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R.J. Bryant , C.P. Hobbs , K.S. Eyre , L.C. Davies , M.E. Sullivan , W. Shields , P. Sooriakumaran , C.L. Verrill , F. Gleeson , R. MacPherson , F.C. Hamdy , S.F. Brewster

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Comparison of prostate biopsy with or without pre-biopsy multi-parametric MRI in prostate cancer detection: an observational cohort study.

Bryant RJ [1,2 ‡], Hobbs CP [1], Eyre KS [1], Davies LC [3], Sullivan ME [1], Shields W [1], Sooriakumaran P [2,4], Verrill CL [2,5], Gleeson F [6], MacPherson R [6], Hamdy FC [1,2], Brewster SF [1].

1 Department of Urology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

2 Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK.

3 Nuffield Department of Population Health, University of Oxford, Oxford, UK.

4 Department of Uro-Oncology, University College London Hospital NHS Foundation Trust, London, UK.

5 Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, UK.

6 Department of Radiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

‡ Corresponding author.

richard.bryant@nds.ox.ac.uk

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The authors have no conflicts of interest to declare.

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RJB, CPH, KSE, WS and PS collected the cohort data and interpreted the results. RJB and LCD undertook the statistical analysis. RJB, MES, PS, CLV, FG, RM, FCH and SB conceived the study. RJB and SB drafted the manuscript, with edits and contributions from all co-authors. All authors approved the final submitted manuscript.

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Abstract

Purpose: We hypothesized that 1) introducing pre-biopsy multiparametric magnetic resonance imaging (PB-mpMRI) increases the diagnostic yield of transrectal prostate biopsy (TRPB), and 2) this would inform recommendations regarding systematic TRPB in the "negative" PB-mpMRI setting.

Materials and methods: Nine hundred and ninety-seven biopsy-naïve patients underwent TRPB alone to June 2016 (cohort A), and seven hundred and ninety-two underwent TRPB following PB-mpMRI thereafter (cohort B). Patients with PB-mpMRI lesions underwent "cognitive-targeted" plus systematic TRPB. Patients without lesions underwent systematic TRPB.

Results: Cohort B comprised younger (68 v 69 years, p=0.01) men with lower PSA (7.6 v 7.9 ng/mL, p=0.024) and prostate volume (56.1 v 62cc, p=0.006). There was no increase in overall PCa detection (57.6 v 56.7%, p=0.701), Gleason grade group (GGG), or number of positive cores (p>0.05 for each) in Cohort B versus Cohort A. Increased multi-focal prostatic intraepithelial neoplasia, maximum PCa core length (≥5mm versus <5mm), and radical surgery/HIFU (p<0.05 for each) was observed in Cohort B. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of a "negative" PB-mpMRI for GGG 2-5 PCa were 88.1%, 59.8%, 67.8% and 84% respectively. For "negative" PB-mpMRIs, a PSAd≥0.15 cut-point only increased "clinically significant" PCa detection if the latter was defined as GGG 3-5 disease and/or tumor length ≥6mm.

Conclusions: Introducing PB-mpMRI in our clinical setting increased the diagnostic yield of PCa per biopsy core. Not performing a systematic TRPB when the PB-mpMRI was "negative" would have led to under-detection of 15.1% (approximately 1 in 6) of GGG≥2 PCa cases.

Keywords

Prostate cancer detection and diagnosis; pre-biopsy mpMRI; PI-RADS; PSA density

Word count (excluding abstract)

2,496

Introduction

Pre-biopsy multi-parametric prostate magnetic resonance imaging (PB-mpMRI) is commonly performed prior to transrectal prostate biopsy (TRPB) in men with suspected prostate cancer (PCa) following PSA-testing, and in active surveillance (AS) (1–3). PB-mpMRI indicates regions of interest using the Prostate Imaging Reporting And Data System (PI-RADS) version 2 (4), which can be targeted at TRPB. Targeting PI-RADS 3-5 lesions increases detection of clinically significant PCa (CS-PCa), and reduces "over-detection" of clinically insignificant PCa, compared with TRPB alone (5).

The advice regarding TRPB if the PB-mpMRI is "negative" (PI-RADS 1-2) is controversial. Some recent guidelines recommend individuals may safely avoid TRPB in this scenario, especially if the PSA density (PSAd) is low, and that "PSA observation" is appropriate (6). These recommendations are based on level 1 evidence suggesting the negative predictive value (NPV) of PB-mpMRI in detecting CS-PCa is 74%-89% (7). In the PRECISION study, patients with PI-RADS 1-2 PB-mpMRI did not undergo systematic TRPB, and were recommended "PSA observation" (5). Incorporating a $\geq$0.15 ng/ml^2 PSAd cut-point may help identify CS-PCa, however data on this are scarce. Given the rapid uptake of PB-mpMRI it is necessary to investigate the effects of its introduction in a "real world" non-trial setting, and investigate the biopsy yield of CS-PCa in individuals with a "negative" mpMRI given suggestions that systematic TRPB can safely be avoided.

PB-mpMRI was incorporated into the PCa diagnostic pathway in our large referral unit in June 2016. Individuals undergoing PB-mpMRI were recommended to undergo “cognitive-targeted” and “systematic” sampling TRPB for PI-RADS 3-5 lesions, and “systematic” TRPB for “normal” (PI-RADS 1-2) PB-mpMRI. We hypothesized that PB-mpMRI increases the TRPB diagnostic yield, and that evaluating the TRPB CS-PCa diagnostic yield of “negative” PB-mpMRIs enables informed recommendations regarding biopsy.

Patients and Methods

With institutional review board approval (Oxford University Hospitals NHS Foundation Trust Audit ID: 4834), all biopsy-naïve patients undergoing TRPB (January 2015 to July 2017) were identified. Approximately 1300 individuals are referred to the Oxford Urology Department annually for investigations for possible PCa. PB-mpMRI was introduced in our PCa diagnostic pathway in June 2016. Retrospective review identified outcomes for individuals receiving TRPB without imaging (Cohort A, n=997 consecutive patients to June 2016), and for those receiving PB-mpMRI plus TRPB (Cohort B, n=792 consecutive patients from June 2016). At the time of investigation, patients in Cohort B receiving PB-mpMRI were generally recommended to undergo systematic PB even if the mpMRI was "normal" (PI-RADS 1-2) as this preceded any any published data or guidance to the contrary.

Results of PB-mpMRI and TRPB for all men with newly diagnosed PCa are reviewed in weekly Uro-Oncology Multi-Disciplinary Team (MDT) meetings. PB-mpMRI images and TRPB results are also reviewed where there is significant discrepancy, for quality assurance and to guide further investigations (options including repeat TRPB or transperineal template biopsy).

mpMRI

PB-mpMRI images were acquired using a 1.5 Tesla or 3 Tesla scanner (GE Medical Systems, Milwaukee, Wisconsin, USA). T2 images were acquired in three planes, along with axial T1, high b-value diffusion weighted images, and dynamic contrast enhanced images. PB-mpMRI were reported by four uro-radiologists with a high volume mpMRI workload and considerable

experience reporting mpMRI in AS (2) and individuals with previous negative TRPB. Whilst historically the mpMRI scans had been "double-reported", with disagreements being reviewed by both reporters plus a third radiologist, this was no longer necessary by June 2016.

Prostate biopsy

TRPBs within our diagnostic pathway are obtained as an 8-, 10- or 12- needle-core procedure under local anesthetic using the 6-12mHz BK Ultrasound (Herlev, Denmark) Flex-focus 800 (previously Falcon) system. Since introducing PB-mpMRI, "cognitively-targeted" plus "systematic" TRPB cores were obtained for PI-RADS 3-5 lesions, whereas "systematic" sampling was performed for "normal" (PI-RADS 1-2) PB-mpMRI. Our historical practice for these cohorts had been to include the "cognitively-targeted" TRPB core(s) in the same formalin pot as ipsilateral systematic cores, with systematic cores from the contralateral prostate being sent in a second pot.

Outcomes and statistical analyses

The main objectives of this study were to investigate 1) whether introducing PB-mpMRI into our PCa investigation pathway resulted in significant differences in identified PCa characteristics, and 2) the NPV of a "negative" (PI-RADS 1-2) PB-mpMRI for detecting CS-PCa (various definitions). Potentially significant differences in baseline cohort demographics were investigated using the Wilcoxon Rank-Sum test (for continuous patient data) or Chi-Square test (for ordinal data). Effects of introducing PB-mpMRI were investigated using the Chi-Square test, Kruskal Wallis test, or Wilcoxon test for trend. Performance characteristics of PB-mpMRI in

detecting “any-grade”, or CS-PCa were determined using prevalence, sensitivity, specificity, PPV and NPV, with PSAd cut-points. A 5% significance level was used.

Results

Baseline characteristics of the cohorts (Cohort 1, "no PB-mpMRI"; Cohort 2, "PB-mpMRI") are outlined in **Table 1**. The "PB-mpMRI" cohort was significantly younger (median age 68 versus 69 years, p=0.01), with a lower PSA (7.6 versus 7.9 ng/ml, p=0.024) smaller prostate volume (56.1 versus 62 ml, p=0.006), and fewer ≤cT1c individuals (48% versus 55%, p=0.002). No significant difference was observed in PSAd, family history, or 5α reductase inhibitor use.

The effects of introducing PB-mpMRI are outlined in **Table 2**. No significant difference was observed in the percentage of men diagnosed with "any-grade PCa" (57.6 versus 56.7%, p=0.701), GGG detected, number of positive biopsy cores per case, or median maximum PCa length. A significant increase in PCa cases ≥5mm length was observed following PB-mpMRI (p=0.041). PB-mpMRI was associated with increased multi-focal prostatic intraepithelial neoplasia (MFPIN) (28.3% versus 21.2%, p=0.023).

Significant correlation was observed between the PB-mpMRI PI-RADS score and the biopsy result (malignant versus benign R=0.628, p<0.001) (**Table 2**). The PB-mpMRI PI-RADS score was significantly associated with PCa GGG (R=0.562, p<0.001). A significantly higher proportion of PB-mpMRI patients underwent radical prostatectomy/high intensity focused ultrasound (HIFU) compared against "no PB-mpMRI' (20.3% versus 11.7%, p<0.001), with fewer men receiving androgen deprivation therapy (ADT) +/- chemotherapy (15.1% versus 25.6%, p<0.001).

To investigate any potential "learning curve" of introducing PB-mpMRI, we compared the first 100 cases in Cohort 2 with the subsequent 692 cases (**Table 3**), and observed a higher percentage of "any grade" PCa cases in the latter 692 cases compared with the initial 100 (59 versus 48%, p=0.038), but no other differences.

We analyzed the performance characteristics of PB-mpMRI in detecting "any-grade", GGG 2-5, and GGG 3-5 PCa, regardless of the number of involved cores, or maximum PCa core length, in the entire PB-mpMRI cohort and the subset of individuals with a benign (≤cT1c) digital rectal examination (DRE) (**Table 4**). The NPV of a "normal" PI-RADS 1-2 PB-mpMRI in the entire cohort was 72.7, 84.9 and 97.8% for "any-grade", GGG 2-5, and GGG 3-5 PCa respectively. This suggests that 27.3% of "any-grade", 15.1% of GGG 2-5, and 2.2% of GGG 3-5 cases would have been undetected if individuals with a "negative" PI-RADS 1-2 mpMRI had not undergone systematic TRPB.

We examined the performance characteristics of PB-mpMRI using various PSAd cut-points (0.1, 0.15, and 0.2 ng/ml^2), and various definitions of CS-PCa (any GGG2-5 disease, GGG2-5 and/or ≥5mm tumor, GGG2-5 and ≥5mm tumor, and GGG3-5 and/or ≥6mm tumor) in the entire PB-mpMRI cohort and benign DRE (≤cT1c) subset (**Table 5** and **Figure 1**). Not undertaking systematic TRPB for a "negative" PI-RADS 1-2 PB-mpMRI would have led to a failure to detect 1 in every 7-25 CS-PCa cases, depending on PSAd cut-point and CS-PCa definition. A PSAd cut-point of 0.15 ng/ml^2 was only able to lead to a significant difference in the detection of CS-PCa as defined as GGG3-5 and/or ≥6mm tumor.

Discussion

Randomized controlled trial (RCT) evidence illustrating benefits from PB-mpMRI when investigating an elevated age-specific PSA has led to rapid uptake of PB-mpMRI to improve PCa detection (1,7–26). There are, however, inconsistencies in the literature, with a recent RCT suggesting PB-mpMRI before biopsy does not improve overall detection of any-grade PCa (27), and this concurs with our observations. Use of PB-mpMRI reduces the false negative rate of biopsies compared with sampling without imaging, which continues to be performed in some centers despite there being an approximately 15-25% risk of missing apical or anterior cancers. The PRECISION study demonstrated that targeted TRPB of PB-mpMRI lesions increased diagnostic yield compared with systematic biopsies, particularly for CS-PCa, and reduces over-detection of clinically insignificant PCa (5). While diagnosing CS-PCa is crucial, it is important to avoid over-detecting low-volume low-risk (GGG1) PCa, this being a downside of performing systematic biopsies in all individuals with elevated age-specific PSA.

There has been rapid uptake of PB-mpMRI in the UK, and in regions of Europe and the USA, ahead of guidelines. PB-mpMRI was introduced in our Institution in 2016, and we evaluated its impact in a “real world” setting outside of a clinical trial. We recognize that differences between our results and those of the PROMIS (PROstate Mr Imaging Study) and PRECISION studies may reflect differences in MRI machines, imaging protocols, PI-RADS scoring, biopsy protocols, and patient characteristics. Our study includes “all-comers”, including those with

mpMRI artifacts, such that our reported experience is likely reflective of clinical practice in similarly sized centers.

We recognize that this study has limitations. It is an observational cohort series, rather than a RCT, and includes "all-comers" undergoing PB-mpMRI to investigate elevated age-specific PSA and suspected PCa. Secondly, both 1.5 Tesla and 3 Tesla MRI scanners were used. Thirdly, our historical practice was to place targeted prostate biopsies in the same pot as the systematic biopsy cores from the contralateral gland, rather than a separate pot, due to histopathology resource limitations. Our practice in this area has since changed. Fourthly, the absolute numbers of men with a PSAd <1.0 or >0.2 ng/ml^2 were small. Moreover, only one specialist uro-radiologist reported each PB-mpMRI, whereas prostate biopsies were undertaken by numerous clinicians and specialist nurses. Inter-observer variability of both PB-mpMRI reporting and biopsy performance could not be thoroughly investigated, however we observed an increase in the proportion of "any grade" PCa cases detected from 48% in the initial 100 PB-mpMRI individuals to 59% in the subsequent 692 men. This effect may partly reflect a learning curve of both the mpMRI reporting and the targeted TRPB procedure, but a separate study would be needed to determine this. PRECISION suggests that despite standardized MRI reporting, there may be only moderate agreement (78%) between radiologists, illustrating the need for improved reporting consistency. The reason for the increase in the proportion of individuals receiving radical prostatectomy/HIFU following PB-mpMRI and biopsy is unknown, but might reflect the longer length of PCa detected, and the fact that the PB-mpMRI images are reviewed in the Uro-Oncology MDT meeting, potentially influencing the treatment offered.

Strengths of our study include evaluation of large numbers of consecutive biopsy-naïve patients in a "real-world" clinical setting. We can also for the first time inform patients in our center of the potential outcomes of systematic TRPB following a "negative" mpMRI on the basis of various definitions of CS-PCa, allowing them to make an informed choice regarding proceeding with TRPB after PB-mpMRI. This is a particular recent issue since the publication of PROMIS and PRECISION, which have been read by well-informed patients.

Having demonstrated benefits from incorporating mpMRI into the investigation pathway for an elevated age-specific PSA (5)(7), few now question the recommendation of targeted biopsies of a PI-RADS 4-5 lesion. There has been uncertainty in how best to inform and advise individuals regarding biopsy if the mpMRI is "normal" (PI-RADS 1-2), including cases with low PSAd. Numerous studies, including this report, demonstrate that systematic biopsies following a PI-RADS 1-2 PB-mpMRI detect CS-PCa (defined as any GGG≥2 disease) in 11-26% patients, and higher-grade cancer in 2-5%. Our finding that 15% of patients with CS-PCa would not have been diagnosed if individuals with a "negative" mpMRI had not received a biopsy is consistent with observations by others (28). While the need to reduce over-detection of clinically insignificant PCa is recognized, it is evident that the diagnosis of some cases of CS-PCa will be missed or delayed if individuals with a "negative" PB-mpMRI undergo "PSA observation", with repeat evaluation if the PSA rises. "PSA observation" has the risk of patient anxiety, repeated investigations, increasing healthcare costs, and delayed diagnosis of CS-PCa. Delay in diagnosing and/or treating intermediate-risk PCa can result in lethal outcomes, as inferred from

the Toronto AS series (29). However, "PSA observation" has the advantage of exposing fewer patients to the risks of biopsy or over-detection of clinically insignificant PCa. Most urology departments in the UK lack the capacity to undertake high volume "PSA observation", though this may be more feasible in the USA. No clinical test is 100% reliable, and clinicians are entrusted to inform of the risks both in proceeding with, or deferring, prostate biopsy following a "negative" PB-mpMRI.

While the PRECISION study demonstrated the benefits of PB-mpMRI (5), individuals with a "negative" PB-mpMRI were not biopsied. We are therefore not informed of the potential detection rate of CS-PCa in such individuals. Moreover, individuals receiving targeted TRPB did not undergo systematic sampling, therefore the true burden of disease remains uncertain. Following these publications, options currently available in clinical practice include: 1) recommending TRPB in all individuals referred with suspected PCa pathway based on an elevated age-specific PSA (with targeted and/or systematic biopsies depending on PB-mpMRI); 2) offering individuals the option of a systematic biopsy if a "negative" mpMRI; 3) to utilize a risk-based refinement such as PSAd, accepting the inherent weaknesses; or 4) to not recommend biopsy if the mpMRI is "negative", and administer "PSA observation" guidance as per PRECISION. Incorporating a PSAd cut-point of 0.15ng/ml^2 improves the NPV of mpMRI for CS-PCa from 92% to 98% for PI-RADS $\leq$3 lesions (30), and studies suggest that combining PI-RADS scores and PSAd can inform decision-making in biopsy naïve patients (28). However, we observed that a PSAd cut-point of 0.15ng/ml^2 only helps distinguish those with CS-PCa from those without, in the context of a "negative" mpMRI for both "all-comers" and those with a benign-feeling prostate, if CS-PCa is defined as ≥GGG3 disease and/or ≥6mm length. Many

would regard any ≥GGG2 disease as CS-PCa, especially in younger men with a good life expectancy, therefore based on an analysis of introducing PB-mpMRI at our institution, there may be concern that current mpMRI technology and "real-world" reporting of "negative" PI-RADS 1-2 images may initially overlook too much CS-PCa disease for a policy of reassurance and potential "PSA observation" without biopsy to be safely adopted. Carefully documented counseling of relative risk with the patient will be required. We recommend PCa diagnostic centers to audit their results to identify the local performance characteristics of PB-mpMRI and TRPB, rather than quoting results from highly optimized RCTs performed elsewhere.

In conclusion, introducing PB-mpMRI at our UK cancer center has increased the diagnostic yield of CS-PCa. Our evaluation of the PB-mpMRI performance characteristics could aid decision-making of our PCa diagnostic pathway patients, particularly regarding whether to proceed to prostate biopsy in the context of "negative" imaging. Depending on how CS-PCa is defined, 1 in every 7 to 25 men with a "negative" PB-mpMRI would have been undiagnosed had they not undergone systematic sampling.

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Demographics	Cohort 1 (No PB-mpMRI; *N*=997)	Cohort 2 (PB-mpMRI; *N*=792)	
Median (range; IQR)			
Age, years	69 (43-90; 63-75)	68 (37-88; 63-73)	*p*=0.01 †
PSA level, ng/ml	7.9 (0.16-15863; 5.8-13.3)	7.6 (0.4-2668; 5.7-11.5)	*p*=0.024 †
Prostate volume, ml	62 (5.97-330; 42.5-88)	56.1 (10.4-244; 40.1-79)	*p*=0.006 †
PSAd, ng/ml^2	0.14 (<0.1-203; 0.08-0.24)	0.13 (<0.1-42.4; 0.09-0.23)	*p*=0.514 †
N (%)			
≤cT1c	**548 (55)**	**370 (48)**	***p*=0.002** ‡
Family history	157 (15.7)	135 (17)	*p*=0.461 ‡
5αRI use	26 (2.6)	24 (3.0)	*p*=0.59 ‡

Table 1. Baseline demographics of the previously biopsy-naïve cohorts. † Wilcoxon Rank-Sum test; ‡ Chi-Square test. Abbreviations: 5αRI – 5 alpha reductase inhibitor; IQR – inter-quartile range; PB-mpMRI – pre-biopsy multi-parametric magnetic resonance imaging; PSA – prostate-specific antigen; PSAd – prostate-specific antigen density.

	Cohort 1 (No PB-mpMRI; *N*=997)	Cohort 2 (PB-mpMRI; *N*=792)	
Negative biopsy result, *N* (%)			
Benign	202 (47)	118 (35)	p=0.018 ‡
Inflammation	33 (7.7)	26 (7.7)	
Unifocal PIN	53 (12.3)	50 (14.9)	
Multifocal PIN	91 (21.2)	95 (28.3)	
ASAP	51 (11.8)	47 (14)	
Positive biopsy result, *N* (%)			
Any-grade prostate cancer	565 (56.7)	456 (57.6)	p=0.701 ‡
Gleason Grade Group, *N* (%)			
1	84 (14.9)	68 (14.9)	p=0.87 §
2	219 (38.8)	171 (37.5)	
3	90 (15.9)	87 (19.1)	
4	53 (9.4)	49 (10.7)	
5	116 (20.5)	80 (17.5)	
1&2 versus 3-5			p=0.66 ‡
1-3 versus 4&5			p=0.55 ‡
Positive Biopsy Cores, *N* (IQR)			
Median positive cores	4 (2-7)	5 (2-8)	p=0.22 †
<3 cores versus ≥3 cores			p=0.56 ‡
Maximum core length			
Median (IQR)			
Maximum length (mm)	7.0 (2.3-11.0)	7.5 (3.0-12.0)	p=0.078 †
<5mm versus ≥5mm length			p=0.041 ‡
mpMRI, *N* (%)			
PI-RADS 1		220 (27.8)	
PI-RADS 2		58 (7.3)	
PI-RADS 3		98 (12.4)	
PI-RADS 4		170 (21.4)	
PI-RADS 5		212 (26.8)	
Artifact*		34 (4.3)	
All biopsy correlation		R=0.628	p<0.001 #
Benign biopsy correlation		R=0.089	p=0.111 #
Gleason Grade correlation		R=0.562	p<0.001 #
Treatment Received, *N* (%)			
Active surveillance / WW	158 (28.0)	106 (23.8)	p=0.14 ‡
Radical surgery / HIFU	66 (11.7)	90 (20.3)	p<0.001 ‡
Brachytherapy	4 (0.7)	8 (1.8)	p=0.11 ‡
Radiotherapy +/- ADT	192 (34.0)	173 (39.0)	p=0.10 ‡
ADT +/- Chemotherapy	145 (25.6)	67 (15.1)	p<0.001 ‡

Table 2. Summary of the effects of introducing PB-mpMRI. Abbreviations: ADT – androgen deprivation therapy; ASAP – atypical small acinar proliferation; HIFU – high intensity focused

ultrasound; IQR – inter-quartile Range; PIN – prostatic intraepithelial neoplasia; PB-mpMRI – pre-biopsy multi-parametric MRI; PI-RADS - Prostate Imaging Reporting And Data System; PSA – prostate-specific antigen; PSAd – prostate-specific antigen density; WW – watchful waiting. * Artifacts precluding PI-RADS include hemorrhage, hip replacement, rectal gas and motion. [‡] Chi-Square test; [†] Kruskal Wallis test; [§] Wilcoxon test for trend.

	PB-mpMRI cohort, first 100 cases	PB-mpMRI cohort, next 692 cases	
Negative biopsy result, *N* (%)			
Benign	**19 (36.5)**	**99 (34.9)**	***p*=0.924 ‡**
Inflammation	**3 (5.8)**	**23 (8.1)**	
Unifocal PIN	**9 (17.3)**	**41 (14.4)**	
Multifocal PIN	**13 (25)**	**82 (28.9)**	
ASAP	**8 (15.4)**	**39 (13.7)**	
Positive biopsy result, *N* (%)			
Any-grade prostate cancer	**48 (48)**	**408 (59)**	***p*=0.038 ‡**
Gleason Grade Group, *N* (%)			
1	**4 (8.3)**	**64 (15.7)**	***p*=0.64 §**
2	**22 (45.8)**	**149 (36.5)**	
3	**7 (14.6)**	**80 (19.6)**	
4	**6 (12.5)**	**43 (10.5)**	
5	**9 (18.8)**	**72 (17.7)**	
1&2 versus 3-5			***p*=0.797 ‡**
1-3 versus 4&5			***p*=0.657 ‡**
Positive Biopsy Cores, *N* (IQR)			
Median positive cores	**5 (3-6)**	**5 (2-8)**	***p*=0.862 †**
<3 cores versus ≥3 cores			***p*=0.607 ‡**
Maximum core length Median (IQR)			
Maximum length (mm)	**8 (3.5-12)**	**7 (3-12)**	***p*=0.628 †**
<5mm versus ≥5mm length			***p*=0.518 ‡**
mpMRI, *N* (%)			
PI-RADS 1	**35 (35)**	**185 (26.7)**	***p*=0.073 §**
PI-RADS 2	**6 (6)**	**52 (7.5)**	
PI-RADS 3	**10 (10)**	**88 (12.7)**	
PI-RADS 4	**21 (21)**	**149 (21.5)**	
PI-RADS 5	**25 (25)**	**187 (27)**	
Artifact*	**3 (3)**	**31 (4.5)**	

Table 3. Sub-analysis of the PB-mpMRI cohort, comparing the first 100 cases with the subsequent 692 cases. Abbreviations: ASAP – atypical small acinar proliferation; IQR – inter-quartile Range; PIN – prostatic intraepithelial neoplasia; PB-mpMRI – pre-biopsy multi-parametric magnetic resonance imaging; PI-RADS - Prostate Imaging Reporting And Data System. * Artifacts precluding PI-RADS include hemorrhage, hip replacement, rectal gas and motion. ‡ Chi-Square test; † Kruskal Wallis test; § Wilcoxon test for trend.

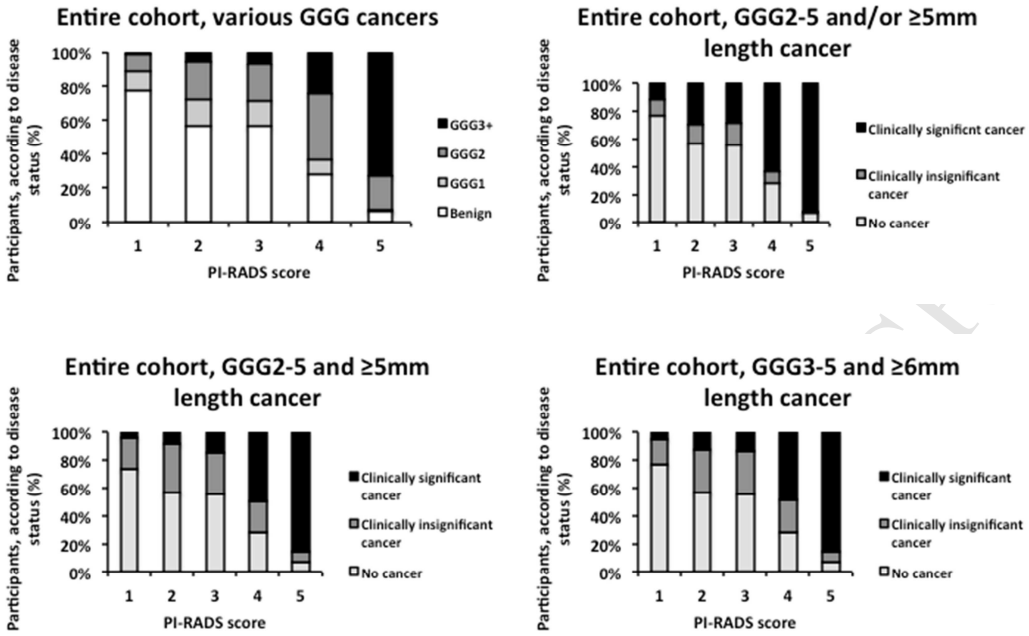
		Full cohort		**≤cT1c (Benign DRE)**	
	Gleason Grade Group	PI-RADS 3-5	PI-RADS 4&5	**PI-RADS 3-5**	**PI-RADS 4&5**
Prevalence	1-5	47.7	57.7	**42.8**	**42.8**
	2-5	49.3	49.3	**31.8**	**31.8**
	3-5	27.6	27.6	**11.6**	**11.6**
Sensitivity	1-5	82.6	72.8	**70.4**	**51.3**
	2-5	88.7	81.2	**79.7**	**62.8**
	3-5	97.1	93.8	**92.7**	**80.5**
Specificity	1-5	63.1	80.3	**68**	**85.2**
	2-5	61.5	79.7	**66.1**	**84.7**
	3-5	49.6	66.2	**57.3**	**76.1**
PPV	1-5	75.4	83.5	**62.2**	**72.2**
	2-5	69.1	79.5	**52.3**	**65.7**
	3-5	42.4	51.4	**22.1**	**30.6**
NPV	1-5	72.7	68.4	**75.4**	**70**
	2-5	84.9	81.4	**87.4**	**83**
	3-5	97.8	96.5	**98.4**	**96.8**

Table 4. Performance characteristics of PB-mpMRI in the detection of any-grade, Gleason Grade Group 2-5, or Gleason Grade Group 3-5 PCa **in the full cohort or in the ≤cT1c (i.e. benign DRE) subset of the cohort**. Abbreviations: **cT1c – clinical stage T1c;** DRE – digital rectal examination; NPV - negative predictive value; PI-RADS - Prostate Imaging Reporting And Data System; PPV – positive predictive value.

	Full cohort				**≤cT1c (Benign DRE)**			
	Definition of clinically significant disease				**Definition of clinically significant disease**			
PI-RADS 1&2 mpMRI	GGG2-5	GGG2-5 and/or ≥5mm	GGG2-5 and ≥5mm	GGG3-5 and/or ≥6mm	**GGG2-5**	**GGG2-5 and/or ≥5mm**	**GGG2-5 and ≥5mm**	**GGG3-5 and/or ≥6mm**
PSAd ≥0.10 versus <0.10								
Chi-Square	0.564	0.798	0.451	1.649	**2.006**	**2.006**	**2.867**	**2.867**
p-value	0.453	0.372	0.502	0.199	**0.157**	**0.157**	**0.09**	**0.09**
Prevalence	14.8	15.2	5	6	**12.1**	**12.1**	**2.2**	**2.2**
Sensitivity	61	61.9	64.3	70.6	**72.7**	**72.7**	**100**	**100**
Specificity	45.3	45.5	44.9	45.4	**43.1**	**43.1**	**42.1**	**42.1**
PPV	16.2	10.2	5.8	7.8	**15**	**15**	**3.7**	**3.7**
NPV	87	87	95.9	95.9	**92**	**92**	**100**	**100**
Missed if no biopsy	1 in 8	1 in 8	1 in 25	1 in 25	**1 in 13**	**1 in 13**	**None**	**None**
PSAd ≥0.15 versus <0.15								
Chi-Square	0.319	0.824	0.068	5.962	**1.813**	**1.813**	**2.1**	**15.499**
p-value	0.572	0.364	0.794	0.015	**0.178**	**0.178**	**0.147**	**<0.001**
Prevalence	14.8	15.2	5	6	**7.8**	**12.1**	**2.2**	**2.2**
Sensitivity	22	23.8	21.4	41.2	**68.2**	**31.8**	**50**	**100**
Specificity	81.8	81.1	81.4	82.7	**19.4**	**80.6**	**79.8**	**80.9**
PPV	17.3	19	5.8	13.5	**10.4**	**18.4**	**5.3**	**10.5**
NPV	85.8	85.4	95.1	95.6	**81.6**	**89.6**	**98.6**	**100**
Missed if no biopsy	1 in 7	1 in 7	1 in 20	1 in 25	**1 in 5**	**1 in 10**	**1 in 71**	**None**
PSAd ≥0.20 versus <0.20								
Chi-Square	0	0.03	0.345	3.911	**0.197**	**0.197**	**0.821**	**17.132**
p-value	0.998	0.958	0.557	0.048	**0.672**	**0.672**	**0.365**	**<0.001**
Prevalence	14.8	15.2	5	6	**12.1**	**12.1**	**2.2**	**2.2**
Sensitivity	9.8	9.5	14.3	23.5	**13.6**	**13.6**	**25**	**75**
Specificity	90.3	90.2	90.5	91.2	**89.4**	**89.4**	**89.3**	**90.5**
PPV	14.8	14.8	7.4	14.8	**15**	**15**	**5**	**15**
NPV	85.2	84.8	95.2	94.8	**88.3**	**88.3**	**98.2**	**99.4**
Missed if no biopsy	1 in 7	1 in 7	1 in 20	1 in 20	**1 in 8**	**1 in 8**	**1 in 50**	**1 in 166**

Table 5. Calculations based on detecting various definitions of "clinically significant" prostate cancer according to various PSA density cut-points (<0.1 or ≥0.1, <0.15 or ≥0.15, and <0.2 or ≥0.2 ng/ml^2) **in the full cohort or in the ≤cT1c (i.e. benign DRE) subset of the cohort**. Abbreviations: **cT1c – clinical stage T1c;** DRE – digital rectal examination: GGG – Gleason grade group; NPV – negative predictive value; PI-RADS - Prostate Imaging Reporting And Data System; PPV – positive predictive value; PSAd – prostate-specific antigen density.

A


Entire cohort, various GGG cancers
Participants, according to disease status (%)
100%
80%
60%
40%
20%
0%
1
2
3
4
5
PI-RADS score
GGG3+
GGG2
GGG1
Benign
Entire cohort, GGG2-5 and/or ≥5mm length cancer
Clinically significnt cancer
Clinically insignificant cancer
No cancer
Entire cohort, GGG2-5 and ≥5mm length cancer
Clinically significant cancer
Clinically insignificant cancer
No cancer
Entire cohort, GGG3-5 and ≥6mm length cancer
Clinically significant cancer
Clinically insignificant cancer
No cancer

B

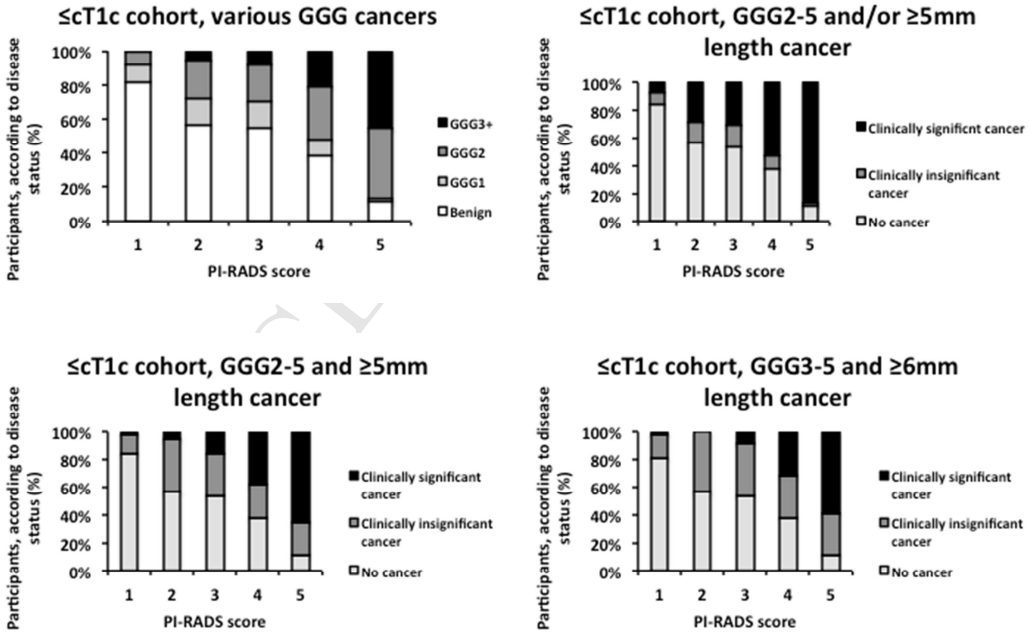

≤cT1c cohort, various GGG cancers
Participants, according to disease status (%)
100%
80%
60%
40%
20%
0%
1
2
3
4
5
PI-RADS score
GGG3+
GGG2
GGG1
Benign
≤cT1c cohort, GGG2-5 and/or ≥5mm length cancer
Clinically significnt cancer
Clinically insignificant cancer
No cancer
≤cT1c cohort, GGG2-5 and ≥5mm length cancer
Clinically significant cancer
Clinically insignificant cancer
No cancer
≤cT1c cohort, GGG3-5 and ≥6mm length cancer
Clinically significant cancer
Clinically insignificant cancer
No cancer

Figure 1. Percentage of men in the PB-mpMRI cohort with clinically significant, clinically insignificant, or no cancer on targeted and systematic prostate biopsy according to PI-RADS score. Results are shown for four different definitions of clinically significance prostate cancer: GGG3+ disease; GG2-5 disease and/or ≥5mm length cancer; GG2-5 disease and ≥5mm length cancer; and GG3-5 disease and ≥6mm length cancer. A) provides results for the entire pre-biopsy mpMRI cohort, and B) provides results for the ≤cT1c (i.e. benign DRE) subset of the cohort. Abbreviations: cT1c – clinical stage T1c; DRE – digital rectal examination; GGG – Gleason grade group; PB-mpMRI – pre-biopsy multiparametric magnetic resonance imaging; PI-RADS - Prostate Imaging Reporting And Data System.

5αRI – 5 alpha reductase inhibitor

ADT – androgen deprivation therapy

AS – active surveillance

ASAP – atypical small acinar proliferation

CS-PCa - clinically significant prostate cancer

DRE – digital rectal examination

GGG - Gleason grade group

HIFU – high intensity focused ultrasound

IQR – interquartile range

MDT - Multi-Disciplinary Team

MFPIN - multi-focal prostatic intraepithelial neoplasia

mpMRI - Multi-parametric prostate magnetic resonance imaging

MRI – magnetic resonance imaging

NHS – National Health Service

NPV - negative predictive value

PB-mpMRI pre-biopsy multiparametric magnetic resonance imaging

PCa – prostate cancer

PIN – prostatic intraepithelial neoplasia

PI-RADS - Prostate Imaging Reporting And Data System

PPV - positive predictive value

PROMIS - PROstate Mr Imaging Study

PSA – prostate specific antigen

PSAd – prostate specific antigen density

RCT – randomized controlled trial

TRPB - transrectal prostate biopsy

TRUS – transrectal ultrasound

UK – United Kingdom

USA – United States of America

WW – watchful waiting