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Prostate Cancer

A Prospective Multicenter Comparison Study of Risk-adapted Ultrasound-directed and Magnetic Resonance Imaging–directed Diagnostic Pathways for Suspected Prostate Cancer in Biopsy-naïve Men

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Abstract

Background: European Association of Urology guidelines recommend a risk-adjusted biopsy strategy for early detection of prostate cancer in biopsy-naïve men. It remains unclear which strategy is most effective. Therefore, we evaluated two risk assessment pathways commonly used in clinical practice.
Objective: To compare the diagnostic performance of a risk-based ultrasound (US)-directed pathway (Rotterdam Prostate Cancer Risk Calculator [RPCRC] #3; US volume assessment) and a magnetic resonance imaging (MRI)-directed pathway.
Design, setting, and participants: This was a prospective multicenter study (MR-PROPER) with 1:1 allocation among 21 centers (US arm in 11 centers, MRI arm in ten). Biopsy-naïve men with suspicion of prostate cancer (age ≥50 yr, prostate-specific antigen 3.0–50 ng/ml, ± abnormal digital rectal examination) were included.
Intervention: Biopsy-naïve men with elevated risk of prostate cancer, determined using RPCRC#3 in the US arm and Prostate Imaging Reporting and Data System scores of 3–5 in the MRI arm, underwent systematic biopsies (US arm) or targeted biopsies (MRI arm).
Outcome measurements and statistical analysis: The primary outcome was the proportion of men with grade group (GG) ≥2 cancer. Secondary outcomes were the proportions of biopsies avoided and GG 1 cancers detected. Categorical (nonparametric) data were assessed using the Mann-Whitney *U* test and χ^2 tests.
Results and limitations: A total of 1965 men were included in the intention-to-treat population (US arm n = 950, MRI arm n = 1015). The US and MRI pathways detected GG ≥2 cancers equally well (235/950, 25% vs 239/1015, 24%; difference 1.2%, 95% confidence interval [CI] −2.6% to 5.0%; p = 0.5). The US pathway detected more GG 1 cancers than the MRI pathway (121/950, 13% vs 84/1015, 8.3%; difference 4.5%, 95% CI 1.8–7.2%; p < 0.01). The US pathway avoided fewer biopsies than the MRI pathway (403/950, 42% vs 559/1015, 55%; difference −13%, 95% CI −17% to −8.3%; p < 0.01). Among men with elevated risk, more GG ≥2 cancers were detected in the MRI group than in the US group (52% vs 43%; difference 9.2%, 95% CI 3.0–15%; p < 0.01).
Conclusions: Risk-adapted US-directed and MRI-directed pathways detected GG ≥2 cancers equally well. The risk-adapted US-directed pathway performs well for prostate cancer diagnosis if prostate MRI capacity and expertise are not available. If prostate MRI availability is sufficient, risk assessment should preferably be performed using MRI, as this avoids more biopsies and detects fewer cases of GG 1 cancer.
Patient summary: Among men with suspected prostate cancer, relevant cancers were equally well detected by risk-based pathways using either ultrasound or magnetic resonance imaging (MRI) to guide biopsy of the prostate. If prostate MRI availability is sufficient, risk assessment should be performed with MRI to reduce unnecessary biopsies and detect fewer irrelevant cancers.

1. Introduction

The European Association of Urology (EAU) guidelines describe the risk of overdiagnosis and related overtreatment in prostate cancer (PCa) diagnosis [1]. The EAU PCa guidelines recommend "an individualized risk-adapted strategy for early detection in well-informed men with life expectancy of at least 10–15 years". It is still unclear which individualized risk-adapted strategy is most effective.

The EAU recently published a position statement outlining a risk-adapted strategy for early detection of PCa [2]. The proposed algorithm is based on prostate-specific antigen (PSA) testing and subsequent risk calculation that includes several clinical parameters. Only when identified as having intermediate or high risk is magnetic resonance imaging (MRI) indicated. MRI-based risk modeling may subsequently identify men with intermediate or high risk who should undergo systematic and MRI-targeted biopsies. This algorithm mitigates overdiagnosis and overtreatment while maintaining the potential individual benefits of early diagnosis.

Parallel to algorithm development for early detection of PCa, population-based screening studies are emerging that incorporate MRI as part of the risk stratification to improve the balance between benefits and harms [3–5]. Despite the many MRI-based risk models currently under investigation, MRI for population-based screening is not yet available. Therefore, risk assessment without MRI is the most likely first step, as also proposed in the EAU position statement [2].

Comparative data for risk assessment using either ultrasound (US)-based risk calculators or MRI-based risk assessment are currently limited. The clinical validity of the US-based Rotterdam Prostate Cancer Risk Calculator #3 (RPCRC#3) [6] has been demonstrated [7] and its use can potentially avoid up to 37% of biopsies at the expense of missing up to 11% of significant cancers [8,9]. In this study, we investigated the effectiveness of two individualized

risk-adapted strategies for early detection while prospectively avoiding biopsies. For this purpose, we compared two diagnostic strategies that utilized risk stratification based on either US (including RPCRC#3) or MRI (including the Prostate Imaging-Reporting and Data System [PI-RADS] risk assessment score).

2. Patients and methods

2.1. Objective

The aim of this prospective multicenter observational clinical effectiveness study conducted in The Netherlands (MR IN PROstate cancer diagnosis and Prior Risk assessment) was to investigate risk-based stratification in a US-directed and an MRI-directed pathway (1:1 allocation) for biopsy-naïve men with suspected PCa.

2.2. Study design

The institutional review board of Erasmus University Medical Center approved the MR-PROPER study (MEC-2017-361; ClinicalTrials.gov NCT03225222). All participants gave written informed consent. The study was conducted in 21 Dutch centers, including five university hospitals, 15 non-university hospitals, and one cancer institute (Supplementary Table 1). Participating centers were not randomized; each center enrolled men only in the study arm that reflected their standard of care, denoted as the US arm (11 centers) or the MRI arm (ten centers; Supplementary Table 2).

2.2.1. US arm and MRI arm

The study design is shown in Figure 1. Men in the US arm underwent US-based RPCRC#3 risk assessment and then US-guided systematic biopsies if they were classified as having elevated risk. Men in the MRI arm underwent MRI scanning with a PI-RADS risk assessment and then targeted biopsy if the MRI findings were positive.

2.2.2. Prospective risk stratification

In the US arm, risk assessment was performed using the US-based RPCRC#3 risk calculator (prostatecancer-riskcalculator.com). Elevated risk was defined as risk of any PCa >20%, or risk of any PCa >12.5% in combination with risk of high-grade PCa >4% [6].

In the MRI arm, risk assessment was performed using prostate MRI. Elevated risk was defined as a PI-RADS (version 2.1) score of 3–5 (MRI-positive) [10,11]. Biopsies were advised for men with elevated risk in both arms, while clinical follow-up was advised for men with low risk.

2.2.3. Safety net

Men at elevated risk in the US arm had the possibility of undergoing an additional MRI assessment with subsequent targeted biopsies after negative systematic biopsies. In the MRI arm, additional systematic biopsies

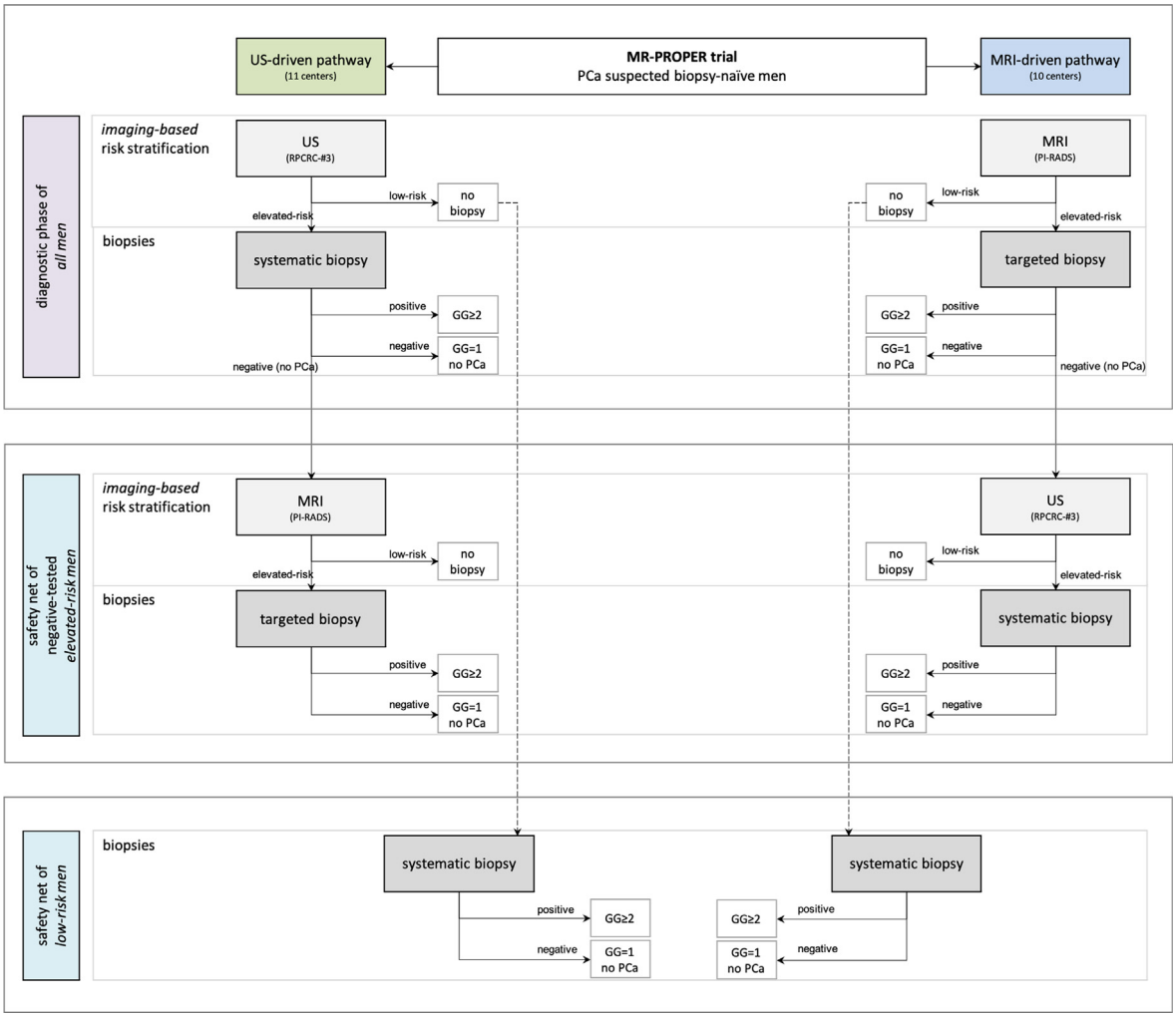

Fig. 1 – Study design for prospective comparison of risk-adapted MRI-directed and US-directed diagnostic strategies for early detection of PCa. MRI = magnetic resonance imaging; PCa = prostate cancer; PI-RADS = Prostate Imaging-Reporting and Data System; RPCRC = Rotterdam Prostate Cancer Risk Calculator; US = ultrasound.

following a negative targeted biopsy procedure could be initiated. In both cases, a shared decision-making process was used (Fig. 1). Some centers preferred to conduct this step in the same visit; however, biopsies were separately stored and analyzed. Furthermore, men with low risk (according to RPCRC#3 or MRI) could undergo additional testing according to shared decision-making.

2.3. Inclusion and exclusion criteria

Men aged ≥50 yr with PSA of 3.0–50.0 ng/ml and/or abnormal digital rectal examination (DRE) and/or a family history of PCa were eligible for the study. Men with previously detected or treated PCa, previous prostate biopsies, stage cT4 tumor on DRE, or contraindications for MRI or biopsy procedures were excluded.

2.4. Biopsy protocol and biopsy analysis

2.4.1. US-guided systematic prostate biopsy

For US-guided systematic biopsies, from ten to 12 cores were sampled (depending on the prostate volume).

2.4.2. MRI-directed targeted prostate biopsy

MRI-positive lesions were biopsied in an MRI-directed biopsy approach (in-bore MRI, MRI-US fusion software, cognitive fusion). In accordance with the PI-RADS guidelines, the prostate MRI protocol consisted of T2-weighted and diffusion-weighted imaging with apparent diffusion coefficient reconstructions [10,11]. Non–contrast-enhanced imaging was permitted [12].

2.4.3. Histopathology analysis

As part of the diagnostic workflow, biopsy cores were graded by local uropathologists by grade group (GG) according to the International Society of Urological Pathology 2014 classification [13].

2.5. Study endpoints

The primary outcome was the proportion of men with GG ≥2 cancers detected in the two study arms. Only results from systematic biopsy in the US arm and results from targeted biopsy in the MRI arm were used for the primary outcome measure.

Secondary outcomes were the proportions of biopsies avoided and PCa-negative (redundant) biopsies, and the proportions of GG 1 cancers detected. In addition, we investigated biopsy outcomes at the "safety net" for each study arm, estimating potential underdiagnosis and overdiagnosis if additional testing was performed. Furthermore, non–imaging-based risk-adapted strategies were investigated (PSA, DRE-based PSA density, and RPCRC#3 DRE; Supplementary material).

2.6. Data analysis

Using a significance level of $\alpha = 5\%$ and power of $\beta = 80\%$, a total of 1296 men with elevated risk (648 men in each arm) was required to show superiority (a difference of at least 7% in cancer detection) of the MRI-directed pathway (intervention arm). We aimed for 1976 men with suspected PCa to account for low-risk cases, exclusions, and dropouts.

All eligible participants were included in the intention-to-treat analysis after giving written informed consent. A modified intention-to-treat analysis was performed that includes only men who underwent the complete diagnostic strategy to which they were assigned. The per-protocol analysis included only men who underwent the imaging procedures to which they were assigned.

Descriptive statistics are used to report clinical, radiological, and pathological characteristics. Categorical nonparametric data were assessed using the Kruskal Wallis (Mann-Whitney *U*) test. The binomial (exact) method was used to calculate confidence intervals (CIs) for categorical data. The χ^2 test was used to test for differences in categorical data between the groups. To correct for known risk factors, we used a multivariable logistic regression model that included PSA density, DRE result, age, and trial arm, with detection of GG ≥2 PCa as the outcome measure. Statistical analyses were performed using SPSS v24.0 (IBM, Armonk, NY, USA).

3. Results

Between December 2017 and September 2020, 2040 consecutive biopsy-naïve men were enrolled, of whom 983 were in the US arm and 1057 were in the MRI arm. Of these, 75 men (US arm $n = 33$; MRI arm $n = 42$) did not meet the inclusion criteria. In total, 1965 men (US arm $n = 950$; MRI arm $n = 1015$) were included in the intention-to-treat analysis (Fig. 2). Men were excluded from the modified intention-to-treat and per-protocol analyses on the basis of patient preferences and loss to follow-up ($n = 21$) and protocol violations ($n = 29$).

3.1. Baseline characteristics

The two arms had equivalent results for PSA level and family history of PCa (Table 1). More DRE abnormalities were found in the US arm than in the MRI arm ($p < 0.01$).

3.2. PCa detection

The primary and secondary outcome measures did not differ between the intention-to-treat, modified intention-to-treat, and per-protocol cohorts (Table 2).

GG ≥2 cancers were detected in 235/950 men (25%, 95% CI 22–28%) in the US arm and 239/1015 (24%, 95% CI 21–26%) in the MRI arm (difference 1.2%, 95% CI −2.6% to 5.0%; $p = 0.5$).

The advice was not to undergo biopsy for 403/950 men (42%, 95% CI 39–46%) in the US arm and 559/1015 (55%, 95% CI 52–58%) in the MRI arm (difference −13%, 95% CI −17 to −8.3%; $p < 0.01$). Biopsy findings were negative in 191/950 men (20%, 95% CI 18–23%) in the US arm and 133/1015 (13%, 95% CI 11–15%) in the MRI arm (difference 7.0%, 95% CI 3.7–10%; $p < 0.01$).

GG 1 cancers were detected in 121/950 men (13%, 95% CI 11–15%) in the US arm and 84/1015 (8.3%, 95% CI 6.7–10%) in the MRI arm (difference 4.5%, 95% CI 1.8–7.2%; $p < 0.01$).

After correcting for PSA density, abnormal DRE, and age, the odds ratio for GG ≥2 PCa detection in the MRI arm in comparison to the US arm as the reference was 1.20 (95% CI 0.93–1.55; $p = 0.16$; Supplementary Table 3).

3.3. Men with elevated risk men after stratification: biopsy results

More men with elevated risk (MRI- or RPCRC#3-positive) had GG ≥2 cancer in the MRI arm (239/462; 52%, 95% CI 47–56%) than in the US arm (235/552; 43%, 95% CI 38–47%; difference 9.2%, 95% CI 3.0–15%; $p < 0.01$; Table 3). For men with elevated risk, there was a nonsignificant difference in the detection of GG 1 cancers between the US arm (121/552; 22%, 95% CI 19–26%) and the MRI arm (84/462; 18%, 95% CI 15–22%; difference −3.7%, 95% CI −8.7% to 1.2%; $p = 0.14$). Fewer men had PCa-negative biop-

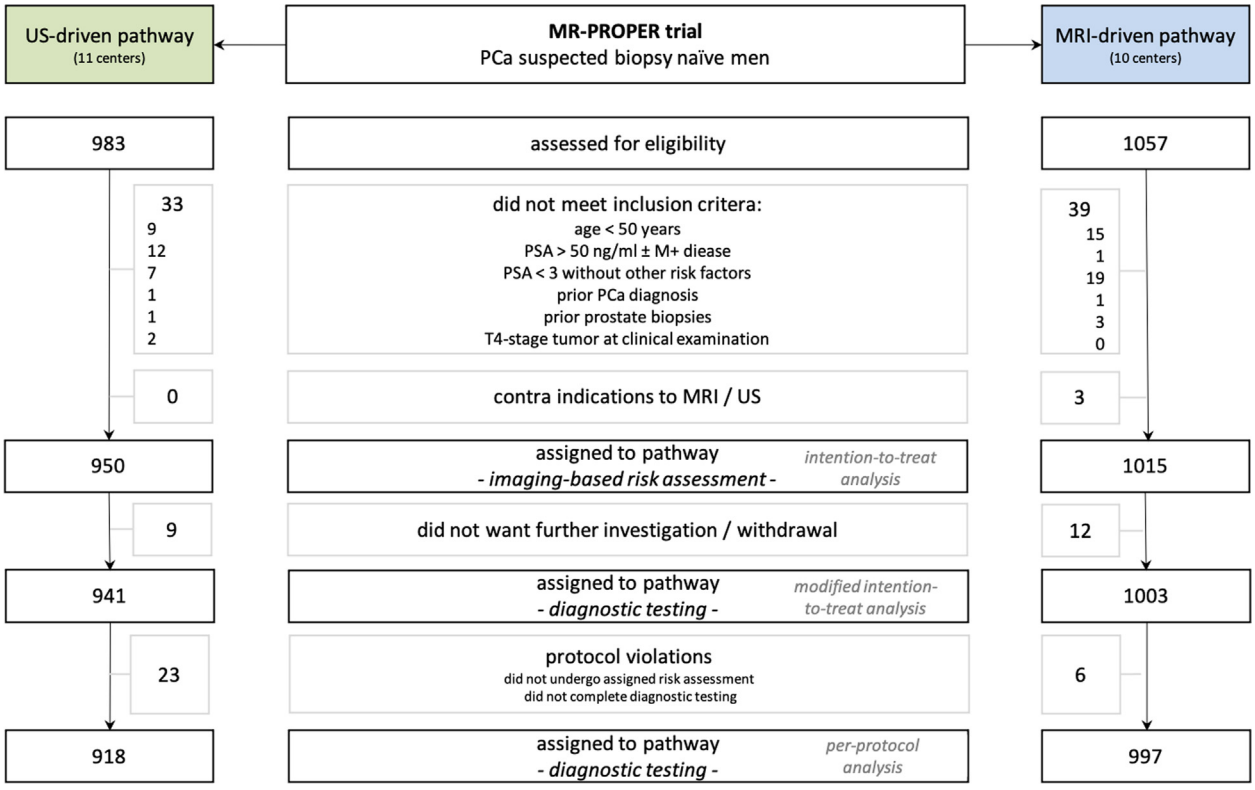

Fig. 2 – Flowchart of participants assigned to the US-directed and MRI-directed arms. MRI = magnetic resonance imaging; PCa = prostate cancer; PSA = prostate-specific antigen; US = ultrasound.

Table 1 – Baseline characteristics of men included in the US and MRI arms

	US arm	MRI arm	*p* value
Participants, *n* (%)	950 (100)	1015 (100)	
Median age, yr (IQR)	69 (64–72)	67 (62–71)	<0.01
Median prostate-specific antigen, ng/ml (IQR)	6.6 (5.0–9.3)	7.1 (5.3–9.6)	0.84
Positive family history, *n* (%)	21 (2.2)	23 (2.3)	0.94
DRE performed, *n* (%)	940 (98.9)	1002 (99.0)	0.64
Mean DRE-estimated prostate volume, ml (SD)	46.8 (12.3)	47.2 (11.4)	0.48
Prostate volume category, *n* (%)			
25 ml	107 (11.5)	72 (7.2)	
40 ml	424 (45.6)	514 (51.3)	
60 ml	398 (42.8)	416 (41.5)	
DRE abnormality felt, *n* (%)	252 (26.8)	213 (21.3)	<0.01

DRE = digital rectal examination; IQR = interquartile range; MRI = magnetic resonance imaging; SD = standard deviation; US = ultrasound.

sies in the MRI arm (133/462; 29%, 95% CI 25–33%) than in the US arm (191/552; 35%, 95% CI 31–39%; difference −5.8%, 95% CI −11% to −0.1%; $p = 0.05$).

3.4. Safety net: additional biopsy results

3.4.1. Men with elevated risk with negative biopsy results

In the MRI arm, 133 men with elevated risk and negative MRI-targeted biopsy were also stratified as having elevated risk according to RPCRC#3 (Table 4). In 25 men (19%), no additional systematic biopsies were performed. Additional systematic biopsies were performed in 108 men, detecting GG ≥2 cancer in ten men and GG 1 cancer in 16, while no cancer was found in 82 men.

In the US arm, 131/191 men (69%) with negative systematic biopsies did not subsequently undergo additional MRI testing. Additional MRI testing was performed in 60 men (31%) with elevated risk. Of the 28 men with MRI-positive findings, 27 underwent MRI-targeted biopsy, which detected GG ≥2 in four men and GG 1 cancer in one, while no cancer was found in 22 men.

3.4.2. Men with low risk

Of the 535 men with MRI-negative findings (low risk), 111 underwent additional testing with systematic biopsies, which detected GG ≥2 cancer in five men (4.5%, 95% CI 0.7–8.4%) and GG 1 in 15 (14%, 95% CI 7.2–20%; Table 4), while 91 biopsy procedures (82%, 95% CI 75–89%) were PCa-negative.

A total of 104/366 men underwent systematic biopsies despite negative RPCRC#3 assessment, which detected GG

Table 2 – Intention-to-treat, modified intention-to-treat, and per-protocol cohorts for analysis by US and MRI arm

Cohort	Patients, *n* (%)		Difference, % (95% CI)	*p* value
	US arm	MRI arm		
Intention-to-treat				
Men included	950	1015		
No biopsy	403 (42.4)	559 (55.1)	−12.7 (−17.0 to −8.3)	<0.01
Biopsy outcome				
Grade group 0 (no prostate cancer)	191 (20.1)	133 (13.1)	7.0 (3.7–10.3)	<0.01
Grade group 1	121 (12.7)	84 (8.3)	4.5 (1.8–7.2)	<0.01
Grade group ≥2	235 (24.7)	239 (23.5)	1.2 (−2.6 to 5.0)	0.53
Modified intention-to-treat				
Men included	941	1003		
No biopsy	394 (41.9)	547 (54.5)	−12.7 (−17.1 to −8.3)	<0.01
Biopsy outcome				
Grade group 0 (no prostate cancer)	191 (20.3)	133 (13.3)	7.0 (3.7–10.4)	<0.01
Grade group 1	121 (12.9)	84 (8.4)	4.5 (1.7–7.2)	<0.01
Grade group ≥2	235 (25.0)	239 (23.8)	1.1 (−2.7 to 5.0)	0.56
Per-protocol-analysis				
Men included	918	997		
No biopsy	371 (40.4)	541 (54.3)	−13.9 (−18.3 to −9.4)	<0.01
Biopsy outcome				
Grade group 0 (no prostate cancer)	191 (20.8)	133 (13.3)	7.5 (4.1–10.8)	<0.01
Grade group 1	121 (13.2)	84 (8.4)	4.8 (2.0–7.5)	<0.01
Grade group ≥2	235 (25.6)	239 (24.0)	1.6 (−2.2 to 5.5)	0.41

CI = confidence interval; MRI = magnetic resonance imaging; US = ultrasound.

Table 3 – Biopsy outcomes for men with elevated risk in the US and MRI arms

	Patients, *n* (%)		Difference, % (95% CI)	*p* value
	US arm	MRI arm		
Men with elevated risk	552	462		
No biopsy	5 (0.9)	6 (1.3)		
Biopsy outcomes				
Grade group ≥2	235 (42.6)	239 (51.7)	9.2 (3.0–15.3)	<0.01
Grade group ≥2 + cribriform	163 (29.5)	162 (35.1)	5.5 (−0.3 to 11.1)	0.06
Grade group ≥3	136 (24.6)	115 (24.9)	0.3 (−5.1 to 5.6)	0.93
Grade group 1	121 (21.9)	84 (18.2)	−3.7 (−8.7 to 1.2)	0.14
Grade group 0 (no prostate cancer)	191 (34.6)	133 (28.8)	−5.8 (−11.5 to −0.1)	0.05

CI = confidence interval; MRI = magnetic resonance imaging; US = ultrasound.

Table 4 – Biopsy outcomes of "safety net" testing for men with elevated risk and a negative biopsy and men with low risk a

	Patients, *n* (%)	
	US arm	MRI arm
Men with elevated risk and a negative biopsy	191	133
No additional biopsy	164 (85.9)	25 (18.8)
Additional MRI testing	60 (31.4)	NA
MRI-negative	32 (53.3)	NA
MRI-positive	28 (46.6)	NA
Additional biopsy testing	27 (14.1)	108 (81.2)
Biopsy outcomes (targeted/systematic biopsy)		
Grade group ≥2	4 (2.1)	10 (7.5)
Grade group ≥2 + cribriform	2 (1.0)	2 (1.5)
Grade group ≥3	2 (1.0)	1 (0.8)
Grade group 1	1 (0.5)	16 (12.0)
Grade group 0 (no prostate cancer)	22 (11.5)	82 (61.7)
Men with low risk with no prior biopsy	366	535
No additional biopsy	262 (71.6)	424 (79.3)
Additional biopsy testing	104 (28.4)	111 (20.7)
Additional biopsy outcomes (systematic biopsy)		
Grade group ≥2	10 (9.6)	5 (4.5)
Grade group ≥2 + cribriform	7 (6.7)	5 (4.5)
Grade group ≥3	4 (3.8)	4 (3.6)
Grade group 1	18 (17.3)	15 (13.5)
Grade group 0 (no prostate cancer)	76 (73.1)	91 (82.0)

MRI = magnetic resonance imaging; NA = not applicable; US = ultrasound.
[a]Statistical testing was not performed owing to the small and unequal data samples.

≥2 cancer in ten men (9.6%, 95% CI 4.7–17%) and GG 1 cancer in 18 (17%, 95% CI 11–26%), while 76 biopsy procedures (73%, 95% CI 64–81%) were negative.

4. Discussion

The goal of risk stratification in PCa diagnosis is to minimize biopsy testing while maintaining a high rate of detection of GG ≥2 cancers and a low rate of detection of GG 1 cancers. Such a strategy was recently proposed by the EAU in a position statement that outlined an algorithm for PSA testing and risk calculation, with subsequent MRI for men with intermediate or high risk [2]. The safe use of such a risk-based strategy in routine practice for early detection of PCa requires verification in prospective studies.

4.1. Design

The MR-PROPER study was designed to reduce biopsies using risk stratification tools prospectively. Two arms applied the recently published EAU PCa guidelines, which suggest a risk-based biopsy-decision protocol to prevent biopsies and to reduce the detection of GG 1 cancers [1]. A total of 21 centers contributed to this study, enrolling patients in either the US (RPCRC#3) arm or the MRI arm. The use of 1.5-T and 3.0-T scanners was permitted, as well as various MRI-targeted biopsy techniques. Therefore, it is likely that our results are generalizable to contemporary clinical practice.

4.2. PCa detection

4.2.1. GG ≥2 cancers

Men with GG ≥2 cancers were equally well detected by the US and MRI risk-adapted pathways (25% vs 24%), even after correction for known risk factors. The GG ≥2 cancer rate in our US arm (25%) is slightly higher than the 20% detected via transrectal US-guided biopsies in a Dutch cohort study of biopsy-naïve men using a biopsy-all strategy (1658 men included between 2007 and 2016) to retrospectively investigate the value of the US (RPCRC#3)-directed pathway [14]. In the Dutch 4M study (626 men included between 2015 and 2017), the GG ≥2 cancer rate detected via transrectal US-guided biopsies in a biopsy-all strategy was 23% [15].

The GG ≥2 cancer rate in our MRI arm (24%) is similar to recently published data for Dutch cohort studies of biopsy-naïve men reporting MRI-directed GG ≥2 cancer rates (25% in the 4M study [15] and 27% in a large Dutch cohort study [16]).

4.2.2. GG 1 cancers and PCa-negative biopsies

GG 1 cancers were detected less frequently in the MRI arm than in the US arm (difference -4.5%). These results are concordant with a Cochrane meta-analysis (difference −7.3%) involving 4079 men from 17 retrospective studies [17] and the 4M study (difference −10%) [15]. Fewer men underwent unnecessary (PCa-negative) biopsies in the MRI arm than in the US arm (difference −7.0%).

4.3. Safe reduction in biopsy testing

The MR-PROPER study prospectively reduced biopsies for men with low risk in the US arm and the MRI arm, demonstrating the value of risk stratification. In the US arm, biopsy tests were avoided by 42% (RPCRC#3-negative, low risk) of men. During routine clinical practice, a subset of these men with low risk underwent systemic biopsies as part of the safety net (Fig. 1). A direct comparison between the US arm and the MRI arm of the proportion of missed cancers is difficult, because only a small subset of men underwent additional biopsies. Of these safety-net biopsies, ten out of 104 GG ≥2 cancers (9.6%) would have been missed in the US arm and five out of 111 (4.5%) in the MRI arm if this safety net had not been applied. These results are comparable with the 7% of GG ≥2 cancers missed according to a retrospective analysis of 1850 men in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) at the same risk thresholds [6]. In the MRI arm, biopsy tests were avoided in the 55% of men who were MRI-negative, similar to the 49% men who were MRI-negative in the 4M study [15]. Omitting systematic biopsies for these MRI-negative men seem justified, because the safety net only detected 2% (five/254) of all GG ≥2 cancers.

4.4. Comparison of outcomes between MR-PROPER and randomized controlled trials

The rates of GG ≥2 cancer detection in the two arms of the MR-PROPER study (25% vs 24%) differ from results for randomized trials such as PRECISION (38% vs 26%; difference 12%, 95% CI 4–20%; p = 0.005) [18] and PRECISE (35% vs 30%; difference 5.2%, 95% CI −3.4% to ∞) [19]. Although the reason for these discrepancies is unclear, differences in histological grading for targeted biopsies may influence final GG ≥2 cancer rates. Furthermore, biopsy avoidance in the MRI arm of the PRECISION (28%) and PRECISE (38%) studies was lower than in MR-PROPER (55%), while the baseline risk (ie, age, PSA, abnormal DRE) was at least as high. Moreover, detection of GG 1 cancers in the US arm (13%) of MR-PROPER was lower than in the US arms of PRECISION (22%) and PRECISE (22%) and in a Cochrane meta-analysis (19%). The latter difference can most likely be explained by the use of RPCRC#3 risk stratification before biopsy.

4.5. Limitations and future perspectives

As part of our protocol, significant PCa that was missed in men with low risk cannot easily be investigated. Several retrospective studies support such a strategy, as these men have a low risk of significant cancer [15,16] and follow-up with PSA monitoring showed very few significant cancers [20]. In contrast to risk assessment via MRI, RPCRC#3 may take other relevant prebiopsy information into account, but may need to be updated to contemporary center-specific settings [21]. Selection bias could have been introduced, since not all patients who were referred for diagnosis were automatically included (depending on day-to-day logistical constraints and the willingness of doctors, nurses, and patients to participate). Significantly more DRE abnor-

malities were found in the US arm than in the MRI arm. We hypothesize that DRE was performed with greater scrutiny in the US arm than in the MRI arm, since DRE is of greater importance in the former because risk assessment relies on clinical parameters including DRE. Small differences in cancer prevalence between the two study arms are possible, but are likely to be negligible because of the large number of participating centers located throughout all regions of the Netherlands. Furthermore, correction for these risk factors showed equivalent cancer detection between the two study arms. Finally, since there is a substantial difference in the proportion of men who underwent safety-net biopsies, a direct comparison of the cancers potentially missed in the two arms is not feasible.

5. Conclusions

This large prospective multicenter study conducted in The Netherlands investigated two commonly used risk-adapted strategies for early detection of PCa. The US-directed pathway, including RPCRC#3 risk assessment, detected men with GG $\geq$2 cancers equally well in comparison to the MRI-directed pathway. The MRI-directed pathway detected fewer men with GG 1 cancers and excluded more men from biopsy tests. We conclude that the risk-adapted US-directed pathway performs well in biopsy-naïve men with suspected PCa if prostate MRI capacity or expertise is not available. If prostate MRI availability is sufficient, risk assessment should preferably be performed with MRI to substantially reduce overdiagnosis and biopsies.

Author contributions: Ivo G. Schoots had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Peer Review Summary

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