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Prostate Cancer

Opportunistic Prostate Cancer Screening with Biparametric Magnetic Resonance Imaging (VISIONING)

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Abstract

Background: This study investigates the use of biparametric magnetic resonance imaging (bpMRI) as primary opportunistic screening for prostate cancer (PCa) without using a prostate-specific antigen (PSA) cut-off.

Objective: The primary endpoint was to assess the efforts and effectiveness of identifying 20 participants with clinically significant prostate cancer (csPCa) using bpMRI.

Design, setting, and participants: Biopsy-naïve men aged over 45 yr were included. All participants underwent 3 Tesla bpMRI, PSA, and digital rectal examination (DRE). Targeted-only biopsy was performed in participants with Prostate Imaging Reporting and Data System (PI-RADS) $\geq$3. Men with negative bpMRI but suspicious DRE or elevated PSA/PSA density had template biopsies. Preintended protocol adjustments were made after an interim analysis for PI-RADS 3 lesions: no biopsy and follow-up MRI after 6 mo and biopsy only if lesions persisted or upgraded.

Outcome measurements and statistical analysis: Biopsy results underwent a comparison using Fisher's exact test and univariable logistic regression to identify prognostic factors for positive biopsy.

Results and limitations: A total of 229 men were enrolled in this study, of whom 79 underwent biopsy. Among these men, 77 displayed suspicious PI-RADS lesions. PCa was detected in 29 participants (12.7%), of whom 21 had csPCa (9.2%). Biparametric MRI detected 21 csPCa cases, while PSA and DRE would have missed 38.1%. Protocol adjustment led to a 54.6% biopsy reduction in PI-RADS 3 lesions. Overall, in this cohort of men with a median PSA value of 1.26 ng/ml, 10.9 bpMRI scans were needed to identify one participant with csPCa. A major limitation of the study is the lack of a control cohort undergoing systematic biopsies.

Conclusions: Opportunistic screening utilising bpMRI as a primary tool has higher sensitivity in detecting csPCa than classical screening methods.

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Patient summary: Screening with biparametric magnetic resonance imaging (bpMRI) and targeted biopsy identified clinically significant prostate cancer in every 11th man, regardless of the prostate-specific antigen (PSA) levels. Preselecting patients based on PSA >1 ng/ml and a positive family history of prostate cancer, as well as other potential blood tests may further improve the effectiveness of bpMRI in this setting.

1. Introduction

Prostate cancer (PCa) is the most prevalent cancer and the second leading cause of cancer death among men in Switzerland [1]. Using prostate-specific antigen (PSA) as a trigger, large population-based screening programmes, such as the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), have shown a reduction of up to 30% in PCa-specific mortality [2,3]. However, PSA alone is suboptimal, evidenced by a receiver operating characteristic curve reporting of 0.52–0.63 for the detection of cancer at prostate biopsy and a relatively high prevalence of clinically significant PCa (csPCa) in men with PSA levels below 3 ng/ml [4–7].

Research indicates that prostate magnetic resonance imaging (MRI) exhibits superior performance to PSA for PCa detection, reducing negative biopsies and identifying more csPCa cases with a high negative predictive value (NPV) ranging between 87.9% and 97.5% [8–13].

While there is currently no recommended standard screening, the Council of the European Union has recently proposed to consider the feasibility of organised PCa screening using PSA and MRI [14].

This study prospectively examines the effectiveness of a purely bpMRI-based opportunistic PCa screening programme with the primary aim of measuring its performance and identifying improvements.

2. Participants and methods

2.1. Ethics

This research was conducted in accordance with the Swiss Association of Research Ethics Committees guidelines (EKNZ Nr. 2018-01965) and is registered at clinicaltrials.gov (NCT03749993).

2.2. Study design

This single-centre prospective cohort study was conducted between January 2019 and May 2023. The study population consisted of men over 50 yr of age (over 45 yr for individuals of African ancestry or with a family history of PCa) without prior prostate biopsies and with life expectancy exceeding 10 yr. Participants were recruited through general practitioners, neighbouring clinics, and urologists in private practice referring interested men. The exclusion criteria were acute urinary tract infections, National Institutes of Health Chronic Prostatitis Symptom Index scores of $\geq$19, International Prostate Symptom Score of $\geq$20, previous biopsy, and contraindications to MRI. All participants underwent biparametric MRI (bpMRI) of the prostate using a 3 T scanner (MAGNETOM Prisma; Siemens Healthineers, Erlangen, Germany) at the University Hospital Basel. The bpMRI protocol (detailed in Supplementary Table 1) included T2-weighted turbo-spin echo and diffusion-weighted imaging for lesion assessment, strictly adhering to the Prostate Imaging Reporting and Data System (PI-RADS) v2.1 guidelines [15]. All MRI images were centrally interpreted by a board-certified radiologist and then independently reviewed by one of two senior radiologists (D.B. and T.H.) with 25 and 20 yr of experience in MRI diagnostics, respectively. Radiologists were blinded to the PSA and digital rectal examination (DRE) results.

2.3. Interim analysis

An interim analysis was planned after the first screening round (phase 1) to assess and refine the study protocol. This analysis occurred following the identification of csPCa in five participants. The protocol's effectiveness was evaluated by comparing the detection rates of PCa using bpMRI against PSA and DRE.

2.4. Indications for biopsy and protocol amendments

In phase 1 of the study, lesions identified as PI-RADS $\geq$3 on MRI were considered suspicious and led to a targeted biopsy. MRI reports classified as PI-RADS 1 and 2 were not biopsied systematically unless accompanied by an abnormal DRE and/or a PSA level of $\geq$10.0 ng/ml. This relatively high PSA threshold was chosen considering the high NPV of bpMRI as well as the fact that participants with an elevated PSA above 3 ng/ml would undergo follow-up PSA controls according to European Association of Urology (EAU) guidelines with their referring doctor.

Following the interim analysis, the protocol for phase 2 was amended to include a no earlier than 6-mo reassessment of initial PI-RADS 3 lesions using multiparametric MRI, with subsequent biopsies for persistent or upgraded lesions. PSA density (PSA-D) of $\geq$0.15 ng/ml^2, calculated using MRI-measured prostate volume, was added as a criterion for systematic biopsy when no PI-RADS $\geq$3 lesion was present (see Fig. 1). The protocol amendments were reviewed and approved by the Swiss Association of Research Ethics Committees.

2.5. Biopsy procedure

The first 36 participants underwent transrectal MRI/ultrasound (US)-fusion biopsies under local anaesthesia, using

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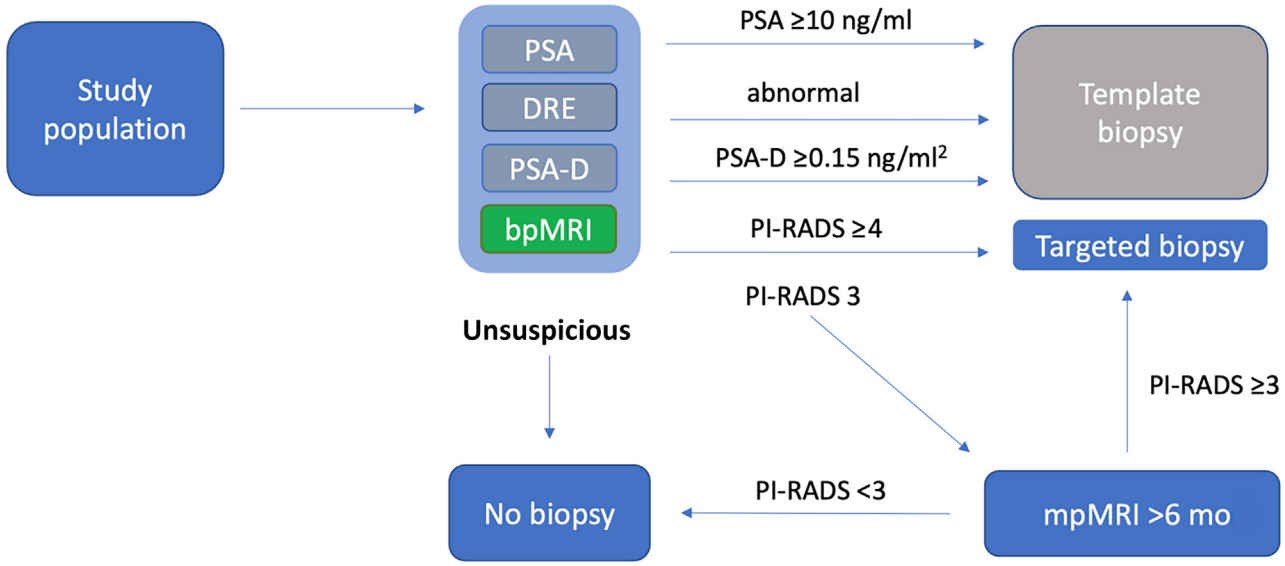

Fig. 1 – Indications for biopsy (template or targeted) and follow-up mpMRI. bpMRI = biparametric MRI; DRE = digital rectal examination; mpMRI = multiparametric MRI; MRI= magnetic resonance imaging; PSA = prostate-specific antigen; PSA-D = PSA density.

a real-time virtual sonography system (Hitachi Medical Corporation, Tokyo, Japan) and magnetic position sensors (3D Guidance Trakstar; Ascension) for targeted biopsies. We then switched to a transperineal method with a robotic-assisted MRI/US-fusion biopsy system (Monalisa; Biobot Surgical Ltd, Singapore) under general anaesthesia for 43 participants. In both methods, two to three biopsy cores were taken from each targeted lesion.

When indicated, a systematic biopsy with on average 18 cores equally distributed over the prostate was performed.

2.6. Histopathological reporting

Gleason score and International Society of Urological Pathology (ISUP) grade were reported for each cancer-positive biopsy. A Gleason score of 3 + 3 = 6 and ISUP 1 were considered clinically nonsignificant PCa (cnsPCa). A Gleason score of 3 + 4 = 7 or above and ISUP ≥2 would be csPCa.

2.7. Analysis and statistical methods

Categorical data were summarised using frequency and percentage, and continuous data using median and range. Fisher's exact test was employed to compare biopsy results across subgroups and univariable logistic regression for the identification of prognostic factors for positive biopsy outcomes. A 5% significance level was used for all statistical tests without adjustment for multiple testing due to the exploratory nature of these analyses. All analyses were performed using SAS 9.4 [16] and R 4.2.1 [17].

3. Results

3.1. Participant enrolment and baseline characteristics

From February 2019 to September 2022, 269 participants were enrolled and 229 participants were ultimately included in the analysis (Fig. 2). Of the 79 participants who underwent a biopsy, all attended follow-up.

The study participants had a median age of 58 yr (interquartile range [IQR], 53–64), a median PSA level of 1.26 ng/ml (IQR, 0.72–2.84), and a median PSA-D of 0.05 ng/ml^2 (IQR, 0.03–0.08; Table 1).

3.2. Interim analysis (phase 1)

In phase 1 (n = 108), 45 participants underwent prostate biopsy, of whom 17.8% (8/45) had PCa ISUP ≥2 (Supplementary Fig. 1). The predefined threshold of detecting n = 5 ISUP ≥2 PCa cases in phase 1 has been surpassed, reaching n = 8 because of the lead time between bpMRI, biopsy, and histopathological report, while the opportunistic screening had continued. If a PSA cut-off of 3 ng/ml had been used, 37.5% (3/8) of the ISUP ≥2 cases detected in phase 1 would have been missed by PSA and DRE alone.

3.3. Overall results (phases 1 and 2)

In total, 79 participants received prostate biopsy after refusal of biopsy by ten participants.

Cancer was detected in 29 of the 229 (12.7%) recruited men, of whom eight (3.5%) had ISUP 1 and 21 (9.2%) had ISUP ≥2. The median PSA level and PSA-D were 2.02 ng/ml (IQR, 1.5–3.21) and 0.067 ng/ml^2 (IQR, 0.049–0.104) for the participants with ISUP 1 cancer, and 3.88 ng/ml (IQR, 2.77–7.53) and 0.111 ng/ml^2 (IQR, 0.075–0.294) for the participants with ISUP ≥2, respectively (Table 2).

Out of the 29 patients with PCa detected by bpMRI screening, 21 were classified to have ISUP ≥2. Interestingly, only 33.3% (seven out of 21) of these ISUP ≥2 cases would have met the criteria for biopsy based on PSA levels, as per our study protocol (Supplementary Fig. 2). Notably, if a PSA cut-off of 3 ng/ml had been utilised, 38.1% (eight out of 21) of ISUP ≥2 cases would have been overlooked by PSA screening. Following protocol amendments after the interim analysis, the rate of negative biopsies in phase 1 was reduced from 73.3% (33/45) to 50% (17/34) in phase

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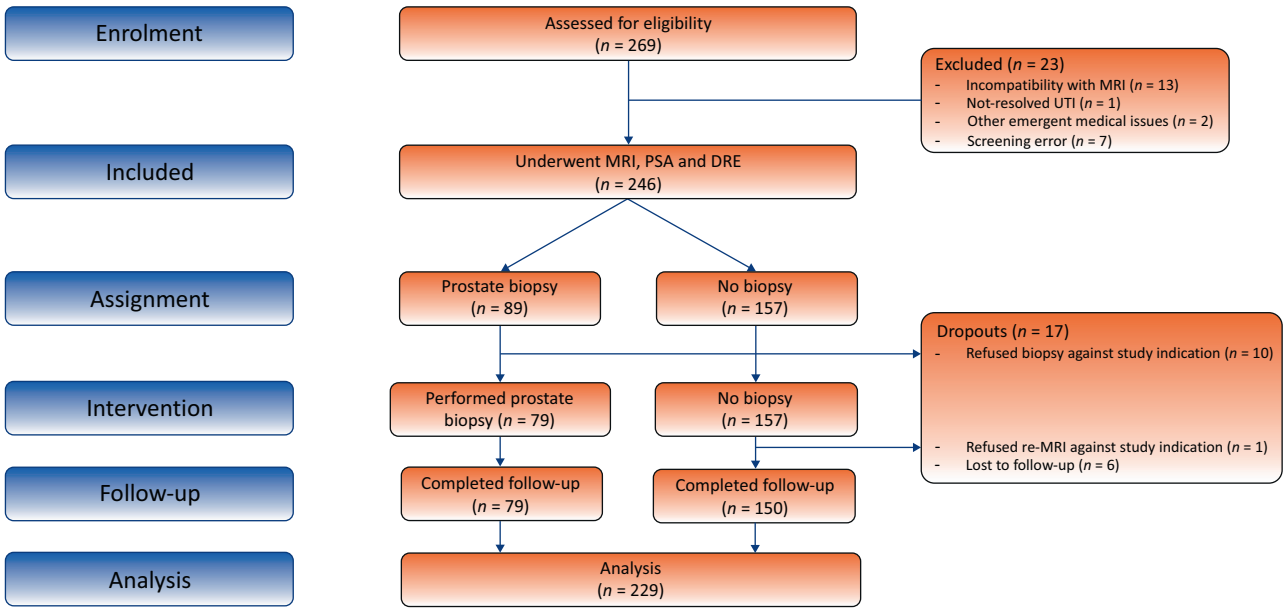

Fig. 2 – CONSORT/TREND flow diagram of the VISIONING study, follow-up, and analysis (according to TREND statement). DRE = digital rectal examination; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; UTI = urinary tract infection.

Table 1 – Baseline characteristics and clinical parameters of all included participants

Baseline characteristics (*n* = 229), median (IQR)	
Age (yr)	58 (53–64)
Prostate volume (ml)	28 (23–39)
PSA (ng/ml)	1.26 (0.72–2.84)
PSA-D (ng/ml^2)	0.05 (0.03–0.08)
Clinical parameters (*n* = 229), *n* (%)	
PSA <1 ng/ml and negative family history for PCa	106 (46.2)
PSA ≥10.0 ng/ml	6 (2.6)
PSA ≥3.0 ng/ml	51 (22.3)
Abnormal DRE	8 (3.5)
Elevated PSA-D (≥0.15 ng/ml^2)	18 (7.9)
Positive family history for PCa	38 (16.6)

DRE = digital rectal examination; IQR = interquartile range; PCa = prostate cancer; PSA = prostate-specific antigen; PSA-D = PSA density.

2 (Supplementary Table 3). Specifically, by avoiding immediate biopsies for men with a PI-RADS 3 score on bpMRI, the rate of MRI-indicated negative biopsies in phase 2 decreased from 72.7% (32/44) to 48.5% (16/33). Consequently, the number of MRI scans needed to detect one ISUP ≥2 case fell from 13.6 to 9.3, while the biopsy detection rate for ISUP ≥2 increased from 17.8% (8/45) to 38.2% (13/34).

In a scenario where participants with a PSA value below 1 ng/ml and no family history of PCa were not assessed further with bpMRI, the detection of ISUP ≥2 PCa would not have been affected. Notably, by doing so, the number of MRI scans required to detect one ISUP ≥2 could have decreased from 10.9 (229/21) to 5.9 (123/21). Consequently, 2.9 (61/21) targeted biopsies would have been necessary to detect one case of ISUP ≥2 (Table 3).

Table 2 – Index lesions, performed biopsy, and biopsy results

	n (%)	PSA (ng/ml) Median (IQR)/[range] [a]	PSA-D (ng/ml^2) Median (IQR)	PSA subgroups (ng/ml)			
				<1	1–2.99	3–9.99	≥10
Index lesion at participant level [b] (*n* = 229)							
PI-RADS 1 or 2	152 (66.4)	1.09 (0.67–2.2)	0.042 (0.027–0.065)	66	63	21	2
PI-RADS 3 [c]	13 (5.7)	1.84 (1.15–3.96)	0.056 (0.033–0.083)	3	6	4	0
PI-RADS 4	55 (24.0)	2.02 (0.89–3.59)	0.056 (0.031–0.099)	15	22	17	1
PI-RADS 5	9 (3.9)	5.67 (2.18–20.0)	0.151 (0.054–0.612)	2	1	3	3
Biopsy intervention (*n* = 229)							
Targeted biopsy	77 (33.6)	2.06 (0.91–3.88)	0.057 (0.031–0.111)	20	29	24	4
Template biopsy	2 (0.9)	9.4 (9.05–9.75)	0.234 (0.196–0.272)	0	0	0	2
No biopsy	150 (65.5)	1.08 (0.67–2.17)	0.042 (0.026–0.064)	66	63	21	0
Biopsy result (*n* = 79)							
ISUP 1	8 (10.1)	2.02 (1.5–3.21) [0.81–4.69]	0.067 (0.049–0.104)	2	4	2	0
ISUP ≥2	21 (26.6)	3.88 (2.77–7.53) [0.8–39.7]	0.111 (0.075–0.294)	1	7	9	4
No cancer	50 (63.3)	1.44 (0.79–3.6) [0.21–12.7]	0.051 (0.026–0.087)	17	18	13	2

IQR = interquartile range; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSA-D = PSA density.
[a] The range was specifically added in this section to display the lowest PSA values in men with prostate cancer.
[b] In case a participant had more than one suspicious PI-RADS lesion, the highest-graded lesion would count as index lesion.
[c] The biopsied PI-RADS 3 lesions were from phase 1 (before the interim analysis) or persistent PI-RADS 3 lesions in follow-up MRI from phase 2.

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Table 3 – Descriptive data of diagnostics and histopathological reports

	PSA subgroups (ng/ml)					
	<1	1–2.99	3–9.99	≥10	Any PSA	≥1 [a]
Biopsy performed	20	29	24	6	79	61
csPCa	1 [b]	7	9	4	21	21
cnsPCa	2	4	2	0	8	6
Negative biopsy	17	18	13	2	50	34
MRI	86	92	45	6	229	123
MRI/ISUP ≥2	86	13.1	5	1.5	10.9	5.9
MRI/PCa	28.7	8.4	4.1	1.5	7.9	4.6
Biopsy/ISUP ≥2	20	4.1	2.7	1.5	3.8	2.9
Biopsy/PCa	6.7	2.6	2.2	1.5	2.7	2.3

cnsPCa = clinically nonsignificant prostate cancer; csPCa = clinically significant prostate cancer; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PCa = prostate cancer; PSA = prostate-specific antigen.
The rows display absolute numbers (*n*) of biopsies performed, csPCa and cnsPCa, negative biopsies (no histological signs of malignancy), MRI count, and ratios of MRI and biopsy per prostate cancer. The columns categorise participants into subgroups by PSA levels.
[a] And/or positive family history of prostate cancer.
[b] This individual had a positive family history of PCa.

Table 4 – Univariable logistic regression for positive biopsy (ISUP ≥2) of risk factors

	Odds ratio (95% CI)	*p* value
PSA	1.17 (1.01–1.36)	0.04
	1.16 [a] (0.99–1.35)	
Family history of prostate cancer (yes vs no)	2.00 (0.66–6.08)	0.2
Age	1.08 (1.01–1.15)	0.021
PSA-D (IQR normalised)	1.84 (1.17–2.89)	0.009
	1.82 [a] (1.15–2.89)	
Positive MRI [b]	1.17 (0.2–6.84)	0.9
	0.93 [a] (0.15–5.62)	
PI-RADS (4–5 vs <4)	1.20 (0.37–3.93)	0.8

CI = confidence interval; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSA-D = PSA density.
[a] Age-adjusted odds ratio.
[b] Positive MRI equals PI-RADS ≥3 in phase 1 and PI-RADS ≥4 or persistent PI-RADS 3 in follow-up MRI in phase 2.

In our univariable regression analysis examining specific risk factors associated with a positive biopsy (Table 4), we found an age-adjusted odds ratio (OR) of 1.16 (95% confidence interval [CI] 0.99–1.35) for PSA and an OR of 1.2 (95% CI 0.37–3.93) for PI-RADS. However, statistical significance was achieved only by PSA, age, and PSA-D.

4. Discussion

In this study, we report the results of a bpMRI-based opportunistic screening programme for PCa, comparing its effectiveness with classical screening methods.

The study encompassed 229 participants, with 21 (26.7%) men diagnosed with ISUP ≥2 in the biopsy group of 79 individuals.

The bpMRI-based screening strategy detected all 21 men with ISUP ≥2, whereas a PSA threshold of 3 ng/ml would have missed 38.1% (8/21) of ISUP ≥2 cases.

Postinterim analysis protocol adjustments postponing immediate biopsy in PI-RADS 3 lesions reduced the negative biopsy rate indicated by bpMRI from 72.7% to 48.5%. However, an even more restrained strategy when indicating biopsy for PI-RADS 3 lesions does not appear to be particularly effective, as the detection rates of ISUP ≥2 in phase 2 for PI-RADS 3 and 4 lesions were 25% (1/4) and 36% (9/25), respectively. On average, 11 participants were screened to detect one man with ISUP ≥2. Notably, the median PSA-D of ISUP ≥2 in our study was 0.111 ng/ml^2 and, as such, below the debated guidelines threshold of 0.15 ng/ml^2 [18].

Comparatively, in the adjusted STHLM3 cohort (adjusted for age, PSA, PSA naivety, family history, and previous negative biopsy using propensity scores to match the current PCa testing cohort), 53.7 participants needed screening to detect one case of ISUP ≥2 with a 62% biopsy rate without cancer detection [19].

It is important to note that our study identified a 27.3% occurrence rate of csPCa in MRI-fusion-guided biopsies, which is lower than the rates reported in other research focusing on the prevalence of PCa in PI-RADS lesions [20]. This difference could be ascribed to the nature of prostate MRI as a reflex test, typically conducted following clinical indications of PCa, rather than within a screening programme.

Regarding a potential selection bias, as we conducted an opportunistic screening and not a screening-by-invitation programme, men with a positive family history of PCa (16.6% in our study) might have been more likely to participate in this study. Another limitation of our study protocol is the absence of a control cohort. Considering the high NPV of MRI for the detection of ISUP ≥2, we balanced the biopsy-related morbidity in a control cohort against the informational benefit and decided not to include a template biopsy control group. Moreover, the nonblinding of the PSA value for participants might have influenced some men with very low PSA levels and PI-RADS 3 or 4 lesions to decide against undergoing a biopsy.

As our analysis was based exclusively on the index lesions and their PI-RADS classification, factors such as the number and size of the lesions were not considered. Concerning this additional diagnostic value of MRI diagnostics, it will be important to implement a continuous control-feedback mechanism comparing the radical prostatectomy specimen with the MRI results, in order to improve the diagnostic process.

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In a recent study conducted by Moore et al [21], a very similar study protocol in an invitation-to-screen setting was utilised. Despite the differing context of invitation to screen as compared with our opportunistic screening setting, the findings of the two studies converge remarkably well. Their parallel findings corroborate the potential use of MRI in the screening for PCa.

Overdetection of cnsPCa remains a challenge that future research needs to address, particularly concerning the use of MRI in prebiopsy assessments [22]. However, in our specific screening trial, the prevalence of cnsPCa detected through MRI-guided biopsies was relatively low (10.4%).

Contrary to our trial's findings that MRI has a higher detection rate than PSA and DRE, the only factors reaching statistical significance in our logistic regression analysis were PSA, PSA-D, and age. While this suggests superior effectiveness of PSA to MRI, we must reiterate the critical role of sensitivity in cancer detection. Economically and ethically, the cost of missing a cancer diagnosis should be given more weight than detecting a benign condition. As such, the clinical value of MRI lies in its ability to lessen the risk of missed diagnoses as compared with conventional screening. An even more effective approach in defining men for further diagnostic screening could be the combined use of PSA and MRI, rather than relying solely on one diagnostic method: exclusion of patients with PSA <1 ng/ml and a negative family history of PCa would potentially reduce MRI scans by 46.3%, lower the negative biopsy rate to 55.7%, and decrease the diagnosis of ISUP 1 PCa by 32%. Under these conditions, only 5.9 bpMRI scans and 2.9 biopsies would have been required without missing any individual with ISUP $\geq$2 in phase 2 of our study (Table 3).

While csPCa currently corresponds to an ISUP grade of $\geq$2, new definitions for csPCa might be needed, especially given that the oncological risk associated with a specific ISUP grade group identified through MRI-guided biopsies may differ from that of the same ISUP grade group detected via systematic biopsies [23], and notably at higher PSA values. Therefore, certain patients with small ISUP grade group II PCa and a low PSA level might still benefit from active surveillance rather than immediately resorting to definitive surgery or radiotherapy.

In order to answer the question of whether the good performance of bpMRI also translates into better survival of men with csPCa, larger and therefore population-based screenings will be required.

5. Conclusions

This pilot study, applying bpMRI as a primary opportunistic screening tool for PCa, demonstrates the superior effectiveness of bpMRI in detecting ISUP $\geq$2 PCa compared with PSA and DRE. Analysing 229 participants, approximately 11 bpMRI scans and four targeted biopsies were required to identify one case of ISUP $\geq$2 PCa. Optimising the screening protocol with a PSA cut-off at 1 ng/ml and excluding men with a negative family history could further decrease the rate of overdiagnoses in ISUP 1 cancers and negative biopsies, resulting in the detection of an ISUP $\geq$2 lesion in every third man undergoing biopsy.

Author contributions: Marc Matthias had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rentsch, Wetterauer, Matthias.
Acquisition of data: Matthias.
Analysis and interpretation of data: Matthias, Rentsch, Wetterauer, Hayoz.
Drafting of the manuscript: Matthias, Wetterauer, Rentsch.
Critical revision of the manuscript for important intellectual content: Matthias, Wetterauer, Rentsch, Seifert, Pueschel, Bubendorf, Winkel, Boll, Merkle, Heye, Hayoz, Deckart, Arbelaez, Mortezavi.
Statistical analysis: Matthias, Hayoz.
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Appendix A. Supplementary data

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