2.45)	<.001
(2) Cancers in the intervention (target + systematic) vs the control group (systematic)	1.90 (1.24, 2.90)	.003	2.16 (1.34, 3.47)	.002
(3) csPCa in the intervention vs the control group	1.63 (1.10, 2.42)	.016	1.79 (1.14, 2.79)	.01

*Adjusted for the Prostate Imaging-Reporting and Data System score (3, 4 or 5), suspicious index lesion size (<6 mm or ≥6 mm in maximal diameter on MRI), age (40-59 or 60-75 years old), and prostate-specific antigen (<10.1 or 10.1-20 ng/ml).

csPCa, clinically significant prostate cancer; OR, odds ratio.

Table 4. Adverse events and serious adverse events reported in the control arm and intervention arm

Characteristic	Control arm	Intervention arm
All men	206	207
Men with adverse events	48 (23%)	64 (31%)
Men with serious adverse events	1 (0.5%)	2 (1.0%)
Cerebral hemorrhage	0 (0.0%)	1 (0.5%)
Sepsis	0 (0.0%)	1 (0.5%)
Urosepsis	1 (0.5%)	0 (0.0%)

Data presented as number of events with percentage

Supplementary Table S1. Cancer distribution map according to Gleason Score and PI-RADS score based on whole mount histopathology

PIRADS vs Gleason score		Gleason score				
		<6	6	7	>7	Total
PI-RADS score	Negative		44	94	4	142
	3	11	0	13	1	25
	4	14	0	47	5	66
	5	3	2	52	20	77
	Total	28	46	206	30	310

Negative indicates PIRADS <3.

Supplementary Table S2. Patient-based MRI reading variability in 160 randomly selected validation cases

Supplementary Table S2a. Lesion based MRI reading agreement in 160 randomly selected cases

Lesion based		First reading				Total
		Negative	PI-RADS 3	PI-RADS 4	PI-RADS 5	
Second reading	Negative		24	28	8	60
	PI-RADS 3	8	10	4	6	28
	PI-RADS 4	17	5	50	22	94
	PI-RADS 5	4	1	4	72	81
Total		29	40	86	108	263

Supplementary Table S2B. Patient based MRI reading variability in 160 randomly selected cases

Patient based		**First reading**		**Total**
		Positive	**Negative**	
Second reading	**Positive**	125 (78%)	5 (3%)	130 (81%)
	Negative	9 (6%)	21 (13%)	30 (19%)
Total		134 (84%)	26 (16%)	160

P_0(accuracy)	91%
P_1	71%
kappa	0.7

Agreement

No agreement

Supplementary Table S3a. Comparison between detection rate for systematic and targeted biopsy in intervention group (n=203)

Biopsy type and outcome	Targeted csPCa	Targeted no csPCa	McNemar Chi-square	Degree of freedom	*P* value*
Systematic csPCa	85	17			
Systematic no csPCa	29	72	3.13	1	.08

*To make the result statistically significant, the adjusted p value for comparison is 0.0125.

Supplementary Table S3b. Difference in prostate cancer detection rate using systematic biopsy in control group and intervention groups

Measurement	Significant prostate cancer	%	Non-significant prostate cancer	%	Pearson Chi-square	Degree of freedom	*P* value*
Systematic biopsy in control group (n=205)	106	52	99	48			
Targeted biopsy in intervention group (n=203)	114	56	89	44	0.81	1	.40

*To make the result statistically significant, the adjusted *P* value for comparison is 0.0125.

Supplementary Table S3c. Systematic biopsy between participants in control group and intervention group

Group	Significant prostate cancer	%	Non-significant prostate cancer	%	Pearson Chi-square	Degree of freedom	*P* value*
Systematic biopsy in Control group	106	52	99	48			
Systematic biopsy in Intervention group	102	50.2	101	49.8	0.09	1	.80

*To make the result statistically significant, the adjusted *P* value for comparison is 0.0125.

Supplementary Table S4a. Summary of MRI detection rates with different biopsy procedures performed: Group 1: Systermatic biopsy only for participants (MRI positive cohort from Control group); Group 2: Systermatic biopsy only for all participants (MRI positive cohort from intervention group); Group 3: Fusion targted biopsy for MRI positive participants and Systemetic biopsy for the rest; Group 4: Fusion targeted+systermatic biopsy for MRI positive participants and Systematic biopsy for the rest; Group 5: systematic biopsy only for participants (MRI positive cohort from both intervention and control group, Group 1+2)

MRI vs biopsy results (inter group comparison)			Biopsy results		
			Non-significant cancer	Significant cancer	Total
MRI	Negative		130	8	138
	Positive	1	99	106	205
		2	100	103	203
		3	89	114	203
		4	71	132	203
		5	199	209	408
	total	1	229	114	343
		2	230	111	341
		3	219	122	341
		4	201	140	341
		5	330	217	546

Supplementary Table S4b. Summary diagnostic accuracy performance for MRI detection rates for different biopsy procedures performed

	mpMRI diagnostic accuracy within different groups	Sensitivity	Specificity	PPV	NPV
1	Control group	93%	57%	51%	94%
2	Systematic biopsy from intervention group	93%	57%	51%	94%
3	Targeted biopsy from intervention group	93%	60%	56%	94%
4	Intervention group	94%	65%	65%	94%
5	Systematic biopsy from both groups	96%	39%	51%	94%

Supplementary Table S5. Adverse events reported in Control arm and intervention arm

Characteristic	Control arm	Intervention arm
All men	206 (100%)	207 (100%)
Men without adverse events	158 (7.7%)	143 (69.1%)
Men with adverse events	48* (23.3%)	64^ (30.9%)
Anorectal discomfort	1 (0.5%)	0 (0.0%)
Back pain	0 (0.0%)	0 (0.0%)
Balance disorder	0 (0.0%)	1 (0.5%)
Cerebral haemorrhage	0 (0.0%)	1 (0.5%)
Chills	0 (0.0%)	1 (0.5%)
Claustrophobia	1 (0.5%)	0 (0.0%)
Diarrhoea	1 (0.5%)	0 (0.0%)
Dysuria	0 (0.0%)	2 (1.0%)
Gastrointestinal infection	0 (0.0%)	1 (0.5%)
Haematospermia	9 (4.4%)	13 (6.3%)
Headache	0 (0.0%)	2 (1.0%)
Hot flush	1 (0.5%)	0 (0.0%)
Hyperhidrosis	0 (0.0%)	1 (0.5%)
Nausea	1 (0.5%)	1 (0.5%)
Paraesthesia	0 (0.0%)	0 (0.0%)
Pollakiuria	0 (0.0%)	1 (0.5%)
Post procedural haematuria	35 (17.0%)	41 (19.8%)
Post procedural haemorrhage	6 (2.9%)	10 (4.8%)
Procedural pain	6 (2.9%)	10 (4.8%)
Proctalgia	0 (0.0%)	1 (0.5%)
Rash	1 (0.5%)	0 (0.0%)
Renal pain	0 (0.0%)	2 (1.0%)
Sepsis	0 (0.0%)	1 (0.5%)

Testicular pain	0 (0.0%)	1 (0.5%)
Urinary hesitation	0 (0.0%)	1 (0.5%)
Urinary tract infection	1 (0.5%)	3 (1.4%)
Urosepsis	1 (0.5%)	0 (0.0%)

*: 64 adverse events recorded in 48 men in control arm.

^: 94 adverse events recorded in 64 men in intervention arm.

Supplementary Table S6 MRI and Ultrasound Information for Host Centre

Siemens Magnetom 3T Trio-PrismaFIT				
Pulse Sequence Name	2D T2 Fast/Turbo Spin Echo	2D EPI-DWI	3D DCE (T1 VIBE)	3D T2 TSE SPACE
TR (ms)	4000-6000	3300	4.76	2000
TE (ms)	100-102	95	2.45	123
Orientation	Sagittal, Transverse, Coronal (oblique)	Transverse (oblique)	Transverse (oblique)	Transverse (oblique)
FOV (mm)	200 (patient dependent)	280	280	256
Phase FOV (%)	100	100	78.1	100
Number of slices	19-35 (patient dependent)	22	22	72
Slice Thickness (mm)	3	3	3	1
Averages	2-3 (patient dependent)	9-12	1	1.5
Filters	2D Distortion Correct, Prescan Normalise, Elliptical	2D Distortion Correct, RAW	2D Distortion Correct, Elliptical	Elliptical
RF Coils	Body Matrix and Spine Array	Body Matrix and Spine Array	Body Matrix and Spine Array	Body Matrix and Spine Array
Fat Suppresion	---	FATSAT	---	---
Pixel Matrix	272-288x320	144x192	138x192	256x256
Phase oversampling	35-100% (patient dependent)	25	0	75
Parallel Imaging	GRAPPA x2	GRAPPA x2	GRAPPA x2	GRAPPA x2
Bandwidth (Hz/Pix)	203-252	1302	540	651
ETL/Turbo Factor (TF)	23-27	144	---	79
RF Pulse Type	Low SAR	Normal	Fast	Normal
Gradient Mode	Normal	Fast	Fast	Fast
b-values (s/mm2)	---	(i) 50, 100, 500, 1000; (ii) 2000	---	-
Voxel Size (mm x mm x mm)	0.7x0.6x3.0	1.9x1.5x3.0	2.0x1.5x3.0	1.0x1.0x1.0
Scan Time (min:sec)	04:10-04:26 (patient dependent)	04:49	03:22:00 (4-6 sec/measure)	05:02
Extras	2 concatenations	Phase Partial Fourier 6/8	Phase Partial Fourier 6/8	Restore Pulse, Slice TF 2

EPI - Echo Planar Imaging, DWI - Diffusion Weighted Imaging: (i) standard acquisition for ADC map calculation; (ii) separate high B-value acquisition DCE - Dynamic Contrast Enhanced, TSE - Turbo Spin Echo, SPACE - Sampling Perfection with Application optimized Contrasts using different flip angle Evolution, TR - Repetition Time, TE - Echo Time, FOV - Field of View, RF – Radiofrequency, GRAPPA - Generalized Auto-Calibrating Partial Parallel Acquisition, ETL - Echo Train Length, SAR - Specific Absorption Rate

Ultrasound MRI fusion software used

Tayside: Olea sphere ® package, Olea-Medical Solutions ltd, Paris, France.

Grampian and Royal Free: Philips DynaCAD 3.3, Phillips Invivo corp, Netherlands

Supplementary Table S7. Gleason 7 (3+4) vs (4+3) cancer by PI-RADS score

		Pathology						
		Negative	6 (3+3)	7 (3+4)	7 (4+3)	8	>8	total
MRI	Negative		44	84	10	0	4	142
	3	11	0	12	1	1	0	25
	4	14	0	35	12	0	5	66
	5	3	2	37	15	9	11	77
	Total	28	46	168	38	10	20	310

Figure legends

Figure 1. Flowchart showing recruitment, randomization and follow-up of men.

Figure 2. Percentages of lesions that were clinically significant prostate cancer lesions, clinically insignificant prostate cancer lesions, and noncancerous lesions identified according to the Prostate Imaging-Reporting and Data System (PI-RADS) v2.0 score. **Clinically significant prostate cancer was defined as a Gleason score (GS) of either ≥3+4 or lesion size >6 mm**

Figure 3. Percentages of men in the intervention group with clinically significant prostate cancer, clinically insignificant prostate cancer, and no cancer identified according to the Prostate Imaging-Reporting and Data System (PI-RADS) v2.0 score. **Clinically significant prostate cancer was defined as a Gleason score (GS) of either ≥3+4 or lesion size >6 mm**

Figure 4. Multiparametric MRI of a prostate in a 60-year-old man, showing a focal lesion (arrow) in the right peripheral zone of the prostate, at the level of the mid gland. It demonstrated low T2 signal on axial (a) and sagittal (b) T2-weighted MRI, marked corresponding restricted diffusion on ADC (c) and high b-value (d) diffusion-weighted MRI, and early contrast enhancement on dynamic contrast enhanced MRI (e). It measured a maximum of 13 mm in transverse axis with a bulge of the prostatic outline but no definite extra-prostatic extension. This was scored as PI-RADS 4. Fused isovolumetric T2 sequence (f) with US image (g). Square marker A placed at the level of proximal prostatic urethra as anatomical landmark. Fusion core revealed a Gleason 3+4 prostate cancer.

Supplementary Figure S1. Flowchart showing design of trial

Supplementary Figure S2. MRI detection rate by Gleason Score