Optimizing Prostate Cancer Screening, Detection and Active Surveillance by Risk Stratification Strategies

Daniël F. Osses

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Het optimaliseren van prostaatkanker screening, detectie en een actief afwachtend beleid door toepassing van risicostratificatie strategieën

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"Queda prohibido no sonreír a los problemas,
no luchar por lo que quieres,
abandonarlo todo por miedo,
no convertir en realidad tus sueños."
- Pablo Neruda

CONTENTS

1

GENERAL INTRODUCTION

PROSTATE CANCER SCREENING AND DETECTION

"Medical research has made such progress, that there are practically no healthy people anymore." – Aldous Huxley (1). This counterintuitive phenomenon as named by Huxley could easily be related to prostate cancer (PCa) care, being often summarized in terms such as 'unnecessary testing', 'overdiagnosis' and 'overtreatment'. The occurrence of these terms and especially how to reduce them at time of detection and initial non-invasive treatment of PCa are extensively discussed in this thesis.

The prostate is a walnut-size gland located in men between the bladder and penis, surrounding the urethra. The prostate is part of the male reproductive system and secretes fluid that nourishes and protects sperm cells produced by the testicles. An enlarged prostate compresses the urethra and irritates the walls of the bladder, interfering with normal urination. More than half of men in their 60s suffer from this benign growth of the prostate called Benign Prostatic Hyperplasia (BPH) (2, 3). Another condition of the prostate, in general developed in men aged 50 years and older due to abnormal growth and division of epithelial cells, is PCa. PCa has the potential to spread to parts outside the prostate, usually the lymph nodes and bones, and can eventually lead to death. PCa is among the top three most lethal cancers in men from most western countries (4, 5). In the Netherlands a total of 12056 men were diagnosed with PCa in 2017, and 2862 men died because of PCa that year (6).

Traditionally, PCa is detected by systematic transrectal ultrasound (TRUS)-guided prostate biopsies (SBx) that are performed in case of clinical suspicion of PCa based on an elevated prostate-specific antigen (PSA) level and/or abnormal digital rectal examination (DRE) (7). PSA is a protein almost exclusively produced by prostate epithelial cells and its serum level is usually elevated in case of PCa presence (8, 9). Therefore, PSA can be used as a marker for early PCa detection (10, 11). However, the serum PSA level can also be elevated due to benign prostate conditions like BPH, prostatitis, prostatic manipulation or instrumentation (12).

Despite the lack of specificity of PSA as a biomarker in PCa detection, opportunistic PSA-based PCa screening as introduced in the early 1990's led to an increase of early PCa diagnoses and, in combination with improved treatment modalities to a reduction in PCa-specific mortality in Europe and the United States of America (USA) (13, 14). The rise of the PSA test and its apparently beneficial effect in PCa diagnostics motivated the initiation of studies exploring the effect of organized PCa screening on mortality and the possibilities of introducing a population-based screening program for PCa, like in the Netherlands nowadays is implemented for breast, cervical and colon cancer (15).

The two largest PSA-based PCa screening studies initiated in the early 1990s are the European Randomized Study of Screening for Prostate Cancer (ERSPC) performed in 8 European countries, and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer screening trial performed in the USA (16, 17). These studies randomized over 250.000 men in total to repeated PSA screening or control groups and show at a median follow-up time of 16 years that with good compliance and no contamination, PSA-based PCa screening can reduce metastatic disease and PCa-specific mortality with approximately 30% and 20%, respectively (18, 19).

The downsides of a purely PSA-based screening algorithm are, however, firstly the high number of men that need to be (repeatedly) tested to identify one men being at risk for potentially life threatening disease. This implies that most men tested will experience no benefit of screening. This is referred to as unnecessary testing. Furthermore, screening will result in a substantial (50%, range 23%-67%; number needed to diagnose [NND] 18, range 5-48) detection of indolent PCa that will never harm a patient, referred to as overdiagnosis (19-23). These cancer findings could primarily affect men's mental health and subsequently actively treating these cancers with surgery or radiation therapy, which still often occurs, will basically not benefit a patients cancer-specific survival but could potentially come with the negative side effects from the active treatment such as incontinence and impotence with (further) reduction of the quality of life (20, 21, 24). This phenomenon is referred to as overtreatment. The estimated numbers of unnecessary testing, overdiagnosis and overtreatment of PSA-based PCa screening on population level are presented in table 1. In summary, on population level the benefits of PSA-based PCa screening do not to very limited outweigh the harms of screening. Therefore, PSA-based PCa screening remains one of the most controversial issues in urological practice.

Harms of PCa screening	Organized PSA-based PCa screening	Opportunistic PSA-based PCa screening (current clinical practice)
Unnecessary testing, % (NNI)	75% (570)	40% (493)
Overdiagnosis, % (NND)	50% (18)	40% (23)
Overtreatment, %	50%	50%

Table 1. An overview of the severity of the harms of organized and opportunistic PSA-based prostate cancer screening on population level. The values are obtained/calculated using data from the main ERSPC and Göteborg screening trials (= average values; results could differ between populations) (19, 22, 23, 25, 26).
PCa: prostate cancer; NNI: number needed to invite; NND: number needed to diagnose; PSA: prostate-specific antigen.

Selecting the right men that will benefit from screening and detection tests with the right tools is mandatory to be able to improve the harm-benefit ratio of PCa screening. In addition, the sampling technique in men identified as being at high risk for aggressive disease should be improved. Key components in identifying which men are suitable for (invasive) screening and detection tests are the estimation of life expectancy, risk of aggressive PCa and potential benefit of PCa treatment which is influenced by the life expectancy, as shown in figure 1. These components are depending on age, comorbidity, the PSA level and other clinical parameters, and expected lead time of PSA screening (27). The selection of men that will benefit from screening and detection tests could potentially be done by upfront risk stratification strategies before embarking to invasive procedures like a prostate biopsy (28).

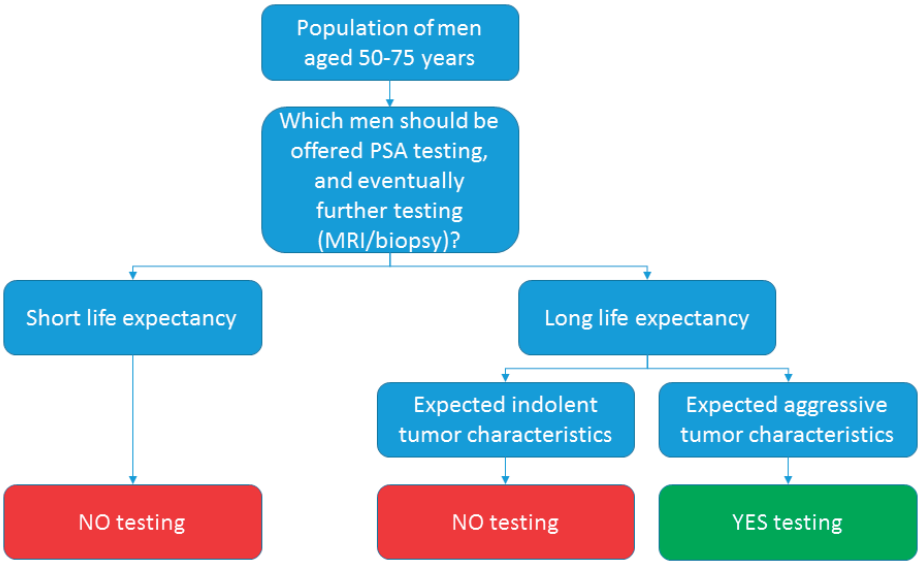

Figure 1. A flowchart showing which men should be selected for prostate cancer screening and detection tests.
PSA: prostate-specific antigen; MRI: magnetic resonance imaging.

ACTIVE SURVEILLANCE

A strategy to potentially counteract some of the harms of overdiagnosis and eventually subsequent overtreatment is Active Surveillance (AS) (29). The aim of AS is to delay or even completely avoid unnecessary invasive treatment of a prostate malignancy to prevent men from treatment related side effects (30). In AS men with a long life expectancy likely to have an overdiagnosed cancer (i.e. low-risk PCa, often defined as Gleason

score [GS] 3+3=6 or International Society of Urological Pathology [ISUP] grade 1 PCa) are closely monitored by repeated PSA measurements, DREs, prostate biopsies and recently also prostate magnetic resonance imaging (MRI), to switch only to active treatment in case of tumor upgrading to higher risk disease (i.e. intermediate/high-risk PCa, often defined as GS ≥3+4 or ISUP grade ≥2 PCa), within the window of curability (31). AS has shown to be safe at long-term follow-up (32, 33). Recently, it was discovered that certain secondary Gleason 4 growth patterns (i.e. cribriform growth and intraductal carcinoma) reflect more aggressive disease than other growth patterns and could be prognostic drivers in cancer-specific survival (34). This implicates that inclusion criteria of AS-protocols could be considered to be extended, allowing the inclusion of limited ISUP grade 2 PCa without the presence of these secondary growth patterns to AS (35).

A downside of the currently applied AS-protocols is, however, the one size fits all approach. This results on one hand in strict monitoring of all low-risk PCa men, but on the other hand in potentially a lot of unnecessary follow-up testing and subsequent costs in men with a (very) low risk of disease upgrading (36). This could result in the opposite effect than intended with AS; to be less burdensome than active treatment and its potential side effects. Therefore, the current protocols of AS should be improved by better selection of those men who are at high risk of disease upgrading and will benefit from follow-up testing and in case of confirmed disease upgrading will also benefit from a subsequent active treatment (37). Life expectancy, the risk of disease upgrading and ability to receive active curative treatment which is influenced by the life expectancy play a major role in identifying the men that will benefit from invasive follow-up testing in AS, as shown in figure 2. Again these aspects are depending on among others age, comorbidity, and PSA and other clinical parameters. Risk-based patient selection for follow-up testing made possible by risk stratification strategies could potentially be the way to go in AS (38, 39).

RISK STRATIFICATION

"Better prediction equals better prioritization." – Asaf Bitton (40). This phrase describes proper risk stratification in effective population health management which is nowadays likely to be necessary to achieve the general aim of better health outcomes, better health care and lower health care costs. Risk stratification is defined as the constellation of activities to determine a person's risk for suffering a particular condition and the need or lack for an intervention (41). Risk stratification has three goals in general: 1) predicting risks, 2) prioritizing interventions and 3) preventing negative outcomes (e.g. death – as well as unnecessary costs).

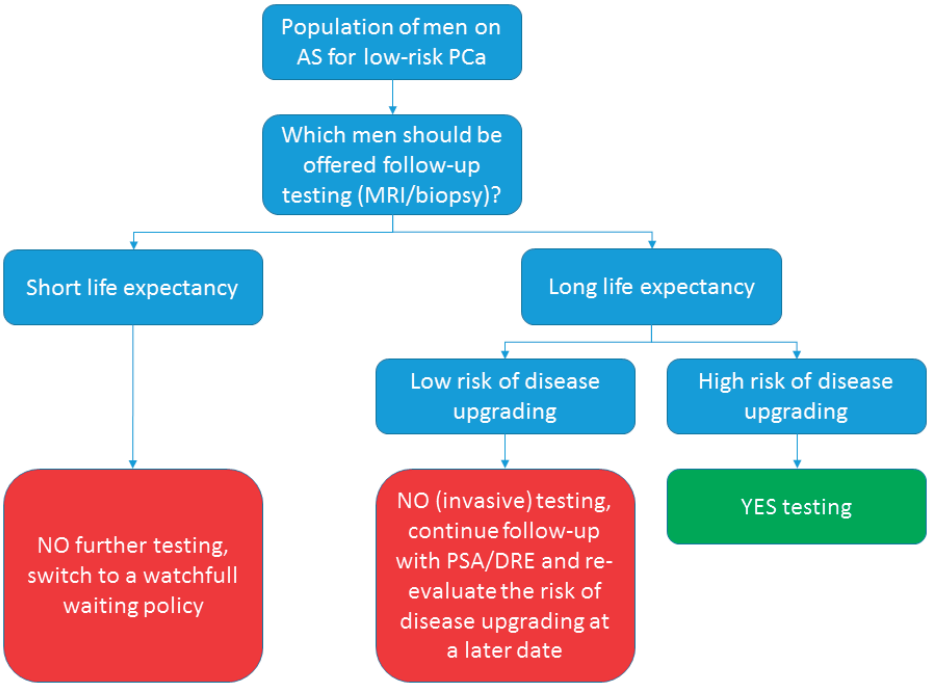

Figure 2. A flowchart showing which men on active surveillance for low-risk prostate cancer should be selected for follow-up (invasive) testing.
AS: active surveillance; PCa: prostate cancer; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; DRE: digital rectal examination.

The PSA test as standalone test already serves as a risk stratification tool. Half of the men at age 60 have a PSA below 1.0 ng/ml, whose 25 year risk of death from PCa turned out to be very low (42-45). However, as mentioned above an elevated PSA level lacks specificity. Therefore, international PCa guidelines also recommend the use of subsequent risk stratification tools for the prediction of a positive prostate biopsy as reflex tests after an elevated PSA level, which have led to the development of so-called risk-adapted screening and detection algorithms (7, 28, 46-48). Risk stratification strategies in PCa care could support the process of shared informed decision-making and could potentially result in less unnecessary testing, less overdiagnosis and less overtreatment. The currently most used risk stratification tools in PCa diagnosis and AS, and also mainly discussed in this thesis, are the combinations of clinical data (e.g. PSA-density [PSA-D]), novel blood- and urine-based (genetic) biomarkers, prediction models (i.e. risk calculators = combinations of [novel] biomarkers and clinical/radiological data) and imaging modalities which next to inform one about the risk at significant PCa also allow the performance of targeted biopsies (TBx) (e.g. prostate MRI with its derived predictive parameters) (28).

GENERAL OBJECTIVE OF THIS THESIS

The general aim of this thesis is to investigate whether the use of risk stratification strategies at time of prostate cancer detection and at initiation and during an active surveillance strategy for low-risk prostate cancer could safely reduce the number of unnecessary referrals/tests, overdiagnosis and eventually subsequent overtreatment, without missing the diagnosis/treatment of clinically significant prostate cancer that potentially could harm a patient if left undetected/untreated.

OUTLINE OF RESEARCH QUESTIONS ADDRESSED IN THIS THESIS

The first part of the thesis will focus on prostate cancer screening and detection, and is divided into five chapters. These five chapters will focus on the following research questions:

- What is the long-term effect of PSA-based prostate cancer screening, and could it add to the ongoing discussion on the balance between harms and benefits of prostate cancer screening? (Chapter 2 and 3)
- Can we select those men at high risk for aggressive disease who need further testing using currently available risk calculators, thereby avoiding unnecessary referrals, MRIs, prostate biopsies and overdiagnosis? (Chapter 2, 4, 5)
- Can magnetic resonance imaging-derived characteristics alone or combined with clinical parameters improve the selection of those men at high risk for aggressive disease who need a biopsy? (Chapter 5 and 6)

The second part of the thesis will focus on active surveillance and is divided into two chapters addressing the following research questions:

- Can we identify those men at high risk of disease upgrading who need a follow-up biopsy using magnetic resonance imaging and clinical parameters, avoiding unnecessary follow-up biopsies in men at low risk of disease upgrading? (Chapter 7 and 8)
- Can serial magnetic resonance imaging be used to monitor low-risk prostate cancer patients during follow-up? (Chapter 8)

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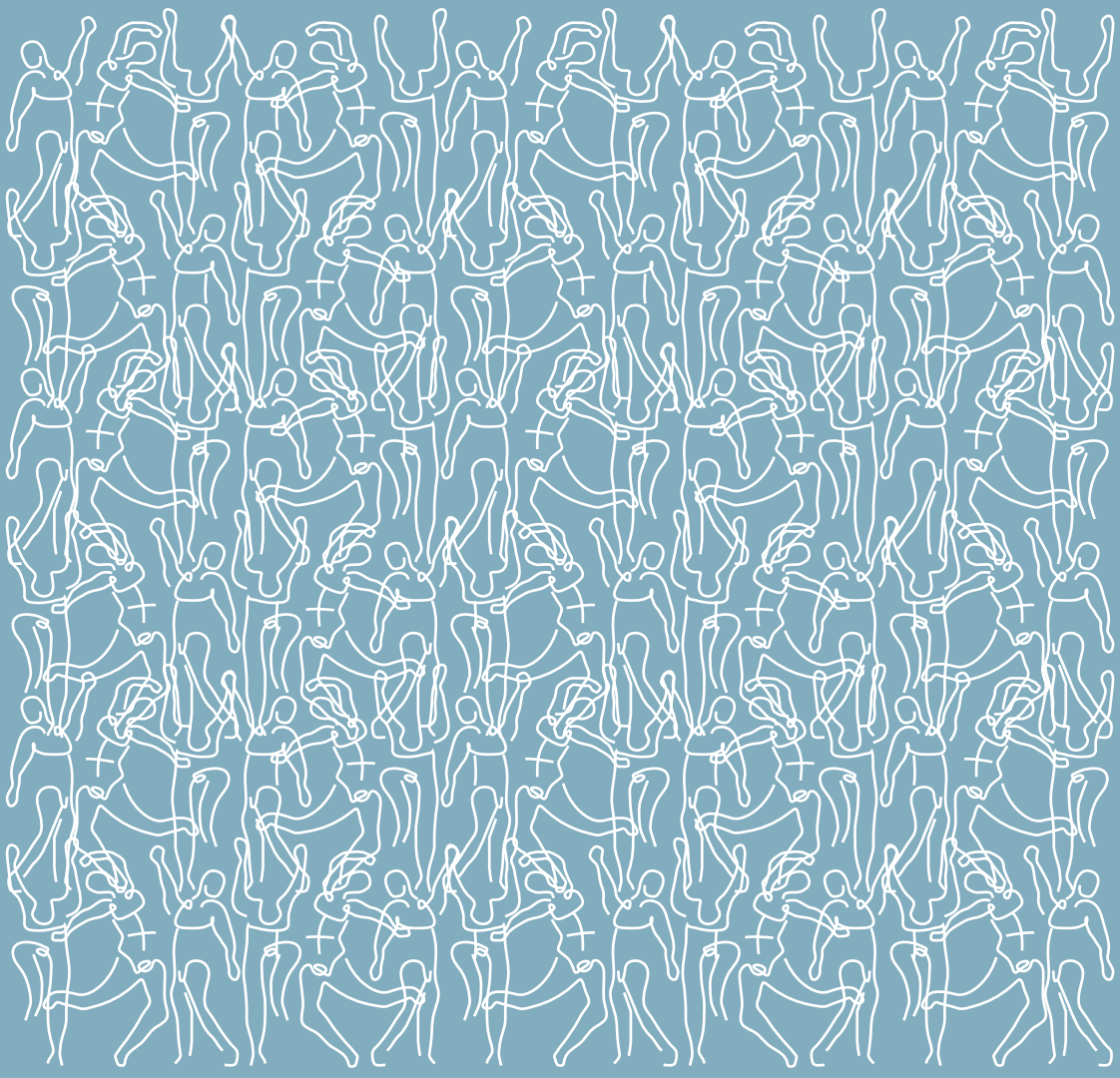
PART I

SCREENING AND DETECTION



2

Prediction medicine: biomarkers, risk calculators and magnetic resonance imaging as risk stratification tools in prostate cancer diagnosis.

Daniël F. Osses
Monique J. Roobol
Ivo G. Schoots

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ABSTRACT

This review discusses the most recent evidence for the currently available risk stratification tools in the detection of clinically significant prostate cancer (csPCa), and evaluates diagnostic strategies that combine these tools. Novel blood biomarkers, such as the Prostate Health Index (PHI) and 4Kscore, show similar ability to predict csPCa. Prostate cancer antigen 3 (PCA3) is a urinary biomarker that has inferior prediction of csPCa compared to PHI, but may be combined with other markers like TMPRSS2-ERG to improve its performance. Original risk calculators (RCs) have the advantage of incorporating easy to retrieve clinical variables and being free accessible as web tool/mobile application. RCs perform similarly well as most novel biomarkers. New promising risk models including novel (genetic) markers are the SelectMDx and Stockholm-3 model (S3M). Prostate magnetic resonance imaging (MRI) has evolved as an appealing tool in the diagnostic arsenal with even stratifying abilities, also in the initial biopsy setting. Merging biomarkers, RCs and MRI results in higher performances than their use as standalone test. In the current era of prostate MRI, the way forward seems to be multivariable risk assessment based on blood and clinical parameters, potentially extended with information from urine samples, as triaging test for the selection of candidates for MRI and biopsy.

Keywords

Prostate cancer detection; risk stratification; biomarker; risk calculator; magnetic resonance imaging; cost-effective diagnostic pathways.

1. INTRODUCTION

Although the European Randomized study of Screening for Prostate Cancer (ERSPC) and the recent analyses from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial show evidence that prostate-specific antigen (PSA)-based screening significantly reduces prostate cancer (PCa)-specific mortality, screening for PCa remains a controversial issue (1-5). False positive PSA tests in patients with benign prostatic hyperplasia (BPH) and/or prostatitis result in unnecessary testing (performance of unnecessary systematic transrectal ultrasound [TRUS]-guided prostate biopsy [SBx]). In addition, PSA-based screening can lead to the overdiagnosis, and potentially overtreatment, of PCa which will never become clinically significant. These harms have a significant effect on the quality of life and therefore diminish the number of quality-adjusted life years (QALYs) due to PSA-based PCa screening. Refinements to the PCa diagnostic pathway, focusing on detecting only those cancers that are potentially life-threatening, are needed to make the pathway less burdensome to patients and as such more cost-effective and acceptable to the general population and health care providers (6).

International guidelines propose such refinements in men requesting their physician to "early detect" PCa by recommending an individualized opportunistic PCa screening policy (7, 8). This opportunistic screening goes along with shared informed decision-making, taking into account the individual potential advantage and damage related to PSA testing (7, 8). Furthermore, guidelines recommend the use of risk stratification tools, such as novel biomarkers, risk calculators (RCs) and magnetic resonance imaging (MRI), for the prediction of a positive prostate biopsy as reflex tests after an elevated PSA level (9-17). This may support the process of shared informed decision-making, reduce the number of unnecessary biopsies by better identification of those men at risk of PCa, and better differentiate aggressive from non-aggressive cancers.

While these risk stratification tools have additional value within the diagnostic pathway, physicians should ask themselves if these tools are necessary in every man with an elevated PSA level, taking into account the height of its additional diagnostic and predictive information, the burden for the patient, the availability and costs for society. Risk stratification could be based on one tool. Performing additional tests only in those men considered to be at high-risk of having clinically significant PCa (csPCa) (defined as Gleason score [GS] ≥ 3+4 or ≥ International Society of Urological Pathology [ISUP] grading group 2) could be an acceptable option (18, 19). The risk of promising "easy-to-perform" tools is extensively (and unnecessary) testing of all men (not only the high-risk men), which could result in the opposite effect than intended; to be specific and cost-effective (20). Clear and explicit directions for diagnostic pathways that combine

risk stratification tools after an elevated PSA level in order to potentially reduce the number of tests without missing csPCa are currently lacking.

The aim of this review is to discuss the most recent advancements of the state-of-the-art risk stratification tools in the detection of csPCa, and their application in contemporary practice. Furthermore, we evaluated diagnostic pathways that combine several stratification tools to potentially realize a high csPCa detection rate together with a high cost-effectiveness.

2. NOVEL BIOMARKERS AND RISK CALCULATORS IN PROSTATE CANCER DIAGNOSIS

Several PSA derivatives have been proposed as PCa biomarkers to improve the specificity of the PSA test. The percentage of free PSA (fPSA) to total PSA (tPSA) was introduced three decades ago but this test improved clinical judgment only when levels reached extreme values (21). More recently, fPSA has been found to include the isoforms benign PSA (bPSA), proPSA (with its most stable form [-2]proPSA) and intact PSA (iPSA) with usefulness in the detection of PCa (22). Combining these isoforms has resulted in the Prostate Health Index (PHI) and four-kallikrein (4K) panel. Furthermore, molecular biology has allowed the study of genes associated with PCa. Next to novel biomarkers many RCs have been developed to predict biopsy outcome. In addition, novel biomarkers have been incorporated into existing RCs and new PCa risk models including novel biomarkers have been developed (e.g. SelectMDx, Stockholm-3 [S3M]) (Table 1).

2.1. Blood-based biomarkers: Prostate Health Index and Four-Kallikrein panel

The PHI test result is based on the following mathematical formula: ([-2]proPSA/fPSA x √PSA) and is developed to predict the probability of any PCa and csPCa at prostate biopsy. PHI is the least expensive ($80 in the USA) of currently available commercial multiplex biomarkers and is suggested in the initial and repeat biopsy setting (8, 23, 24). On average, using PHI with a cut-off of ≥25 to biopsy could avoid 40% of biopsies and reduce 25% of GS 6 diagnoses at the cost of missing 5% csPCa (25). Recently, Chiu et al. compared the performance of PHI in different ethnic groups from nine sites (1688 Asian and 800 European men), concluding that PHI was more effective in safely reducing biopsies in Asian men compared to European men (56% versus 40% biopsy reduction) (26).

The 4Kscore is based on serum biomarkers (i.e. the 4K-panel = tPSA, fPSA, iPSA and human kallikrein 2 [hK2]) and includes clinical variables like age, digital rectal examination (DRE) and prior biopsy results to predict the risk of csPCa on biopsy. The 4Kscore is a commercially available assay, is not available in Europe and costs around $500 in the USA (27). Its use is recommended in patients undergoing initial and repeat biopsy (28). A systematic review to evaluate the performance of the 4Kscore in the pre-biopsy setting showed a pooled area under the curve (AUC) above 0.80 for the discrimination of csPCa, which was highly consistent across 11 studies involving over 10000 subjects (29). The AUC of the receiver operating characteristic (ROC)-curve summarizes the value of a test. The higher the AUC of the ROC-curve is, the more combinations of high sensitivity and specificity are available, thus the better the test performs. On average, using the 4Kscore with a cut-off risk of 9% csPCa to indicate systematic biopsy (SBx) could avoid 43% biopsies at the cost of missing 2.4% csPCa (12, 30, 31). In a comparative study including 531 men undergoing first-time biopsy, Nordström et al. found that the PHI test and 4Kscore showed similar ability to predict the detection of csPCa (AUC 0.71 versus 0.72) (32). In summary, the serum based biomarkers PHI and 4Kscore show comparable performance but are substantially different in price.

2.2. Urine-based biomarkers: PCA3, TMPRSS2-ERG, HOXC6, TDRD1 and DLX1 genes

Prostate cancer antigen 3 (PCA3) is a gene that transcribes a long non-coding messenger RNA (mRNA) that is overexpressed in PCa tissue and is detectable in urine after DRE. The PCA3 score is calculated measuring the concentration of PCA3 mRNA in relation to PSA mRNA and costs around $300 in the USA (33). Guidelines recommend using a cut-off of 35 in men with moderately elevated PSA for whom repeat biopsy is being considered (8, 28). Numerous studies indicate that the PCA3 score has greater accuracy for overall PCa detection in the repeat biopsy setting compared to tPSA and fPSA (34-36). Data about the association of the PCA3 score with csPCa are, however, conflicting (37-40). In recent years, comparative studies have demonstrated that PHI outperforms PCA3 for the prediction of csPCa on biopsy (41, 42). As the current paradigm emphasizes detection of csPCa, the potential of PCA3 as a reflex test is questionable.

Another gene associated with PCa and detectable in urine after DRE is TMPRSS2-ERG fusion. Studies demonstrated that the TMPRSS2-ERG fusion gene has a greater diagnostic accuracy than tPSA, with a high specificity (93%) and positive predictive value (PPV) (94%) for the detection of PCa (43, 44). Unlike PCA3, TMPRSS2-ERG levels were associated with csPCa. However, its low sensitivity reduces its value as a standalone test. Combining PCA3 with TMPRSS2-ERG can improve the prediction of csPCa (15, 43, 44). A commercial test, the MiProstate Score (MiPS), incorporates PSA, PCA3 and TMPRSS2-ERG

Risk stratification tool	Indication (biopsy setting)	Reduced MRIs (%)	Reduced biopsies (= SBx and/or TBx) (%)	Reduced low-risk PCa diagnoses (= GS 6 or GG 1) (%)	Missed csPCa (≥GS 3+4 or ≥GG 2) (%)	Costs ($ or €)*
Blood-based biomarkers:						
PHI (cut-off ≥25) --> SBx	Initial and repeat	N/A	40	25	5	$80
4Kscore (cut-off ≥9% csPCa) --> SBx	Initial and repeat	N/A	43	ND	2	$500
Urine-based biomarkers:						
PCA3 (cut-off ≥35) --> SBx	Repeat	N/A	67	40	21	$300
PCA3 (cut-off ≥25) plus TMPRSS2-ERG (cut-off ≥10) --> SBx	Initial and repeat	N/A	35	19	10	ND
Original risk calculators (including PSA and standard clinical data):						
ERSPC RPCRC (cut-off ≥4% csPCa) --> SBx	Initial and repeat	N/A	32	25	5	Free of charge
PCPT 2.0 (cut-off ≥4% csPCa) --> SBx	Initial and repeat	N/A	16	15	3	Free of charge
Sunnybrook (cut-off ≥4% csPCa) --> SBx	Initial and repeat	N/A	25	22	5	Free of charge
New risk calculators (including novel biomarkers):						
4Kscore-ERSPC RPCRC combined (cut-off ≥5% csPCa) --> SBx	Initial	N/A	66	14	2	$500
PCA3-based nomogram Hansen (cut-off ≥30% PCa) --> SBx	Initial	N/A	55	ND	2	$300
MiPS-PCPT RC (cut-off ≥40% PCa) --> SBx	Initial and repeat	N/A	47	10	2	$700
SelectMDx (cut-off ≥-2.8 risk score) --> SBx	Initial and repeat	N/A	42	ND	2	€ 300
S3M (cut-off ≥10% csPCa) --> SBx	Initial	N/A	38	17	6	ND
Magnetic Resonance Imaging:						
Upfront MRI + TBx	Initial	0	32	37	4	$1000
After previous negative SBx --> MRI + TBx	Repeat	0	32	38	2	$1000
Novel biomarkers and MRI merged together:						
PHI (cut-off ≥35) + MRI suspicion score --> TBx + SBx	Repeat	0	42	13	5	$1080
PHI-density (cut-off ≥0.44) + MRI suspicion score --> TBx + SBx	Repeat	0	35	ND	8	$1080

4Kscore (cut-off <7.5% csPCa) + MRI suspicion score --> TBx + SBx	Initial and repeat	0	15	ND	2	$1500
Risk calculators including MRI data:						
MRI-ERSPC RPCRC 3 (cut-off ≥10% csPCa) --> TBx + SBx	Initial	0	14	13	10	$1000
MRI-ERSPC RPCRC 4 (cut-off ≥10% csPCa) --> TBx + SBx	Repeat	0	36	15	4	$1000
Van Leeuwen model (cut-off ≥10% csPCa) --> TBx + SBx	Initial	0	28	13	3	$1000
Truong model (cut-off <70% benign) --> TBx	Repeat	0	29	14	8	$1000
Mehralivand model (cut-off ≥20% csPCa) --> TBx + SBx	Initial and repeat	0	38	ND	11	$1000
Diagnostic strategies combining tools:						
Initial 4Kscore (cut-off ≥7.5% csPCa) --> MRI + TBx	Initial and repeat	25	83	75	33	$500 - $1500
Initial PCA3 (cut-off ≥35) --> MRI + TBx	Initial	52	76	87	48	$300 - $1300
Initial ERSPC RPCRC 3 --> MRI + TBx + SBx	Initial	37	37	23	6	$0 - $1000
Initial ERSPC RPCRC 4 --> MRI + TBx	Repeat	37	55	66	17	$0 - $1000
Initial SelectMDx (cut-off ≥10% csPCa) --> MRI + TBx + SBx	Initial and repeat	35	35	52	2	€300 - €1300
Initial S3M (cut-off ≥10% csPCa) --> MRI + TBx + SBx	Initial and repeat	38	38	42	8	ND

Table 1. Summary table with the performances of the currently available risk stratification tools (as standalone tests and merged together) and the diagnostic pathways that combine the tools in the detection of clinically significant prostate cancer (csPCa) (all on average; results can differ between populations). *including only the estimated costs of the risk stratification tool(s); excluding the costs of biopsy procedures, consultations etc.
Red = disadvantage, Orange = neutral, Green = advantage.
MRI: magnetic resonance imaging; SBx: systematic biopsy; TBx: MRI-targeted biopsy; PCa: prostate cancer; GS: gleason score; GG: grade group; csPCa: clinically significant prostate cancer; PHI: Prostate Health Index; N/A: not applicable; ND: not determined; 4K: four-kallikrein; PSA: prostate-specific antigen; ERSPC: European Randomized study of Screening for Prostate Cancer; RPCRC: Rotterdam Prostate Cancer Risk Calculator; PCPT: Prostate Cancer Prevention Trial; MiPS: MiProstate Score; S3M: Stockholm-3 model.

to predict the risk of PCa and csPCa. MiPS costs around $700 in the USA and is a promising test following PSA screening, but has not yet been validated in prospective studies and directly compared with other biomarkers (45, 46).

Microarray analysis of mRNA from PCa tissue compared with normal prostate tissue revealed 39 potential biomarker candidates (40). Among them, eight mRNAs were upregulated in precipitates of urine obtained after DRE from men with PCa. From these eight genes a panel (HOXC6, TDRD1 and DLX1) was selected for the detection of PCa and in particular csPCa (47, 48). This urinary three-gene panel showed higher accuracy (AUC 0.77) to predict csPCa in biopsies compared with the PCA3 score or serum PSA.

2.3. Combinations of biomarkers and clinical data = risk calculators

2.3.1. Risk calculators including only standard clinical parameters

RCs have the advantage of incorporating easy to retrieve clinical variables. A systematic review identified 127 existing RCs in the field of PCa (9). Only six RCs to predict biopsy outcome have been externally validated in more than five study populations other than the development population: the ERSPC Rotterdam Prostate Cancer Risk Calculator (RPCRC), the Finne model, the Chun model, the Karakiewicz model, the Prostate Cancer Prevention Trial (PCPT) model and the ProstataClass model (10, 49-53). Besides PSA, the DRE was the most common predictor variable to be included in the risk models, followed by age, fPSA and transrectal ultrasound (TRUS) prostate volume (PV). In a recent head-to-head comparison, RCs incorporating PV showed to be superior in identifying men at risk of csPCa (54). Therefore, incorporation of PV into RCs is recommended (54-56). The same study showed that the above-mentioned RCs and the so-called Sunnybrook RC have a moderate to well discriminatory ability when predicting any PCa (AUCs from 0.64 to 0.72) (54, 57). The ERSPC RPCRC was shown to be slightly superior in predicting men at risk of csPCa. On average, using the ERSPC RPCRC with biopsy at a cut-off of 4% csPCa risk could avoid 32% of biopsies and reduce 25% of GS 6 diagnoses while keeping a 95% sensitivity for detecting csPCa (54).

Another advantage of RCs using only readily available clinical data is that they are available as web tool and mobile applications (Apps), making (most of) them free accessible for everyone (58). A recent systematic review assessing the everyday functionality and utility of the currently available RC Apps showed that based on the Mobile Application Rating Scale, the ERSPC RPCRC App performed well (59).

2.3.2. Risk calculators including novel biomarkers next to clinical parameters

The original RCs were virtually all developed in the 1990s. That means that they do not include later-developed biomarkers. The addition of PHI to the ERSPC RPCRC three

(initial biopsy) and four (repeat biopsy) significantly improved the prediction of csPCa (60, 61). More recently, Loeb et al. confirmed the added value of PHI when incorporated into the PCPT RC and ERSPC RPCRC, and created a new PHI-based prediction model with an AUC of 0.75 (62).

The 4Kscore is in fact a risk prediction model combining novel biomarkers (i.e. the 4K-panel) and standard clinical data. Verbeek et al. recently investigated in a cohort of 2872 men (initial biopsy) the clinical impact of the 4Kscore, ERSPC RPCRC and the combination of both for predicting csPCa (63). In this study the 4Kscore and ERSPC RPCRC had similar AUCs (0.88 versus 0.87). The 4Kscore-ERSPC RPCRC combination significantly improved the AUC to 0.89 (64). Gain in net benefit must, however, be weighed against additional costs and the availability of tests.

The PCA3 score has also been investigated in conjunction with other variables. Hansen et al. designed a PCA3-based nomogram specifically to predict initial prostate biopsy results (65). This model could lead to the avoidance of 55% biopsies while missing 2% of patients with csPCa. PCA3 has also been incorporated into existing prediction tools for men undergoing initial or repeat biopsy, such as the ERSPC RPCRC, PCPT RC (updated in 2018 with TMPRSS2-ERG added) and Chun model (66-70). Incorporation of PCA3 improved the diagnostic accuracy of all RCs, which is perhaps the most appropriate application of PCA3 (71). Similarly, the addition of MiPS to the PCPT RC was superior to a base model (46). Using various cut-offs, the MiPS-PCPT RC model would avoid 35%-47% of biopsies while missing 6%-10% low-risk PCa and 1.0%–2.3% csPCa.

Based on the high predictive accuracy for csPCa of the urinary three-gene panel - HOXC6, TDRD1 and DLX1 -, Van Neste et al. developed a new risk model combining HOXC6 and DLX1 with clinical parameters (age, PSA, DRE, PV and family history). This model is available as the SelectMDx test and costs around €300,- in Europe (40, 72). The European Association of Urology (EAU) guidelines suggest considering the use of SelectMDx in deciding whether to take an initial or repeat biopsy (8). The model demonstrated an AUC of 0.86 for csPCa and outperformed the base model without mRNA markers and the PCPT RC. Decision curve analysis suggested that SelectMDx could reduce 42% of biopsies while missing 2% csPCa. Recently, analyses showed that with SelectMDx quality-adjusted life years (QALYs) could be gained while saving healthcare costs in the initial diagnosis of PCa, making the use of SelectMDx before proceeding to biopsy potentially a cost-effective strategy (73-75). As stated by Van Neste et al. the SelectMDx model is mainly driven by the strong predictive value of PSA-density (72).

Another new risk model is the S3M. This model is based on plasma protein biomarkers (PSA, fPSA, iPSA, hK2, MSMB, MIC1) combined with genetic polymorphisms (232 single nucleotide polymorphisms) and clinical variables (age, DRE, PV, family and biopsy history). The model was created using data from the Stockholm-3 study, with PSA-density being once more the strongest predictor (76). The S3M is not available outside of Sweden and it is difficult to judge its exact price (77). The S3M is proposed to be used in the initial biopsy setting. In a screening cohort, the S3M performed significantly better than PSA alone for the detection of csPCa (AUC 0.74 versus 0.56) (76). At the same level of sensitivity as the PSA test using a cut-off of ≥3.0 ng/mL to diagnose csPCa, use of the S3M could reduce the number of biopsies by 32% and avoid 17% GS 6 diagnoses (78). Recently, the S3M was updated and showed a slightly improved AUC (77). In a contemporary independent cohort, the S3M also performed well (38% biopsy avoidance at the cost of missing 6% csPCa) (79). The S3M's performance characteristics should be compared with other biomarkers and RCs before wide incorporation in daily practice.

3. MAGNETIC RESONANCE IMAGING (MRI) AS CLINICAL "BIOMARKER" IN PROSTATE CANCER DIAGNOSIS

With the technological advancements in recent years and increasing experience among technicians, radiologists, urologists and pathologists, MRI has evolved as an appealing tool in the diagnostic arsenal (8). MRI has shown to be the preferred imaging modality for detecting areas suspicious for csPCa and allowing guidance for targeted biopsy (TBx), with a total cost of $700 - $3000 depending on regional differences in health-care systems outside of Europe (80, 81). In Europe, the costs of a prostate MRI is estimated to be €300 - €500 (81). TBx can be performed using in-bore MR-guided biopsy, cognitive fusion biopsy and software fusion biopsy, without significant differences in the detection rate of csPCa among the three techniques (82). TBx is most often performed in combination with SBx. Guidelines for standardized prostate MR image acquisition and reporting are published (83). The Prostate Imaging – Reporting and Data System (PI-RADS) describes the assessment of MRI lesions, judged on a likelihood scale from 1 to 5. A PI-RADS assessment score of 3 to 5 is mostly used as definition for a suspected lesion on MRI (83). Strategies incorporating MRI as a (subjective) "biomarker" in different clinical settings have been undergoing investigation or are still being investigated. In addition, to better identify those men who would benefit from TBx and/or additional SBx after an MRI scan, MRI data have been combined with (objective) novel biomarkers and incorporated into existing and new developed risk models (Table 1).

3.1. Initial biopsy setting

Although MRI with or without TBx (MRI strategy), in addition to or as a replacement of SBx, is increasingly investigated in the initial biopsy setting, guidelines do not yet recommend a pre-biopsy MRI or an upfront MRI-directed biopsy management in biopsy-naïve men (8, 28). Over the last years studies have shown that MRI in combination with TBx significantly improved the detection rate of csPCa in the repeat biopsy setting but not (yet) in biopsy naïve men (80, 84). High-level evidence for csPCa detection by the MRI strategy as compared to SBx in biopsy-naïve men has been scarce until 2018.

Recently, two multicenter randomized controlled trials (RCTs) in biopsy-naïve men investigated the performance of the MRI strategy versus SBx (17, 85). The PRECISION trial showed that MRI in combination with TBx detected 12% more csPCa and 13% less low-risk PCa (= GS 6 PCa or ISUP grading group 1) than SBx, while a 28% reduction of biopsies was realized. Porpiglia et al. also concluded that the MRI strategy outperformed SBx. Furthermore, two prospective multicenter studies investigating the agreement of PCa detection between the MRI strategy (i.e. without additional SBx) and SBx in biopsy-naïve men have been published recently (86, 87). In the 4M-study and MRI-FIRST trial the proportion of detected csPCa by MRI with or without TBx (25%-32%) was similar to the proportion csPCa detected by SBx (23%-30%). However, the MRI strategy detected significantly less low-risk PCa compared to SBx and MRI could have avoided 18%-49% of biopsy procedures at the cost of missing 5% csPCa. Lastly, a Cochrane review determined in a mixed biopsy population (initial and repeat) that at a prevalence of 30% csPCa, the negative predictive value (NPV) for MRI, MRI-TBx, MRI strategy and SBx was 90%, 93%, 90% and 87% (using template biopsy as reference standard), respectively (88). An additional agreement analysis showed an equivalent proportion of detected csPCa by MRI with or without TBx (22%) and SBx (20%) in biopsy-naïve men. However, the MRI strategy beneficially avoided the detection of a significant proportion (37%) of low-risk PCa and reduced 32% of biopsy procedures (negative MRI) at the cost of missing 4% csPCa, across 20 included studies involving over 5000 biopsy-naïve subjects.

3.2. Repeat biopsy setting

Guidelines recommend the use of MRI and TBx in the setting of persistent clinical suspicion of PCa after previous negative SBx (8, 28, 89). Studies have shown that the MRI strategy can significantly improve the detection of csPCa while reducing the detection of low-risk PCa and number of performed biopsy procedures in comparison to repeat SBx (80, 84, 90-93). The NPV of the MRI strategy in this setting is, however, also not 100% (94-96).

The Cochrane review from Drost et al. included 10 studies involving over 1500 subjects to determine the agreement of PCa detection between the MRI strategy and SBx in the repeat biopsy setting (88). The analysis showed that the MRI strategy detected 44% more csPCa than SBx. Furthermore, the MRI strategy avoided the detection of a significant proportion (38%) of low-risk PCa and reduced 32% of biopsies at the cost of missing 2% csPCa.

3.3. Novel biomarkers and MRI merged together

Gnanapragasam et al. showed in 279 men requiring a repeat biopsy that adding PHI to the MRI suspicion score improved csPCa prediction (AUC 0.75) compared to PSA + MRI alone (AUC 0.69). Using a PHI cut-off ≥35, 13% of low-risk PCa and 5% of csPCa was missed while 42% of men potentially spared a repeat biopsy (97). Recently, Druskin et al. showed in men with previous negative biopsy that PHI-density and PI-RADS score were complementary, with a PI-RADS score ≥3 or, if PI-RADS score ≤2, a PHI-density ≥0.44, being 100% sensitive for csPCa. Using 0.44 as a threshold for PHI-density combined with MRI, 35% of biopsies could have been avoided at the cost of missing 8% csPCa (98).

In a population of 300 men (initial and repeat biopsy) the combined use of 4K and prostate MRI showed to be superior in the prediction of csPCa (AUC 0.82) and patient's selection for biopsy, compared to using the 4Kscore (AUC 0.70) or PI-RADS score (AUC 0.74) individually (99). If one was to defer a biopsy in men with a negative MRI and a 4Kscore <7.5%, one would avoid 15% of the biopsies and miss 2% csPCa.

3.4. Risk calculators including MRI data

Kim et al. determined the added value of MRI to the PCPT RC in the detection of csPCa on TBx and/or SBx in 339 men requiring initial or repeat biopsy (100). In patients with an estimated risk of csPCa ≤10%, the use of MRI in addition to the PCPT RC provided a significant improvement in clinical risk discrimination (AUC 0.60 versus 0.69). Radtke et al. added pre-biopsy MRI data (PI-RADS v1 score) to the ERSPC RPCRC parameters and developed newly fitted RCs that were superior to ERSPC RPCRC and PI-RADS score alone in their study cohort (101). However, net benefit of these RCs was observed only beyond the 10% risk threshold for csPCa. Recently, Alberts et al. improved the ERSPC RPCRCs. They used a multicenter cohort of 961 men who underwent SBx with or without TBx, and added next to PI-RADS v1 score age as parameter to the ERSPC RPCRCs (102). For the MRI-ERSPC RPCRC 3 net benefit was only observed above a 10% risk threshold for csPCa, which would result in 14% biopsies avoided while missing low-risk PCa in 13% and csPCa in 10% of biopsy-naïve men. The MRI-ERSPC RPCRC 4 would have avoided 36% of repeat biopsies, missing low-risk PCa in 15% and csPCa in 4% of men.

Other groups developed new MRI-based prediction models. Van Leeuwen et al. constructed a model based on the data of 393 biopsy-naïve men undergoing template biopsy with or without TBx incorporating the same parameters as used in the MRI-ERSPC RPCRCs. Using a csPCa risk threshold of 10% would have avoided 28% of biopsies in their cohort, missing 13% low-risk PCa and 3% csPCa (103). Truong et al. developed a nomogram for predicting benign pathology on TBx in the setting of an abnormal MRI after previous negative biopsy (104, 105). The model (PSA, age, PV and PI-RADS v2 score) had an AUC ranging from 0.77 to 0.80. At a benign pathology risk threshold of 70% to biopsy, 29% of biopsies could be avoided with 14% low-risk PCa and 8% csPCa being missed. Recently, Mehralivand et al. constructed a RC to differentiate among patients with positive MRI findings who would benefit from TBx and SBx from those who would not (106). At a csPCa risk threshold of 20% to biopsy, 38% of biopsies could have been avoided while identifying 89% of csPCa.

Again, we are close to being confronted with dozens of RCs predicting biopsy outcome using amongst others MRI results. To avoid this, it is strongly advised that the publication of yet another model should only be pursued after performance is compared with already available models that have shown good discriminative capability. Calibration to a particular setting is relatively easy to do (provided that the predictive effects of other covariates are similar between the development and designated clinical setting), as now is stated in the new MRI-ERSPC RPCRC App. In that way we will create a situation where the best-performing model (both with respect to discrimination and calibration) will be used and that results can be compared that may potentially lead to further refinement.

4. DIAGNOSTIC PATHWAYS THAT COMBINE RISK STRATIFICATION TOOLS IN PROSTATE CANCER DIAGNOSIS

Prostate MRI seems to be the most useful risk stratification tool because of its ability to detect suspicious lesions and guide for TBx, next to inform one about the risk at csPCa (PI-RADS score). However, in a considerable proportion of patients the MRI will not show any abnormalities making it thereby potentially a redundant test. In addition, some patients will have false positive abnormalities on MRI (i.e. benign pathology or low-risk PCa) resulting in unnecessary TBx. The state-of-the-art challenge in the current MRI era is to identify those men who will benefit from an MRI with TBx, for maximum csPCa detection while reducing the number of unnecessary MRIs, biopsies and diagnoses of low-risk PCa. An option could be upfront risk stratification with a novel biomarker or RC (with or without novel biomarker(s) included), and if indicated subsequent MRI with if indicated subsequent biopsy (Table 1 and Figure 1).

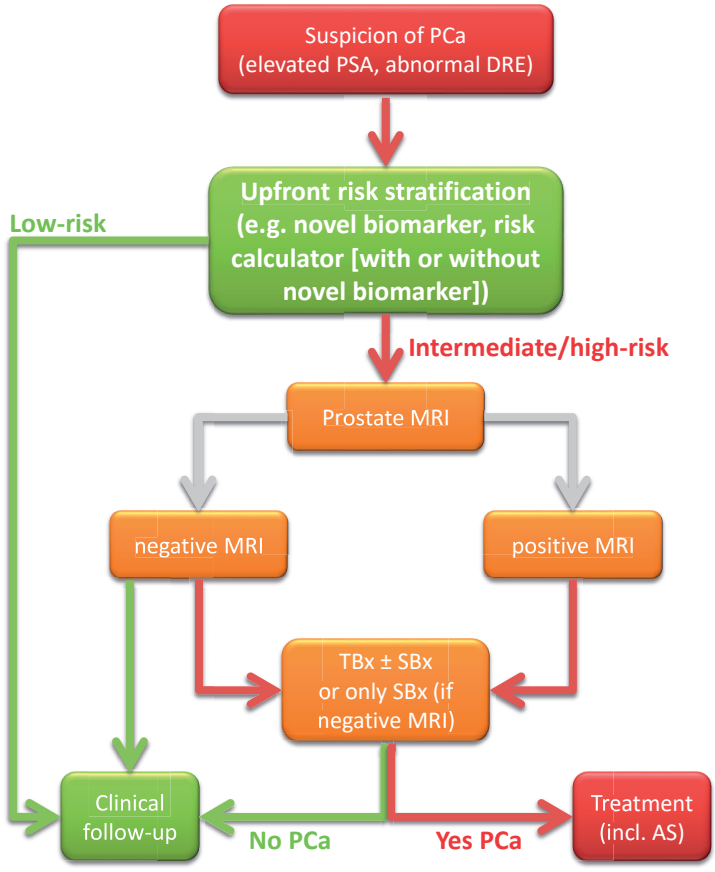

Figure 1. Flowchart of men with elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE), with the combination of upfront risk stratification and if indicated prostate MRI and biopsy.
PSA: prostate-specific antigen; DRE: digital rectal examination; PCa: prostate cancer; MRI: magnetic resonance imaging; PI-RADS: MRI suspicion score; TBx: MRI-targeted biopsy; SBx: systematic biopsy; AS: active surveillance.

4.1. Upfront novel biomarker and if indicated subsequent MRI and biopsy

PHI has been tested as a predictor of a positive MRI in men requiring repeat biopsy (97). PHI scores were generally higher in men with an MRI lesion. However, using PHI only marginally increased predictive value compared to PSA in this study suggesting that PHI is unlikely to be useful as a triaging test in deciding if an MRI will be positive. Punnen et al. looked at different sequencing strategies to combine the 4Kscore and MRI in a mixed biopsy population (initial and repeat) (99). A strategy of doing an initial 4Kscore, followed by an MRI if the 4Kscore was greater than 7.5% and a subsequent TBx if the MRI was positive showed a 25%, 83% and 75% reduction in the number of

MRIs, biopsies and low-risk PCa diagnoses, respectively. However, this strategy resulted in 33% of csPCa being missed. A similar pathway using PCA3 score ≥35 as threshold would result in 52% MRI reduction, 76.4% reduction of biopsies and 86.6% less diagnoses of low-risk PCa, at the cost of missing 47.5% csPCa (107). All studies conclude that optimized sequencing of novel biomarkers and MRI is the other way around, i.e. an initial MRI followed by a novel biomarker among only those men with a low to moderate suspicion score on MRI. However, that still would mean at least an MRI in every man with a suspicion of PCa.

4.2. Upfront risk calculator including only standard clinical parameters and if indicated subsequent MRI and biopsy

Alberts et al. studied whether upfront risk stratification with the ERSPC RPCRC could be used before the decision to perform an MRI in men confronted with a previous negative SBx while having a persistent suspicion of csPCa (19). The analysis was restricted to TBx outcomes. In their cohort, upfront ERSPC RPCRC-based patient selection for MRI would have avoided 51% of MRIs, 69% of biopsies and 25% of low-risk PCa diagnoses, while missing 10% csPCa. In a repeat biopsy setting, Drost et al. found that upfront use of the ERSPC RPCRC to select men for MRI with TBx could diagnose most of the csPCa (83%), while saving 37% of MRIs, 55% of biopsies and 66% of low-risk PCa diagnoses (108).

Recently, Mannaerts et al. showed in a retrospective biopsy-naïve cohort of 200 men that a pathway of initial ERSPC RPCRC, followed by an MRI if the ERSPC RPCRC advised to perform biopsy and subsequent SBx with additional TBx in case of a positive MRI, would reduce 37% of MRIs and biopsies, 23% of low-risk PCa diagnoses while missing 6% csPCa (109). A TBx-only strategy after ERSPC RPCRC would have missed 27% of csPCa in this cohort. Currently, a Dutch prospective study (MR PROPER) evaluating the MRI strategy versus SBx in biopsy-naïve men (3000 inclusions aimed), both after initial risk stratification with the ERSPC RPCRC, is ongoing and will provide more clarity about the value of the ERSPC RPCRC-MRI pathway (110). In any case, results obtained till now argue for an ERSPC RPCRC-based selection for MRI with performance of only MRI with or without TBx in repeat biopsy men considered to be at high-risk of csPCa according to the ERSPC RPCRC, while biopsy-naïve men considered to be at high-risk should undergo both MRI with or without TBx and SBx.

4.3. Upfront risk calculator including novel biomarker(s) and if indicated subsequent MRI and biopsy

In a retrospective study the SelectMDx score was significantly higher in patients with a suspicious lesion on MRI compared to patients with a negative MRI. For the prediction of MRI outcome, the AUC of SelectMDx was 0.83 compared to 0.66 for PSA and 0.65 for

PCA3, suggesting a positive association between SelectMDx and the final PI-RADS v2 score (111). Trooskens et al. presented data on the use of SelectMDx (including TRUS PV) to exclude low-risk patients from undergoing an MRI (112). A strategy of doing upfront SelectMDx, followed by an MRI if the risk for csPCa was greater than 10% and subsequent SBx with additional TBx if the MRI was positive (defined as PI-RADS score ≥4), would reduce 35% of MRIs and biopsies, 52% of low-risk PCa diagnoses while missing 2% csPCa.

Grönberg et al. recently investigated the combination of S3M and MRI in a cohort of 532 men who were referred for PCa workup (initial and repeat biopsy). Performing MRI with or without TBx and additional SBx only in men with a risk >10% for csPCa using the S3M would reduce the number of MRIs and biopsies with 38%, while diagnosing 42% less low-risk PCa at the cost of missing 8% csPCa cases (113). The strategy of performing only MRI with or without TBx for men with a positive S3M test would save even more biopsies (42%) and low-risk PCa diagnoses (46%), however, at the cost of missing 19% csPCa.

On average, the value of upfront risk stratification with one of the new risk models seems similar to the upfront use of the ERSPC RPCRC to select candidates for MRI. Taking into account the costs and availability of the tests, the ERSPC RPCRC might be preferable. However, to determine the most cost-effective diagnostic pathway in PCa diagnosis ideally a large prospective cohort study of men biopsied irrespective of risk stratification tool outcome and retrospectively compared performance of all relevant stratification tools should become available for both the initial and repeat biopsy setting.

5. CONCLUSIONS

There are numerous risk stratification tools available that can help increase the specificity of PSA for the detection of csPCa in the initial and repeat biopsy setting. These tools may thereby refine the PCa diagnostic pathway, improving diagnostic outcome, reducing the burden for patients and making it more cost-effective and acceptable to the general population and health care providers. All risk stratification tools result in a considerable decrease in unnecessary testing and carry a generally small risk of missing csPCa.

Taking into account the costs, RCs using PSA and clinical parameters which perform similarly well as novel, most often more expensive, biomarkers seem to be the preferred choice. However, head-to-head-comparisons of all biomarkers and RCs are necessary.

Pre-biopsy prostate MRI has shown to have more added value in men requiring repeat biopsy than in biopsy-naïve men. Recent studies show evidence for an MRI-directed biopsy management in all men, including biopsy-naïve men.

Merging novel biomarkers, RCs and MRI results in higher diagnostic accuracies and net benefit than the use of these risk stratification tools as standalone test. However, in the state-of-the-art clinical decision-making, the patient should benefit from further testing and treatment, even when the diagnostic test is "easy-to-perform". Therefore, the way forward in the current era of prostate MRI is to have an accurate predictive low-cost risk stratification tool. This risk stratification tool as triaging test for the selection of candidates for further testing (e.g. MRI, biopsy) seems to be multivariable risk assessment based on blood and clinical parameters, potentially extended with information from urine samples, which is free of use, available everywhere, extensively externally validated, and calibrated for different populations. Large prospective and comparative studies remain, however, necessary to fully assess the potentials and risks of these combined strategies.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

3

Results of prostate cancer screening in a unique cohort at 19yr of follow-up.

Daniël F. Osses
Sebastiaan Remmers
Fritz H. Schröder
Theo van der Kwast
Monique J. Roobol

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ABSTRACT

We assessed the effect of screening in the European Randomized study of Screening for Prostate Cancer (ERSPC) Rotterdam pilot 1 study cohort with men randomized in 1991-1992. A total of 1134 men were randomized on a 1:1 basis to a screening (S) and control (C) arm after prostate-specific antigen (PSA) testing (PSA ≥10.0 ng/ml was excluded from randomization). Further PSA testing was offered to all men in the S-arm with 4-yr intervals starting at age 55 yr and screened up to the age of 74 yr. Overall, a PSA level of ≥3.0 ng/ml triggered biopsy. At time of analysis, 63% of men had died. Overall relative risk of metastatic (M+) disease and prostate cancer (PCa) death was 0.46 (95% confidence interval [CI]: 0.19-1.11) and 0.48 (95% CI: 0.17-1.36) respectively, in favor of screening. This ERSPC Rotterdam pilot 1 study cohort, screened in a period without noteworthy contamination, shows that PSA-based screening could result in considerable reductions of M+ disease and mortality which if confirmed in larger datasets should trigger further discussion on pros/cons of PCa screening.

Patient summary

In a cohort with 19 yr of follow-up we found indications for a more substantial reduction in metastatic disease and cancer-specific mortality in favor of prostate cancer screening than previously reported. If confirmed in larger cohorts, these findings should be considered in the ongoing discussion on harms and benefits of prostate cancer screening.

MAIN REPORT

The European Randomized study of Screening for Prostate Cancer (ERSPC) has shown that prostate-specific antigen (PSA)-based screening results in a significant prostate cancer (PCa) mortality reduction at 13 yr of follow-up (FU) (1). In contrast to the ERSPC, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial did not show a cancer-specific mortality reduction due to screening in their intention-to-screen analysis (2). However, recently published (modeling) analyses show that the ERSPC and PLCO trials in fact provide compatible evidence that screening reduces PCa mortality (3, 4). Despite these observed reductions, unnecessary testing and overdiagnosis still preclude PSA-based PCa screening from adoption as public health policy. However, the results of the ERSPC and PLCO trials may be affected by a relatively short FU and PSA contamination. Here, we assessed the effect of PSA-based PCa screening in an ERSPC Rotterdam study cohort (pilot 1 study) with men randomized in the period 1991-1992 (an era in which PSA testing was uncommon) and enabling us to report on the basis of long-term FU.

ERSPC Rotterdam started with a series of five pilot studies in October 1991. Full capacity screening started in June 1994. In this work, we describe the results of the first pilot study of ERSPC Rotterdam. The participants of this ERSPC pilot 1 study are not included in the Rotterdam section of the main ERSPC trial. The other pilot studies were not included in the current analyses due to their period of randomization, length of FU and substantial differences in administrative procedures/screening processes. The pilot 1 study protocol characteristics are described in earlier publications (5, 6). Briefly, 3331 men aged 55-74 yr selected from the population registry of Rotterdam were invited for screening. The only exclusion criterion was a previous PCa diagnosis. Men who responded (n = 1186; recruitment rate of 35.6%) by returning the intake questionnaire and who provided signed informed consent were included and randomized after PSA testing (n = 1134) on a 1:1 basis to a screening (S) and control (C) arm. Men (n = 30) with a PSA level ≥10.0 ng/ml were excluded from randomization and directly referred to their general practitioner. The screening protocol consisted of PSA, digital rectal examination and transrectal ultrasound (TRUS) and was offered to all men in the S-arm with a 4-yr interval and applying the upper age limit of 74 yr (maximum of five consecutive screening rounds). In general, a PSA level ≥3.0 ng/ml triggered TRUS-guided biopsy. The primary endpoint was PCa-specific mortality. We also assessed the clinical/pathological features of the cancers detected (at time of diagnosis) and calculated the relative risk (RR) of metastatic (M+) disease (defined as N1 and/or M1 and/or PSA >100 ng/ml), including M+ disease at diagnosis and during FU. Finally, we retrospectively randomized the initially excluded men (PSA ≥10.0 ng/ml) using the bootstrap procedure (n = 5000

iterations) to calculate risk reductions including all PSA values (hypothetical situation). Descriptive statistics were used to evaluate patient/tumor characteristics. Cumulative progression to M+ disease and PCa-specific mortality by arm were calculated using the Nelson-Aalen method (7). Numbers needed to screen (NNS) to avert one M+ disease and PCa death were calculated as the inverse of the absolute risk reduction and number needed to diagnose (NND) as the NNS multiplied by the excess PCa incidence in the S-arm. All analyses were performed using R, version 3.4.3.

Of the 1134 men with a PSA level <10.0 ng/ml, 553 (49%) were randomized to the S-arm and 581 (51%) to the C-arm. Median PSA level at baseline in S- and C-arm was 1.2 ng/ml (interquartile range [IQR]: 0.5-2.2) and 1.1 ng/ml (IQR: 0.5-2.1), respectively. Further PSA measurements in the C-arm are not available. The median age at randomization and FU time was 64 (IQR: 60-69) and 19 yr (IQR: 12-24), respectively. Cumulative PSA contamination rate in the C-arm was estimated to be ± 4.5% (questionnaire data), with the first 4 yr a rate of 1.8%. In the S-arm 71 PCas were detected versus 57 PCas in the C-arm (Table 1). Excess incidence due to screening is 32 PCa cases per 1000 men randomized. The M+ disease was detected in three screened men versus eight men in the C-arm. During FU, seven men in the S-arm and 16 men in the C-arm progressed to M+ disease, resulting in an overall RR of M+ disease of 0.46 (95% confidence interval [CI]: 0.19-1.11) and a 19 yr-specific RR of M+ disease of 0.42 (95% CI: 0.16-1.08), in favor of screening (Figure 1A). At time of analysis, 63% (718/1134) of all men had died. Five men in the S-arm and 11 men in the C-arm died because of PCa. Overall RR of PCa death in men allocated to the S-arm relative to the C-arm was 0.48 (95% CI: 0.17-1.36); 19 yr-specific RR of PCa death was 0.47 (95% CI: 0.14-1.50) in favor of screening (Figure 1B). The absolute risk reduction in M+ disease and PCa mortality was 14.9 (95% CI: -2-32) and 9.9 (95% CI: -5-25) per 1000 men, respectively. NNS to avert one M+ disease and PCa death is 67 (95% CI: 30-ND) and 101 (95% CI: 39-ND), respectively. NND was three (101/1000*32). In the S-arm, 75% of the PCa cases underwent treatment versus 25% underwent surveillance. In the C-arm, 53% of the PCa cases underwent treatment versus 30% surveillance (in 17% of the cases in C-arm, the choice of treatment was unknown). Among the 30 men initially excluded from randomization, 19 were diagnosed with PCa including eight with M+ disease (Table 1). Of these men, 26 (87%) died including five PCa deaths. Retrospectively randomizing these 30 men resulted in an overall RR (in favor of screening and averaged over 5000 randomization procedures) of M+ disease and PCa death of 0.57 (95% CI: 0.27-1.20) and 0.59 (95% CI: 0.25-1.44), respectively.

This ERSPC Rotterdam pilot 1 study cohort, systematically screened in a period largely without PSA contamination and with more than 60% of the men deceased, confirms

that PSA-based PCa screening reduces M+ disease and PCa-specific mortality. The reductions are, although statistically insignificant, considerable and if confirmed in larger datasets should again be weighed against the harms of unnecessary testing and overdiagnosis. Previous ERSPC reports on lead time of advanced disease (± 3 yr), M+ disease

	Screening arm (n = 553)		Control arm (n = 581)		Total excluded cohort (n = 30)	
	No.	%	No.	%	No.	%
T-stage						
T1	29	41	20	35	5	26
T2	27	38	24	42	8	42
T3	14	20	7	12	5	26
T4	1	1	6	11	1	5
N-stage						
NX	37	52	34	60	8	42
N0	34	48	19	33	9	47
N1	-	-	4*	7	2**	11
M-stage						
MX	25	35	25	44	4	21
M0	43	61	25	44	12	63
M1	3	4	7*	12	3**	16
PSA >100 ng/ml	-	-	-	-	5***	26
Gleason score						
3+3	39	55	26	46	-	-
≥3+4	23	32	28	49	1	5
Unknown	9	13	3	5	18	95
Survival status – all men						
Alive	189	34	227	39	4	13
Death	364	66	354	61	26	87
Survival status – PCa men						
Alive	50	70	40	70	3	16
Death	21	30	17	30	16	84
Cause of death						
PCa	5	1	11	3	5	19
Other cause	359	99	343	97	21	81

Table 1. The clinical/pathological features (TNM-staging, Gleason grading) of the cancers detected (at time of diagnosis). Survival status and cause of death from both the screening and control arm of the men included and randomized with a prostate-specific antigen (PSA) level <10.0 ng/ml (n = 1134) as well as of the men excluded because of a PSA level ≥10.0 ng/ml (n = 30).
*Three men had both N1 and M1 disease. **One man had both N1 and M1 disease. ***One man had both M1 disease and PSA >100 ng/ml at time of diagnosis.
PSA: prostate-specific antigen; PCa: prostate cancer.

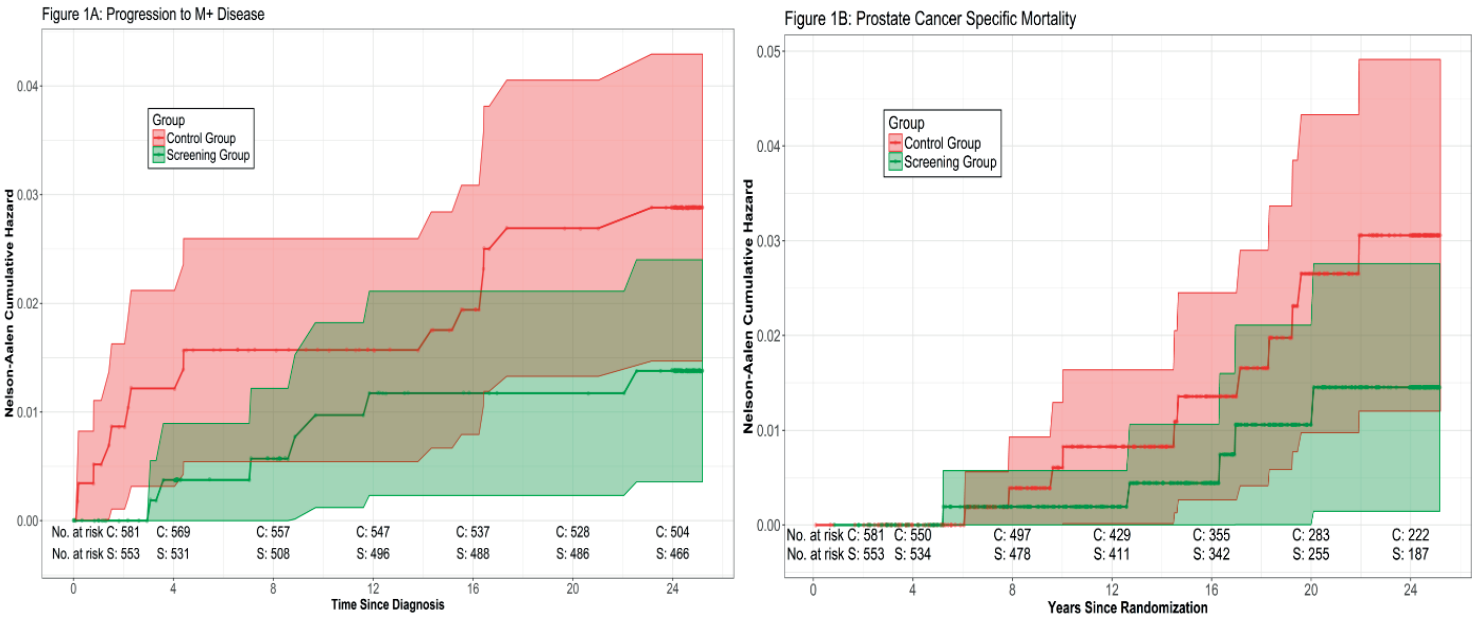

Figure 1. – (A) Nelson-Aalen estimates of cumulative progression to metastatic disease (including 95% confidence intervals) for the men randomized with a PSA level <10.0 ng/ml. (B) Nelson-Aalen estimates of cumulative prostate cancer-specific mortality (including 95% confidence intervals) for the men randomized with a PSA level <10.0 ng/ml.

C-arm: control arm; M+ disease: metastatic disease; PSA: prostate-specific antigen; S-arm: screening arm.

developing despite screening, and reduction of M+ disease preceding PCa mortality reduction are also confirmed, proving the validity of our findings (8, 9). The reductions in M+ disease and PCa mortality are, however, substantially larger than the main ERSPC trial (54% vs 30% and 52% vs 21%, respectively) (1-4). This could be explained by the relatively long FU of this study implying that FU in the ERSPC trial could still be too short to see the full effect of screening, given the long natural history of screen-detected PCa (15-25 yr) and the fact that there was almost no PSA contamination in the C-arm of this study (10). We note that inclusion of men with high PSA values and therefore more likely to have disease beyond cure even if detected earlier resulted in the decrease in relative reduction of both M+ disease and PCa-specific mortality. The strengths of the present study include the relatively long FU, almost no PSA contamination, and more than 60% of men deceased at time of analysis. Therefore, this study is an appropriate comparison between screening and no screening and can be regarded as a good indicator of the full effect of PCa screening. Limitations to this work include the small sample size and low event rates necessitating confirmation of our findings in the ongoing randomized trials. It can, however, not be excluded that the magnitude of the RRs in this pilot study will be confirmed in the main ERSPC trial when having the availability of 19 yr of FU.

In conclusion, long term data predominantly coming from an era with hardly any contamination show that PSA-based PCa screening could result in a considerable reduction of both M+ disease and PCa-specific mortality which, if confirmed in larger datasets, should refuel the discussion on harms and benefits of PCa screening.

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CONFLICTS OF INTEREST

We have no conflicts of interest to disclose.

4

Multivariable risk-based patient selection for prostate biopsy in a primary health care setting: referral rate and biopsy results from a urology outpatient clinic.

Daniël F. Osses
Arnout R. Alberts
Gonny C.F. Bausch
Monique J. Roobol

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ABSTRACT

Background

According to their guidelines, Dutch general practitioners (GPs) refer men with prostate-specific antigen (PSA) level ≥3.0 ng/ml to the urologist for risk-based patient selection for prostate biopsy using the Rotterdam Prostate Cancer Risk Calculator (RPCRC). Use of the RPCRC in primary care could optimize the diagnostic pathway even further by reducing unnecessary referrals. To investigate this, we calculated the risk and assessed the rate of men referred to the urologist with PSA level ≥3.0 ng/ml by implementing the RPCRC in a primary health care setting.

Methods

In January 2014, an exploratory study was initiated in collaboration with the primary health care facility of the GP laboratory in Rotterdam. GPs were given the possibility to refer men with a suspicion of prostate cancer (PCa) or a screening wish to this primary care facility (STAR-SHL) where further assessment was performed by specially trained personnel. Risk-based advice on referral to the urologist was given to the GP on the basis of the RPCRC results. If requested, advice on the treatment of lower urinary tract symptoms (LUTS) was provided. All men signed informed consent.

Results

Between January 2014 and September 2017, a total of 243 men, median age 64 (interquartile range [IQR], 57-70) years were referred for a consultation at the primary care facility. Of the 108 men with PSA level ≥3.0 ng/ml and a referral related to PCa, GPs were advised to refer 58 men to the urologist (54%). Of the men with available follow-up (FU) data (n=187, median FU, 16 [IQR, 9-25] months) 54 men were considered high-risk (i.e. had an elevated risk of PCa as calculated by the RPCRC). Of these men, 51 (94%) were actually referred to secondary care by their GP, and so far 38 men underwent biopsy. PCa was detected in 30 men (47% had Gleason score [GS] ≥3+4 PCa), translating to an overall positive predictive value (PPV) of 79%. Within the available FU time, 2 out of 38 (5%) men with PSA level ≥3.0 ng/ml which were considered low-risk have been diagnosed with GS 3+3 PCa.

Conclusions

Risk-stratification with the RPCRC in a primary health care setting could prevent almost half of referrals of men with PSA level ≥3.0 ng/ml to the urologist. In more than three-quarters of men referred for prostate biopsy, the suspicion of PCa was confirmed and almost half of men had clinically significant PCa (GS ≥3+4 PCa). These data show a huge potential for multivariable risk-stratification in primary care.

Keywords

Primary care; prostate cancer; prostate volume; prostate-specific antigen (PSA); risk-stratification.

INTRODUCTION

Unnecessary testing, overdiagnosis and treatment with accompanying health care costs preclude that prostate-specific antigen (PSA)-based prostate cancer (PCa) screening can be adopted as a public health policy (1, 2). The delicate benefit-harm ratio of population-based screening is, however, difficult to translate to the individual patient (3). Therefore, guidelines recommend individualized opportunistic PCa screening along with shared informed decision-making, taking into account the individual potential advantage and damage related to PSA testing (4).

Risk calculators for the prediction of a positive prostate biopsy have been developed to support physicians in this informed decision-making, and to reduce the number of unnecessary biopsies by better identification of those men at risk of PCa (5). The European Randomized Study of Screening for Prostate Cancer (ERSPC)-based Rotterdam Prostate Cancer Risk Calculator (RPCRC), for instance, reduces the percentage of unnecessary, potentially harmful, and costly transrectal ultrasound systematic biopsy (TRUS-Bx) by ±33% when using PSA level ≥3.0 ng/ml and RPCRC risk ≥12.5% as cut-off values in the urology outpatient clinic (6-11). When adopting this strategy, only a small amount of potentially aggressive PCa would be missed.

The guidelines for Dutch general practitioners (GPs) lowered the PSA cut-off value for referral to the urologist from 4.0 to 3.0 ng/ml, under the condition that the urologist uses the RPCRC for patient selection for biopsy (12). This policy results in an increased number of referrals to secondary care. This seems controversial, considering the current demand of the Dutch government to reduce health care costs by keeping more care in the primary care. However, to adhere to government's request, introduction of the RPCRC into the primary care setting could potentially result in further optimization of the diagnostic pathway by reducing unnecessary referrals to secondary care and, thereby reducing the number of biopsies, costs and workload. The implementation of PCa diagnostic risk models, like the RPCRC, based on PSA, digital rectal examination (DRE) and prostate volume on transrectal ultrasound (TRUS) and their impact on patient selection in primary care have never been investigated.

As such, the aim of this study was to assess the rate of men referred to the urologist with a PSA level ≥3.0 ng/ml by implementing multivariable risk-stratification with the RPCRC in a primary health care setting. In addition, we assessed adherence of GPs to the RPCRC risk prediction results and of those men biopsied we assessed the PCa detection rates and clinical characteristics.

METHODS

Study design and population

In January 2014, this prospective observational study was initiated by the Erasmus MC in collaboration with the primary health care facility of the GP laboratory in Rotterdam (STAR-SHL). GPs were given the possibility of referring men with a suspicion of PCa or a screening wish to this primary care facility. Patients were then offered a so-called 'prostate consultation'. Inclusion criteria for study participation were prostate biopsy naïve or previously negative biopsied men of 18 years or older of all ethnic backgrounds who were referred by their GP for a prostate consultation and had sufficient understanding of the Dutch language. Men with previously diagnosed PCa were excluded. All men signed informed consent before enrolment. The study was approved by our institutional review board (METC Erasmus MC, number: MEC-2013-572) and conformed to the provisions of the Declaration of Helsinki.

Procedures and data collection

Patients were offered an assessment including DRE and TRUS, regardless of their PSA level , at the primary care facility. DRE was carried out to estimate the prostate volume and search for abnormalities of the prostate. TRUS of the prostate was performed to measure the prostate volume and presence of hypo-echogenic lesions. Study participation included prospective registration of these data in an anonymized database; no additional investigations were done. In case a man did not give his informed consent for data collection, he could still undergo all the examinations and the risk calculation, however, without any data registration for research purposes.

All described examinations are considered routine clinical practice in a urology outpatient clinic to evaluate lower urinary tract symptoms (LUTS) or PCa. The examinations were performed by specially trained Erasmus MC personnel from the department of Urology. With the collected data, the risk of finding any PCa and potentially aggressive PCa in case of performing a prostate biopsy was calculated using the RPCRC calculators 3 or 4 (http://www.prostatecancer-riskcalculator.com/). Based on the outcome of the RPCRC, recommendations on referral to the urologist were formulated as follows:

- Risk of positive prostate biopsy < 12.5%: no biopsy;
- Risk of positive prostate biopsy 12.5%-20%: consider a biopsy, depending on the comorbidity of the patient and on the risk of a high grade or extended PCa (>4%);
- Risk of positive prostate biopsy > 20%: prostate biopsy.

The findings, the calculated risk of finding PCa and the risk-based advice on referral to the urologist were reported to the GP using the electronic patient chart. He or she

subsequently decided whether or not to refer the patient to a urologist for prostate biopsy. If requested, advice on the treatment of LUTS was provided.

The calculated risks and the associated advice were matched with information on actual referral and biopsy rates. Biopsy outcome if applicable was also assessed. In case of a PCa diagnosis initial treatment was recorded together with available follow-up (FU) data. All information was retrieved through direct contact with the different GP practices. GPs were initially not aware of the fact that they would be contacted to provide FU information.

Outcomes

The primary outcome of this study was to assess the rate of men with a PSA level ≥3.0 ng/ml considered at high-risk (i.e. having an elevated calculated PCa risk) on the basis of the RPCRC. The secondary outcomes were the compliance rate of GPs and patients to the RPCRC based advice, the rate of detected (clinically significant) PCa in the urology outpatient clinic and the rate of missed PCa within the available FU time. Clinically significant PCa (csPCa) was defined as any Gleason score (GS) ≥3+4 PCa found in biopsy specimens.

Statistical analysis

Demographic characteristics are presented for the overall group of men. Categorical data are reported as count (percentage). Continuous data are reported as median (interquartile range [IQR]). Descriptive statistics were used to evaluate the primary and secondary outcomes. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 21.0. IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

Between January 2014 and September 2017, a total of 243 men were referred by their GP for a prostate consultation at the primary care facility. Median age and PSA level was 64 (IQR, 57-70) years and 2.5 (IQR, 0.9-5.8) ng/ml, respectively. The largest group of men (44%) were referred by their GP because of a PCa screening wish and/or advice for LUTS. Of the 243 men, 46% (n=112) had a PSA level ≥3.0 ng/ml. Other relevant baseline characteristics are presented in table 1.

Characteristic	Median	Interquartile range
Age (years)	64	57-70
PSA (ng/ml)	2.5	0.9-5.8
Prostate volume on TRUS (ml)	38	26-59.5
	No.	**%**
PSA:		
<3.0 ng/ml	131	54
≥3.0 ng/ml	112	46
Abnormal DRE	42	17
Abnormal TRUS	32	13
Previous biopsy	6	3
Indication:		
PCa screening	104	43
LUTS	31	13
Screening & LUTS	108	44
Previously screened	72	30
PCa in family	32	13
Already LUTS medication	24	10
Total cohort	**243**	**100**

Table 1. Patient characteristics of the total group (n=243).
PSA: prostate-specific antigen; TRUS: transrectal ultrasound; DRE: digital rectal examination; PCa: prostate cancer; LUTS: lower urinary tract symptoms.

RPCRC results

A substantial part of men (71%) with PSA level <3.0 ng/ml were referred for LUTS. The majority of men (n=108, 96%) with PSA level ≥3.0 ng/ml had a referral related to PCa (Table 2). Of these 108 men, 54% (n=58) were considered high-risk and advised to be referred to the urologist by their GP. Eight men with PSA level <3.0 ng/ml, who according to the guidelines should not be referred, were advised to be referred for prostate biopsy on the basis of the RPCRC results. The rest of the men were considered low-risk and based on the RPCRC would not benefit from a PCa-related visit to the urologist (Figure 1). The median calculated risk of finding any PCa and potentially aggressive PCa in the 66 men considered high-risk was 37% (IQR, 21-59%) and 14% (IQR, 5-39%), respectively.

PSA	PCa screening	Screening & LUTS	Only LUTS	Total cohort
<3.0 ng/ml	38	66	27	131
≥3.0 ng/ml	66	42	4	112
Total cohort	**104**	**108**	**31**	**243**

Table 2. Referral reasons for consultation stratified for PSA level subgroup in total cohort (n=243).
PCa: prostate cancer; LUTS: lower urinary tract symptoms; PSA: prostate-specific antigen.

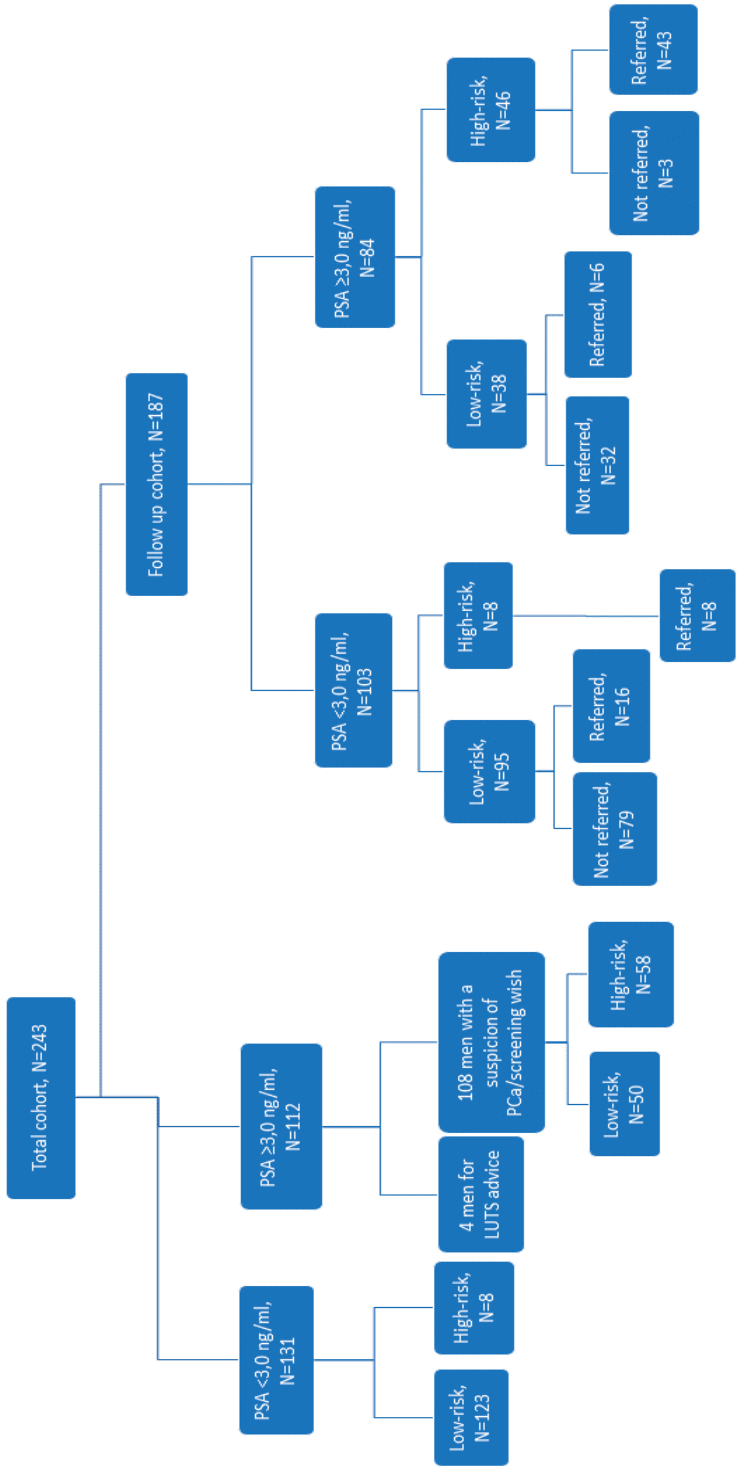

Figure 1. Flow-chart of the Rotterdam Prostate Cancer Risk Calculator results for both PSA level subgroups in the total cohort and in the follow-up cohort. In the follow-up cohort the number of referrals is also showed.
PSA: prostate-specific antigen; LUTS: lower urinary tract symptoms; PCa: prostate cancer.

Referral rate, biopsy outcomes and treatment types

Of the total of 243 men, FU data were available of 187 men (FU cohort). Median FU time was 16 (IQR, 9-25) months. Of these 187 men, 45% (n=84) had a PSA level ≥3.0 ng/ml; this was similar to the rate of men with PSA level ≥3.0 ng/ml in the total cohort. In the FU cohort, 54 men (8 men with PSA level <3.0 ng/ml and 46 men with PSA level ≥3.0 ng/ml) were considered high-risk (Figure 1). The median calculated risk of finding any PCa and potentially aggressive PCa in prostate biopsy in these 54 men was also 37% (IQR, 21-59%) and 14% (IQR, 5-39%), respectively. The rates of men considered low- and high-risk in this FU cohort were similar to the rates in the total cohort for both PSA level subgroups. 94% (n=51) of men considered high-risk were actually referred to secondary care and so far 38 (75%) men underwent prostate biopsy. The median calculated risk of finding any PCa and potentially aggressive PCa in these 38 men was 47% (IQR, 32-67%) and 19% (IQR, 9-44%), respectively. Any PCa was detected in 30 men, including 14 (47%) men with GS ≥3+4 PCa. This constitutes an overall positive predictive value (PPV) of 79%. Only 6 of 38 men with PSA level ≥3.0 ng/ml considered low-risk and therefore not advised to be referred were, however, referred to the urologist by their GP. Within the available FU time, in two of these men GS 3+3 PCa was detected, resulting in an overall negative predictive value (NPV) of 96% for any PCa and 100% NPV for csPCa. An overview of treatments applied to the 30 PCa patients is presented in table 3. The majority of men (80%, n=24) underwent active curative treatment (i.e. radiation therapy or radical prostatectomy [RARP]).

Treatment type	Number	%
Active Surveillance	5	17
Brachytherapy	3	10
EBRT	14	47
RARP	7	23
ADT ± chemotherapy	1	3
Total	**30**	**100**

Table 3. Overview of treatment types undergone by the men with PCa (n=30).
EBRT: external beam radiation therapy; RARP: robot assisted radical prostatectomy; ADT: androgen deprivation therapy.

DISCUSSION

In 2016, the incidence of PCa was 11.064 and the 10-year prevalence of PCa was 79.223 in the Netherlands (13). The number of new PCa cases is expected to increase by 49% in 2030 and consequently the PCa health care costs will rise as well. The importance of an effective diagnostic algorithm in PCa is therefore high. The primary health care

could help to further refine PCa detection strategies to become more acceptable to the general population and health care providers (e.g. costs of the prostate consultation at the primary care facility are 85 versus 592 Euros for a same consultation at a Dutch urologist). However, GPs are still uncertain about managing PCa screening, and for that reason men with PCa suspicion or a screening wish receive different care depending on their GP's reasoning and practice preferences (14, 15). The implementation of validated PCa diagnostic risk models in primary care could be a solution for this problem and may help the GP to facilitate informed decision-making and improve patient selection for referral to secondary care.

The present study is the first study evaluating a risk calculator for patient selection for prostate biopsy in primary care. We show that by implementing multivariable risk-stratification with the RPCRC in a primary health care setting the rate of men referred to the urologist for prostate biopsy with PSA level ≥3.0 ng/ml could be reduced with almost 50%. In more than 75% of men referred for biopsy according to the advice of the RPCRC, the suspicion of PCa has been confirmed and almost half of these men had GS ≥3+4=7 PCa. The vast majority of those men diagnosed with PCa received active treatment with curative intent (only 17% of men were followed-up on active surveillance [AS]). This seems to indicate a favourable ratio between clinically significant and insignificant PCa after multivariable risk-stratification with the RPCRC in primary care. Within the available FU time, in only 5% of men with PSA level ≥3.0 ng/ml who were considered low-risk based on the RPCRC non-csPCa (GS 3+3=6) has been missed. The RPCRC uses readily available information like PSA and DRE. DRE is already often performed in the GP setting for volume estimation. In addition, abdominal ultrasound instead of TRUS could be used in GP practices for more accurate volume estimation. This is thought to easily be performed by GPs or trained nurses. Our study thereby suggests an important and relevant role for multivariable risk-stratification in primary care to improve patient selection for referral to secondary care.

Health care systems with a strong primary care component are more cost-effective than those that are predominantly led by hospital specialists (16). No previous studies have, however, described the use of PCa diagnostic risk models in the GP setting. Some papers recommend that PSA levels should no longer be referred to as "normal" or "elevated" but should be incorporated into appropriate multivariable risk-based strategies to provide individualized risk information for decision making in primary care practices (17-19). Only a few studies from primary care have examined signs next to an elevated PSA level that could predict PCa and improve patient selection for referral to secondary care this way. In the present study, the RPCRC showed an overall PPV of 79% for PCa. This is significantly higher than the PPV for any PCa (ranging from 12% to 42%) of

DRE alone or DRE in combination with weight loss and nycturia in primary care patients found by Walsh et al. and the CAPER studies (20, 21).

Several studies have investigated the use of PCa risk calculators, including the RPCRC, in secondary care. Our rates of referrals/biopsies avoided, missed PCa and doctors' compliance are in line with these previously well-established results of PCa risk calculators in secondary care (5, 7, 9, 22-24). In contrast to these secondary care results, the rate of detected PCa in men considered high-risk was significantly higher in our cohort (79% vs. 15-49% in the other publications). The rate of detected csPCa was, however, similar. The benefits for the PCa diagnostic pathway obtained by using risk calculators for patient selection for biopsy seem similar in both primary and secondary care; probably being even more cost-effective when performing this risk-stratification in the primary care setting.

Unexpectedly, the compliance rate of GPs to the RPCRC-based advice on referral to secondary care was very high (94%). Within the short FU time already 75% of the men considered high-risk have actually been biopsied. It must be noted, that despite the very high PPV in those men considered at high-risk and actually biopsied it seems that there is room for improvement. More than half of men had a GS 3+3 PCa and based on only their Gleason grading could be considered as being overdiagnosed. In principle, based on their grading these men are eligible for AS. However, most men (69%) in whom GS 3+3 PCa (without taking into account e.g. tumour volume, MRI characteristics) was detected underwent active treatment, which could be considered as overtreatment. This implies that if we really aim to counterbalance the harms of PSA testing we should not only focus on reducing unnecessary referrals but also aim to uncouple diagnosis from treatment (25).

The strength of the present study is that all the examinations and risk calculation were performed in a true primary care population with prostate-related questions without any pre-selection. Therefore, we were able to test the RPCRC also in men with a PSA level <3.0 ng/ml who were referred mainly for LUTS advice and not specifically for PCa. On the basis of the RPCRC results, eight of these men (PSA levels ranging from 0.7 to 2.8 ng/ml) were advised to be referred for further analysis; in two of these men PCa was detected. This reinforces the argument to implement PCa risk models in primary care since men considered high-risk according to the RPCRC and subsequently diagnosed with PCa are found in both PSA ranges. The fact remains that men with a PSA level <3.0 ng/ml are mainly seen by GPs because the majority of them are not referred to the urologist.

The present study is limited by the fact that the examinations were performed at the primary care facility by specially trained Erasmus MC personnel from the Department of Urology. Given that measuring the prostate volume with TRUS is not common practice for GPs and requires additional training and a TRUS-device, it still remains difficult to translate our study results to the real GP's office. However, risk-stratification with the RPCRC could also be performed with only PSA and a DRE-based prostate volume. Both information is available in the GP setting. Besides, volume measurement with simple abdominal ultrasound instead of TRUS could be performed by trained GPs or nurses and could help to more accurately estimate the prostate volume. These measures might result in comparable RPCRC results as shown in the present study. The second limitation of this study is the fact that the diagnostic accuracy of the RPCRC in our primary care cohort could not be investigated within the full cohort since not all men considered high-risk underwent prostate biopsy. When additional FU data become available this will give new insight in PCa detection not only in these men but possibly also in those men initially considered as low-risk according to the calculations of the RPCRC.

In conclusion, our study shows that individualized multivariable risk-stratification for prostate biopsy based on PSA, DRE and prostate volume on TRUS in primary care may reduce unnecessary referrals to secondary care and, thereby reduce the number of biopsies, costs and workload in the urology outpatient clinic. Further studies in larger cohorts need to be performed, including the inclusion of GPs or trained nurses to actually perform the DRE and/or (abdominal) ultrasound, to confirm these findings and validate the use of PCa risk calculators in primary care.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

5

Risk assessment and MR imaging in initial prostate cancer diagnosis: an impact analysis – MR PROPER study.

Daniël F. Osses
Monique J. Roobol
Ivo G. Schoots
The MR PROPER Registry Investigators

MANUSCRIPT IN PREPARATION.

ABSTRACT

Introduction & Objectives

To investigate the clinical performances of a prostate cancer (PCa) diagnostic pathway consisting of upfront individual risk prediction with the Rotterdam Prostate Cancer Risk Calculator (RPCRC) and in addition a magnetic resonance imaging (MRI)-driven diagnostic pathway in only those biopsy-naïve men that are considered to be at intermediate/high-risk of having a potentially life-threatening PCa.

Materials & Methods

This prospective multicenter observational non-randomized clinical effectiveness study was conducted in 21 centers in the Netherlands. Participating centers included men in the study arm that reflected their standard clinical practice (i.e. MRI- or transrectal ultrasound [TRUS]-driven pathway). Between 2017 and 2020, a total of 2040 biopsy-naïve men with a suspicion of PCa were recruited. Upfront risk prediction was performed with the RPCRC-3. Low-risk men were advised to undergo clinical follow-up. Intermediate/high-risk men underwent initially TRUS- or MRI-driven biopsies. Outcome measurements were prostate MRI and biopsy avoidance, detection of indolent (non-csPCa [= ISUP 1]) and significant cancer (csPCa [= ISUP ≥2]), and missed csPCa.

Results

After exclusion of 96 men, 1944 men were included for analyses. The RPCRC-MRI pathway focusing on the MRI-targeted biopsy (TBx) outcomes only resulted in a csPCa detection rate of 27% (225/807) and a non-csPCa detection rate of 9% (75/807) in high-risk men. The RPCRC-MRI pathway could potentially result in 20% (196/1003) prostate MRI avoidance and, with 49% (396/807) of the performed MRIs in high-risk men being negative, a total of 59% (592/1003) biopsy procedures avoided. The RPCRC-MRI pathway would miss in 4% (22/592) of men (i.e. low-risk men and high-risk men with a negative MRI) a diagnosis of csPCa.

Conclusion

The RPCRC-MRI pathway results in a high csPCa detection rate with a substantial reduction of the non-csPCa detection rate, numbers of prostate MRIs and biopsy procedures performed, at the cost of missing only a limited number of csPCa diagnoses. This is the first large prospective study to demonstrate that a risk-based MRI PCa diagnostic pathway is a worthwhile approach for the future.

INTRODUCTION

The prostate cancer (PCa) diagnostic pathway needs to be optimized to reduce unnecessary testing and to avoid the 'over'diagnosis and subsequently 'over'treatment of those cancers that will never harm a patient if left undetected (i.e. low-grade/clinically insignificant PCa [non-csPCa]) (1). Traditionally, PCa is detected by systematic transrectal ultrasound (TRUS)-guided prostate biopsies (SBx) that are performed in case of a clinical suspicion of PCa based on an elevated prostate-specific antigen (PSA) level and/or abnormal digital rectal examination (DRE) (2). This strategy is associated with substantial overdiagnosis, overtreatment and the risk of missing aggressive life-threatening cancers (i.e. high-grade/clinically significant PCa [csPCa]) (3). These are difficult manageable problems for men themselves, the healthcare system and the society-at-large that bear the financial costs of this diagnostic cascade. Therefore, we need more accurate diagnostic methods and better pre-biopsy risk stratification (4, 5).

Risk calculators (or nomograms) (RC) for the prediction of a positive prostate biopsy have been developed to support physicians in clinical decision-making with respect to the individual patient and reduce the number of unnecessary biopsies. PCa risk calculators improve the diagnostic value of PSA by increasing its sensitivity and specificity by adding other potential predictive risk factors to the decisional process and as such provide an individual risk estimation of having a biopsy-detectable csPCa (6, 7). In a urology outpatient clinic risk prediction using the Rotterdam Prostate Cancer Risk Calculator (RPCRC) with biopsy at a cut-off of 4% csPCa risk can avoid up to 33% of unnecessary SBx and reduce 25% of low-grade PCa while keeping a 95% sensitivity for detecting csPCa at initial biopsy (8, 9).

Over the last years magnetic resonance imaging (MRI) and MRI-targeted prostate biopsies (MRI-TBx) have been increasingly used next to SBx in PCa diagnosis. In clinical practice there is a clear shift going on from a TRUS-driven to an MRI-driven diagnostic pathway for both the biopsy-naïve (i.e. initial) and repeat-biopsy (i.e. previous negative) setting, as also recommended by the recently updated international PCa guidelines (2, 10-12). Studies have shown that MRI has a high negative predictive value (NPV) for csPCa and thereby can avoid a biopsy procedure in 28%-49% of men, reducing the detection of low-grade PCa with 13% (13-16). The MRI pathway is considered to be superior to the TRUS pathway, as it improves diagnostic accuracy and it limits both the amount of invasive diagnostic procedures, overdiagnosis and overtreatment (17).

In the Netherlands in the pre-MRI era approximately 40.000 SBx procedures for initial PCa diagnosis were performed per year. With the ongoing shift to an MRI-driven PCa

diagnostic pathway, we are on the verge of yearly 40.000 prostate MRIs for initial PCa diagnosis in the Netherlands. However, performing a prostate MRI in all men with an elevated PSA level is a challenge due to limits in resources, capacity and availability of expertise. In addition, a considerable proportion of men with a clinical PCa suspicion will have a negative MRI or a false positive MRI making it thereby potentially a redundant test (4). Retrospective studies have shown that about one-third of the prostate MRIs could potentially be avoided by pre-MRI risk stratification by for example usage of the RPCRC, at the cost of missing only a limited number of csPCa (4%) (18-20). To date, no prospective large-cohort data are available yet on the MRI-driven diagnostic strategy following multivariable risk prediction in biopsy-naïve men.

The MR PROPER study aimed to investigate a refined PCa diagnostic pathway in biopsy-naïve men, consisting of an upfront individual risk prediction with the RPCRC in case of an initial PCa suspicion and in addition an MRI-driven diagnostic pathway in only those men that are considered to be at intermediate/high-risk of having a potentially life-threatening PCa (Figure 1). The diagnostic performances, cost-effectiveness and quality of life of this RPCRC-MRI pathway were compared to those of a SBx pathway in biopsy-naïve men, also following upfront risk stratification with the RPCRC. Here, we present the first clinical outcomes of the MR PROPER study, a large prospective multicenter clinical effectiveness study conducted in the Netherlands.

MATERIALS & METHODS

Study design and participants

This prospective multicenter observational non-randomized clinical effectiveness study was approved by the Institutional Review Board of the Erasmus University Medical Center (MEC-2017-361), and written informed consent with guarantee of confidentiality was obtained from all study participants. The study was registered in ClinicalTrials.gov under identifier NCT03225222. The study was conducted in 21 centers in the Netherlands: 5 university hospitals, 15 non-university hospitals and the Dutch Cancer Institute. Within the observational study design it was not attempted to randomize patients to each arm. Participating centers included men in the study arm that reflected their standard clinical practice; i.e. three existing clinical algorithms labelled as the MRI-'first' (=10 centers), TRUS-'first' (=8 centers) and TRUS-'only' (=3 centers) diagnostic pathways were followed. For analytical purposes the TRUS-'first' and TRUS-'only' arms have been merged together to one combined TRUS-arm (i.e. control arm). The flowchart of the study is shown in figure 2.

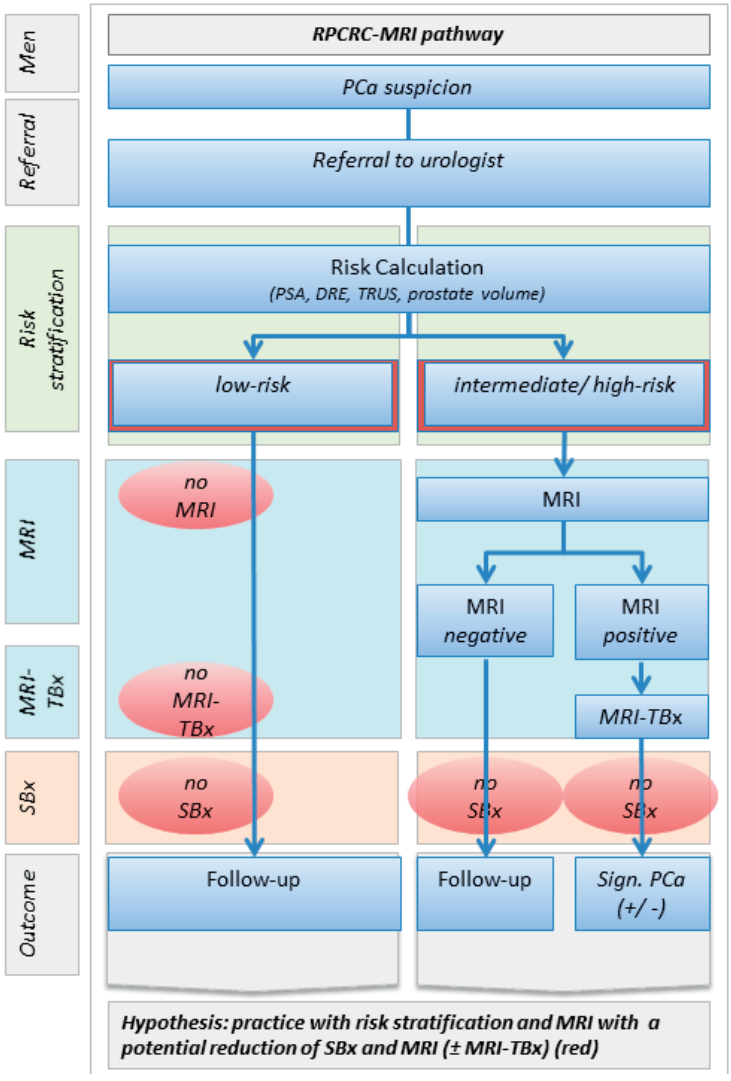

Figure 1. The MRI pathway with upfront risk stratification.
MRI: magnetic resonance imaging; TBx: targeted biopsy; SBx: systematic biopsy; RPCRC: Rotterdam Prostate Cancer Risk Calculator; PCa: prostate cancer; PSA: prostate-specific antigen; DRE: digital rectal examination; TRUS: transrectal ultrasound.

Between December 2017 and September 2020, a total of 2040 (MRI-'first' n=1057, TRUS-'first' n=679 and TRUS-'only' n=304) consecutive biopsy-naïve men, aged ≥50 year with a suspicion of PCa based on regular PSA blood test (≥3.0 ng/ml) and/or abnormal DRE and/or family history of PCa and fit to undergo all protocol procedures were recruited in this study. Exclusion criteria were previously detected or treated PCa, previous (negative) prostate biopsies, clinical T4-stage tumor on DRE, PSA level >50ng/

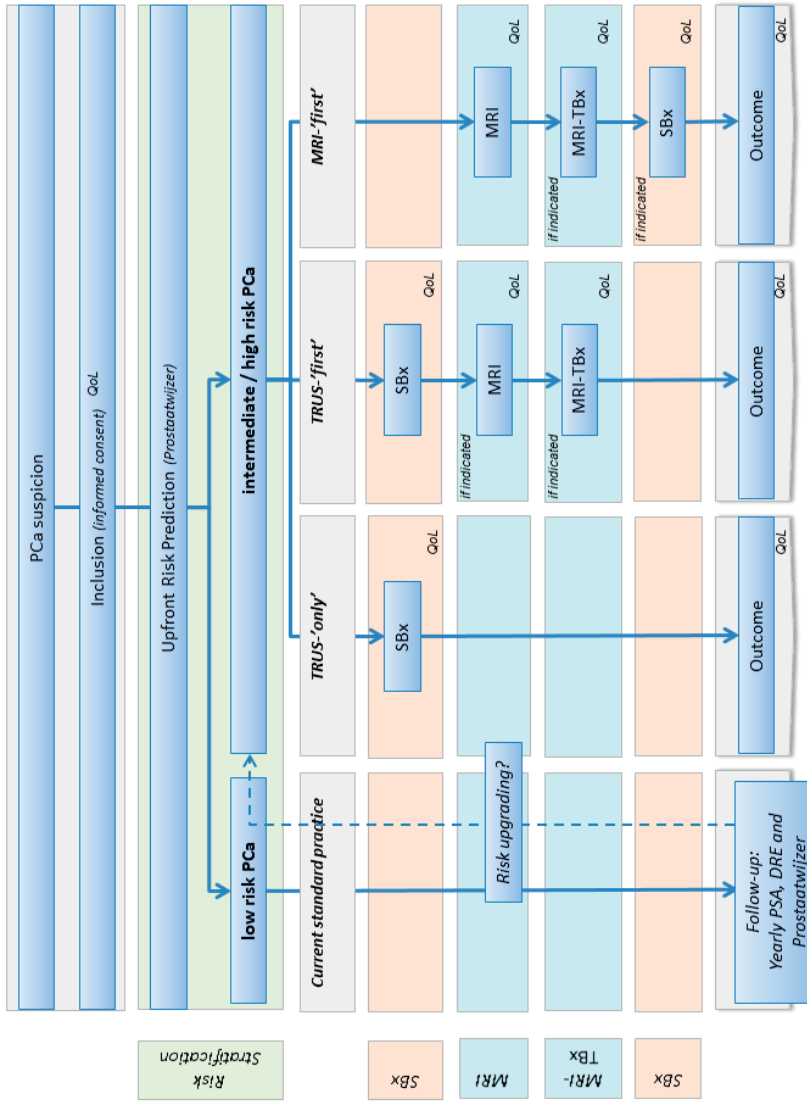

Figure 2. Flowchart of the study.
MRI: magnetic resonance imaging; TBx: targeted biopsy; SBx: systematic biopsy; RPCRC: Rotterdam Prostate Cancer Risk Calculator; PCa: prostate cancer; QoL: quality of life; DRE: digital rectal examination; TRUS: transrectal ultrasound.

ml and a suspicion of metastatic disease at time of diagnosis, contra-indications to MRI (e.g. claustrophobia, pacemaker, eGFR ≤ 30, known or expected allergy to contrast media) or biopsy procedures, previous history of hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work and any other medical condition precluding procedures described in the protocol (Figure 3).

Study procedures

Upfront risk stratification

Following enrolment in the study, individual risk prediction was performed with the RPCRC-3 (including DRE with or without TRUS findings) (http://www.prostatecancer-riskcalculator.com/) in all men. The cut-off for stratifying men to intermediate/high-risk of PCa was:

a) >20% risk for any PCa or
b) >12.5% risk for any PCa in combination with a >4% risk for high-grade PCa.

Men considered to be at low-risk of PCa were advised to undergo clinical follow-up according to the standard follow-up protocol of their participating center (i.e. no direct biopsy intervention). If indicated by their treating urologist or in case of a strong patient's desire a biopsy procedure could be performed in low-risk men (TRUS- or MRI-driven; depending on the standard clinical algorithm in their participating center). All available follow-up data were collected.

Men considered to be at intermediate/high-risk of PCa underwent initially TRUS- or MRI-driven prostate biopsies according to the standard clinical practice in their participating center (i.e. TRUS-'only', TRUS-'first' or MRI-'first' diagnostic pathway). The TRUS-'only' diagnostic pathway used only TRUS-guided biopsies (SBx) without prostate MRI (i.e. traditional diagnostic PCa pathway). The TRUS-'first' diagnostic pathway started with TRUS-guided biopsies (SBx), and subsequently additional MRI and MRI-targeted biopsies (MRI-TBx) were performed when indicated by the treating urologist. The MRI-'first' diagnostic pathway started with a prostate MRI, and subsequently additional MRI-targeted biopsies (MRI-TBx) and/or TRUS-guided biopsies (SBx) were performed if indicated (Figure 2).

Systematic TRUS-guided prostate biopsy

Systematic TRUS-guided biopsy (SBx), using 18G needle and a periprostatic block (optional) was the standard of care. The biopsy scheme for the primary SBx procedure consisted of sextant lateral biopsies with a minimum of two additional medial cores, based on prostate volume, and a maximum of 12 biopsy cores. If hypo-echoic lesions were visualized by TRUS, additional targeted biopsy could be performed based on the

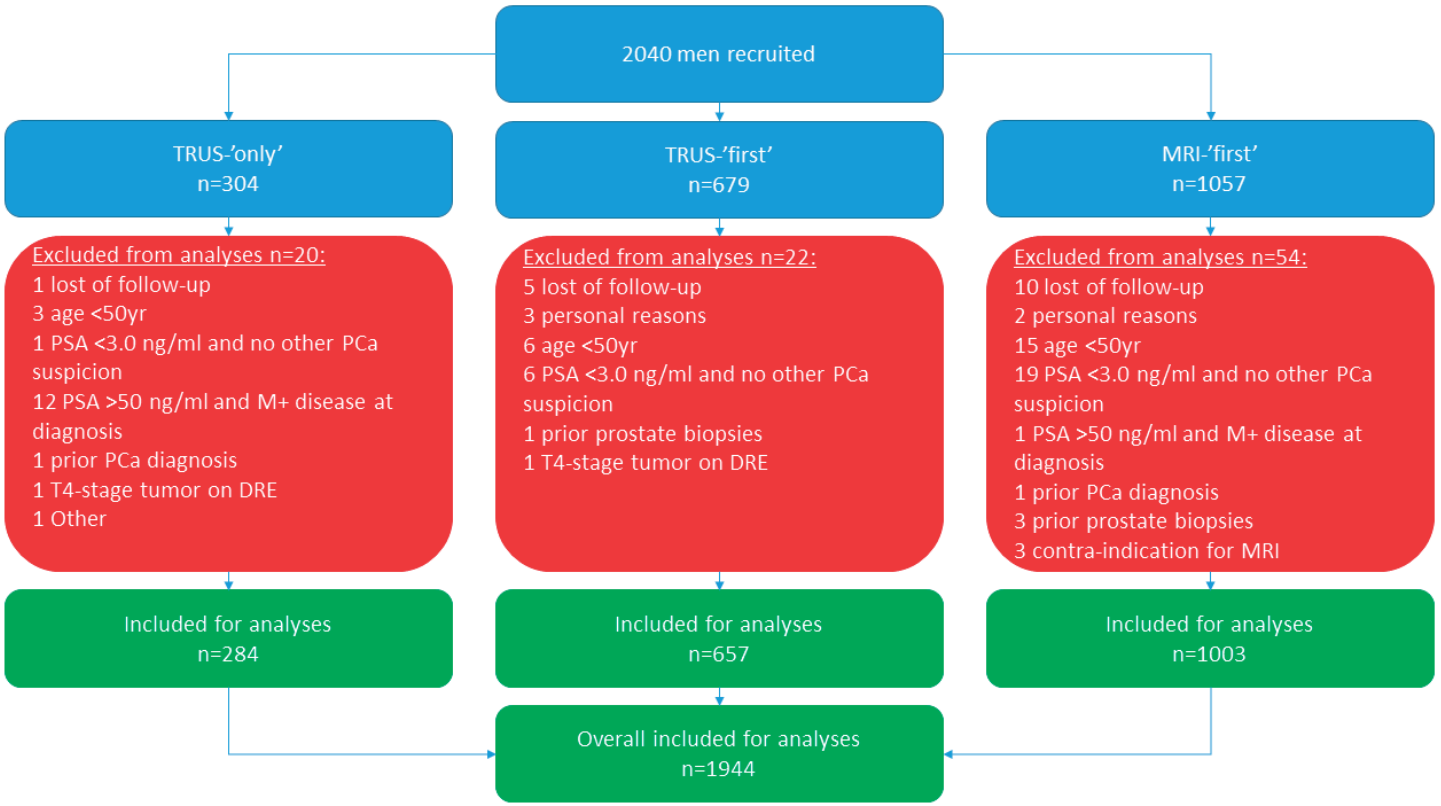

Figure 3. Included and excluded men in the study.
TRUS: transrectal ultrasound; PSA: prostate-specific antigen; PCa: prostate cancer; M+: metastatic disease; DRE: digital rectal examination; MRI: magnetic resonance imaging.

preference of the urologist. In case SBx was performed after a prostate MRI the operator performing the biopsies was not blinded to the MRI findings, as this was part of routine clinical practice.

Multiparametric MRI and MRI-targeted prostate biopsy

MRI protocols were according to the Guidelines by the European Society of Urogenital Radiology and the American Society of Radiology (21, 22). MRI protocols consisted of T2-weighted (T2W) imaging, and diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) reconstructions. Additional dynamic contrast enhanced (DCE) imaging was optional, based on the preferred hospital protocol. Prostate MRI scans were performed on 1.5-Tesla or 3-Tesla systems (different vendors: Philips Healthcare, Siemens Healthcare, General Electric Healthcare) using different pelvic phased-array coils. The images were analyzed by expert radiologists (>250 prostate MRIs). Individual lesions, as well as the whole prostate, were scored with the version 2 of the Prostate Imaging Reporting and Data System (PI-RADS) 5-point likelihood scale for csPCa (21, 22). Individual lesions with a PI-RADS score ≥3 were classified as suspicious. In case of multiple suspicious lesions on MRI, the highest PI-RADS score lesion was used as index lesion. Prostate volume on MRI was calculated by the MRI-based prolate ellipsoid formula with three dimensions (axial images left-right, sagittal images basis-apex, anterior-posterior) multiplied by 0.52. Suspected lesions were measured in three dimensions (on axial images left-right and anterior-posterior, on sagittal images, basis-apex), based on the sequence the lesions were most reliably depicted.

All suspicious MRI lesions were biopsied with an MRI targeted approach. This could be 1) in-bore MRI, 2) with MRI-TRUS fusion software (different vendors), or 3) with a cognitive fusion approach. All suspicious lesions were targeted with biopsies on T2W-images, based on the areas with the lowest b-values on the ADC-maps. The number of MRI-TBx was at the discretion of the physician performing the biopsies, however, a minimum of 2 and maximum of 5 targeted cores were performed. MRI-TBx procedures were performed by expert physicians (>100 biopsy procedures).

Histopathology

Uro-pathologists from each participating center analyzed the biopsies taken in their hospital, and gave a final grading for further diagnostic and treatment work-flow according to the International Society of Urological Pathology (ISUP) 2014 modified Gleason score (GS)/Grade (G) Group system (23). The presence of an invasive cribriform growth pattern (CR) and/or intraductal carcinoma (IDC) was routinely recorded. According to the most recent European Association of Urology (EAU) guidelines, low-grade PCa (i.e. non-csPCa) and high-grade PCa (i.e. csPCa) were defined in this study as ISUP grade 1

PCa and ISUP grade 2 and higher PCa, respectively (2). The outcome of the combined biopsies (MRI-TBx and/or SBx) was used as overall reference standard.

Study endpoints

The primary outcomes were the overall detection rates of csPCa and non-csPCa for all diagnostic pathways; especially the RPCRC-MRI versus RPCRC-TRUS pathway (focusing on the biopsy outcomes of MRI-TBx with and without SBx versus SBx with and without MRI-TBx, respectively). The secondary outcomes were the proportions of prostate MRI scans and biopsies that have been avoided by the RPCRC-MRI pathway, the number of detected csPCa in men considered to be at low-risk of PCa by the RPCRC and the number of detected csPCa in men with a negative prostate MRI.

Statistical analysis

For analytical purposes the TRUS-'first' and TRUS-'only' arms have been merged together to one combined TRUS-arm (i.e. control arm). Descriptive statistics were used to report the clinical, radiological and pathological characteristics. Categorical data are reported as count (percentage). Continuous data are reported as median (interquartile range [IQR]). Statistically significant differences in continuous non-parametric data were assessed with the Mann-Whitney U test; in case of more than two groups the Kruskal–Wallis test was used. The Chi-square test for trend was used to test for differences in categorical data. PSA-density (PSA-D) was calculated by dividing the PSA level by the maximum measured prostate volume by DRE-, TRUS- or MRI (depending on the performed investigations per patient). Analyses were performed using Statistical Package for the Social Sciences (version 24.0; IBM, Armonk, NY, USA).

RESULTS

Patient characteristics

After exclusion of 96 men, 1944 men were included in this study for analyses (Figure 3). Patient and diagnostic characteristics are summarized in table 1. Overall, the median age (IQR) and PSA-D (IQR) of the included men were 68 years (63-72) and 0.13 ng/ml^2 (0.09-0.18), respectively. The majority of men had no abnormalities on DRE and TRUS examinations. According to the RPCRC, 30% (577/1944) of all men were considered to be at low-risk of PCa. The majority of men underwent a prostate MRI during follow-up. Men in the MRI-'first' and TRUS-'first' arms had significantly higher PSA levels than men in the TRUS-'only' arm. The majority of men in the MRI-'first' arm did not undergo a TRUS examination at time of risk stratification, meaning that most men in this arm underwent upfront risk stratification with the RPCRC based on PSA level and DRE findings only.

Characteristic	Overall cohort (n=1944)	TRUS-'only' (n=284)	TRUS-'first' (n=657)	MRI-'first' (n=1003)	*p-value*
Age (yr), median (IQR)	68 (63-72)	69 (64-74)	69 (65-71)	67 (61-71)	*<0.001*
PSA level (ng/ml), median (IQR)	6.8 (5.1-9.5)	5.8 (4.6-8.2)	7 (5.2-9.8)	7.1 (5.3-9.6)	*<0.001*
Prostate volume on DRE (ml), median (IQR)	40 (35-60)	40 (35-60)	40 (40-60)	40 (35-60)	*0.67*
Prostate volume on TRUS (ml), median (IQR)	48 (36-65)	48 (35-70)	50 (37-68)	45 (35-57)	*<0.001*
Prostate volume on MRI (ml), median (IQR)	53 (40-73)	N/A	52 (38-67)	54 (40-73)	*0.185*
PSA-density (ng/ml/ml), median (IQR)	0.13 (0.09-0.18)	0.12 (0.09-0.16)	0.13 (0.09-0.19)	0.13 (0.09-0.18)	*0.016*
Positive family history for PCa, n (%)	44 (2)	6 (2)	15 (2)	23 (2)	*0.983*
DRE findings, n (%)					
T0	1470 (75)	196 (69)	489 (74)	785 (78)	*0.004*
T2a	281 (15)	42 (15)	88 (13)	151 (15)	
T2b	64 (3)	23 (8)	25 (4)	16 (2)	
T2c	32 (2)	3 (1)	18 (3)	11 (1)	
T3a	62 (3)	13 (5)	25 (4)	24 (2)	
T3b	25 (1)	6 (2)	9 (1)	10 (1)	
Unknown	10 (1)	1 (1)	3 (1)	6 (1)	
TRUS findings, n (%)					
no TRUS	616 (32)	13 (5)	69 (11)	534 (53)	*<0.001*
Benign	1125 (58)	211 (74)	479 (73)	435 (43)	
Suspected	203 (10)	60 (21)	109 (17)	34 (3)	
RPCRC, n (%)					
low-risk	577 (30)	121 (43)	260 (40)	196 (20)	*<0.001*
intermediate/high-risk	1367 (70)	163 (57)	397 (60)	807 (81)	
RPCRC risk any PCa, median (IQR)	26 (14-43)	20 (10-42)	24 (12-46)	27 (18-41)	*<0.001*
RPCRC risk high-grade PCa, median (IQR)	7 (3-18)	5 (2-18)	6 (2-21)	7 (4-16)	*<0.001*
Prostate MRI, n (%)					
no MRI	772 (40)	284 (100)	482 (73)	6 (1)	*0.019*
PI-RADS 1-2	613 (31)	N/A	77 (12)	536 (53)	
PI-RADS 3	79 (4)	N/A	15 (2)	64 (6)	
PI-RADS 4	252 (13)	N/A	52 (8)	200 (20)	
PI-RADS 5	228 (12)	N/A	31 (5)	197 (20)	
Overall pathology at biopsy, n (%)					
no PCa / no Biopsy	1182 (61)	168 (59)	382 (58)	632 (63)	*0.108*
ISUP I	239 (12)	44 (16)	87 (13)	108 (11)	
ISUP II	252 (13)	34 (12)	81 (12)	137 (14)	
ISUP III	104 (5)	13 (5)	45 (7)	46 (5)	
ISUP IV	88 (5)	14 (5)	23 (4)	51 (5)	
ISUP V	79 (4)	11 (4)	39 (6)	29 (3)	

Table 1. Patient and diagnostic characteristics.
PSA: prostate-specific antigen; DRE: digital rectal examination; TRUS: transrectal ultrasound; MRI: magnetic resonance imaging; PCa: prostate cancer; DRE: digital rectal examination; RPCRC: Rotterdam Prostate Cancer Risk Calculator; PI-RADS: Prostate Imaging-Reporting and Data System; ISUP: International Society of Urological Pathology.

From the MRI-'first' men 20% (196/1003) were considered to be at low-risk of PCa according to the RPCRC, compared to approximately 40% of men in both TRUS arms (*p<0.001*).

Overall prostate cancer detection

The overall PCa detection rate was 39% (762/1944). Non-csPCa and csPCa were detected in 12% (239/1944) and 27% (523/1944) of all men, respectively (Table 1). The PCa detection rates of all three study arms were comparable. The most csPCa was detected in the TRUS-'first' arm (i.e. 29% versus 27% [= MRI-'first'] and 26% [= TRUS-'only']), while the least non-csPCa was detected in the MRI-'first' arm (i.e. 11% versus 16% [= TRUS- 'only'] and 13% [= TRUS-'first']).

RPCRC-MRI versus RPCRC-TRUS pathway

High-risk men in the combined TRUS arm had significantly higher PCa risk probabilities than high-risk men in the MRI-'first' arm (Table 2). The RPCRC-TRUS pathway focusing on the SBx outcomes only resulted in a csPCa detection rate of 43% (236/560) and a

Characteristic	Combined TRUS arm (n=560)		MRI-'first' (n=807)		*p-value*
	RPCRC-SBx	*RPCRC-SBx-MRI-TBx*	*RPCRC-MRI-TBx-SBx*	*RPCRC-MRI-TBx*	
RPCRC risk any PCa, median (IQR)	39 (27-63)	39 (27-63)	32 (23-46)	32 (23-46)	*<0.001*
RPCRC risk high-grade PCa, median (IQR)	14 (7-41)	14 (7-41)	9 (6-20)	9 (6-20)	*<0.001*
Prostate MRI, n (%)					
no MRI	560 (100)	422 (75)	0 (0)	0 (0)	*0.025*
PI-RADS 1-2		52 (9)	396 (49)	396 (49)	
PI-RADS 3		13 (2)	55 (7)	55 (7)	
PI-RADS 4		43 (8)	178 (22)	178 (22)	
PI-RADS 5		30 (5)	178 (22)	178 (22)	
Pathology at biopsy, n (%)					
no PCa / no Biopsy	203 (36)	196 (35)	466 (58)	507 (63)	*<0.001*
ISUP I	121 (22)	113 (20)	95 (12)	75 (9)	
ISUP II	99 (18)	110 (20)	125 (16)	115 (14)	
ISUP III	55 (10)	57 (10)	43 (5)	48 (6)	
ISUP IV	34 (6)	35 (6)	49 (6)	35 (4)	
ISUP V	48 (9)	49 (9)	29 (4)	27 (3)	

Table 2. The performances of the RPCRC-MRI versus RPCRC-TRUS pathways in high-risk men. RPCRC: Rotterdam Prostate Cancer Risk Calculator; PCa: prostate cancer; MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; ISUP: International Society of Urological Pathology; TRUS: transrectal ultrasound; SBx: systematic biopsy; TBx: targeted biopsy.

non-csPCa detection rate of 22% (121/560) in high-risk men. The RPCRC-TRUS pathway focusing on the SBx and (if performed) MRI-TBx outcomes resulted in a csPCa detection rate of 45% (251/560) and a non-csPCa detection rate of 20% (113/560). The RPCRC-MRI pathway focusing on MRI-TBx and (if performed) SBx outcomes resulted in a csPCa detection rate of 31% (246/807) and a non-csPCa detection rate of 12% (95/807), which are both significantly lower than the PCa detection rates of the RPCRC-TRUS pathway. The RPCRC-MRI pathway focusing on the MRI-TBx outcomes only resulted in a csPCa detection rate of 27% (225/807) and a non-csPCa detection rate of 9% (75/807) in high-risk men (Table 5).

Prostate MRIs and biopsies avoided by the RPCRC-MRI pathway

The RPCRC-TRUS pathway could potentially result in 40% (381/941) biopsy procedure avoidance (i.e. low-risk men) (Table 3). The RPCRC-MRI pathway could potentially result in 20% (196/1003) prostate MRI avoidance and, with 49% (396/807) of the performed MRIs in high-risk men being negative, a total of 59% (592/1003) biopsy procedures avoided (Table 5).

Characteristic	Combined TRUS arm (n=381)		MRI-'first' (n=196)		*p-value*
	RPCRC-SBx	*RPCRC-SBx-MRI-TBx*	*RPCRC-MRI-TBx-SBx*	*RPCRC-MRI-TBx*	
RPCRC risk any PCa, median (IQR)	10 (8-13)	10 (8-13)	12 (9-14)	12 (9-14)	*0.006*
RPCRC risk high-grade PCa, median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	*<0.001*
Prostate MRI, n (%)					
no MRI	381 (100)	344 (90)	6 (3)	6 (3)	*0.208*
PI-RADS 1-2		25 (7)	140 (71)	140 (71)	
PI-RADS 3		2 (1)	9 (5)	9 (5)	
PI-RADS 4		9 (2)	22 (11)	22 (11)	
PI-RADS 5		1 (1)	19 (10)	19 (10)	
Pathology at biopsy, n (%)					
no PCa / no Biopsy	358 (94)	354 (93)	166 (85)	173 (88)	*0.011*
ISUP I	16 (4)	18 (5)	13 (7)	9 (5)	
ISUP II	5 (1)	5 (1)	12 (6)	9 (5)	
ISUP III	0 (0)	1 (1)	3 (2)	3 (2)	
ISUP IV	2 (1)	2 (1)	2 (1)	2 (1)	
ISUP V	0 (0)	1 (1)	0 (0)	0 (0)	

Table 3. The performances of the RPCRC-MRI versus RPCRC-TRUS pathways in low-risk men. RPCRC: Rotterdam Prostate Cancer Risk Calculator; PCa: prostate cancer; MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; ISUP: International Society of Urological Pathology; TRUS: transrectal ultrasound; SBx: systematic biopsy; TBx: targeted biopsy.

MRI PI-RADS score	Overall cohort, PCa detection				Low-risk men, PCa detection				High-risk men, PCa detection			
	no PCa, n (%)	non-csPCa, n (%)	csPCa, n (%)	Total	no PCa, n (%)	non-csPCa, n (%)	csPCa, n (%)	Total	no PCa, n (%)	non-csPCa, n (%)	csPCa, n (%)	Total
PI-RADS 1-2	140 (78)	30 (17)	9 (5)	**179**	22 (85)	4 (15)	0 (0)	**26**	118 (77)	26 (17)	9 (6)	**153**
PI-RADS 3	45 (59)	13 (17)	18 (27)	**76**	7 (78)	1 (11)	1 (11)	**9**	38 (57)	12 (18)	17 (25)	**67**
PI-RADS 4	76 (30)	73 (29)	102 (41)	**251**	16 (53)	4 (13)	10 (33)	**30**	60 (27)	69 (31)	92 (42)	**221**
PI-RADS 5	19 (8)	29 (13)	180 (79)	**228**	5 (25)	6 (30)	9 (45)	**20**	14 (7)	23 (11)	171 (82)	**208**
Total	**280**	**145**	**309**	**734**	**50**	**15**	**20**	**85**	**230**	**130**	**289**	**649**

Table 4. PI-RADS score distribution and prostate cancer detection.
MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; PCa: prostate cancer; csPCa: clinically significant prostate cancer.

Detected csPCa in low-risk men and in men with a negative MRI

Within the available follow-up of the 577 men considered to be at low-risk of PCa, csPCa was detected in 5% (26/577) of men (Table 3). Significantly more csPCa was detected in low-risk men of the MRI-'first' arm compared to low-risk men of the combined TRUS-arm (9% versus 2%).

In the overall cohort, csPCa was detected in 5% (9/179) of the biopsied men with a negative prostate MRI (Table 4). Related to the total number of negative MRIs (n=613) in the study, this rate decreases to 1%. All these significant cancers were detected in men considered to be at high-risk of PCa according to the RPCRC. In total, the RPCRC-MRI pathway would miss in 4% (22/592) of men (i.e. low-risk men and high-risk men with a negative MRI) a diagnosis of csPCa (Table 5).

Diagnostic pathway	csPCa detection (%)	non-csPCa detection (%)	Prostate MRI avoidance (%)	Biopsy procedure avoidance (%)	Missed csPCa (%)
RPCRC-TRUS / SBx	43	22	N/A	40	2
RPCRC-MRI-TBx	27	9	20	59	4

Table 5. Summary table of performances.
RPCRC: Rotterdam Prostate Cancer Risk Calculator; TRUS: transrectal ultrasound; MRI: magnetic resonance imaging; csPCa: clinically significant prostate cancer; SBx: systematic biopsy; TBx: targeted biopsy.

DISCUSSION

PCa has become the second most frequent cancer worldwide, resulting in an increasing burden of PCa to our society. Therefore, there is an urgent need for an individualized risk-adapted diagnostic pathway for the early detection of csPCa that could reduce the number of unnecessary prostate MRIs and biopsy procedures, and minimize the over-detection and overtreatment of low-grade PCa. Recently, Van Poppel et al. on behalf of the EAU presented a widely applicable, intelligible algorithm as a guidance in whom, and how to apply early detection of life-threatening PCa in 2020 and beyond, based on state-of-the-art knowledge and expert opinion (24). This proposed algorithm has not yet been prospectively analyzed. The MR PROPER study is the first large prospective study that investigated the performances of such an MRI-driven PCa diagnostic pathway following upfront multivariable risk prediction in biopsy-naïve men; a risk-adapted strategy that is comparable to the diagnostic algorithm proposed by Van Poppel et al. (24). The first clinical outcomes of the MR PROPER study show that the RPCRC-MRI pathway could result in an acceptable high csPCa detection with a considerable reduction of non-csPCa detection, prostate MRIs and biopsy procedures performed at the

cost of missing only limited csPCa diagnoses. These results suggest that the RPCRC-MRI pathway has the potential to improve the harm-benefit ratio in PCa diagnostics.

Similar to previous studies comparing the MRI- and TRUS-driven diagnostic PCa pathways (i.e. without upfront risk stratification) in biopsy-naïve men, the MR PROPER study shows that the MRI-pathway is non-inferior to the TRUS-pathway with regard to csPCa detection but is superior for detecting fewer non-csPCa and reducing biopsy procedures (15-17). The RPCRC-MRI pathway as studied in the MR PROPER study resulted in men considered to be at high-risk of PCa according to the RPCRC in a csPCa and non-csPCa detection rate of approximately 30% and 10%, respectively. Restricting prostate MRIs and biopsies to only high-risk men selected by the RPCRC could reduce 20% of MRIs and 59% of biopsies, at the cost of missing only 4% csPCa. A retrospective analysis from Mannaerts et al. showed comparable results with even up to 40% of prostate MRIs potentially being avoided after initial risk stratification with the RPCRC (19). This difference in number of MRIs avoided could potentially be explained by the fact that only half of the men in the MRI-'first' arm of our study underwent a TRUS examination with accurate prostate volume estimation at time of initial risk stratification. A study from Reesink et al. that investigated a diagnostic pathway consisting of upfront RPCRC followed by a biparametric MRI and eventually biopsies resulted in 47% of MRIs avoided, 71% of biopsies avoided, 15.7% csPCa detection and 6.9% non-csPCa detection (20). An important difference to our study is the prevalence of csPCa in their cohort (19%) versus the csPCa prevalence (27%) in our cohort, which could explain the different performances of a comparable diagnostic strategy. Disease prevalence impacts the clinical utility of risk calculators and prostate MRI.

Other potential risk stratification methods to select candidates for MRI and subsequent biopsy have also been investigated in the literature. Recently, Hendriks et al. showed that upfront use of the SelectMDx-test with subsequently restriction of MRI to men with a positive SelectMDx-test could result in 38% MRI and 60% biopsy avoidance at the cost of missing 13% csPCa (25). Falagario et al. showed similar findings making use of upfront risk stratification with the 4Kscore (18). The value of upfront risk stratification with one of these risk models seems similar to the upfront use of the RPCRC to select candidates for MRI and biopsy. This could probably be explained by the strong predictive value of PSA-density in all risk models. To determine the most cost-effective diagnostic pathway in PCa diagnosis, ideally a large prospective cohort study of men biopsied irrespective of risk stratification tool outcome and retrospectively compared performance of all relevant stratification tools should become available.

Unexpectedly, 20% of men from the MRI-'first' arm were considered to be at low-risk of PCa according to the RPCRC compared to 40% of men in the combined TRUS-arm. On average in the literature, use of the RPCRC in biopsy-naïve men with a cut-off of 4% csPCa risk has shown to result in one out of three men considered to be at low-risk of PCa (8). Theoretically, there could be a difference in a priori risk of PCa between the study arms in the MR PROPER study. However, only half of the men in the MRI-'first' arm underwent a TRUS examination with accurate prostate volume estimation at time of initial risk stratification, compared to almost all men in the combined TRUS-arm. Thus, most men in the MRI-'first' arm underwent upfront risk stratification with the RPCRC based on PSA level and DRE findings only. An accurately measured prostate volume is known to play an important role in the prediction of PCa (9, 26). It could, therefore, be hypothesized that volume estimation based on DRE would underestimate the actual prostate volume which potentially could result in an overestimation of the actual PCa risk. Volume estimation based on a TRUS examination could be more accurate, thereby assessing more precisely the PCa risk. Since the PSA-density (calculated by dividing the PSA level by the maximum measured prostate volume by DRE-, TRUS- or MRI) was similar for all study arms, there seems not be a large difference in a priori PCa risk between the different arms. By performing a TRUS examination in all men at time of initial risk stratification potentially more men could have been classified as being at low-risk of PCa according to the RPCRC and thereby potentially more prostate MRIs could have been avoided in the MRI-'first' arm. Further future analyses in the MR PROPER study will provide more clarity on this topic.

The major strength of the MR PROPER study is the fact that it is the first large multicenter prospective study reporting on the performance of an individualized risk-adapted MRI diagnostic PCa pathway in biopsy-naïve men. By including patients from 21 participating centers (both university and non-university hospitals) in the Netherlands, the study results are more generally representative by giving an overall view of the nationwide real-world setting of current PCa diagnostics in daily practice. Therefore, the study outcomes and the investigated RPCRC-MRI pathway could be more easily implemented in urological centers and (national) guidelines for more evidence-based practice. It must, however, still be noted that every institution should know their own test performance statistics when making clinical decisions based on prostate MRI findings, because of existing differences in the prevalence of csPCa, radiology, targeted biopsy and pathology learning curves per institution.

Some limitations of our study should be highlighted. First, the observational study design and the fact that at some points the indication for further investigations was left to the treating urologist resulted in no standardly performed prostate biopsies in low-risk

men or in men with a negative prostate MRI or next to MRI-TBx of suspicious lesions in men with a positive MRI. Therefore, it is difficult to make hard inferences about the numbers of missed csPCa. However, aim of the MR PROPER study was also to implement upfront risk stratification with the RPCRC in daily clinical practice to save MRIs and biopsies. If indicated by the treating urologist further investigations have been performed according to the standard care of the participating center as mentioned in the study protocol. Second, in case SBx was performed after a prostate MRI the operator performing the biopsies was not blinded to the MRI findings, as this was part of routine clinical practice. Third, the RPCRC is based on SBx outcomes. Adjustments to the risk model using MRI and MRI-TBx data could further improve its performance for MRI-TBx outcomes. Lastly, the RPCRC-MRI pathway was evaluated using SBx and MRI-TBx histopathology results as reference standard for the presence of csPCa. Whole-mount prostatectomy would be a better gold standard. However, the MR PROPER study reflects daily clinical practice and it is unethical to perform a prostatectomy in men without detected PCa.

CONCLUSION

The first clinical outcomes of the MR PROPER study show that the RPCRC can be used as upfront triaging test for the selection of biopsy-naïve candidates for a prostate MRI and subsequent MRI-driven prostate biopsy procedure. This so-called RPCRC-MRI pathway results in a high csPCa detection rate with a substantial reduction of the non-csPCa detection rate, numbers of prostate MRIs and biopsy procedures performed, at the cost of missing only a limited number of csPCa diagnoses. The RPCRC-MRI pathway could therefore be considered as a way forward in the current era of prostate MRI to reduce harms and increase the benefits of the current PCa diagnostic pathway. Future in-depth analyses of the MR PROPER data will follow and will provide us a more detailed insight in the diagnostic performances, and also the cost-effectiveness and quality of life of the RPCRC-MRI pathway.

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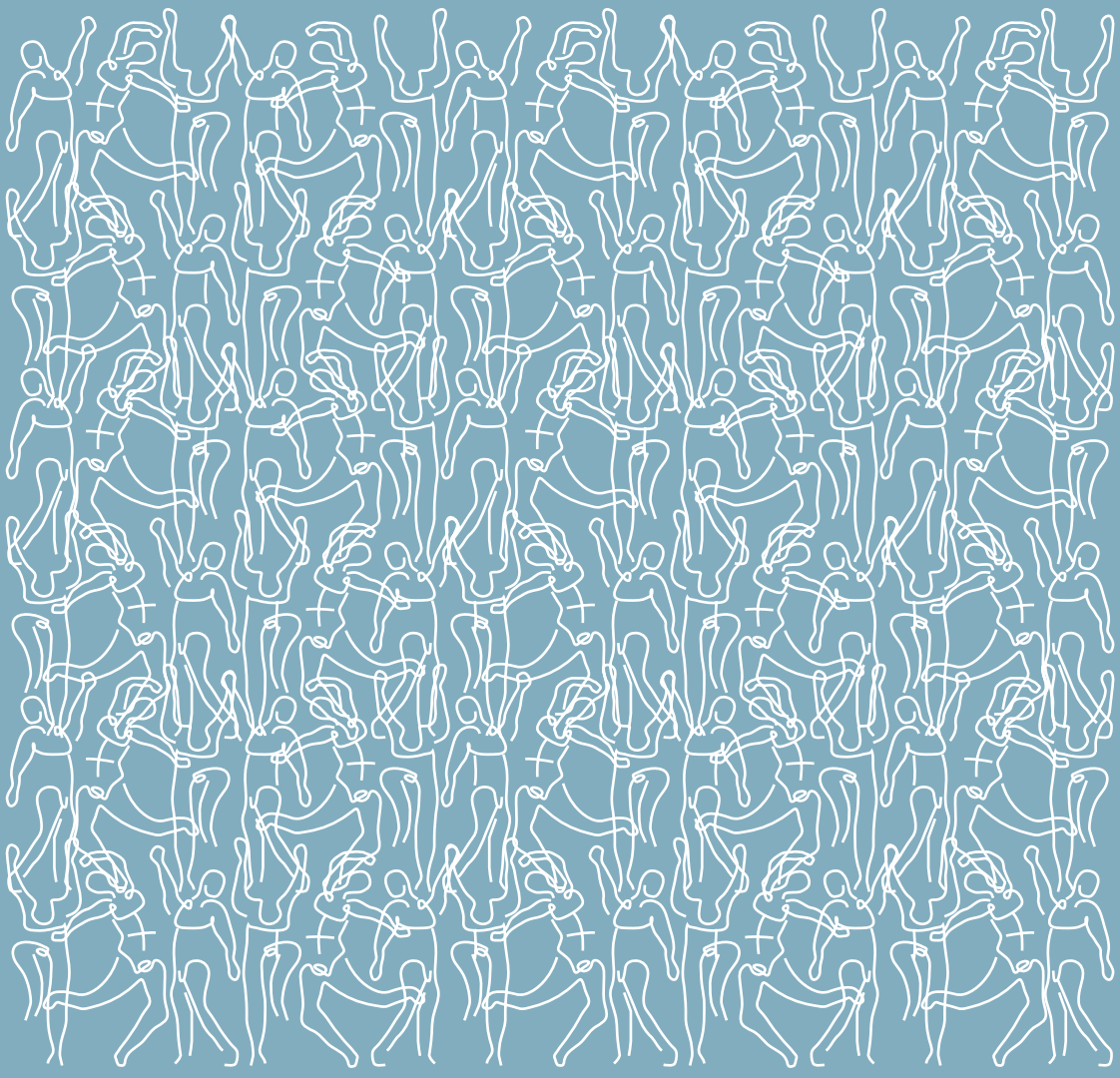
CONFLICTS OF INTEREST

The authors declare no conflict of interest.



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Equivocal PI-RADS three lesions on prostate magnetic resonance imaging: risk stratification strategies to avoid MRI-targeted biopsies.

Daniël F. Osses
Christian Arsov
Lars Schimmöller
Ivo G. Schoots
Geert J.L.H. van Leenders
Irene Esposito
Sebastiaan Remmers
Peter Albers
Monique J. Roobol

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ABSTRACT

We aimed to investigate the relation between largest lesion diameter, prostate-specific antigen density (PSA-D), age, and the detection of clinically significant prostate cancer (csPCa) using first-time targeted biopsy (TBx) in men with Prostate Imaging – Reporting and Data System (PI-RADS) 3 index lesions. A total of 292 men (2013-2019) from two referral centers were included. A multivariable logistic regression analysis was performed. The discrimination and clinical utility of the built model was assessed by the area under the receiver operation curve (AUC) and decision curve analysis, respectively. A higher PSA-D and higher age were significantly related to a higher risk of detecting csPCa, while largest index lesion diameter was not. The discrimination of the model was 0.80 (95% CI 0.73-0.87). When compared to a biopsy-all strategy, decision curve analysis showed a higher net benefit at threshold probabilities of ≥2%. Accepting a missing ≤5% of csPCa diagnoses, a risk-based approach would result in 34% of TBx sessions and 23% of low-risk PCa diagnoses being avoided. In men with PI-RADS 3 index lesions scheduled for first-time TBx, the balance between the number of TBx sessions, the detection of low-risk PCa, and the detection of csPCa does not warrant a biopsy-all strategy. To minimize the risk of missing the diagnosis of csPCa but acknowledging the need of avoiding unnecessary TBx sessions and overdiagnosis, a risk-based approach is advisable.

Keywords

Clinically significant prostate cancer; equivocal PI-RADS lesions; prostate MRI; risk stratification; targeted biopsies.

INTRODUCTION

The Prostate Imaging – Reporting and Data System (PI-RADS) score is important for standardized prostate magnetic resonance imaging (MRI) acquisition and reporting (1-4). Depending on the nature of the cohort and by following the PI-RADS guidelines, a not negligible number of lesions will be scored as PI-RADS 3, which is termed equivocal (5). The prevalence of clinically significant prostate cancer (csPCa, often defined as International Society of Urological Pathology [ISUP] grade ≥2 PCa) in biopsied PI-RADS 3 cases varies from 3% to 50% in the literature (6, 7).

PI-RADS 3 lesions are challenging because their characteristics in MRI have a great overlap with benign conditions (8, 9). On the other hand, tumors that are less visible by using T2-weighted (T2W) and apparent diffusion coefficient (ADC)-based tissue contrast might be classified as PI-RADS 3, despite the presence of Gleason ≥4 patterns (10). The PI-RADS guidelines propose recommendations for MRI-directed biopsy strategies, but do not clearly state how to deal with these category 3 imaging findings. In men with an overall PI-RADS score 3 on prostate MRI, an MRI-directed biopsy should be considered; however, biopsy can be avoided or deferred in carefully chosen patients if they are not at high risk of csPCa (2). Thus, while a targeted biopsy (TBx) may appear to be the logical next step in PI-RADS 3 cases, monitoring lesion characteristics with follow-up MRI and thereby postponing biopsies also seems to be an acceptable option (11).

The risk stratification of suspicious MRI lesions could help to avoid unnecessary biopsies. Studies on sub-classifying PI-RADS 3 lesions are limited and include most often small cohorts. The available data indicate that prostate-specific antigen density (PSA-D) might be useful in predicting the presence of csPCa (7, 11-17). From the perspective that size matters, subcategorizations of PI-RADS 3 lesions based on size have been proposed (18-21). However, sufficient evidence to develop clear directions on lesion characteristic-specific management of PI-RADS 3 lesions in csPCa diagnosis is still lacking, especially in men scheduled for MRI and TBx for the first time.

Using one of the largest series of men with an overall PI-RADS score of 3 on prostate MRI undergoing a first TBx session currently available, we aimed to investigate whether stratifying PI-RADS 3 lesions based on the largest (index) lesion diameter could aid in avoiding TBx sessions and low-risk PCa diagnoses without missing the diagnosis of csPCa. In addition, acknowledging earlier publications of its potential usefulness we also studied PSA-D as stratification tool and combined this information with the largest index lesion diameter and age in a multivariable prediction model.

MATERIALS & METHODS

Study population

This retrospective study was approved by the institutional review boards of the University Düsseldorf Medical Faculty and Erasmus University Medical Center with a waiver of written informed consent (NL45884.078.13/A301321).

Between October 2013 and July 2019, a total of 2557 consecutive men with clinical suspicion of PCa (initial/repeat biopsy) or on active surveillance (AS) for low-risk PCa underwent a multiparametric MRI (mpMRI) and, if indicated, TBx of suspicious MRI lesions with additional systematic prostate biopsy (SBx) if applicable to guidelines at one of the two tertiary referral centers. A total of 1809 men had a positive MRI, defined as an overall PI-RADS score ≥3. In the current study, we included the 292 men with an overall PI-RADS score 3 undergoing a first TBx session (Figure 1).

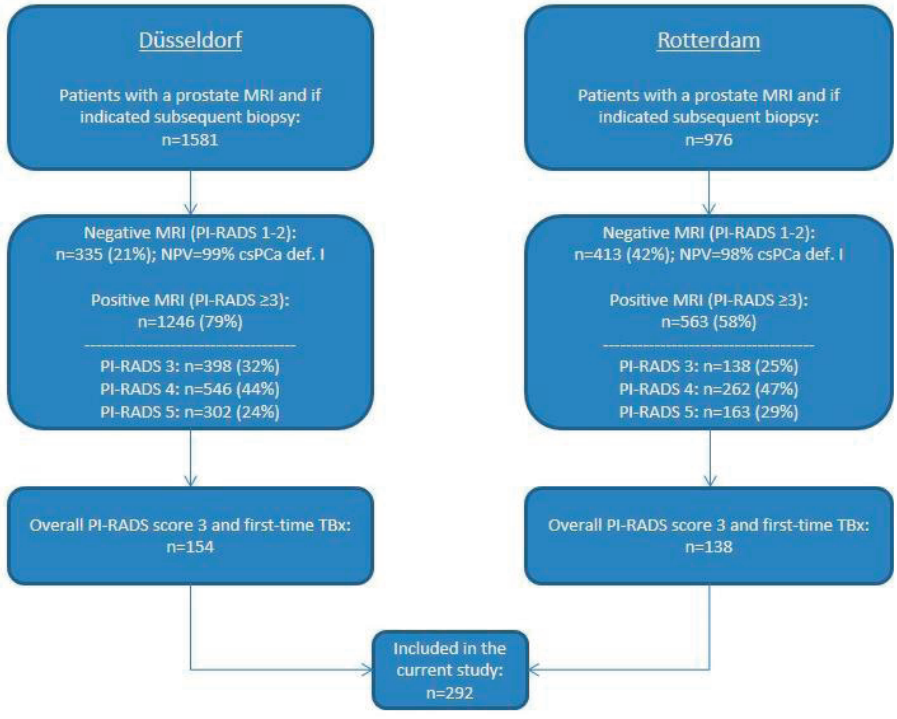

Figure 1. Flowchart of patients included in this study.
MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System; NPV: negative predictive value; csPCa: clinically significant prostate cancer; def.: definition; TBx: targeted biopsy.

Multiparametric MRI

MRIs were performed on a 3.0-Tesla MR scanner (Magnetom Trio Siemens [Düsseldorf, Germany] or Discovery MR750 GE Healthcare [Rotterdam, The Netherlands]) with a 32-channel pelvic phased-array coil. MRI protocols included T2W, diffusion-weighted imaging (DWI) with ADC reconstructions and dynamic contrast enhanced (DCE) imaging. MRIs were reviewed by radiologists with 5 to 9 years of prostate MRI experience according to the PI-RADS version 1 or version 2 guidelines (1, 4). MRI lesions with a PI-RADS score from 3 to 5 were defined as suspicious. Prostate volume on MRI was calculated using the prolate ellipsoid formula (length × width × height × π/6). Reported largest lesion diameter measurements were indicative for TBx decision management in daily practice, not for scientific volume estimations. Largest lesion diameter was preferably measured on an axial image, or otherwise on the image which best depicted the finding. Peripheral and transition zone lesions were preferably measured on ADC and T2W imaging, respectively, or otherwise on the sequence that allowed the best visualization of the lesion.

Prostate biopsy

MRI-TBx was performed using an MRI-transrectal ultrasound (TRUS) fusion system (UroNav® Invivo [Düsseldorf, Germany] or UroStation™ Koelis [Düsseldorf, Germany, Rotterdam, The Netherlands]). The suspicious MRI lesions were targeted with 2-5 cores per lesion, depending on the lesion size. If indicated, an additional SBx (8-12 cores, depending on the prostate volume) was performed by the same operator. All the biopsy procedures were performed by a transrectal approach and by experienced operators.

Pathological review of biopsy specimens

Biopsy specimens were reviewed by experienced pathologists according to the ISUP 2014 modified Gleason score (GS)/Grade Group (G) system (22). The presence of an invasive cribriform growth pattern (CR) and/or intraductal carcinoma (IDC) was recorded. In general, csPCa and thereby the recommendation for treatment was defined as any GS ≥3+4 PCa or ISUP grade ≥2 PCa found by TBx and/or SBx. Since our aim is to avoid TBx sessions, analyses are based on the TBx histopathology outcomes. The results of SBx were not used.

Study endpoints

Analyses of the largest (index) lesion diameter were performed at the patient and lesion level (= Supplementary Material). Analyses including PSA-D and age were performed at the patient level only.

Three definitions for csPCa were analysed:
I: ISUP grade ≥2 PCa (currently the most used, = primary outcome);
II: ISUP grade ≥2 with CR and/or IDC PCa;
III: ISUP grade ≥3 PCa.

Two definitions of "TBx avoided" were used:
- patient level = a complete TBx session avoided per patient;
- lesion level = a TBx procedure avoided per lesion (= Supplementary Material).

Primary outcomes:
- PCa detection in TBx specimen of men with equivocal MRI result (PI-RADS score 3);
- results in terms of avoiding TBx sessions and the detection of low-risk PCa of a risk stratification strategy based on the largest index lesion diameter accepting missing ≤5% of csPCa diagnoses (definition I).

Secondary outcomes:
- results in terms of avoiding TBx sessions and the detection of low-risk PCa of a risk stratification strategy based on PSA-D accepting missing ≤5% of csPCa diagnoses (definition I);
- performance and clinical utility of a multivariable prediction model including age, largest index lesion diameter, and PSA-D for TBx decision management in men with equivocal MRI result (PI-RADS score 3).

Statistical analysis

Descriptive statistics were used to report the patient characteristics. Categorical data are reported as count (percentage). Continuous data are reported as median (interquartile range [IQR]). Statistically significant differences in continuous non-parametric data were assessed with the Mann-Whitney U test. The Chi-square test for trend was used to test for differences in categorical data; in case of small numbers the Fischer's exact test was used. PSA-D was calculated by dividing the PSA level by the MRI-measured prostate volume. The relation of largest index lesion diameter, PSA-D and age at time of biopsy, and csPCa (I) detection was assessed using (multivariable) logistic regression. Age was included as a potential predictor in order to comply with the large age range of men in daily clinical practice, and because recent prostate MRI-risk calculators have shown that age could significantly add to original PCa risk calculators (23). For a better interpretation of the coefficients, we used the age per 10 years and multiplied the PSA-D value by 10. The discrimination of the resulting multivariable prediction model was assessed by the area under the receiver operation curve (AUC). The confidence interval of the AUC was calculated with 2000 bootstrap samples. The clinical utility of the model

was assessed with decision curve analysis. Analyses were performed using Statistical Package for the Social Sciences (version 24.0; IBM, Armonk, NY, USA) and R version 3.5.1.

RESULTS

Cohort characteristics and prostate cancer detection

The Düsseldorf and Rotterdam cohorts significantly differed in all reported patient characteristics, except the time of follow-up (Table 1). The majority of men had a previous negative SBx procedure, and more than one PI-RADS 3 lesion on MRI. Any PCa, csPCa (I), csPCa (II) and csPCa (III) was detected in 32% (92/292), 13% (39/292), 7% (20/292) and 3% (10/292) of all men, respectively. In men with an initial suspicion of PCa, the csPCa (I) detection was significantly lower compared to men with previous negative SBx and men on AS. In the Düsseldorf cohort consisting of mostly biopsy-naïve men (42%) and men with a previous negative biopsy (53%), csPCa (I) was detected in 3% (4/154) of men. In the Rotterdam cohort consisting of mostly men on AS (51%) and men having a previous negative biopsy (45%), csPCa (I) was detected in 25% (35/138) of men.

The 292 men included had a total of 525 PI-RADS 3 lesions (Table 2). The median (IQR) largest lesion diameter was 11 (9-13) mm. The majority of PI-RADS 3 lesions was located in the transition zone of the prostate. In these lesions, any PCa, csPCa (I), csPCa (II) and csPCa (III) was detected in 21% (108/525), 8% (43/525), 4% (20/525) and 2% (10/525), respectively. There was no significant difference in csPCa (I) detection between peripheral- and transition-zone PI-RADS 3 lesions.

Risk stratification for TBx decision based on largest index lesion diameter

In this PI-RADS 3 cohort, in univariate analysis the largest index lesion diameter is not a statistically significant predictor (p=0.70) of csPCa (I) (Table 3). It must be noted that csPCa (I) is more often detected in men with larger PI-RADS 3 index lesions compared to men with smaller index lesions. When accepting missing ≤5% of csPCa (I) diagnoses, a threshold for largest index lesion diameter of ≥7mm would result in 10% fewer TBx sessions and 26% of low-risk PCa diagnoses being avoided (Table 4, Supplementary Table 1).

Risk stratification for TBx decision based on PSA-density

In this PI-RADS 3 cohort, in univariate analysis PSA-D is a statistically significant predictor ($p<0.001$) of csPCa (I) (Table 3). Men with csPCa (I) had significantly higher PSA-D than men without csPCa (I). When accepting missing no more than 5% of csPCa (I) diagnoses, a PSA-D threshold of ≥0.11ng/ml² would result in avoiding 25% of TBx sessions and 11% of low-risk PCa diagnoses (Table 4).

	Total cohort (n=292)	Düsseldorf (n=154)	Rotterdam (n=138)	*p value*
Age (yr), median (IQR)	64 (58-69)	61 (53-67)	67 (61-72)	*<0.001*
Follow-up time (yr), median (IQR)	2 (1-3)	3 (2-4)	2 (1-3)	*0.083*
PSA level (ng/ml), median (IQR)	8.1 (6-12.2)	7.3 (5.5-11)	9.5 (6.6-13.1)	*0.001*
Prostate volume on MRI (ml), median (IQR)	52.3 (36-78.8)	58 (44.8-83.3)	46 (31-68.5)	*<0.001*
PSA-density (ng/ml/ml), median (IQR)	0.16 (0.11-0.25)	0.13 (0.1-0.18)	0.23 (0.13-0.31)	*<0.001*
Indication of prostate MRI, no. (%)				
Initial PCa diagnosis	69 (24)	64 (42)	5 (4)	*<0.001*
Previous negative biopsy	144 (49)	82 (53)	62 (45)	
Active Surveillance	79 (27)	8 (5)	71 (51)	
DRE findings, no. (%)				
Benign	191 (65)	75 (49)	116 (84)	*<0.001*
Suspected	60 (21)	38 (25)	22 (16)	
Unknown	41 (14)	41 (27)	0 (0)	
PI-RADS 3 lesions on MRI, no. (%)				
1	132 (45)	16 (10)	116 (84)	*<0.001*
2	89 (31)	69 (45)	20 (15)	
3	69 (24)	67 (44)	2 (1)	
4	2 (1)	2 (1)	0 (0)	
Highest grade at TBx, no. (%)				
no PCa	200 (69)	141 (92)	59 (43)	*<0.001*
G 1	53 (18)	9 (6)	44 (32)	
G 2	19 (7)	2 (1)	17 (12)	
G 2 with CR and/or IDC	10 (3)	0 (0)	10 (7)	
G 3	9 (3)	2 (1)	7 (5)	
G 4-5	1 (1)	0 (0)	1 (1)	

Table 1. Patient characteristics.
IQR: interquartile range; PSA: prostate-specific antigen; MRI: magnetic resonance imaging; PCa: prostate cancer; DRE: digital rectal examination; PI-RADS: Prostate Imaging Reporting and Data System; TBx: targeted biopsy; G: grade; CR: cribriform growth pattern; IDC: intraductal carcinoma.

Multivariable risk prediction for TBx decision

Multivariable logistic regression showed that a higher PSA-D and a higher age at time of biopsy were significantly (*p≤0.001*) related to a higher risk of csPCa (I) diagnosis in PI-RADS 3 cases, while the largest index lesion diameter was not (*p=0.51*) (Table 3). To avoid data-dependent variable selection for the regression model, the largest index lesion diameter is included in the model despite not being a significant predictor. The discrimination of this model is 0.80 (95% CI 0.73-0.87). The model has a higher net benefit compared to a biopsy-all PI-RADS 3 patients strategy at threshold probabilities of ≥2% (Figure 2). Applying a risk-based threshold of 5% would result in 23% fewer

TBx sessions and 13% fewer low-risk PCa diagnoses at the cost of missing 3% csPCa (I). Table 5 shows the numbers of avoided TBx sessions, low-risk PCa diagnoses and missed csPCa (I) for the model using a risk threshold range of 2% to 10%. When accepting missing no more than 5% of csPCa (I) diagnoses, a risk threshold of 7% would result in 34% fewer TBx sessions and 23% low-risk PCa diagnoses avoided. When not accepting missing the diagnosis of csPCa (I), a risk threshold of 3% should be applied resulting in avoiding 10% of TBx sessions and almost no reduction in the diagnosis of low-risk PCa.

	Total PI-RADS 3 lesions (n=525)	PI-RADS 3 lesions Düsseldorf (n=363)	PI-RADS 3 lesions Rotterdam (n=162)	*p value*
Lesion size (largest diameter, mm), median (IQR)	11 (9-13)	12 (10-13)	10 (7-12)	*<0.001*
Lesion zone, no. (%)				
Peripheral zone	186 (35)	107 (30)	79 (49)	*<0.001*
Transition zone	324 (62)	246 (68)	78 (48)	
Central zone	2 (1)	0 (0)	2 (1)	
>1 zone	13 (3)	10 (3)	3 (2)	
Lesion location, no. (%)				
Anterior	340 (65)	258 (71)	82 (51)	*<0.001*
Posterior	178 (34)	103 (28)	75 (46)	
Both	7 (1)	2 (1)	5 (3)	
Grade at TBx, no. (%)				
no PCa	417 (79)	346 (95)	71 (44)	*<0.001*
G 1	65 (12)	10 (3)	55 (34)	
G 2	23 (4)	5 (1)	18 (11)	
G 2 with CR and/or IDC	10 (2)	0 (0)	10 (6)	
G 3	9 (2)	2 (1)	7 (4)	
G 4-5	1 (1)	0 (0)	1 (1)	

Table 2. PI-RADS 3 lesion characteristics.
IQR: interquartile range; TBx: targeted biopsy; PCa: prostate cancer; G: grade; CR: cribriform growth pattern; IDC: intraductal carcinoma; PI-RADS: Prostate Imaging Reporting and Data System.

	Univariable analysis			Multivariable analysis (model)		
Variable	**Odds ratio**	**95% CI**	***p value***	**Odds ratio**	**95% CI**	***p value***
Age (per 10 years)	2.62	1.62 – 4.25	*<0.001*	2.31	1.43 – 3.92	*0.001*
Largest index lesion diameter	1.01	0.96 – 1.01	*0.70*	1.02	0.96 – 1.08	*0.51*
PSA-density (multiplied by 10)	1.65	1.31 – 2.10	*<0.001*	1.53	1.21 – 1.97	*<0.001*

Table 3. Output of the logistic regression analyses.
PSA: prostate-specific antigen.

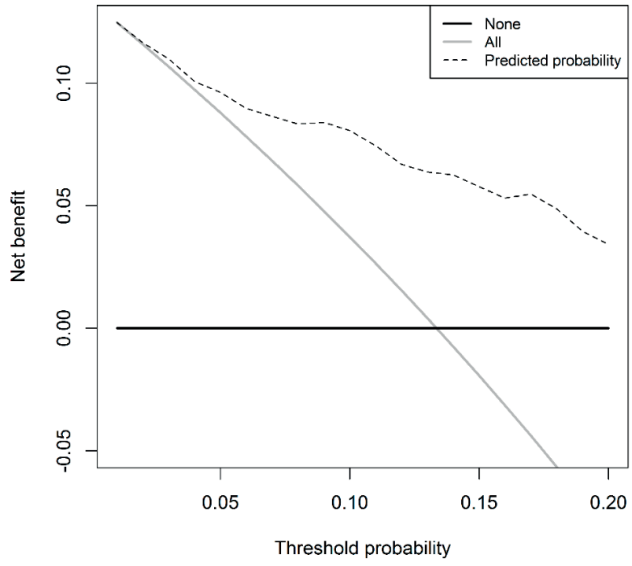

Figure 2. Decision curve for clinically significant prostate cancer in the targeted biopsy of the prediction model.

Thresholds		TBx sessions	ISUP grade 1 PCa	ISUP grade ≥2 PCa	ISUP grade ≥2 with CR and/or IDC PCa	ISUP grade ≥3 PCa
Largest index lesion diameter	**PSA-density**	**Avoided (n, %)**	**Not detected (n, %)**	**Missed diagnosis (n, %)**	**Missed diagnosis (n, %)**	**Missed diagnosis (n, %)**
Monitor all patients		292 (100%)	53 (100%)	39 (100%)	20 (100%)	10 (100%)
Biopsy all patients		0 (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
≥4mm	-	3 (1%)	3 (6%)	0 (0%)	0 (0%)	0 (0%)
≥5mm	-	11 (4%)	5 (9%)	1 (3%)	1 (5%)	0 (0%)
≥6mm	-	19 (7%)	10 (19%)	1 (3%)	1 (5%)	0 (0%)
≥7mm	-	29 (10%)	14 (26%)	2 (5%)	2 (10%)	1 (10%)
≥8mm	-	41 (14%)	16 (30%)	5 (13%)	3 (15%)	2 (20%)
-	**≥0.05ng/ml²**	5 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
-	**≥0.10ng/ml²**	55 (20%)	4 (1%)	2 (5%)	1 (5%)	1 (10%)
-	**≥0.11ng/ml²**	73 (25%)	6 (11%)	2 (5%)	1 (5%)	1 (10%)
-	**≥0.12ng/ml²**	91 (31%)	9 (17%)	3 (8%)	1 (5%)	1 (10%)
-	**≥0.15ng/ml²**	141 (48%)	14 (26%)	5 (13%)	1 (5%)	1 (10%)
-	**≥0.20ng/ml²**	183 (63%)	19 (36%)	10 (26%)	2 (10%)	2 (20%)

Table 4. Summary table of the avoided targeted biopsy sessions and prostate cancer diagnoses missed, when using the largest index lesion diameter or PSA-density as a stratification tool.
PSA: prostate-specific antigen; TBx: targeted biopsy; ISUP: International Society of Urological Pathology; PCa: prostate cancer; CR: cribriform growth pattern; IDC: intraductal carcinoma.

Threshold	TBx sessions	ISUP grade 1 PCa	ISUP grade ≥2 PCa
Risk of csPCa	Avoided (n, %)	Not detected (n, %)	Missed diagnosis (n, %)
Monitor all patients	292 (100%)	53 (100%)	39 (100%)
Biopsy all patients	0 (0%)	0 (0%)	0 (0%)
≥2%	10 (3%)	1 (2%)	0 (0%)
≥3%	30 (10%)	2 (4%)	0 (0%)
≥4%	47 (16%)	4 (8%)	1 (3%)
≥5%	65 (23%)	7 (13%)	1 (3%)
≥6%	84 (30%)	9 (17%)	2 (5%)
≥7%	97 (34%)	12 (23%)	2 (5%)
≥8%	119 (42%)	16 (30%)	3 (8%)
≥9%	137 (48%)	20 (38%)	3 (8%)
≥10%	150 (53%)	22 (42%)	4 (10%)

Table 5. Performance and clinical utility of the prediction model: numbers of avoided TBx sessions, low-risk PCa diagnoses and missed csPCa using a risk threshold range of 2% to 10%.
CsPCa: clinically significant prostate cancer; TBx: targeted biopsy; ISUP: International Society of Urological Pathology; PCa: prostate cancer.

DISCUSSION

Patients with PI-RADS 3 index lesions scheduled for first-time TBx represent a diagnostic problem, as there is controversy regarding whether these men should be biopsied or could safely be monitored with follow-up MRI. In this study, using a large international dataset, we found that csPCa with a detection percentage of 3%-13% (based on different definitions) on first-time TBx was uncommon in PI-RADS 3 cases. This could imply that PI-RADS score 3 cases represent a category of men in whom initially monitoring with follow-up MRI could be a realistic option. The csPCa (I) detection at the patient level was 13% in our total population, with almost half of the cancers being not higher than ISUP grade 2 PCa without CR and/or IDC. Our csPCa (I) detection percentage is in line with the recent meta-analysis of Maggi et al. which included 25 studies, showing a csPCa detection percentage in PI-RADS 3 cases of 18.5% (95% CI 16.6-20.3; range 3.4-47) (7). The reasons for the wide range of csPCa detection in PI-RADS 3 index lesions in the literature include, among others, the considerable interobserver variability in the characterization of equivocal lesions caused by reader experience and differences in technical performance, the prevalence of csPCa in different populations and TBx-related factors. These factors could potentially also explain the difference in csPCa (I) found between the Düsseldorf and Rotterdam cohorts. The low event rate in the Düsseldorf cohort limited us to perform logistic regression analyses separately per cohort. For these analyses the two cohorts were regarded as one, in line with analyses on heterogeneous cohorts (24).

Instead of a monitoring all or a biopsy-all PI-RADS 3 patients strategy, a more realistic approach to avoid TBx sessions and low-risk PCa diagnoses would be to apply a risk stratification strategy. Risk stratification for TBx decision solely based on the largest index lesion diameter did not aid in avoiding TBx sessions while assuring csPCa (I) detection. On the contrary, risk stratification based on PSA-D only or a multivariable approach including next to the largest index lesion diameter, PSA-D, and age could result in avoiding a substantial number of TBx sessions and low-risk PCa diagnoses at the cost of missing only limited numbers of csPCa (I) diagnoses. These results suggest that when TBx is considered in men with PI-RADS 3 index lesions scheduled for first-time TBx, risk stratification based on PSA-D or preferably a multivariable model-based risk stratification approach is advisable.

To the best of our knowledge, this is the first study to investigate largest (index) lesion diameter as a stratification tool in a large daily clinical cohort of men with PI-RADS 3 index lesions. According to our results, largest index lesion diameter is not a significant predictor of csPCa in PI-RADS 3 cases. To lower the risk of statistical overfitting, largest index lesion diameter is included in the multivariable prediction model (25). In our cohort, slightly more csPCa (I) was detected in PI-RADS 3 index lesions with a diameter ≥10mm (14%, 31/217), compared to index lesions with a diameter <10mm (11%, 8/75). This finding could suggest that csPCa is relatively rare in smaller PI-RADS 3 index lesions. Rais-Bahrami et al. suggest that small MRI index lesions (≤7mm) may correspond to benign lesions or indolent cancers (18). Furthermore, Rosenkrantz et al. proposed to upgrade a PI-RADS 3 to a PI-RADS 4 lesion on the basis of larger size (20, 26). These assumptions do, however, not take into account the scenario that in the studied series small PI-RADS 3 index lesions harboring csPCa could have been mis-sampled by TBx. The absence of csPCa in the TBx specimens would then mean that csPCa was missed and not that there was no csPCa present (6, 27). However, if this would really be the case follow-up of the lesions with MRI could overcome the problem of missing a timely csPCa diagnosis.

PSA-D showed to be a significant clinical predictor of csPCa in our cohort. Applying solely PSA-D as risk stratification tool could result in 25% less TBx sessions and 11% less low-risk PCa diagnoses missing only 5% csPCa (I). This high predictive value of PSA-D in PI-RADS 3 cases is in line with previous studies, and also with studies reporting on TBx and SBx histopathology outcomes (17). Venderink et al. showed that offering a biopsy to only PI-RADS 3 men with a PSA-D of ≥0.15ng/ml^2 resulted in 42% of biopsy sessions avoided at the cost of missing 6% csPCa. Lowering the threshold to ≥0.12ng/ml^2 would result in 26% of biopsy sessions avoided, missing no csPCa (28). Therefore, PSA-D may represent a good index to decide which PI-RADS 3 men should undergo a

biopsy (29). The risk stratification of PI-RADS 3 cases could further be improved by a model-based approach in which PSA-D, largest index lesion diameter, and age are combined in a multivariable prediction model that predicts the risk of csPCa of a PI-RADS 3 man, as shown by our findings. To the best of our knowledge, our study is one of the first studies, next to the work of Di Trapani et al., to show the high added value of such a model-based approach in safely avoiding TBx sessions and low-risk PCa diagnoses in specifically PI-RADS 3 cases (29).

Next to the most often used definitions for csPCa, we studied the prevalence of PI-RADS 3 lesions related to the presence of CR and IDC in TBx specimens. CR and IDC are prognostic drivers in cancer-specific survival, even more than other Gleason 4 patterns (30, 31). Although ISUP grade ≥2 PCa was our primary outcome measure for csPCa, the incorporation of this secondary growth patterns information into the risk stratification could further improve the selection of men who will benefit from treatment, especially because almost half of the detected ISUP grade ≥2 PCa in our cohort was ISUP grade 2 without CR and/or IDC PCa. Therefore, we may argue that the threshold for csPCa should be ISUP grade ≥2 with CR and/or IDC PCa to save even more TBx sessions in men with PI-RADS 3 index lesions and thereby avoid the (over)detection of ISUP grade 2 PCa, which potentially could never harm a patient if left undetected (32).

The strength of our study is the inclusion of data from two centers, resulting in one of the largest series of men with an overall PI-RADS score 3 undergoing first-time TBx. This makes our study results more generally representative by giving more an overall view of the real-world setting of PI-RADS 3 lesions in daily practice, compared to reporting single center results. It must, however, be noted that every institution should know their own test performance statistics when making clinical decisions based on prostate MRI findings, because of existing differences in radiology, fusion biopsy and pathology learning curves per institution (33). Furthermore, our analysis of different csPCa definitions including the presence of secondary growth patterns is of high added value for further clinical decision-making.

Some limitations of our study should be highlighted. First, our study has a retrospective design and could thereby introduce a selection bias. However, our study represents a cohort of consecutive men. Second, men included were treated over a long time frame in which changes in the PI-RADS classification also occurred. However, the newer PI-RADS versions may not necessarily be better regarding diagnostic accuracy than the original PI-RADS version (34-36). Third, we did not include SBx or prostatectomy outcomes as reference standard in our analyses. Some literature suggests to perform a combined biopsy strategy in PI-RADS 3 cases (7). However, since our primary objective was to

establish directions for lesion characteristic-specific management of PI-RADS 3 lesions in csPCa diagnosis, SBx outcomes would not have been of added value to answer our research questions. Furthermore, our results are similar to studies investigating PSA-D as stratification tool but reporting on TBx and SBx outcomes (17). This suggests that the TBx-only strategy could be similar in csPCa detection to the combined biopsy strategy in PI-RADS 3 cases. Nevertheless, when considering a biopsy in PI-RADS 3 men, we advise that adding SBx to TBx should be discussed at an individual level taking into account the benefits and harms. Fourth, although we have found potential predictors of csPCa in men with a PI-RADS 3 index lesion, the constructed prediction model is not (yet) usable in clinical practice for TBx decision management. To construct a more robust prediction model for TBx decision in PI-RADS 3 cases, more data are necessary and an external validation of the model is advised before its application in clinical practice. Lastly, the lesion measurements, although measured according to the PI-RADS recommendations, were not standardized. We acknowledge that standardized MRI lesion measurement should be the gold standard (37, 38). However, as long as this is not implemented in routine clinical practice, lesion measurement according to the PI-RADS guidelines is the daily workflow in most hospitals.

CONCLUSIONS

Overall, in men with PI-RADS 3 index lesions scheduled for first-time TBx, the balance between the number of TBx sessions, detection of low-risk PCa and detection of csPCa does not warrant a biopsy-all strategy. If the (low) risk of not diagnosing csPCa in these men is accepted, monitoring these men with follow-up prostate MRI could be considered as the optimal strategy avoiding TBx and the detection of low-risk PCa. To minimize the risk of missing the diagnosis of csPCa while acknowledging the need to avoid unnecessary TBx sessions and overdiagnosis, a model-based risk stratification approach including at least PSA-D could be considered. More data are necessary to construct a robust clinically useful prediction model for TBx decision management in PI-RADS 3 cases. Future large-scale studies should also focus on the need, optimal intervals, and frequencies for follow-up MRIs in these men.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIALS

The supplementary materials are available online at: http://www.mdpi.com/2075-4426/10/4/270/s1

Threshold	No. of TBx sessions		No. of ISUP grade 1 PCa		No. of ISUP grade ≥2 PCa		No. of ISUP grade ≥2 with CR and/or IDC PCa		No. of ISUP grade ≥3 PCa	
Largest diameter of index lesion	Performed	Avoided (% total)	Detected	Not detected (% total)	Detected	Missed diagnosis (% total)	Detected	Missed diagnosis (% total)	Detected	Missed diagnosis (% total)
Biopsy all patients	292	0 (0%)	53	0 (0%)	39	0 (0%)	20	0 (0%)	10	0 (0%)
Monitor all patients	0	292 (100%)	0	53 (100%)	0	39 (100%)	0	20 (100%)	0	10 (100%)
≥1mm	292	0 (0%)	53	0 (0%)	39	0 (0%)	20	0 (0%)	10	0 (0%)
≥2mm	292	0 (0%)	53	0 (0%)	39	0 (0%)	20	0 (0%)	10	0 (0%)
≥3mm	290	2 (1%)	51	2 (4%)	39	0 (0%)	20	0 (0%)	10	0 (0%)
≥4mm	289	3 (1%)	50	3 (6%)	39	0 (0%)	20	0 (0%)	10	0 (0%)
≥5mm	281	11 (4%)	48	5 (9%)	38	1 (3%)	19	1 (5%)	10	0 (0%)
≥6mm	273	19 (7%)	43	10 (19%)	38	1 (3%)	19	1 (5%)	10	0 (0%)
≥7mm	263	29 (10%)	39	14 (26%)	37	2 (5%)	18	2 (10%)	9	1 (10%)
≥8mm	251	41 (14%)	37	16 (30%)	34	5 (13%)	17	3 (15%)	8	2 (20%)
≥9mm	233	59 (20%)	30	23 (43%)	32	7 (18%)	15	5 (25%)	8	2 (20%)
≥10mm	217	75 (26%)	28	25 (47%)	31	8 (21%)	15	5 (25%)	8	2 (20%)
≥11mm	190	102 (35%)	23	30 (57%)	27	12 (31%)	14	6 (30%)	8	2 (20%)
≥12mm	170	122 (42%)	19	34 (64%)	24	15 (38%)	14	6 (30%)	8	2 (20%)
≥13mm	129	163 (56%)	13	40 (75%)	16	23 (59%)	12	8 (40%)	7	3 (30%)
≥14mm	96	196 (67%)	10	43 (81%)	14	25 (64%)	10	10 (50%)	6	4 (40%)
≥15mm	76	216 (74%)	10	43 (81%)	11	28 (72%)	8	12 (60%)	4	6 (60%)
≥16mm	57	235 (80%)	6	47 (89%)	7	32 (82%)	5	15 (75%)	2	8 (80%)
≥17mm	46	246 (84%)	6	47 (89%)	7	32 (82%)	5	15 (75%)	2	8 (80%)
≥18mm	37	255 (87%)	5	48 (91%)	5	34 (87%)	3	17 (85%)	2	8 (80%)
≥19mm	30	262 (90%)	4	49 (92%)	5	34 (87%)	3	17 (85%)	2	8 (80%)

≥20mm	28	264 (90%)	3	50 (94%)	5	34 (87%)	3	17 (85%)	2	8 (80%)

Supplementary Table 1. Performed and avoided targeted biopsy sessions and numbers of prostate cancer diagnoses detected and missed in PI-RADS 3 patients with different thresholds for clinically significant prostate cancer, when using largest index lesion diameter only as stratification tool.
TBx: targeted biopsy; ISUP: International Society of Urological Pathology; PCa: prostate cancer; CR: cribriform growth pattern; IDC: intraductal carcinoma.

Threshold	No. of TBx procedures		No. of ISUP grade 1 PCa		No. of ISUP grade ≥2 PCa		No. of ISUP grade ≥2 with CR and/or IDC PCa		No. of ISUP grade ≥3 PCa	
Largest lesion diameter	Performed	Avoided	Detected	Not detected	Detected	Missed diagnosis	Detected	Missed diagnosis	Detected	Missed diagnosis
Biopsy all lesions	525	0	65	0	43	0	20	0	10	0
Monitor all lesions	0	525	0	65	0	43	0	20	0	10
≥1mm	525	0	65	0	43	0	20	0	10	0
≥2mm	525	0	65	0	43	0	20	0	10	0
≥3mm	522	3	62	3	43	0	20	0	10	0
≥4mm	516	9	58	7	42	1	19	1	10	0
≥5mm	505	20	54	11	42	1	19	1	10	0
≥6mm	492	33	50	15	41	2	19	1	10	0
≥7mm	478	47	45	20	40	3	18	2	9	1
≥8mm	451	74	42	23	37	6	17	3	8	2
≥9mm	406	119	31	34	34	9	14	6	7	3
≥10mm	364	161	27	38	33	10	14	6	7	3
≥11mm	298	227	20	45	27	16	12	8	6	4
≥12mm	240	285	18	47	24	19	12	8	6	4
≥13mm	168	357	11	54	16	27	10	10	5	5
≥14mm	120	405	9	56	14	29	8	12	4	6
≥15mm	90	435	9	56	10	33	6	14	2	8
≥16mm	65	460	6	59	6	37	4	16	1	9
≥17mm	50	475	6	59	6	37	4	16	1	9
≥18mm	41	484	5	60	4	39	2	18	1	9
≥19mm	33	492	4	61	4	39	2	18	1	9

	≥20mm	30	495	3	62	4	39	2	18	1	9	

Supplementary Table2. Performed and avoided targeted biopsies procedures and numbers of prostate cancer diagnoses detected and missed in PI-RADS 3 lesions with different thresholds for clinically significant prostate cancer, when using largest lesion diameter as stratification tool.
TBx: targeted biopsy; ISUP: International Society of Urological Pathology; PCa: prostate cancer; CR: cribriform growth pattern; IDC: intraductal carcinoma.

Discovery MR750 GE Healthcare

Sequence	T2 TSE	T2 TSE	T2 TSE	EPI DWI	T1 LAVA/FLEX	DCE dynamic T1 LAVA
Orientation	Sagittal	Coronal	Axial	Axial	Axial	Axial
TR (ms)	8941	n.a.	5660	3203	-	-
TE (ms)	140	n.a.	140	Min.	-	-
Flip Angle (deg)	125	n.a.	125	-	12	12
Matrix size	256	n.a.	320	128	300	160
# Slices/ Thickness(mm)	30 slices 3 mm	n.a.	30 slices 3 mm	30 slices 3 mm	24 slices 4 mm	24 slices 4 mm
Gap	0%	n.a.	0%	0 %	-	-
Voxel size (mm)	0.7x0.7x3	n.a.	0.6x0.6x3	2x2x3	1.2x1.2x4	1.5x1.5x3
Averages/NEX	2	n.a.	4	-	-	-
FOV	190	n.a.	190	240	360	240
Phase enc Dir	S/I	n.a.	A/P	Unswap	R/L	R/L
Fat suppres	None	n.a.	None	Fat sat.	None	None
b-values (sec/mm2)	-	n.a.	-	50, 400, 800, 1500 (calculated)	-	-
Measurements	1	n.a.	1	1	1	20
Contrast agent	-	n.a.	-	-	-	0.1 mmol/Kg gadolinium
Acquisition time	2:58	n.a.	4:39	5:04	3:07	3:02

Magnetom Trio® Siemens	Sequence	T2 TSE	T2 TSE	T2 TSE	EPI DWI	T1 TSE	DCE dynamic T1 Vibe
	Orientation	Sagittal	Coronal	Axial	Axial	Axial	Axial
	TR (ms)	11330	11330	10630	4700	650	3.62
	TE (ms)	103	103	117	90	13	1.27
	Flip Angle (deg)	150	150	150	-	-	12
	Matrix size	256	256	256	136	320	128
	# Slices/ Thickness(mm)	30 slices 3 mm	30 slices 3 mm	30 slices 3 mm	30 slices 3 mm	30 slices 3 mm	20 slices 3 mm
	Gap	0%	0%	0%	0 %	-	-
	Voxel size (mm)	0.7x0.7x3	0.7x0.7x3	0.5x0.5x3	1.5x1.5x3	1.3x0.9x5	1.5x1.5x3.3
	Averages/NEX	1	1	2	8	-	-
	FOV	170	170	128	200	300	192
	Phase enc Dir	H>>F	R>>L	R>>L	R>>L	R>>L	R>>L
	Fat suppres	None	None	None	Fat sat.	None	None
	b-values (sec/mm2)	-	-	-	0, 500, 1000 + 1400 (acquired)	-	-
	Measurements	1	1	1	1	1	22
	Contrast agent	-	-	-	-		0.1 mmol/Kg gadolinium
	Acquisition time	4:11	4:11	8:21	4:31	5:15	3:36

Supplementary Table3. Specifications of applied mpMRI scan protocols.
TSE: turbo spin echo; EPI: echo-planar imaging; DWI: diffusion weighted imaging; DCE: dynamic contrast enhanced; TR: repetition time; TE: echo time; FOV: field of view; NEX: number of excitation; H: head; F: feet; R: right; L: left.

PART II

ACTIVE SURVEILLANCE

7

Reduction of MRI-targeted biopsies in men with low-risk prostate cancer on active surveillance by stratifying to PI-RADS and PSA-density, with different thresholds for significant disease.

Ivo G. Schoots
Daniël F. Osses*
Frank-Jan H. Drost*
Jan F.M. Verbeek
Sebastiaan Remmers
Geert J.L.H. van Leenders
Chris H. Bangma
Monique J. Roobol

*These authors contributed equally to this work.

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ABSTRACT

Background

The fear of undergrading prostate cancer (PCa) in men on active surveillance (AS) have led to strict criteria for monitoring, which have resulted in good long-term cancer-specific survival, proving the safety of this approach. Reducing undergrading, MRI-targeted biopsies are increasingly used in men with low-risk disease despite their undefined role yet. The objective of this study is to investigate the rate of upgrading using MRI-targeted biopsies in men with low-risk disease on AS, stratified on the basis of PI-RADS and PSA-density, with the aim to reduce potential unnecessary repeat biopsy procedures.

Methods

A total of 331 men were prospectively enrolled following the MRI-PRIAS protocol. MR imaging was according to Prostate Imaging Reporting and Data System (PI-RADSv2) guidelines. Suspicious MRI lesions (PI-RADS 3-5) were additionally targeted by MRI-TRUS fusion biopsies. Outcome measure was upgrading to Gleason score (GS) ≥3+4 with MRI-targeted biopsies, stratified for PI-RADS and PSA-density.

Results

In total, 25% (82/331) of men on AS showed upgrading from GS 3+3. Only 3% (11/331) was upgraded to GS ≥8. In 60% (198/331) a suspicious MRI lesion was identified, but in only 41% (82/198) of men upgrading was confirmed. PI-RADS 3, 4 and 5 categorised index lesions, showed upgrading in 30%, 34% and 66% of men, respectively. Stratification to PI-RADS 4-5, instead of PI-RADS 3-5, would have missed a small number of high volume Gleason 4 prostate cancer in PI-RADS 3 category. However, further stratification into PI-RADS 3 lesions and PSA-density <0.15 ng/mL^2 could result in a safe targeted biopsy reduction of 36% in this category, without missing any upgrades.

Conclusions

Stratification with the combination of PI-RADS and PSA-density may reduce unnecessary additional MRI biopsy testing. Overall, the high rate of detected upgrading in men on AS may result in an unintended tightening of continuing in AS. Since patients, included under current AS criteria showed extremely favorable outcome, there might be no need to further restrict continuing on AS with MRI and targeted biopsies.

Keywords

Prostate cancer; biopsy; magnetic resonance imaging; MRI-guided targeted biopsy; PSA-density; PI-RADS; risk stratification.

INTRODUCTION

In the Western world, about one half of all patients diagnosed with prostate cancer (PCa) has low-risk disease (1). In low-risk disease, active treatment hardly yields survival benefit (2). Therefore, active surveillance (AS) is the recommended option for the initial management of low-risk disease (3, 4).

Monitoring in AS is based on repeated PSA measurements, clinical T-staging based on digital rectal exams, and repeated random systematic transrectal ultrasound (TRUS)-guided biopsies (3). Repeated biopsies are cumbersome for patients and have severe complication risks. Moreover, sampling errors lead to underestimation of the Gleason grading (5).

The fear of undergrading PCa in men on AS has however led to strict criteria for monitoring, which has resulted in good long-term cancer-specific survival, proving the safety of this approach (6). To reduce the fear of undergrading, MRI and MRI-targeted biopsies are increasingly used in the management of patients with clinically low-risk PCa, despite their role has not yet been established definitively (7). The use of MR imaging in AS has improved the inclusion of true low-grade PCa; targeted biopsies of suspected lesions on MRI may result in excluding those men found with intermediate/high-grade PCa (8).

However, this additional testing by MRI and MRI targeted biopsy may result in an unintended reclassification to perceived higher risk. This is termed as 'risk inflation'; a cancer that is stable may be more accurately sampled at MRI-targeted biopsy and found to include higher risk features than when it was sampled in a routine systematic manner (9). This lesion targeting results in an increase in risk attribution if traditional criteria (i.e. Gleason score [GS], cancer core length and the proportion of positive cores on routine sampling) are still applied. It would therefore be wrong to falsely encourage men to cease AS because of an apparent increase in risk (reclassification) rather than a true change in their cancer.

Appropriate risk thresholds are not yet understood when MRI and MRI-targeted biopsies are used. In this study we investigate the upgrading with MRI and MRI-targeted biopsies in men with low-risk disease on AS, and examine the potential reduction of targeted biopsies by stratifying to PI-RADS and PSA-density. We explore the possible risk inflation by MRI and targeted biopsies, and look into the potential extension of GS thresholds for continuing in AS when using MRI in strict monitoring.

METHODS

The study was HIPAA compliant and was approved by the institutional ethical review board (NL45884.078.13/A301321). Written informed consent with guarantee of confidentiality was obtained from the participants. Men with low-risk PCa are prospectively enrolled in our in-house database as part of our AS protocol. From November 2013 until October 2017 a total of 347 consecutive men on AS for low-grade (GS 3+3) PCa detected by TRUS guided biopsy received a first multi-parametric MRI and targeted biopsies of visible suspicious MRI lesions at our tertiary referral center.

A total of 331 men were included in the current study. Men were excluded (16/347), as they did not undergo additional targeted biopsy, despite of having a positive MRI (n=8 PI-RADS 3 lesions, n=8 PI-RADS 4 lesions). Results of part of this prospective cohort have been previously published (10).

In 50% (166/331) men were participants of the PRIAS study (www.prias-project.org), an international web-based AS study with strict criteria for inclusion at diagnosis (GS 3+3, T-stage ≤cT2, PSA ≤10 ng/ml, ≤2 positive cores, PSA density <0.2) and follow-up (11). Within the MRI-PRIAS side study protocol an MRI and targeted biopsies (if indicated) are performed at baseline (3 months after diagnosis) and during every repeat standard TRUS-guided biopsies, scheduled at 1, 4, 7 and 10 years after diagnosis. Inclusion in the MRI-PRIAS side study is also possible after ≥1 repeat TRUS-guided biopsies. The only reclassification criterion in the MRI-PRIAS side study is the presence of high-grade PCa (GS ≥3+4) at MRI-targeted biopsy. A head-to-head comparison of MRI-targeted with standard TRUS-guided biopsies was only available in repeat biopsies, and was not further investigated in this study.

The remaining 165/331 (50%) men in the present study had low-grade PCa based on standard TRUS-guided biopsy findings, but were followed-up outside of the PRIAS protocol as they did not meet the strict PRIAS inclusion criteria or were referred from a center not participating in PRIAS. All men were included in our prospective, institutional review board approved database, which is HIPPA compliant.

Multi-parametric MRI

The institutional MRI protocol included T2-weighted imaging (T2w), diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) reconstructions, and dynamic contrast enhanced (DCE) imaging, as previously described (12), according to the Prostate Imaging Reporting and Data System (PI-RADS) version 2 guidelines (13). MRI was performed on a 3-T system (Discovery MR750, General Electric Healthcare, USA) using a

32-channel pelvic phased-array coil. All MRIs were reviewed by one urogenital radiologist (IGS) with over 5 years of prostate MRI experience. Individual lesions were scored according to the PI-RADSv2 5-point likelihood scale for high-grade PCa, and the index lesions were annotated and delineated (13). Visible MRI lesions with a PI-RADS score from 3 to 5 were defined as suspicious.

MRI-targeted biopsy

The MRI-TRUS fusion technique was used (UroStation™, Koelis, France) to perform the targeted biopsies of all suspicious lesions, identified on MRI. The suspicious MRI lesions, delineated on DICOM images, were targeted with 2 – 4 cores under ultrasound guidance. Experienced operators (FHD, DFO, JFV) performed the biopsy procedures.

Pathological review of biopsy specimens

One expert uropathologist (GJvL) reviewed all biopsy specimens according to the International Society of Urological Pathology (ISUP) 2014 modified Gleason Score (14). GS upgrading was defined as any GS ≥3+4 PCa found by MRI-targeted biopsies.

Study objectives

The primary objective of this study was to identify upgrading with MRI and MRI-targeted biopsies (benefit) in men on AS with GS 3+3. In line with this objective, the absence of upgrading (harm) despite of additional testing with MRI and targeted biopsies, was also assessed. The outcome measure is the presence/absence of upgrading to GS ≥3+4.

The secondary objective was to assess the value of risk-stratification based on MRI (PI-RADS) and PSA-density for the presence/absence of additional upgrading. Additional analysis was performed with the outcome measure of GS ≥4+3, focussing on risk inflation with MRI.

Statistical analysis

In accordance with the START recommendations, the outcome measure of clinically significant PCa for MRI and targeted biopsies is the biopsy result of GS 3+4 and higher (15). The PSA density was calculated using the MRI-measured prostate volume. The MRI-measured volume was calculated by the prolate ellipsoid formula (length x width x height x π/6). The PSA density cut-off point of 0.15 and 0.20 ng/mL^2 was used for stratification (16-19). Histograms of the stratified PI-RADS and GS biopsy outcomes were constructed to visualize in which men GS upgrading did or did not occur.

Statistical tests were two-sided with the criterion of significance set at $P<0.05$. Statistically significant differences in continuous non-parametric patient characteristics were

assessed with the Mann-Whitney U test, while the χ^2 test for trend was used to test for differences in categorical patient characteristics; in case of small numbers the Fischer's exact test was used. Statistical analyses were performed with SPSS for Windows (Version 21.0. Armonk, NY: IBM Corp.). In addition, R version 3.4.2 and R-package ggplot2 (20) were used for visualization. Gleason scores were dichotomized using cut-off score Gleason ≥3+4, and Gleason ≥4+3, in which a zero indicated a GS below the cut-off and a one indicated a GS above the cut-off score.

RESULTS

In 331 men on AS for GS 3+3 PCa, the median (interquartile range) age and PSA level at diagnosis were respectively 67 (range, 62–72) years and 8.0 (range 5.6–12.0) ng/mL (Table 1). A total of 66/331 (20%) men had more than two positive systematic biopsy cores at diagnosis. A total of 155/331 (47%) men received their first MRI at baseline, while 176/331 (53%) men received their first MRI at confirmatory biopsy or at surveillance biopsy. In these men no previous MRI was performed. Men included in PRIAS did not significantly differ from men not included in PRIAS, accept for a small PSA and PSA-density difference (Table 1), reflecting PRIAS inclusion criteria.

Benefit of additional testing with MRI and targeted biopsies

Upgrading in all men on AS

In total, 25% (82/331) of men on AS showed upgrading from GS 3+3, due to additional testing by MRI and if indicated targeted biopsies. The majority (71%) was upgraded to GS 3+4, only 16% (13/82) and 13% (11/82) to GS 4+3 and GS ≥4+4, respectively. Most of the upgraded index lesions (82%) were categorized into PI-RADS 4 and 5. Highest GS's were associated with PI-RADS 4 and 5.

Upgrading in men with a suspicious MRI index lesion

In 60% (198/331) a suspicious lesion was identified on MRI, and was additionally biopsied (Figure 1). 41% (82/198) of these suspicious lesions showed upgrading from GS 3+3 to GS 3+4 or higher. In PI-RADS 3, 4 and 5 index lesions, the upgrading was 30% (15/50), 36% (36/101) and 66% (31/47), respectively.

Upgrading in men with a PI-RADS 3 lesion

Of all suspicious index lesions on MRI, 25% (50/198) was categorised into PI-RADS 3 (Figure 1), meaning that the MRI abnormalities are equivocal to high- or low-grade PCa. An upgrade to GS 3+4 and GS 4+3 was proven in 22% (11/50) and 8% (4/50)

Men on Active Surveillance			Men included in PRIAS protocol			Men not included in PRIAS protocol			*P value* *
based on standard TRUS-guided biopsy findings (GS 3+3)									
Median (IQR) or n (%)			Median (IQR) or n (%)			Median (IQR) or n (%)			
Age (years)	67	62-72	Age (years)	67	62-72	Age (years)	67	62-72	0,574
Time since diagnosis (months)	11,5	4-33	Time since diagnosis (months)	12	4-37	Time since diagnosis (months)	11	3-29	0,124
PSA (ng/ml)	8,0	5,6-12	PSA (ng/ml)	7,6	5,3-10	PSA (ng/ml)	8,6	6-13,5	**0,001**
Prostate volume on MRI (ml)	46	32-65	Prostate volume on MRI (ml)	47	34-67	Prostate volume on MRI (ml)	44	31-64	0,272
PSA-density (ng/ml2)	0,17	0,11-0,28	PSA-density (ng/ml2)	0,14	0,09-0,26	PSA-density (ng/ml2)	0,20	0,11-0,31	**0,001**
No. of positive cores at diagnosis	1	1-2	No. of positive cores at diagnosis	1	1-2	No. of positive cores at diagnosis	2	1-2,5	0,112
No. of suspicous MRI lesions	1	0-1	No. of suspicous MRI lesions	1	0-1	No. of suspicous MRI lesions	1	0-1	0,591
DRE			DRE			DRE			
cT1	224	(68%)	cT1	128	(77%)	cT1	96	(58%)	0,142
cT2	62	(19%)	cT2	27	(16%)	cT2	35	(21%)	
cT3	5	(2%)	cT3	1	(1%)	cT3	4	(2%)	
n.a.	40	(11%)	n.a.	10	(6%)	n.a.	30	(19%)	
Total	331	(100%)	Total	166	(100%)	Total	165	(100%)	

Table 1. Patient characteristics.

* Mann-Whitney U, Chi-square, Fisher's Exact.

IQR: interquartile range; TRUS: transrectal ultrasound; PSA: prostate specific antigen; DRE: digital rectal examniation; MRI: magnetic resonance imaging; n.a.: not available.

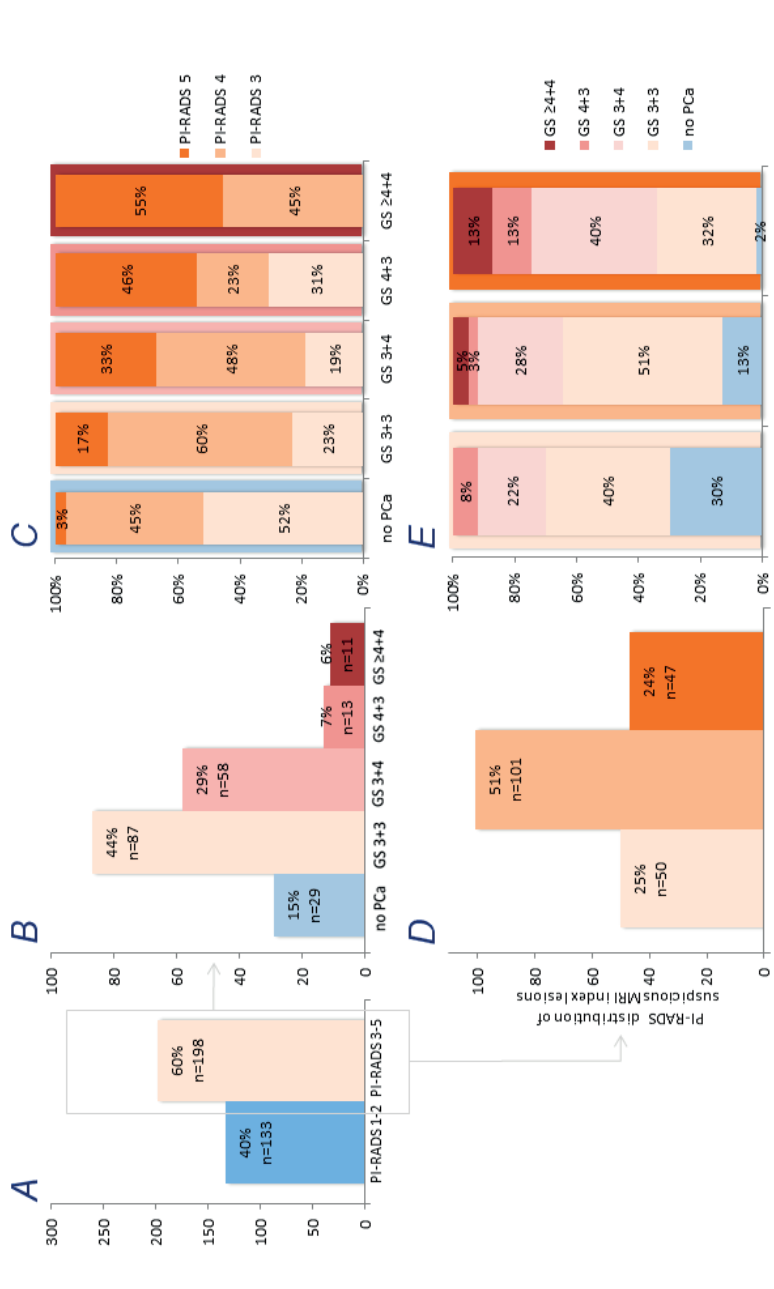

Figure 1. Suspicious prostate MRIs in men with initially low-risk disease on active surveillance, who underwent targeted biopsies. (A) positive (PI-RADS 3-5) and negative MRIs (PI-RADS 1-2); (B) positive MRIs, divided into Gleason score; (C) positive MRIs, divided into Gleason score in direct relation to PI-RADS score; (D) positive MRIs, divided into PI-RADS score; (E) positive MRIs, divided into PI-RADS score in direct relation to Gleason score.
MRI: magnetic resonance imaging; PI-RADS: MRI suspicion score; PCa: prostate cancer; GS: Gleason score.

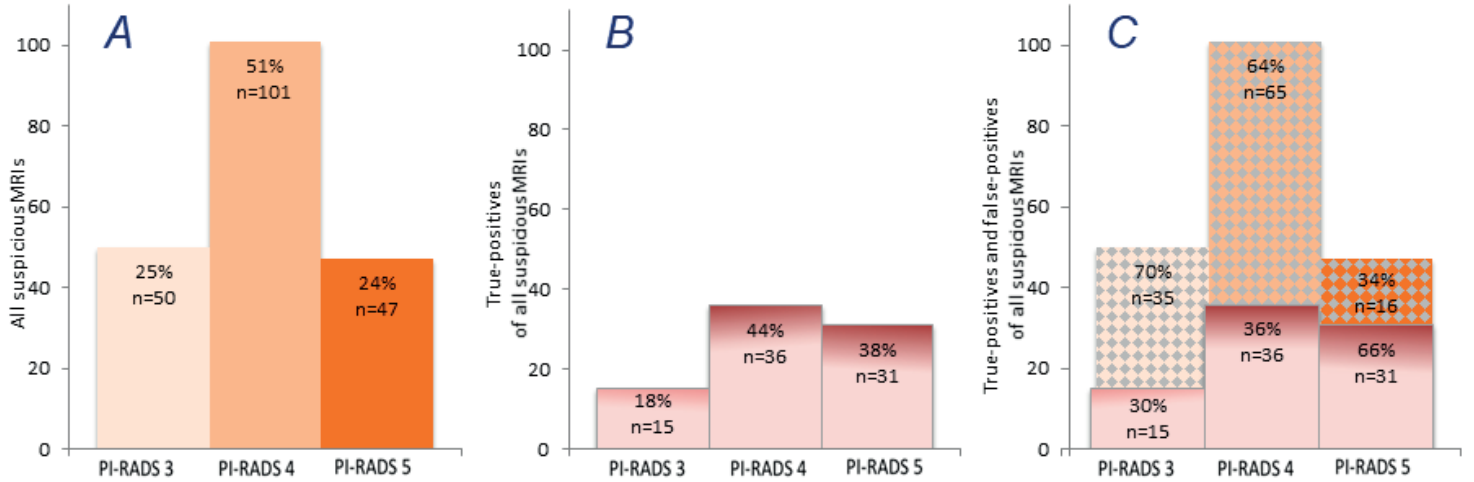

Figure 2. PI-RADS distribution of (A) all men in active surveillance with a suspicious initial MRI, (B) men upgraded following targeted biopsies (true-positives) using outcome measure Gleason score (GS) ≥3+4, and (C) men without upgrading (true-negatives) in comparison to men with upgrading (true-positives). The right graph (C) depicts the unnecessary targeted biopsies in PI-RADS assessment category 3, 4 and 5 (dotted areas).
MRI: magnetic resonance imaging; PI-RADS: MRI suspicion score.

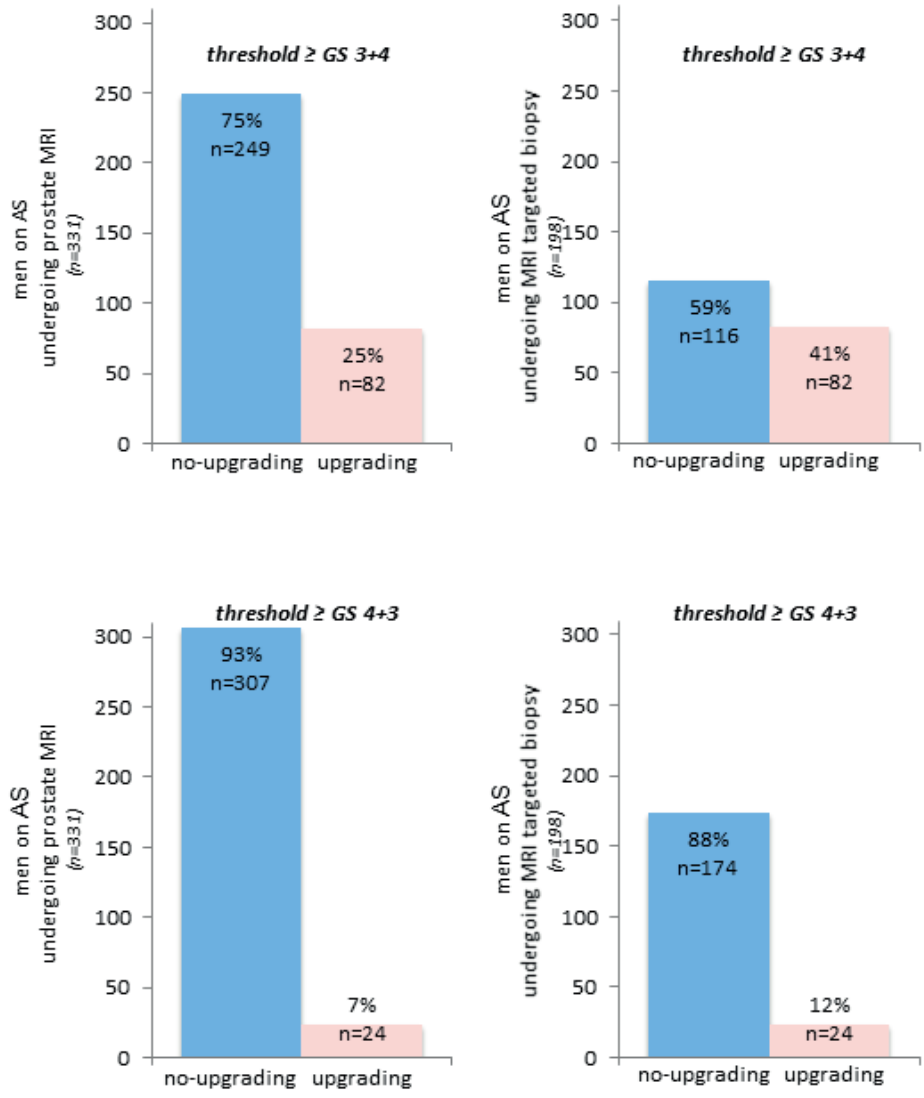

Figure 3. Unnecessary MRIs (blue in left graphs) (left) and unnecessary targeted biopsies (blue in right graphs) for Gleason cut-off score GS ≥3+4 (upper half) and GS ≥4+3 (lower half), for detecting clinically significant prostate cancer (red) in men with initially low-risk disease, based in traditional criteria.
AS: active surveillance; GS: Gleason score; MRI: magnetic resonance imaging; PI-RADS: MRI suspicion score.

respectively, showing the additional value of targeting these PI-RADS 3 lesions. None of these lesions however showed GS ≥4+4.

All suspicious MRI index lesions						*Stratified to Gleason score and PSA density*										*Threshold csPCa: GS ≥3+4*				*Threshold csPCa: GS ≥4+3*			
		PSA density				No PCa		GS 3+3		GS 3+4		GS 4+3		GS ≥4+4		PSA density				PSA density			
PI-RADS	Men	<0.15		≥0.15		<0.15	≥0.15	<0.15	≥0.15	<0.15	≥0.15	<0.15	≥0.15	<0.15	≥0.15	<0.15		≥0.15		<0.15		≥0.15	
3	50	18	*36%*	32	*64%*	12	3	6	14	0	11	0	4	0	0	0	*0%*	15	*100%*	0	*0%*	4	*100%*
4	101	43	*43%*	58	*57%*	6	7	28	24	8	20	0	3	1	4	9	*25%*	27	*75%*	1	*13%*	7	*88%*
5	47	13	*28%*	34	*72%*	0	1	6	9	5	14	1	5	1	5	7	*23%*	24	*77%*	2	*17%*	10	*83%*
	198	74	*37%*	124	*63%*	18	11	40	47	13	45	1	12	2	9	16	*20%*	66	*80%*	3	*13%*	21	*88%*

All suspicious MRI index lesions						*Stratified to Gleason score and PSA density*										*Threshold csPCa: GS ≥3+4*				*Threshold csPCa: GS ≥4+3*			
		PSA density				No PCa		GS 3+3		GS 3+4		GS 4+3		GS ≥4+4		PSA density				PSA density			
PI-RADS	Men	<0.20		≥0.20		<0.20	≥0.20	<0.20	≥0.20	<0.20	≥0.20	<0.20	≥0.20	<0.20	≥0.20	<0.20		≥0.20		<0.20		≥0.20	
3	50	22	*44%*	28	*56%*	12	3	8	12	2	9	0	4	0	0	2	*13%*	13	*87%*	0	*0%*	4	*100%*
4	101	54	*53%*	47	*47%*	8	5	33	19	11	17	1	2	1	4	13	*36%*	23	*64%*	2	*25%*	6	*75%*
5	47	19	*40%*	28	*60%*	0	1	9	6	8	11	1	5	1	5	10	*32%*	21	*68%*	2	*17%*	10	*83%*
	198	95	*48%*	103	*52%*	20	9	50	37	21	37	2	11	2	9	25	*30%*	57	*70%*	4	*17%*	20	*83%*

Figure 4. Number of positive MRIs with Gleason score outcome of MRI-targeted biopsies, stratified to PI-RADS and PSA-density.
Blue: beneficial outcome of the test results, stratified to PI-RADS and PSA-density; light red: low detection of clinically significant prostate cancer, stratified to PI-RADS and PSA-density; red: high detection of clinically significant prostate cancer, stratified to PI-RADS and PSA-density.
MRI: magnetic resonance imaging; PSA: prostate specific antigen; GS: Gleason score; csPCa: clinically significant prostate cancer; PI-RADS: MRI suspicion score.

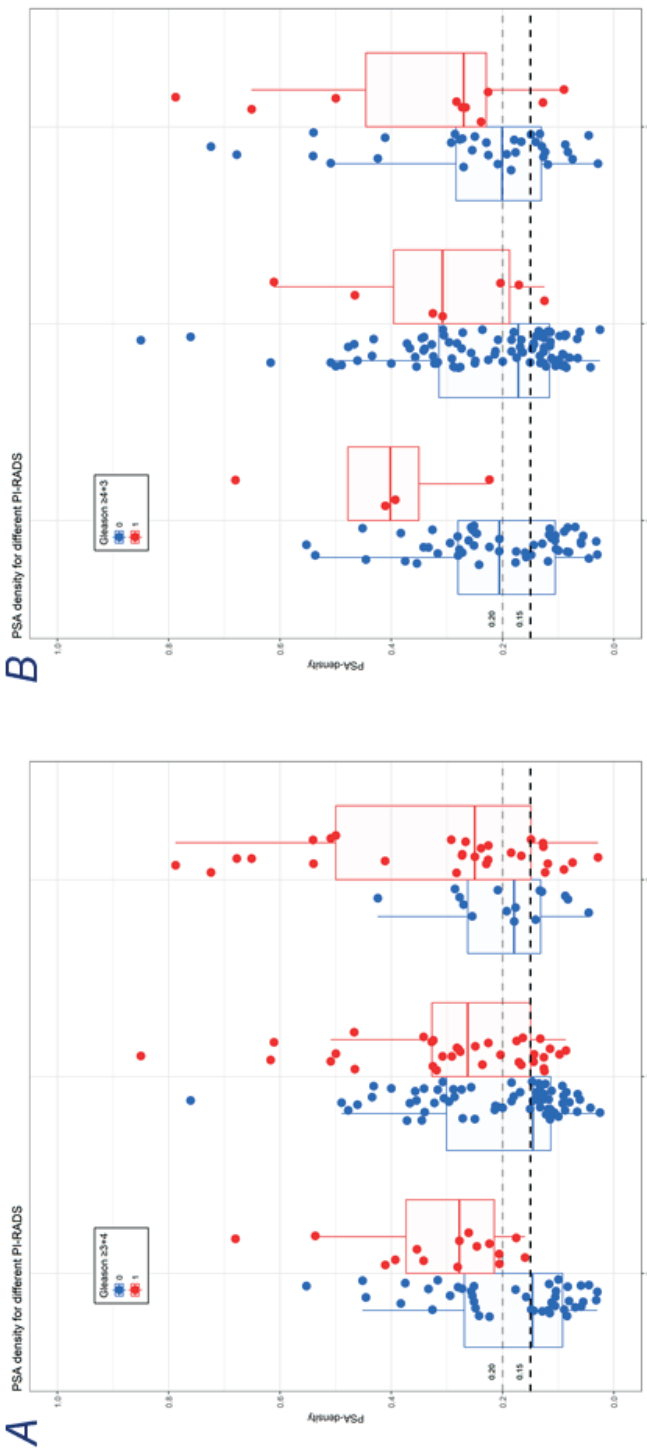

Figure 5. Dot-plots (and integrated box-plots) of men included in active surveillance. The PI-RADS assessment category 3, 4, and 5 (x-axis) are plotted against the PSA-density (y-axis). The outcome measure is Gleason score (GS), which is dichotomized using cut-off score GS ≥3+4 (A), and GS ≥4+3 (B) for clinically significant prostate cancer. Zero [0] indicated a Gleason score below the cut-off (blue dots and boxplots), and a one [1] indicated a Gleason score above the cut-off score (red dots and boxplots).
PI-RADS: MRI suspicion score; PSA: prostate specific antigen.

Harms of additional testing with MRI and targeted biopsies

Abundantly or unnecessary MRI and targeted biopsies

In 40% (133/331) of men, no suspicious lesions on MRI were identified. In these men MRI testing did not result in MRI-targeted biopsies, and no further harm was attributed.

In 59% (116/198) of men with a suspicious MRI, additional MRI-targeted biopsies did not result in upgrading: GS 3+3 PCa was confirmed in 44% (87/198), and no PCa was detected in 15% (29/198). These biopsies can be considered as harm and this was most prominent in the PI-RADS 3 category (70% GS 3+3 or no PCa) (Figure 2). Similar analysis for PI-RADS 4 and PI-RADS 5 category resulted in 64% and 34% unnecessary targeted biopsies.

Abundantly or unnecessary MRI and targeted biopsies adjusted to risk inflation

When looking at the detection of GS ≥4+3 PCa additional testing did not result in upgrading in respectively 93% (307/331) of all MRIs, and in 88% (174/198) of all MRI-targeted biopsies (Figure 3).

Potential strategies to reduce further harm

Excluding PI-RADS 3 lesions from targeted biopsies

Excluding PI-RADS 3 index lesions from targeted biopsies would result in a reduction of 25% (50/198) targeted biopsies, however, still missing 18% (15/82) of all upgrades to GS ≥3+4. Missed upgrading to GS ≥4+3 would be 5% (4/82).

Stratifying to PSA-density before targeting suspicious MRI lesions

Figures 4 and 5 show the number of men with targeted biopsies, stratifying to PIRADS and to PSA-density.

PSA-density cut-off ≥0.15 ng/mL^2

Upgrades to GS ≥3+4 in PI-RADS 3 lesions were all identified in men with a PSA-density of ≥0.15 ng/mL^2. Hence, when first stratifying according to a PSA-density cut-off ≥0.15 ng/mL^2 in men with a PI-RADS 3 lesion, would result in a MRI-targeted biopsy reduction of 36% (18/50) in this category, without missing any upgrade to GS 3+4 or higher. These results are plotted in figure 5 to visualize the amount of additional MRI testing with targeted biopsies, in men with initially low-risk disease on AS. The PSA-density thresholds of 0.15 and 0.20 ng/mL^2 are depicted as dotted lines.

Even for PI-RADS 4 lesions, risk stratification by PSA-density could be beneficial if adjustment to potential risk inflation is performed: only 1% (1/82) of all upgrades would have been missed, reducing 43% (43/101) of targeted biopsies in this category.

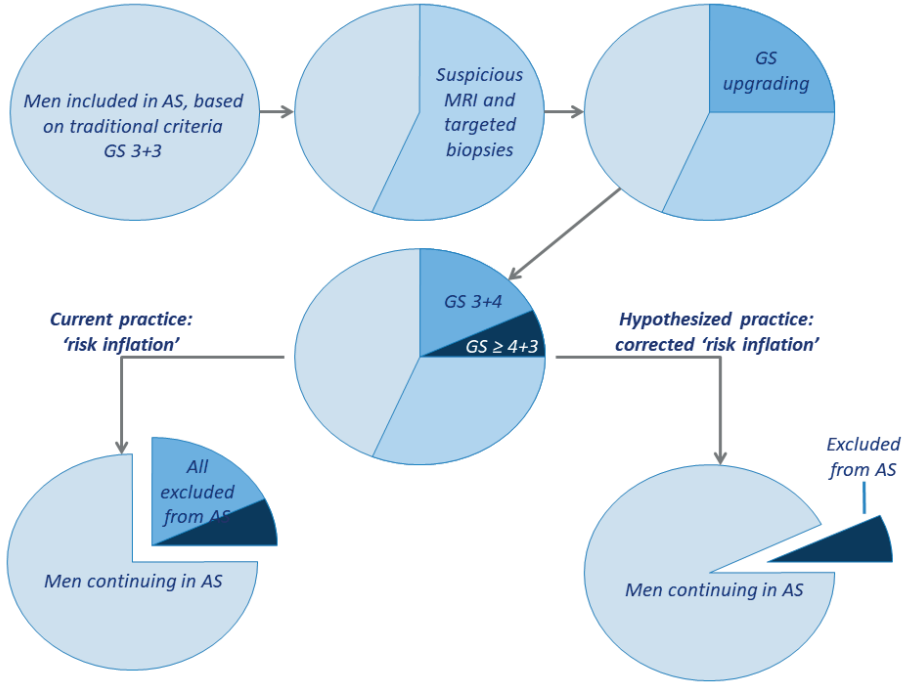

Figure 6. Active surveillance and initial MRI. Men included in active surveillance (circle 1), based on traditional criteria (PSA, clinical T-stage and Gleason score by systematic ultrasound-guided biopsies) have excellent prognosis as shown by long-term follow-up of several clinical trial (6,30,35). Nowadays, men undergo additional MRI, as suggested by recent reviews (8,36). These MRIs show in more than half at least one suspicious lesion. Subsequently, these lesions are biopsied by MRI-targeted approach (circle 2). A significant proportion shows upgrading (circle 3), of which the majority is Gleason score (GS) 3+4 (circle 4). In current clinical practice all upgraded men are advocated to cease active surveillance and change into active treatment, despite good prognosis (circle 5). This suggests 'risk inflation'. In the hypothesized clinical practice, only men with upgrading to primary Gleason 4 pattern and higher are excluded from active surveillance (circle 6), correcting the present initiated 'risk inflation' by MRI.
AS: active surveillance; GS: Gleason score; MRI: magnetic resonance imaging.

PSA-density cut-off ≥0.20 ng/mL²

Stratifying according to the PSA-density cut-off ≥0.20 ng/mL² would result in a targeted biopsy reduction of 44% (22/50) of all PI-RADS 3 index lesions, at the cost of missing 2% (2/82) upgrades; these 2 index lesions were classified as GS 3+4. When changing outcome to GS ≥4+3, the reduction of 44% in targeted biopsies of PI-RADS 3 lesions, coincides with not missing any upgrades to GS 4+3 or higher (Figures 4 and 5).

DISCUSSION

In our data on men on AS, additional testing with MRI and targeted biopsies could be regarded as beneficial in 25% of men: additional testing resulted in an upgrade to GS ≥3+4 as compared to the GS 3+3 PCa based on systematic TRUS-guided biopsy findings. Our results matches well with upgrading data of other studies on AS, varying from 16% to 29% (21-27). This rate of upgrading was even higher (41%) as we consider only those men who had a positive MRI, defined as PI-RADS 3 to 5. However, the relevance of identifying and acting on this upgrading cannot be adequately interpreted without the presence of long-term data on cancer-specific survival. In fact, a similar cohort of men with low-risk disease, without additional testing by MRI and targeted biopsies, has a 15-year cancer-specific survival of 94,3% (6).

Autopsy data show that many men with intermediate-risk disease (Gleason 7) are never diagnosed and therefore have clinically 'insignificant' cancer (28, 29). The Prostate Testing for Cancer and Treatment (ProtecT) trial, which compared in a randomized controlled manner three modalities of management (active monitoring, radical prostatectomy, and external beam radiotherapy) on patients with localized PCa (30), demonstrated no significant difference in the 10-year cancer-specific survival or overall survival.

	Threshold csPCa: GS ≥3+4		Threshold csPCa: GS ≥4+3	
MRI index lesions	**no targeted biopsy**	**targeted biopsy**	**no targeted biopsy**	**targeted biopsy**
Stratification into PSAD <0.15 and ≥0.15				
PI-RADS 3	P3 and PSAD <0.15	P3 and PSAD ≥0.15	P3 and PSAD <0.15	P3 and PSAD ≥0.15
PI-RADS 4		P4 and any PSAD	P4 and PSAD <0.15	P4 and PSAD ≥0.15
PI-RADS 5		P5 and any PSAD		P5 and any PSAD
Stratification into PSAD <0.20 and ≥0.20				
PI-RADS 3	P3 and PSAD <0.20	P3 and PSAD ≥0.20	P3 and PSAD <0.20	P3 and PSAD ≥0.20
PI-RADS 4		P4 and any PSAD		P4 and any PSAD
PI-RADS 5		P5 and any PSAD		P5 and any PSAD

Table 2. Summarised strategies to reduce targeting biopsies in low-risk men in active surveillance based on current data.
CsPCa: clinically significant prostate cancer; GS: Gleason score; PSAD: prostate specific antigen-density; PI-RADS: MRI suspicion score.

In the ProtecT trial there was a difference in metastasis rate, however, favouring radical treatment at 10 years follow-up. This difference in metastasis rate is considered to result from the 25% of men who had intermediate- or high-risk disease, for whom active

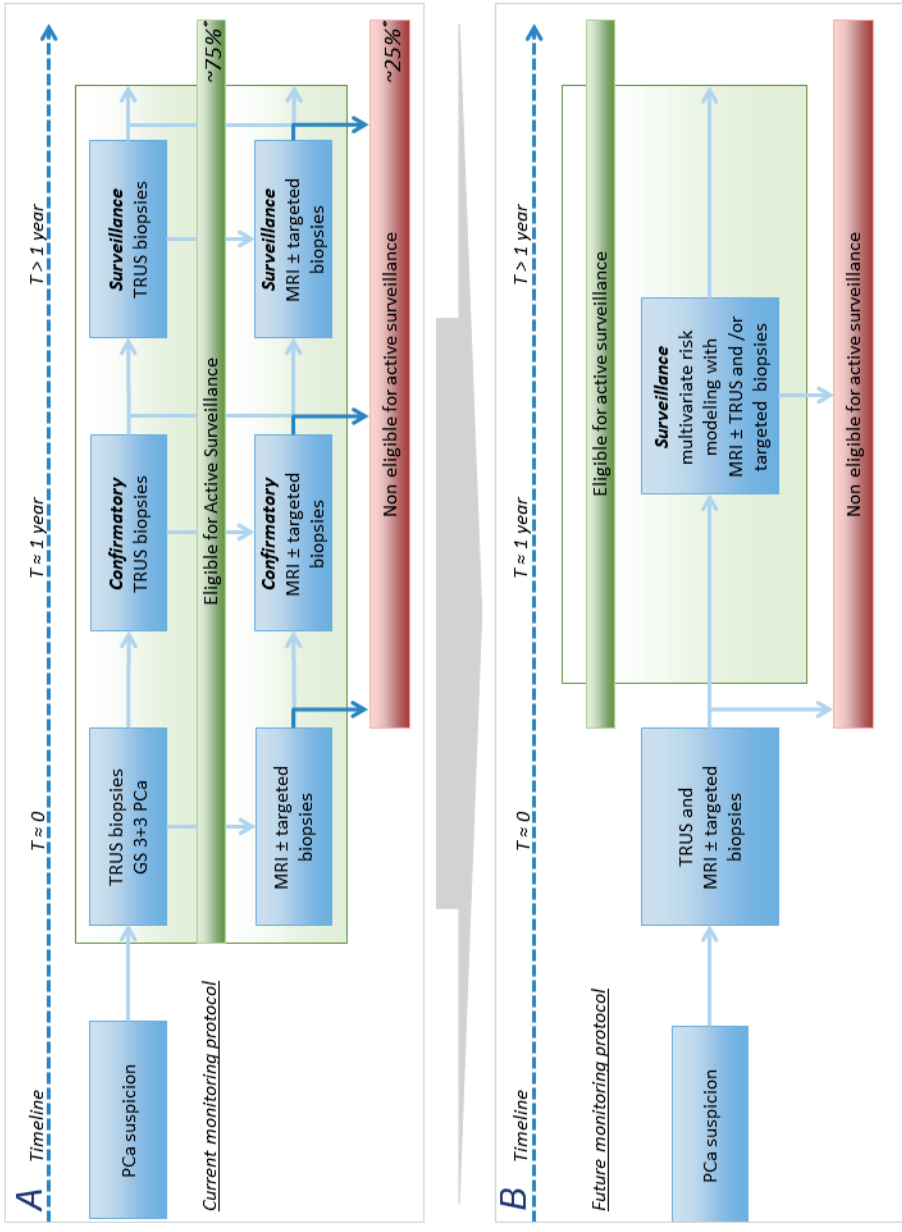
A
Timeline
T ≈ 0
T ≈ 1 year
T > 1 year
PCa suspicion
TRUS biopsies
GS 3+3 PCa
Confirmatory
TRUS biopsies
Surveillance
TRUS biopsies
MRI ± targeted
biopsies
Confirmatory
MRI ± targeted
biopsies
Surveillance
MRI ± targeted
biopsies
Eligible for Active Surveillance
~75%
Non eligible for active surveillance
~25%
Current monitoring protocol
B
Timeline
T ≈ 0
T ≈ 1 year
T > 1 year
PCa suspicion
TRUS and
MRI ± targeted
biopsies
Eligible for active surveillance
Surveillance
multivariate risk
modeling with
MRI ± TRUS and /or
targeted biopsies
Non eligible for active surveillance
Future monitoring protocol

Figure 7. Current and future surveillance protocol. (A) Current surveillance protocol of men with low-risk prostate cancer. Within the MRI-PRIAS side study protocol an MRI and targeted biopsies (if indicated) are performed at baseline (3 months after diagnosis) and during every repeat standard TRUS-guided biopsies, scheduled at many time points after diagnosis. This study identified a 25% upgrading to Gleason 7 and higher, based on MRI and targeted biopsies. (B) Incorporating prostate MRI at primary prostate cancer diagnosis will result in better discrimination between true low-risk disease and intermediate-/high-risk disease. If TRUS-guided biopsies combined with MRI and targeted biopsies are able to minimize misclassification of prostate cancer, we may abandon the currently used confirmation biopsy testing at 1 year in active surveillance management. We may hypothesize that surveillance management of men with low-risk prostate cancer will incorporate results from MRI and targeted biopsies into multivariate risk models in nearby future.
*, indicative % as a result from this study.
PCa: prostate cancer; GS: Gleason score; TRUS: transrectal ultrasound; MRI: magnetic resonance imaging.

monitoring is clearly associated with an increased risk of progression. Nonetheless, the lack of a mortality difference emphasizes that the majority of Gleason 7 patients are not at risk in the 10-year time frame.

In the Sunnybrook surveillance cohort the 15-year metastasis rate was at least 20% in Gleason 7 cancer at initial diagnosis (31). In a recent study, however, no increase in metastasis rate or progression of intermediate risk patients on surveillance was reported compared to low risk, with up to 10 year follow-up (32). This suggests that many intermediate risk patients may still be candidates for AS (33).

The experiences described were from the pre-MRI era: men with Gleason 7 PCa at standard systematic biopsy sampling might have consisted partially of men with higher Gleason grades. Today, such patients will have the benefit of an MRI and targeted biopsies, with a high likelihood of a more accurate biopsy and hence better representative histopathology results (34). This may result in an unintended tightening of inclusion for AS, as schematically depicted (Figure 6) (35, 36).

We detected 25% upgrading to Gleason 7 and higher, however, only 3% was Gleason 8 and higher, identical to other published reports (26, 37). It is likely that only these men with Gleason 8 and higher disease significantly influenced cancer-specific survival in men classified as having low-risk disease, in which the overall prognosis showed to be excellent in the pre-MRI era (6). We may argue that low-risk patients upgraded with targeted biopsies to intermediate-risk disease should not be excluded from AS based on the Gleason criterion alone. The higher precision of MRI and targeted biopsies may create the opportunity to specify new risk thresholds that potentially could open AS to a larger group of patients. Treatment decisions should be based on multiple parameters next to patient age and co-morbidity, including percentage of Gleason 4, growth patterns (e.g. cribriform), PSA-density, and MRI findings.

Therefore, the major challenge is accurate patient selection for AS, without the burden of intensively additional testing. The additional testing by MRI and targeted biopsies, recommended in recent reviews on MRI in AS (8, 36), comes with an extra invasive procedure, increasing the burden for patients staying in AS.

In this study, MRIs were abundantly or unnecessary performed in 75% of men in AS. Furthermore, unnecessary targeted biopsies were performed in 59% in men with a suspicious MRI (Figure 3), most prominent in PI-RADS 3 and 4 assessment category (Figure 2). Unnecessary testing would even be 93% for MRI and 88% for targeted biopsies, if we accept GS 3+4 as less significant disease. This critical evaluation of additional invasive

testing is not to devaluate MRI, instead, this evaluation supports exploring refinements in the role of MRI at primary diagnosis and in AS, as proposed in figure 6.

The PI-RADS steering committee recommended to biopsy lesions with PI-RADS category 4 and 5, and not lesions with PI-RADS category 1 and 2 (13). For findings with PI-RADS category 3, biopsy may or may not be appropriate, depending on factors other than MRI alone. In our study we biopsied all PI-RADS category 3 lesions, and detected high volume Gleason 4 pattern in 8% PI-RADS 3 lesions (all GS 4+3, no GS ≥4+4). We may argue that in some circumstances this might be acceptable, reducing the additional harms of additional biopsies. However, further stratification by PI-RADS to biopsy only PI-RADS category 4 and 5 would result in missing high volume Gleason 4 pattern, as also confirmed by other studies (23, 38).

We therefore additionally investigated the combination of PSA-density and MRI to further tailor the patient risk stratification in reducing unnecessary biopsies and improving the balance between the benefit and harms of additional testing. Using the PSA-density cut-off ≥0.15 ng/mL^2 in men with a PI-RADS 3 lesion would result in a targeted biopsy reduction of 36% in this category, without missing any upgrade to GS 3+4 or higher (Figures 4 and 5). Even for PI-RADS 4 lesions, tailored risk stratification by PSA-density could be beneficial if adjustment to risk inflation is performed (Figures 4 and 5, Table 2).

Others have confirmed this correlation, however, data in men on AS is limited (37, 39-41). In a multivariate cox-regression analysis, the PSA-density was shown to be a positive predictor to detect upgrading in men on AS, with a hazard ratio of 1.72 (40). In a receiver operating characteristic (ROC) analysis by Lai et al. the optimal PSA-density cut-off point was 0.18 ng/mL^2 with an AUC of 0.77 (39). The optimal cut-off in men on AS should be further determined in larger cohorts. In a cohort of men with initially diagnosed low-risk disease by MRI/US fusion biopsy and monitoring with serial fusion biopsies, still PSA-density was an important predictor of subsequent upgrading (41). Our study clearly suggests that men on AS with a PI-RADS 3 index lesion and a PSA-density of <0.15 ng/mL^2 may not benefit from a follow-up biopsy.

Incorporating prostate MRI at primary PCa diagnosis will result in better discrimination between true low-risk disease and intermediate-/high-risk disease. If TRUS-guided biopsies combined with MRI and targeted biopsies are able to minimize misclassification of PCa, we may abandon the currently used confirmation biopsy testing at 1 year in AS management, as depicted in figure 7. MRI and targeted biopsies are increasingly used in the surveillance management of patients with clinically low-risk PCa; however, their role has not yet been established definitively (7). We may hypothesize that surveillance

management of men with low-risk PCa will incorporate results from MRI and targeted biopsies into multivariate risk models in nearby future (Figure 7B) (42).

Our study comes with some limitations. First, our study is a retrospective design. Retrospective studies are known for their risk of selection bias. However, our study represents a prospectively monitored cohort of consecutive men on AS, with strict monitoring (within or without the PRIAS protocol). Second, we did not perform co-reading of MRIs, which likely would have increased detection sensitivity. However, even without co-reading the MRI detection rate in our cohort is comparable to those reported in recent publications on MRI in AS (21-27). Third, clinicians involved were not blinded to clinical data and MRI results. Hence, this process is daily clinical practice and therefore can be extrapolated to other hospitals. Fourth, the presence of standard systematic biopsy results in this study next to MRI-targeted biopsies would have shown the imperfection of MRI in detection all clinically significant PCa. Studies evaluating this added value are reporting up to 11% additionally found clinically significant PCa (8). As part of the monitoring protocol, the majority of men received their initial MRI without additional systematic biopsies. However, this group of men will decrease as a result of the increased introduction of MRI and targeted biopsies at the primary diagnostic work-up.

We acknowledge that the outcome measurement of our analysis was upgrading, based on MRI-revealed Gleason grading as recommended by the START consortium (15). Instead, the cancer-specific survival rate in long-term follow-up would have been more appropriate, especially in disputing the relevance of this high upgrading rate due to MRI targeted biopsies. However, this outcome may be debatable in a cohort of men with mostly low-risk disease that exhibits excellent long-term cancer-specific survival (6), and furthermore experiences most shifts from AS to active treatment during the first 2 years of follow-up (43).

CONCLUSIONS

In this study on AS, we detected by MRI-targeted biopsies an upgrading to Gleason 7 and higher in 25%, however, only 3% was Gleason 8 and higher. This rate of upgrading was even higher (41%) as we consider only those men who had a suspicious finding on prostate MRI, defined as PI-RADS 3 to 5. Further stratification to PI-RADS 4-5 would have missed a small number of primary Gleason 4 PCa in the PI-RADS 3 category. Stratification with the combination of PI-RADS and PSA-density may reduce unnecessary additional

MRI biopsy testing. We showed that men on AS with a PI-RADS 3 index lesion and a PSA-density of <0.15 ng/mL^2 will not benefit from a follow-up targeted biopsy.

The high rate of detected upgrading may result in an unintended tightening of continuing in AS. Since patients, included under current surveillance criteria showed extremely favorable outcome, there might be no need to further restrict continuing on AS with MRI and targeted biopsies. The higher precision of MRI and targeted biopsies may create the opportunity to specify new risk thresholds that potentially could open AS to a larger group of patients.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

8

Prostate cancer upgrading with serial prostate magnetic resonance imaging and repeat biopsy in men on active surveillance: are confirmatory biopsies still necessary?

Daniël F. Osses
Frank-Jan H. Drost
Jan F.M. Verbeek
Henk B. Luiting
Geert J.L.H. van Leenders
Chris H. Bangma
Gabriel P. Krestin
Monique J. Roobol
Ivo G. Schoots

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ABSTRACT

Objectives

To investigate whether serial prostate magnetic resonance imaging (MRI) may guide the utility of repeat targeted (TBx) and systematic biopsy (SBx) when monitoring men with low-risk prostate cancer (PCa) at 1-year of active surveillance (AS).

Patients and Methods

We retrospectively included 111 consecutive men with low-risk (International Society of Urological Pathology [ISUP] Grade 1) PCa, who received protocolled repeat MRI with or without TBx and repeat SBx at 1-year of AS. TBx was performed in Prostate Imaging-Reporting and Data System (PI-RADS) score ≥3 lesions (MRI-positive men). Upgrading defined as ISUP Grade ≥2 PCa (I), Grade ≥2 with cribriform growth/intraductal carcinoma PCa (II), and Grade ≥3 PCa (III) was investigated. Upgrading detected by TBx only (not by SBx) and SBx only (not by TBx) was investigated in MRI-positive and -negative men, and related to radiological progression on MRI (Prostate Cancer Radiological Estimation of Change in Sequential Evaluation [PRECISE] score).

Results

Overall upgrading (I) was 32% (35/111). Upgrading in MRI-positive and -negative men was 48% (30/63) and 10% (5/48) (*P <0.001*), respectively. In MRI-positive men, there was upgrading in 23% (seven of 30) by TBx only and in 33% (10/30) by SBx only. Radiological progression (PRECISE score 4-5) in MRI-positive men was seen in 27% (17/63). Upgrading (I) occurred in 41% (seven of 17) of these MRI-positive men, while this was 50% (23/46) in MRI-positive men without radiological progression (PRECISE score 1-3) (*P =0.534*). Overall upgrading (II) was 15% (17/111). Upgrading in MRI-positive and -negative men was 22% (14/63) and 6% (three of 48) (*P =0.021*), respectively. In MRI-positive men, there was upgrading in three of 14 by TBx only and in seven of 14 by SBx only. Overall upgrading (III) occurred in 5% (five of 111). Upgrading in MRI-positive and -negative men was 6% (four of 63) and 2% (one of 48) (*P =0.283*), respectively. In MRI-positive men, there was upgrading in one of four by TBx only and in two of four by SBx only.

Conclusion

Upgrading is significantly lower in MRI-negative compared to MRI-positive men with low-risk PCa at 1-year of AS. In serial MRI-negative men, the added value of repeat SBx at 1-year surveillance is limited and should be balanced individually against the harms. In serial MRI-positive men, the added value of repeat SBx is substantial. Based on this

cohort, SBx is recommended to be performed in combination with TBx in all MRI-positive men at 1-year of AS, also when there is no radiological progression.

Keywords

Low-risk prostate cancer; active surveillance; prostate MRI; PI-RADS; PRECISE; upgrading.

INTRODUCTION

Active surveillance (AS) is a widely used strategy for managing men with low-risk prostate cancer (PCa) to reduce overtreatment and treatment-related side-effects, with confirmed oncological safety at long-term follow-up (1). The fear of under grading at time of diagnostic biopsy has led to the development of AS protocols with strict criteria for inclusion and monitoring, like the Prostate cancer Research International Active Surveillance (PRIAS) study (www.prias-project.org) (2).

Today, magnetic resonance imaging (MRI) and targeted biopsy (TBx) are increasingly used in the evaluation of patients with low-risk PCa who initially opt for AS, based on systematic transrectal ultrasound-guided prostate biopsy (SBx) findings (3). The additional use of a first pre-biopsy MRI and subsequent TBx in these men can aid in the exclusion of higher risk men with International Society of Urological Pathology (ISUP) Grade (G) 2 and higher PCa, irrespective of the timing of the MRI during follow-up (i.e. at baseline, confirmatory or surveillance biopsy) (4-9). A first pre-biopsy MRI in the evaluation of men on AS for low-risk PCa has therefore recently been adopted in the European Association of Urology (EAU) PCa guidelines (10).

An MRI-based monitoring strategy in men with low-risk PCa on AS is attractive to health systems and patients, potentially avoiding a prostate biopsy procedure with its attendant morbidities as much as reasonably possible. The Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) criteria could help to qualify radiological risk of progression on serial prostate MRI (11, 12). However, the role of MRI in monitoring and its potential to guide the indication for repeat biopsies (i.e. confirmatory and surveillance biopsies) during AS is still unclear. Unanswered issues in clinical practice are whether SBx could be omitted in cases of a negative follow-up MRI, whether only TBx should be performed in cases of a positive follow-up MRI, and whether biopsies should only be performed in cases of radiological disease progression on follow-up MRI. Recent studies provide contradictory findings in men on AS for low-risk PCa as to whether or not serial MRI could obviate the need for repeat biopsies (13-24). Hamoen et al. showed an overall added value for repeat (confirmatory) SBx at 1-year of AS of 42% as compared to 7% added value for serial MRI with or without TBx (MRI ± TBx) (18). However, Thurtle et al. and Elkjaer et al. found much more added value for serial MRI ± TBx (30%-50%), and less added value for repeat SBx (9%-12%) in their cohorts (19, 20). Substantial evidence on implementing prostate MRI as a monitoring tool in men on AS for low-risk PCa is still lacking.

As virtually all AS protocols advise a repeat biopsy procedure after 1 year on AS, we aimed to determine the potential guidance of serial prostate MRI (i.e. positive or negative MRI, with or without radiological progression) in the utility of repeat TBx and SBx in men with low-risk PCa at 1-year of AS, using different definitions for clinically significant PCa (csPCa) as outcome measures.

PATIENTS AND METHODS

Study population

This retrospective study was approved by our Institutional Review Board (IRB; NL45884.078.13/A301321), and written informed consent with guarantee of confidentiality was obtained from all study participants. No additional data other than already collected as part of this IRB-approved study was sought for the analyses done in this study. Men with low-risk PCa (ISUP Grade 1) were prospectively enrolled in our in-house clinical database as part of our AS protocol. All men were followed according to the MRI-PRIAS study protocol (www.prias-project.org). In summary, they underwent an MRI ± TBx at baseline (3 months after the detection of low-risk PCa on diagnostic SBx), and during every repeat SBx scheduled at 1 year (confirmatory biopsy), and 4, 7 and 10 years (surveillance biopsy) after diagnosis (Figure 1). The only upgrading or re-classification criterion was the presence of ISUP Grade 2 (Gleason score [GS] 3+4) and higher PCa at biopsy.

From November 2013 to May 2019, 517 consecutive men on AS for ISUP Grade 1 PCa underwent at least one prostate MRI during follow-up. At time of analysis, 252 men had undergone an MRI ± TBx at baseline. Results of part of this cohort have been previously published (8, 9). In all, 70/252 (28%) men had upgrading after first MRI-TBx and therefore ceased AS, and 71/252 (28%) men had not yet undergone a second MRI ± TBx at time of analysis. In the present study, we included 111 men on AS for low-risk PCa who had undergone both an MRI ± TBx at baseline and at the time of the scheduled confirmatory SBx 1 year after initiation of AS (Figure 1).

Multiparametric MRI

Multiparametric MRI (mpMRI) at both time points was performed on a 3.0-Tesla MR scanner (Discovery MR750; General Electric Healthcare, Chicago, IL, USA) with a 32-channel pelvic phased-array coil. The institutional MRI protocol included T2-weighted imaging (T2w), diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) reconstructions, and dynamic contrast enhanced (DCE) imaging, according to the Prostate Imaging-Reporting and Data System (PI-RADS) version 1 and 2 guidelines (25). All MRIs

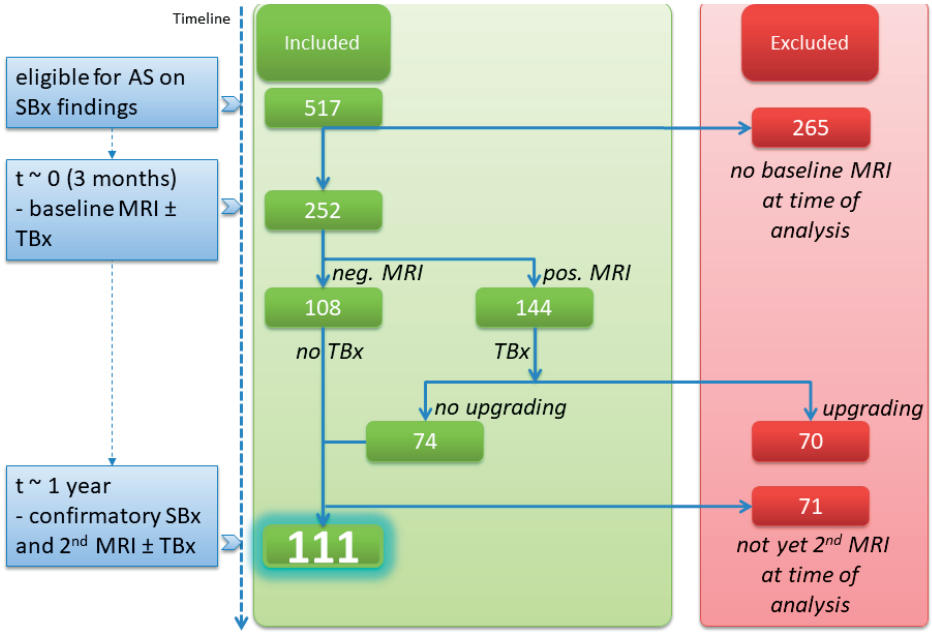

Figure 1. Flowchart of patients included in this study.
AS: active surveillance; SBx: systematic biopsy; MRI: magnetic resonance imaging; TBx: targeted biopsy.

were reviewed by one urogenital radiologist with >7 years' experience of prostate MRI. Individual lesions were scored according to the PI-RADS 5-point likelihood scale for csPCa, and the index lesions were annotated and delineated (25). Visible MRI lesions with a PI-RADS score of 3-5 were defined as suspicious.

Serial MRI scans were all compared to the initial imaging by the reporting radiologist according to the PRECISE criteria (11, 12). The PRECISE recommendations use a 5-point likelihood scale to qualify radiological progression on MRI in men on AS with serial prostate MRIs. PRECISE score 1-2 corresponds to resolution/regression of previous features suspicious on MRI (based on a decreased radiological size/stage/conspicuity/PI-RADS score), PRECISE score 3 corresponds to radiological stable disease, and PRECISE score 4-5 to disease progression on MRI (based on an increased radiological size/stage/conspicuity/PI-RADS score). In clinical practice, a positive serial MRI without radiological progression is defined as PRECISE score 1-3.

MRI-targeted biopsy and systematic biopsy

Biopsies were performed in a separate session. All men with a positive (serial) MRI underwent TBx. An MRI-ultrasound fusion system (UroStation™, Koelis, France) was

used to take TBx of all suspicious lesions identified on MRI. The suspicious MRI lesions, delineated on Digital Imaging and Communications in Medicine (DICOM) images, were targeted with 2-5 cores/lesion. An additional SBx (8-12 cores, depending on the prostate volume) was taken in all men at the time of confirmatory biopsy and was not blinded from MRI results. The biopsy procedures were performed by four experienced operators.

Pathological review of biopsy specimens

One expert uropathologist reviewed all biopsy specimens according to the ISUP 2014 modified Gleason score/Grade Group system (26). The presence of an invasive cribriform growth pattern (CR) and/or intraductal carcinoma (IDC) was routinely recorded. Upgrading, and thereby the recommendation to switch to active treatment, was defined in clinical practice as any ISUP Grade ≥2 PCa found by MRI ± TBx and/or SBx.

Study endpoints

We compared the percentage of upgrading of ISUP Grade 1 PCa to csPCa between the results of MRI ± TBx and SBx in MRI-positive and -negative men on AS at the time of confirmatory biopsy (1-year surveillance). In addition, we assessed the percentage of upgrading related to the PRECISE score (i.e. regressive, stable and progressive features on prostate MRI). The percentage of upgrading was calculated using three different definitions of csPCa: (definition I) ISUP Grade 2 and higher PCa, (definition II) ISUP Grade 2 with CR and/or IDC and higher PCa, and (definition III) ISUP Grade 3 and higher PCa.

Primary outcomes are:

1) upgrading (definition I) in MRI-positive and -negative men.
2) upgrading (definition I) related to the radiological changes between first and second MRI (PRECISE score), in MRI-positive and -negative men.

Secondary outcome is:

1) upgrading based on higher thresholds (definition II and III) for csPCa.

Statistical analysis

Descriptive statistics were used to report the clinical patient characteristics and percentages of upgrading. Statistically significant differences in continuous non-parametric data were assessed with the Mann-Whitney U test and Wilcoxon signed rank test. The Chi-square test for trend, McNemar test and Wilcoxon signed rank test were used to test for differences in categorical data. In accordance with the Standards of reporting for MRI-targeted biopsy studies (START) recommendations, cross-tabulation of the confirmatory biopsy outcomes was performed to compare the percentage of upgrading

detected by MRI ± TBx vs SBx (27). Analyses were performed using Statistical Package for the Social Sciences (version 24.0; IBM, Armonk, NY, USA), with a two-tailed level of significance set at P <0.05.

RESULTS

Patients' characteristics

The clinical patients' characteristics with subsequent low-risk PCa profiles did not show significant differences (except for age) at baseline and at confirmatory biopsy at 1-year of AS (Table 1).

Upgrading (definition I) at 1-year surveillance, in MRI-positive and -negative men

At 1-year surveillance, 57% (63/111) of men had a positive follow-up MRI and 43% (48/111) had a negative follow-up MRI. Overall upgrading (definition I) occurred in 32% (35/111, 95% CI 23-41), as a result of TBx and/or SBx (Table 2). Upgrading in MRI-positive and -negative men was 48% (30/63, 95% CI 35-61) and 10% (five of 48, 95% CI 4-23) (*P <0.001*, 95% CI for the difference 21-51), respectively. In MRI-positive men, upgrading was 23% (seven of 30) by TBx only, 33% (10/30) by SBx only, and 43% (13/30) by both TBx and SBx (Suppl. Table 1 for cross-tabulation of biopsy data).

In a total of 23 MRI-positive men, SBx detected upgrading. 43% (10/23, 95% CI 23-66) of the detected upgrading by SBx in these men was (also) located on the contralateral side of the suspicious MRI lesion(s). The overall upgrading in MRI-positive men increased with the PI-RADS score from 38% (five of 13, 95% CI 14-68) in PI-RADS score 3, 48% (19/40, 95% CI 32-64) in PI-RADS score 4, 60% (six of 10, 95% CI 26-88) in PI-RADS score 5 MRIs. Based on TBx results no correlation was found of upgrading related to higher PI-RADS score.

Upgrading (definition I) at 1-year surveillance, related to changes on MRI in MRI-positive and -negative men

Radiological progression (PRECISE score 4-5, i.e. from non-suspicious to suspicious and suspicious to more suspicious) in MRI-positive men was observed in 27% (17/63). Upgrading (definition I) in these men was 41% (seven of 17, 95% CI 18-67), as a result of TBx and/or SBx. Upgrading occurred in three of seven by TBx only and in three of seven by SBx only (Table 3). No radiological progression (PRECISE score 1-3) in MRI-positive men occurred in 73% (46/63). Upgrading in these men was 50% (23/46, 95%

Characteristic	Baseline Total cohort (n=111)	Confirmatory biopsy (1-year surveillance) Total cohort (n=111)	*p value**
Age (yr), median (IQR)	66 (60-70)	67 (61-71)	*<0.001*
PSA level (ng/ml), median (IQR)	6.8 (5.1-9.1)	6.9 (5.2-9.4)	*0.352*
Prostate volume (ml), median (IQR)	42 (30-56)	41 (31-55)	*0.695*
PSA density (ng/ml/ml), median (IQR)	0.17 (0.11-0.25)	0.15 (0.12-0.27)	*0.864*
Clinical stage, n (%)			
T1c	85 (77)	80 (72)	*0.665*
T2a	22 (20)	25 (23)	
T2b	2 (2)	4 (4)	
T2c	1 (1)	2 (2)	
T3a	1 (1)	0 (0)	
TRUS findings, n (%)			
Benign	93 (84)	91 (82)	*0.774*
Suspected	18 (16)	20 (18)	
Number of positive diagnostic cores, n (%)			
1	46 (41)	N/A	*N/A*
2	36 (32)	N/A	
3	19 (17)	N/A	
4	7 (6)	N/A	
5	2 (2)	N/A	
6	1 (1)	N/A	
PI-RADS score of MRI, n (%)			
1-2	52 (47)	48 (43)	*0.303*
3	15 (14)	13 (12)	
4	35 (32)	40 (36)	
5	9 (8)	10 (9)	
PRECISE score of MRI, n (%)			
1-2	N/A	14 (13)	*N/A*
3	N/A	80 (72)	
4-5	N/A	17 (15)	
Time between MRIs (months), median (IQR)	N/A	10 (9-13)	*N/A*
Overall ISUP Grade at biopsy, n (%)			
no PCa	N/A	31 (28)	*N/A*
G 1	111 (100)	45 (41)	
G 2	N/A	18 (16)	
G 2 with CR and/or IDC	N/A	12 (11)	
G 3	N/A	5 (5)	
G 4-5	N/A	0 (0)	

Table 1. Patients' characteristics at baseline and at 1-year confirmatory biopsy.
*p values calculated based on the comparison between the baseline and confirmatory characteristics for the total cohort.
IQR: interquartile range; PSA: prostate-specific antigen; TRUS: transrectal ultrasound; PI-RADS: Prostate Imaging Reporting and Data System; MRI: magnetic resonance imaging; PRECISE: Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; ISUP: International Society of Urological Pathology; PCa: prostate cancer; G: Grade; CR: cribriform growth pattern; IDC: intraductal carcinoma; N/A: not applicable.

		Follow-up MRI at one-year surveillance	Definition I					Definition II						Definition III					
				No upgrading	Upgrading			No upgrading	Upgrading					No upgrading	Upgrading				
		N (% of total)		Overall, n (%, n/N)	All biopsy	Biopsy technique, n (% of overall)		Overall, n (%, n/N)	All biopsy	TBx + SBx	SBx only	TBx only		Overall, n (%, n/N)	All biopsy	TBx + SBx	SBx only	TBx only	
						TBx + SBx	SBx only	TBx only											
Total		111 (100)	76 (68)	35 (32)	13 (37)	15 (43)	7 (20)	94 (85)	17 (15)	4 (24)	10 (59)	3 (18)	106 (95)	5 (5)	1 (20)	3 (60)	1 (20)		
Positive MRI	PI-RADS 3-5	63 (57)	33 (52)	30 (48)	13 (43)	10 (33)	7 (23)	49 (78)	14 (22)	4 (29)	7 (50)	3 (21)	59 (94)	4 (6)	1 (25)	2 (50)	1 (25)		
Negative MRI	PI-RADS 1-2	48 (43)	43 (90)	5 (10)	x	5 (100)	x	45 (94)	3 (6)	x	3 (100)	x	47 (98)	1 (2)	x	1 (100)	x		

Table 2. Upgrading in MRI-positive and -negative men per definition for clinically significant prostate cancer at 1-year surveillance.
N: number; MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System; TBx: targeted biopsy; SBx: systematic biopsy.

Follow-up MRI at one-year surveillance		Definition I						Definition II					Definition III				
			No upgrading	Upgrading				No upgrading	Upgrading				No upgrading	Upgrading			
		N (% of total)	Overall, n (%, n/N)	Overall, n (%, n/N)		Biopsy technique, n (% of overall)		Overall, n (%, n/N)	Overall, n (%, n/N)		Biopsy technique, n (% of overall)		Overall, n (%, n/N)	Overall, n (%, n/N)		Biopsy technique, n (% of overall)	
					All biopsy	TBx + SBx	SBx only	TBx only		All biopsy	TBx + SBx	SBx only	TBx only		All biopsy	TBx + SBx	SBx only	TBx only
Total	PRECISE 4-5	17 (15)	10 (59)	7 (41)	1 (14)	3 (43)	3 (43)	14 (82)	3 (18)	0 (0)	3 (100)	0 (0)	16 (94)	1 (6)	0 (0)	1 (100)	0 (0)
	PRECISE 1-3	94 (85)	66 (70)	28 (30)	12 (43)	12 (43)	4 (14)	80 (85)	14 (15)	4 (29)	7 (50)	3 (21)	90 (96)	4 (4)	1 (25)	2 (50)	1 (25)
Positive MRI	PRECISE 4-5	17 (27)	10 (59)	7 (41)	1 (14)	3 (43)	3 (43)	14 (82)	3 (18)	0 (0)	3 (100)	0 (0)	16 (94)	1 (6)	0 (0)	1 (100)	0 (0)
	PRECISE 1-3	46 (73)	23 (50)	23 (50)	12 (52)	7 (30)	4 (17)	35 (76)	11 (24)	4 (36)	4 (36)	3 (27)	43 (93)	3 (7)	1 (33)	1 (33)	1 (33)
Negative MRI	PRECISE 4-5	N/A															
	PRECISE 1-3	48 (100)	43 (90)	5 (10)	x	5 (100)	x	45 (94)	3 (6)	x	3 (100)	x	47 (98)	1 (2)	x	1 (100)	x
	PRECISE 3	*42 (88)*	*38 (90)*	*4 (10)*	*x*	*4 (100)*	*x*	*40 (95)*	*2 (5)*	*x*	*2 (100)*	*x*	*41 (98)*	*1 (2)*	*x*	*1 (100)*	*x*
	PRECISE 1-2	*6 (13)*	*5 (83)*	*1 (17)*	*x*	*1 (100)*	*x*	*5 (83)*	*1 (17)*	*x*	*1 (100)*	*x*	*6 (100)*	*0 (0)*	*x*	*0 (0)*	*x*

Table 3. Upgrading related to radiological changes on MRI in MRI-positive and -negative men per definition for clinically significant prostate cancer at 1-year surveillance.

MRI: magnetic resoncance imaging; N: number; PRECISE: Prostate Cancer Radiological Estimation of Change in Sequential Evaluation; TBx: targeted biopsy; SBx: systematic biopsy.

CI 35-65), found by TBx and/or SBx. Upgrading was 17% (four of 23) by TBx only and 30% (seven of 23) by SBx only.

PRECISE score 3 (i.e. stable radiological features) in MRI-negative men was observed in 88% (42/48), in whom upgrading occurred in 10% (four of 42, 95% CI 3-23) (Table 3). Radiological regression from suspicious to non-suspicious findings (PRECISE score 1-2) in follow-up MRI-negative men was observed in 13% (six of 48), in whom upgrading occurred in 17% (one of six, 95% CI 1-64).

Upgrading at 1-year surveillance, based on higher thresholds (definition II and III) for clinically significant prostate cancer

Overall upgrading (definition II) was 15% (17/111, 95% CI 9-23). Upgrading in MRI-positive and -negative men was 22% (14/63, 95% CI 13-35) and 6% (three of 48, 95% CI 1-17) (*P =0.021*, 95% CI for the difference 2-28), respectively. In MRI-positive men, there was upgrading in three of 14 by TBx only, and in seven of 14 by SBx only (Table 2). Related to PRECISE, upgrading was 18% (three of 17, 95% CI 4-43) for PRECISE score 4-5 and 15% (14/94, 95% CI 8-24) for PRECISE score 1-3 (Table 3).

Overall upgrading (definition III) was 5% (five of 111, 95% CI 2-10). Upgrading in MRI-positive and -negative men was 6% (four of 63, 95% CI 2-16) and 2% (one of 48, 95% CI 1-11) (*P =0.283*, 95% CI for the difference -5-13), respectively. In MRI-positive men there was upgrading in one of four by TBx only, and in two of four by SBx only (Table 2). Related to PRECISE, upgrading was 6% (one of 17, 95% CI 1-29) for PRECISE score 4-5 and 4% (four of 94, 95% CI 1-11) for PRECISE score 1-3 (Table 3).

DISCUSSION

The guidance of serial prostate MRI in the utility of repeat biopsies, when monitoring low-risk PCa men on AS, has not been clearly established. In our clinical practice of men with low-risk PCa on AS with subsequent MRI at baseline and at 1-year follow-up, overall upgrading from low- to intermediate/high-risk PCa (definition I) at 1-year surveillance was 32%. Upgrading was significantly lower in MRI-negative men (10%) compared to MRI-positive men (48%). In MRI-positive men, SBx detected a substantial additional proportion of upgrading not detected by TBx; almost half detected on the contralateral side of the suspicious MRI lesion(s). Upgrading was similar in MRI-positive men with radiological progression and without radiological progression. In these two groups the additional value of SBx in upgrading to ISUP Grade 2 and higher PCa was 43% and 30%, respectively. This argues for additional repeat SBx in men with and in men without

radiological progression on positive MRI. The other studied thresholds for upgrading ([definition II] ISUP Grade ≥2 with CR and/or IDC PCa, and [definition III] ISUP Grade ≥3 PCa) resulted in a lower overall upgrading (15% and 5%, respectively). At these thresholds, similar results were found with only limited upgrading in MRI-negative men and substantial added value of SBx in MRI-positive men. These results suggest that in serial MRI-negative men with low-risk PCa, repeat SBx at 1-year surveillance should be balanced against the harms on an individual basis. The risk of missing a timely diagnosis of high-risk PCa is low. In serial MRI-positive men, however, repeat SBx combined with TBx should be performed in all MRI-positive low-risk PCa men at 1-year surveillance to gain maximal diagnostic precision. This strategy could save a repeat biopsy procedure at 1-year follow-up in 43% of men at the cost of missing 2%-10% of csPCa (depending on the threshold used) in our population.

Two important clinical implications from our present results are: to consider omitting SBx in serial MRI-negative men at 1-year AS, and to perform both SBx and TBx in serial MRI-positive men. Previous studies have also investigated the value of serial MRI and TBx in monitoring men on AS for low-risk PCa. With respect to the applied AS protocol (i.e. the time interval between follow-up testing), the studies of Thurtle et al., Elkjaer et al. and Hamoen et al. are similar to our present study (18-20). Our present results of overall upgrading (32%) and added value of repeat SBx in MRI-positive (33%) and MRI-negative men (10%) at 1-year surveillance of low-risk PCa are mostly in line with the results of Hamoen et al. (25% overall upgrading and an added value of repeat SBx in serial MRI-positive men of 36%, while in MRI-negative men of 50%). The difference in added value of SBx in MRI-negative men is probably caused by the fact that in our present study 48 (43%) men had a negative MRI and repeat SBx, while only 8 (11%) men of Hamoen et al.'s cohort had a negative MRI and SBx. Our overall percentage of upgrading is also consistent with the stable 25% re-classification found at each repeat SBx in the entire PRIAS study (without the use of MRI) (2). This finding confirms the high value of re-sampling the prostate with SBx in men at 1-year AS, which after upfront risk stratification with MRI appears to have the most added value in MRI-positive men.

Thurtle et al. and Elkjaer et al. showed, however, a lower overall upgrading (14%-16%) at confirmatory biopsy in their cohorts and less added value of repeat SBx (12%-18% added value of repeat SBx in serial MRI-positive men and 5%-7% in MRI-negative men). These differences to our present study could be explained by our daily clinical practice AS cohort of men with low-risk PCa as opposed to the men with very low-risk PCa included in their studies. Furthermore, in the Hamoen et al. study and in our present study, the repeat SBx was not taken blinded from the MRI results which, could beneficially influence the SBx outcomes.

Consistent with the upgrading results in other studies, most men, if upgraded, were upgraded from ISUP Grade 1 to Grade 2 PCa in our present cohort. This is probably (partially) caused by previous sampling error, as low-risk PCa profiles remained equal. This confirms the finding that most men following an AS programme rarely have high-risk disease (ISUP Grade 3 and higher PCa) during follow-up and therefore have a good cancer-specific survival (1, 28).

Our present results indicate performing SBx in combination with TBx in all MRI-positive men at 1-year AS, and also when there is no radiological progression, which is in line with the recommendations from Hsiang et al. and Chesnut et al. (23, 24). In the total cohort, we detected more upgrading in men with a PRECISE score 4-5 (41%) compared to men with a PRECISE score 1-3 (30%) on follow-up MRI. This finding is in line with Dieffenbacher et al., who studied the impact of serial MRIs in AS using the PRECISE score at 4-years follow-up (21). However, they showed a much better discrimination of the PRECISE scoring system for AS disqualification, with only 10% upgrading detected in men with a PRECISE score 1-3. Differences might be explained by the fact that we analyzed a cohort at 1-year of AS with substantial added value of repeat prostate sampling with SBx, while they analyzed a cohort at time of third follow-up saturation biopsy (4-years after initial diagnosis). This has probably resulted in an improved patient selection for AS with only limited added value of repeat sampling of the whole prostate at time of their analysis. In addition, the fact remains that the assessment of serial MRIs in men on AS is challenging, as upgrading still occurs with some regularity in men with an apparent stable low-risk disease on positive MRI due to the high value of repeat prostate sampling. Therefore, serial MRIs and the PRECISE criteria need to be investigated more often in clinical AS cohorts of men with low-risk PCa to help with the creation of a robust dataset to define proper radiological thresholds of clinically significant disease in men on AS.

The present study is the first to investigate the role of serial prostate MRIs in a daily clinical practice of AS (following a strict protocol) related to the presence of CR and IDC in biopsy specimens. CR and IDC are prognostic drivers in survival, even more than other Gleason 4 subpatterns (29). Kweldam et al. showed that men with ISUP Grade 2 PCa with the presence of CR/IDC were associated with a worse disease-specific survival (67%) at 15-years follow-up, compared to men with ISUP Grade 2 PCa without the presence of CR/IDC (94%) and men with Grade 1 PCa (99%) (30). Identifying these Gleason 4 patterns in men on AS may therefore be of high clinical relevance, with subsequently a large population staying on AS without CR/IDC. In our present population, overall upgrading defined by ISUP Grade ≥2 with CR and/or IDC PCa (definition II) decreased from 32% to 15%, potentially saving even more biopsy procedures (e.g. in PI-RADS score 3

men) and keeping more men on AS. Incorporation of this tumour-specific information into risk stratification could further improve selection of men who will benefit from active treatment. We may argue that the threshold for upgrading in men on AS should be changed to ISUP Grade ≥2 with CR and/or IDC PCa, to (falsely) exclude less men from AS and thereby to reduce the rate of overtreatment and treatment-related side-effects.

Some limitations of our study should be highlighted. First, our study has a retrospective design and could thereby introduce a selection bias. However, our study represents a prospective cohort of consecutive men on AS with strict monitoring. Second, clinicians involved were not blinded to clinical data and MRI results. Hence, this process is daily clinical practice and therefore can be extrapolated to other hospitals. Third, the sample size of our study is relatively small, which could reduce generalizability. However, in comparison to similar studies in recent literature it is the second largest sample size available in a study on the use of serial MRI in men on AS at 1-year surveillance for low-risk PCa. Lastly, the median follow-up time is limited to 33 months. We acknowledge that the outcome measurement of our analysis was upgrading at 1-year surveillance. The cancer-specific survival rate in a long-term follow-up would have been more appropriate to make hard inferences about the need for and frequencies of surveillance testing. This outcome may, however, be debatable in a cohort of men with low-risk disease who exhibit excellent long-term cancer-specific survival and who furthermore experience most shifts from AS to active treatment during the first 2 years of follow-up (31).

In conclusion, at 1-year surveillance the performance of repeat SBx in serial MRI-negative men should be discussed per individual based on one's balance between benefits (e.g. not missing any intermediate/high-risk disease) and harms (e.g. unnecessary biopsy, biopsy complications). In serial MRI-positive men, repeat SBx should be performed together with MRI-TBx in all MRI-positive men, and also when there is no radiological progression. These findings are irrespective of upgrading threshold. Future large-scale studies should confirm this and focus on other surveillance issues in the current MRI era, such as the need for, the intervals and frequencies of surveillance testing from 2 years after the diagnosis of low-risk PCa.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIALS

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Serial MRI ± TBx outcome (ISUP grade), n		Repeat SBx outcome (ISUP grade), n						
			no PCa	G 1	G 2	G 2 with CR and/or IDC	G 3	G 4-5	Total
	Negative MRI (PI-RADS 1-2)	**no targets**	23	20	2	2	1	0	48
	Positive MRI (PI-RADS 3-5) + TBx	**no PCa**	8	1	1	1	0	0	11
		G 1	2	22	4	3	1	0	32
		G 2	2	4	5	1	1	0	13
		G 2 with CR and/or IDC	0	0	2	3	0	0	5
		G 3	0	1	0	0	1	0	2
		G 4-5	0	0	0	0	0	0	0
		Total	35	48	14	10	4	0	**111**

Supplementary Table 1. Cross-tabulation of serial MRI with or without targeted biopsy results vs repeat systematic biopsy results, at 1-year surveillance.
MRI: magnetic resonance imaging; TBx: targeted biopsy; ISUP: International Society of Urological Pathology; PI-RADS: Prostate Imaging Reporting and Data System; TBx: targeted biopsy; SBx: systematic biopsy; PCa: prostate cancer; G: grade; CR: cribriform growth pattern; IDC: intraductal carcinoma.

PART III

DISCUSSION

9

GENERAL DISCUSSION

As described in the introduction section (Chapter 1) of this thesis, the main objective was to study whether the use of risk stratification strategies could reduce a) the harms of PSA-based prostate cancer screening (i.e. unnecessary testing and overdiagnosis; Part I) and b) overtreatment (i.e. active treatment in those cases that have an indolent course; Part II) without affecting the benefit of screening (i.e. reducing suffering and dying from the disease). Several research questions regarding this objective will be answered in this general discussion. In addition, future perspectives will be discussed.

PART I: CAN RISK STRATIFICATION AT TIME OF PROSTATE CANCER DETECTION REDUCE UNNECESSARY REFERRALS/TESTS, OVERDIAGNOSIS AND OVERTREATMENT WITHOUT MISSING CLINICALLY SIGNFICANT PROSTATE CANCER THAT COULD HARM A PATIENT IF LEFT UNDETECTED?

What is the long-term effect of PSA-based prostate cancer screening, and could it add to the ongoing discussion on the balance between harms and benefits of prostate cancer screening?

The aim of PCa screening is to find a potentially harmful csPCa within the window of curability, which in the case of PCa implies that screening involves men that do not have any symptoms related to PCa. Whether a man can truly benefit from an early detection and treatment of his PCa depends on the interaction of how aggressive (and sensitive for treatment) the potentially present disease is and how long the patient will live (1). Therefore, the European Association of Urology (EAU), the United States Preventive Services Task Force (USPSTF) and the American Urological Association (AUA) guidelines state that in men with a life expectancy of more than 10-15 years PCa screening could be considered after the process of shared-informed decision making (2-4) (Chapter 2).

To understand the impact of untreated localized PCa on life expectancy and quality of life, knowledge on the natural history of screen-detected PCa is important. Swedish long-term data on initial untreated early-stage PCa show that after 30 years of follow-up and 99% of men in the study cohort deceased, 17% of men died because of PCa; the majority died 15-25 years after the initial diagnosis (5, 6). This finding was confirmed by the Prostate Cancer Intervention Versus Observation Trial (PIVOT) which showed an excellent 15- and 20-years disease-specific survival for low- to intermediate-risk PCa without initial curative treatment (7, 8). The two largest randomized controlled trials (RCTs) on PCa screening, reporting results with approximately 9 years follow-up after diagnosis can therefore not yet be representative for the full effect of screening in reducing metastatic disease and PCa mortality. Many screen-detected cancers are, at

time of detection, low or intermediate risk and as such will have a long natural history (15-25 years) (9-12).

Next to a limited follow-up time, PSA contamination in the control arms of the ERSPC and PLCO trials is another phenomenon that affects the relative result of mortality reduction when comparing the two arms of the trials. The reported rate of PSA contamination in the control arms of the ERSPC and PLCO trials ranges from 19% to 70% (13, 14). Studies have shown that after adjustment for nonattendance and PSA contamination the effect of organized PCa screening as conducted in the Rotterdam section of the ERSPC could increase, with a reduction of the risk of dying from PCa up to 51% for an individual man choosing to be screened repeatedly as compared to a man that was not screened (15, 16). Reporting on the effect of screening with long-term follow-up data without (or individually identified) PSA contamination is therefore valuable in gaining more insight into the full effect of PSA-based PCa screening. Having those data will contribute to the ongoing discussion on the balance between harms and benefits of PCa screening.

In Chapter 3 it was shown that data from the first pilot study of the ERSPC Rotterdam section (median follow-up time of 19 years, almost no PSA contamination and more than 60% of men deceased at time of analysis) suggest that there could be a more substantial relative reduction in metastatic disease (54%) and PCa-specific mortality (52%) in favor of PSA-based PCa screening than previously reported (17). Obviously, the relatively small sample size and low event rates resulted in wide confidence intervals and statistically insignificant reductions, and for now, limit drawing definitive conclusions.

It can however not be excluded that the magnitude of the relative risks in the first ERSPC Rotterdam pilot study will be confirmed in the main ERSPC trial when having the availability of 19 years or more of follow-up, as rates of metastatic disease and PCa death in the screening arms of both studies do not differ much. The most recent update of the main ERSPC trial at 16 years of follow-up already shows that the absolute reduction in PCa mortality still increases, compared to earlier publications (12). More importantly, longer follow-up in the main ERSPC trial seems to go along with a reduction of the harms of PCa screening on a population level. The number needed to invite (NNI) to prevent one PCa death was 570 at 16 years follow-up compared with 1947 at 9 years and 742 at 13 years. The number of cases needed to diagnose (NND) to avert one PCa death declined from 48 at 9 years of follow-up to 18 in the recent update at 16 years (9, 12, 18). With extended follow-up the NND will likely continue to decrease (but this should be interpreted with some caution since the PCa incidence in the control group is gradually catching up with the screening arm). Similar findings have been reported from

the Swedish section of the ERSPC trial, having the availability of 18 years of follow-up and suggesting that the results of PSA-based PCa screening could be more beneficial than previously thought (19). It remains to be seen whether the ERSPC trial as a whole will confirm these observations. Differences in study populations, a-priori risks of PCa, screening protocols and screening duration between centers influence the main outcome of the trial (20).

So, although there are indications that in the long run the harm-benefit ratio of PSA-based PCa screening could be more beneficial than reported so far and an introduction of a population-based screening program for PCa could become a possibility in the near future, the finding that to detect 5000 prostate cancers more than 20000 biopsy procedures were needed, i.e. a positive predictive value (PPV) of only 24%, should trigger all stakeholders to work on improvement (12, 21). By following the current protocols many men will experience short-term screening related harms, while only a selected number of men would benefit from the potentially considerable beneficial long-term effect of PSA-based PCa screening on metastatic disease and PCa-specific mortality, as suggested by the findings in Chapter 3. These short-term harms should be minimized and experienced by as few men as possible. If this could be achieved it would open the door to PCa screening on a large scale, like recently proposed for the European setting by proponents within the EAU (22-24). Recent developments in risk stratification and targeted tissue sampling will hopefully convince those stakeholders that consider overdiagnosis and overtreatment unavoidable, insurmountable and unethical impacts on men's quality of life (25). Therefore, to identify and treat the prostate cancers that have impact while leaving aside the rest of the detectable cancers we should not focus too much on the question 'To screen or not to screen?', but much more on the question 'If we screen, what is the optimal way to do that?'. Examples of adjustments to optimize screening and detection pathways of PCa to get the best for our patients will be discussed in detail in the next sections of the general discussion, and a new screening and detection strategy will be proposed.

Can we select those men at high risk for aggressive disease who need further testing using currently available risk calculators, thereby avoiding unnecessary referrals, MRIs, prostate biopsies and overdiagnosis?

Multivariable risk-based patient selection for referral to the urologist

To predict whether a man harbors a potentially harmful csPCa and whether the events (i.e. metastases and death) of this harmful csPCa will occur before the competing risk of death from another cause, is difficult. However, our understanding of which men may benefit from PSA-based PCa screening has improved over the past few years (e.g. men

with a positive family history, men from African descent, men with a life expectancy of >10-15 years) (26-28). Unfortunately, detailed analyses of the population of men screened within the trials has up to now not succeeded in a clear-cut strategy that substantially improves the harm-benefit ratio (29). For example, when using a purely PSA-based screening algorithm screening within a wider age range, narrowing the screening intervals or lowering the PSA threshold for referral to biopsy would indeed increase the detection of csPCa but at the same time increase the number of unnecessary screening tests and overdiagnosis (30, 31). One of the biggest challenges in PCa screening remains to decrease its harms without affecting its benefits.

In the Netherlands a screening and detection algorithm based on PSA only (threshold of 3.0 ng/ml) to select for a referral to the urologist and potentially (invasive) further testing would result in a benign outcome in 60%-75% of biopsied men, and up to half of the detected PCa being clinically insignificant (12, 32, 33). Better prediction of a patient's risk of harboring csPCa and thereby better selection for referral for further testing (i.e. MRI, biopsy) could reduce the percentage of unnecessary testing and cause a more favorable clinically significant to insignificant ratio of PCa detected (34, 35). Multivariable risk calculators (RCs) for the prediction of a positive prostate biopsy have been developed to support physicians to better identify those men at risk of csPCa. Among six extensively externally validated RCs, the ERSPC Rotterdam Prostate Cancer Risk Calculator (RPCRC) showed to be slightly superior in predicting men at risk of csPCa (36, 37). On average, using the ERSPC RPCRC in a urology outpatient clinic with biopsy at a cut-off point of 4% csPCa risk could avoid 32% of biopsies and 25% of low-risk PCa diagnoses while keeping a 95% sensitivity for detecting csPCa (34, 38) (Chapter 2).

In the Dutch health care system general practitioners (GPs) play an important role since they are the first link in the chain of many diagnostic pathways. Men with a suspicion of PCa or a PCa screening wish first visit their GP, where after balancing the individual potential advantages and damages related to screening, a PSA test and if indicated, a referral to the urologist will be conducted. Therefore, this is the first point within the PCa diagnostic pathway where optimization of the pathway by better risk stratification should take place (39). GPs are, however, still uncertain about managing PCa screening and detection, and for that reason men receive different care depending on their GP's reasoning and practice preferences (40, 41). The implementation of validated PCa diagnostic risk models in primary care could be a solution for this problem and may help the GPs to facilitate informed decision-making and improve patient selection for referral.

In Chapter 4 it was shown that use of the ERSPC RPCRC in a primary care setting (centralized GP laboratory and test center) could reduce the rate of men with a PSA level

≥3.0 ng/ml referred to the urologist with almost 50%, without missing any csPCa in men considered low risk (42). Although in more than 75% of the high-risk men referred for biopsy the suspicion of PCa was confirmed, almost half of the detected PCa among these men was low-risk disease according to the Gleason grading. This indicates that there is room for improvement of this strategy. Nevertheless, the considerable reduction in unnecessary referrals to the urologist suggests an important and relevant role for multivariable risk stratification in primary care. To further validate and translate these findings to the individual GP's offices, studies with GPs or trained nurses performing the tests necessary to calculate individual risk are indicated. DRE is not unknown in the GP setting, and could also be used for prostate volume estimation after training. In addition, simple abdominal ultrasound instead of transrectal ultrasound (TRUS) could be used in GP practices for more accurate volume estimation (43).

Based on the findings in Chapter 4 it can be concluded that (at least) for the Dutch primary health care setting multivariable risk stratification for patient selection for referral to the urologists, is the first step in optimizing the pathway of PCa screening and detection. Large-scale implementation should be top priority when considering the introduction of a population-based PCa screening program. Therefore, risk stratification starting at the GP's office is the first step of the proposed PCa screening and detection strategy (Figure 1) in this thesis.

Multivariable risk-based patient selection for prostate MRI and biopsy

The recently updated Dutch, European and North-American PCa guidelines recommend to perform a pre-biopsy prostate MRI in all men with a (initial or persistent) suspicion of csPCa (i.e. biopsy-naïve and repeat biopsy setting), before embarking to a prostate biopsy procedure (44-49). MRI is a useful tool because of its ability to detect suspicious lesions in the prostate and as a guidance for targeted prostate biopsies (TBx). In addition, the MRI based PI-RADS score provides information on the likelihood of having a csPCa. The MRI PCa diagnostic pathway is considered to be superior to the traditional TRUS diagnostic pathway, as it improves diagnostic accuracy and it limits both the amount of invasive procedures, overdiagnosis and overtreatment (44). However, performing a prostate MRI in all men with an elevated PSA level is a challenge due to limits in resources, capacity and availability of expertise. In addition, in a considerable proportion of patients the MRI will not show any abnormalities making it thereby potentially a redundant test. Furthermore, some patients will have false positive abnormalities on MRI (i.e. benign pathology or low-risk PCa) resulting in unnecessary TBx (Chapter 2). Multivariable risk stratification could potentially help to better select upfront which men will benefit from a prostate MRI and subsequent biopsies (50-53). In that way, upfront pre-MRI risk stratification could optimize the PCa diagnostic pathway by avoid-

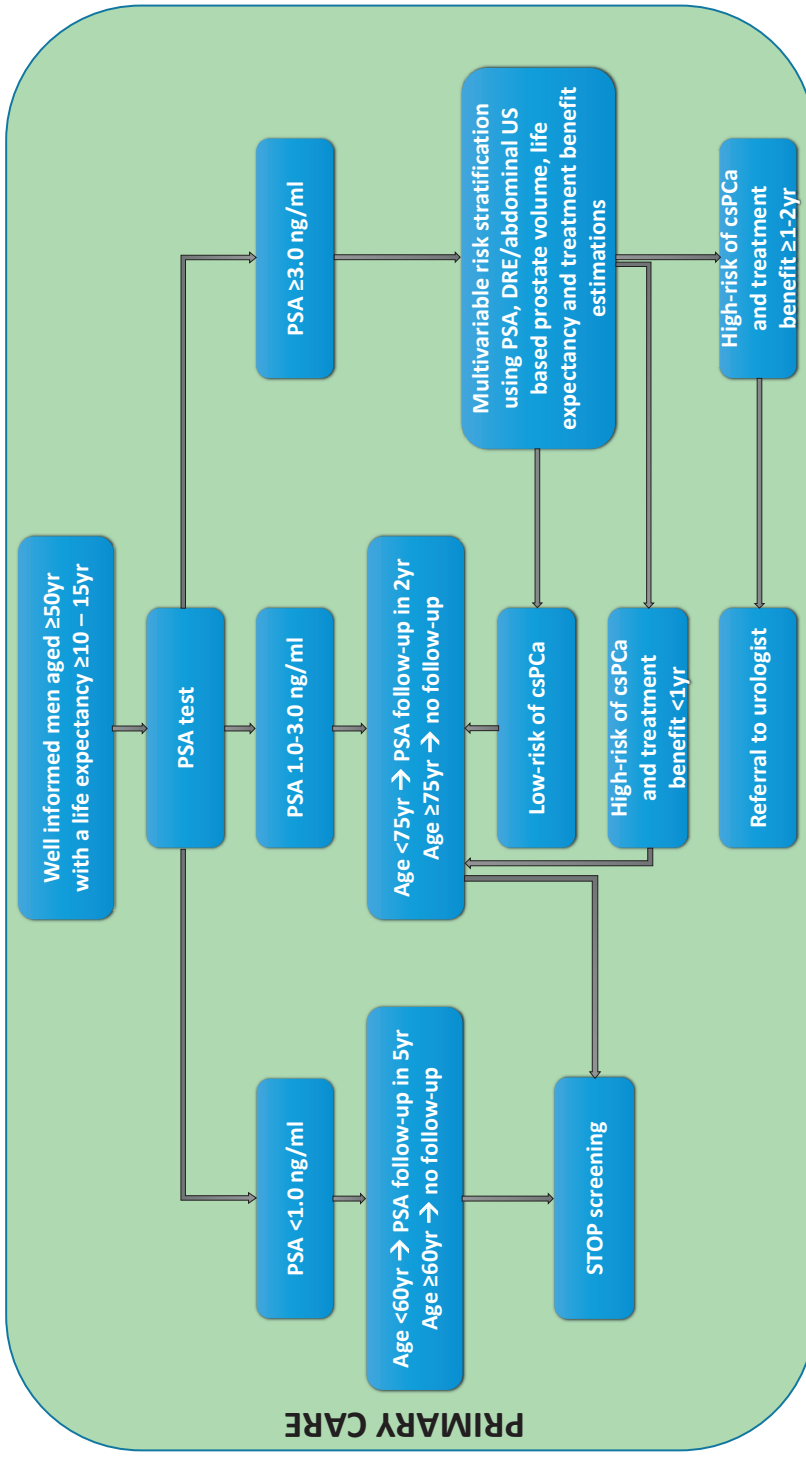

Figure 1. Proposed new prostate cancer screening and detection pathway for primary care.
PSA: prostate-specific antigen; DRE: digital rectal examination; csPCa: clinically significant prostate cancer; US: ultrasound.

ing the performance of unnecessary pre-biopsy prostate MRIs and thereby potentially avoiding (even more) unnecessary biopsies and diagnoses of low-risk PCa.

Recently, Van Poppel et al. presented a new risk-adapted algorithm as a guidance in whom, and how to apply early detection of csPCa in 2020 and beyond. It should however be mentioned that the proposed algorithm was not based on prospective research data but on state-of-the-art knowledge and expert opinion (24). Chapter 5 of this thesis shows the preliminary results of a prospective multicenter clinical effectiveness study conducted in the Netherlands among 21 centers, investigating the performances of such a new risk-based PCa diagnostic strategy. This so-called MR PROPER study aims to compare the diagnostic performance, cost-effectiveness and quality of life of an MRI-driven PCa diagnostic pathway versus a systematic biopsy (SBx) driven pathway in biopsy-naïve men with a suspicion of PCa, based on an upfront individual multivariable risk stratification using the ERSPC RPCRC. The first clinical outcomes of the MR PROPER study provide evidence that the ERSPC RPCRC can be used as upfront risk stratification tool for the selection of biopsy-naïve candidates for a prostate MRI and subsequent biopsy procedure (54). The ERSPC RPCRC-MRI pathway resulted in men considered to be at high-risk of PCa according to the ERSPC RPCRC in a csPCa and low-risk PCa detection rate of 27% and 9%, respectively. Restricting prostate MRIs and biopsies to only high-risk men selected by the ERSPC RPCRC could reduce 20% of MRIs and 59% of biopsies, at the cost of missing only 4% csPCa. The MR PROPER study is herewith the first large prospective study to demonstrate that a risk-based MRI PCa diagnostic pathway is the approach for the future. Careful evaluation of patients with a need for a diagnostic work-up with prostate MRI would not only avoid costs and resources but could also improve the performance of the MRI pathway itself.

In line with previous studies, the MR PROPER study shows that the MRI pathway is non-inferior to the TRUS pathway in biopsy-naïve men with regard to csPCa detection, but is superior for detecting fewer low-risk PCa and reducing biopsy procedures. In other words, the MRI pathway can reduce the harms of PCa diagnostics without affecting the benefit. The reduction of harms can further be increased by better upfront selection of whom will benefit from the MRI pathway. This selection can be done with multivariable risk stratification tools like the ERSPC-RPCRC but also tests like e.g. the SelectMDx-test or 4Kscore could play a role here (50-54). The value of upfront risk stratification with one of these risk models in avoiding prostate MRIs, biopsies and low-risk PCa diagnoses is comparable (Table 1). The common denominator in all these tools is inclusion of the strong predictive value of the PSA-density (PSA-D). Therefore, at time of pre-MRI risk stratification accurate prostate volume estimation with e.g. a TRUS examination is advisable.

Summarizing the above, it can be concluded that multivariable risk stratification should be performed before selecting men for prostate MRI and subsequent biopsies to improve the harm-benefit ratio of the PCa diagnostic pathway. The MRI pathway with upfront risk stratification could be considered as a way forward in the current era of prostate MRI in PCa diagnosis. Therefore, pre-MRI multivariable risk stratification is a crucial part of the optimal PCa screening and detection pathway as proposed in this thesis (Figure 2).

Multivariable risk calculator including MRI data for prostate biopsy selection
To better identify those men who will benefit from TBx and/or additional SBx after a prostate MRI, MRI parameters have been incorporated into existing and new developed risk models. In Chapter 2 promising results of multivariable prediction models including MRI parameters (mostly the PI-RADS score) for both the initial and repeat biopsy setting are shown. The MRI risk prediction models have a high accuracy with area's under (AUC) the receiver-operating characteristic curves (ROC) ranging from 0.69 to 0.93 (55-61). On average, usage of the risk models could result in 30% biopsy (i.e. TBx and/or SBx) procedures and 15% low-risk PCa diagnoses avoided, at the cost of missing 5% csPCa diagnoses (21). The added value of multivariable risk stratification after the performance of an MRI depends on the a-priori risk of csPCa and the degree of pre-MRI risk stratification in a population. Furthermore, it is important to realize that the creation of dozens of MRI risk models on limited sample size, often single center study populations should be avoided. Preferably, a situation is created where high quality, good performing, already available models (both with respect to discrimination and calibration) are extensively externally validated and calibrated for different populations. This could lead to further refinement and improvement of the models (62, 63). Recently, Püllen et al. performed an external validation and head-to-head comparison of three existing MRI risk prediction models (64). The accuracy and potential of all three models are confirmed in this study, with the best results in avoiding unnecessary biopsies shown by the MRI-ERSPC risk calculator (Table 1).

MRI risk calculators should preferably be applied as third stratification tool after the performance of a PSA test (i.e. first stratification step) and upfront multivariable risk-based patient selection for prostate MRI (i.e. second stratification step) with the aim to not only reduce prostate biopsies and overdiagnosis but also the number of unnecessary MRIs (65). MRI risk calculators could support physicians and patients in several aspects of biopsy decision-making. Their added value in avoiding unnecessary biopsies holds especially for those men considered being at high(er) risk of csPCa before MRI, but that subsequently after MRI have a PI-RADS score 1-3. This new knowledge when used in another risk stratification step, including MRI result, could lead to a change from

Risk stratification tool	Biopsy setting	Reduced MRIs (%)	Reduced biopsies (%)	Reduced low-risk PCa diagnoses (%)	Missed csPCa (%)
Risk calculators including MRI data:					
MRI-ERSPC RPCRC 3 (cut-off ≥10% csPCa) --> TBx + SBx	Initial	0	26	13	4
Model Distler (cut-off ≥10% csPCa) --> TBx + SBx	Initial	0	0	ND	0
Model Radtke (cut-off ≥10% csPCa) --> TBx + SBx	Initial	0	3	ND	1
Diagnostic strategies combining tools:					
Initial 4Kscore (cut-off ≥7.5% csPCa) --> MRI + TBx + SBx	Initial	21	34	33	3
Initial ERSPC RPCRC 3 (cut-off ≥5% csPCa) --> MRI + TBx + SBx	Initial	20-37	59	59	4
Initial SelectMDx (cut-off ≥13% csPCa) --> MRI + TBx + SBx	Initial	38	60	58	13

Table 1. An updated overview of the performances of MRI risk calculators and risk-based PCa diagnostic strategies (all on average; results can differ between populations). (adapted from table 1, Chapter 2)
MRI: magnetic resonance imaging; PCa: prostate cancer; csPCa: clinically significant prostate cancer; ERSPC: European Randomized Study of Screening for Prostate Cancer; RPCRC: Rotterdam Prostate Cancer Risk Calculator; TBx: targeted biopsy; SBx: systematic biopsy; ND: not determined; 4K: four-kallikrein.

being at high(er) risk for csPCa to being at low(er) risk of harboring csPCa. Furthermore, MRI risk calculators can aid in the choice on method of biopsy in case the MRI is positive. For instance, patients considered being at high risk of csPCa according to multivariable risk stratification with an obvious PI-RADS 5 lesion on MRI could be biopsied by only TBx, i.e. omitting the SBx procedure of an additional 12 cores. On the other hand, in men considered being at high risk of csPCa with a PI-RADS 3 or small PI-RADS 4 lesion, the combined result of an elevated risk estimation and MRI location indicates the need for TBx and SBx to gain maximal diagnostic yields (66, 67). Therefore, there is without doubt added value for multivariable risk stratification including MRI data to decide for a subsequent prostate biopsy (and potentially biopsy strategy) within the PCa detection pathway. Hence, multivariable risk stratification after MRI is part of the optimal screening and detection strategy as proposed in this thesis (Figure 2).

Can magnetic resonance imaging-derived characteristics alone or combined with clinical parameters improve the selection of those men at high risk for aggressive disease who need a biopsy?

Magnetic Resonance Imaging-derived parameters

Important for standardized prostate MRI acquisition and reporting is the PI-RADS score (45, 68, 69). The MRI-derived parameters that are included in the PI-RADS score are, among other things, the degree of hypo-intensity, the greatest lesion dimension, the ADC value and the degree of contrast enhancement. Combining these MRI-derived parameters into the PI-RADS score is known as a strong predictor of csPCa, with up to 80% csPCa found in PI-RADS score 5 lesions (70). Some urologists and radiologists in the field of PCa diagnosis therefore suggest that the PI-RADS score on prostate MRI should serve as standalone test to select those men at high risk for csPCa who need a prostate biopsy (45, 71-73). This suggestion could be confirmed with data from the MR PROPER study (Chapter 5) showing a csPCa detection rate of 5% in men with a negative MRI and 79% in men with a PI-RADS score 5. Whether the MRI-derived parameters that are combined into the PI-RADS score are useful as standalone risk stratification tests to predict csPCa is debatable.

Studies on ADC values in predicting the diagnosis of PCa show promising results that the ADC value can help differentiate clinically insignificant from csPCa. Especially quantitative measurement of the mean ADC improved differentiation of benign versus malignant prostate lesions, compared with clinical assessment (74, 75). Radiomic machine learning had comparable but not better performance than mean ADC assessment (76, 77). From the perspective that lesion size could matter, Rais-Bahrami et al. suggested that small MRI index lesions (≤7mm) may correspond to benign lesions or indolent cancers (78). Furthermore, Rosenkrantz et al. proposed additional criteria to adjust the current PI-RADS version 2 guidelines, and to upgrade a PI-RADS 3 to a PI-RADS 4 lesion on the basis of lesion size (using thresholds of ≥10mm or ≥15mm), since substantial more csPCa would be detected in the larger lesions (79). In Chapter 6 of this thesis, it was investigated whether stratifying PI-RADS 3 lesions based on largest (index) lesion diameter could aid in avoiding TBx sessions and low-risk PCa diagnoses without missing the diagnosis of csPCa. Largest lesion diameter appeared not be a significant predictor of csPCa in the studied PI-RADS 3 cases (80). Perhaps that the lack of standardized MRI lesion measurement influenced the predictive value of lesion diameter in this study (81).

Hence, the PI-RADS score on prostate MRI could be used to select those men at high risk for csPCa who need a prostate biopsy. In men with a PI-RADS score 1-2 primarily

clinical and if indicated further radiological follow-up rather than performing directly SBx could be considered. In the rest of men (i.e. PI-RADS score ≥3) a biopsy procedure (i.e. TBx with or without SBx) could be considered, preferably after further risk stratification with specific MRI-derived parameters like the ADC value. The value of lesion size (i.e. lesion diameter or lesion volume) as standalone test in predicting the presence of csPCa needs further investigation, preferably after performing standardized MRI lesion measurements.

MRI-derived parameters combined with clinical data

An important clinical predictor of csPCa is PSA-density (i.e. PSA divided by prostate volume [PSA-D]). In 1992 Benson et al. already reported that PSA-D had better ability to predict PCa than PSA alone (82). Especially in the PSA range of 4-20ng/ml, PSA-D could improve cancer risk stratification compared with PSA alone. In a more recent head-to-head comparison, PCa risk calculators incorporating PSA and prostate volume (i.e. PSA-D) were shown to be superior in identifying men at risk of csPCa (36). The incorporation of prostate volume into risk calculators is therefore recommended (Chapter 2) (83, 84).

In Chapter 6 the added value of PSA-D in predicting csPCa in PI-RADS 3 cases is shown. Applying solely PSA-D as risk stratification tool in PI-RADS 3 men could result in 25% less TBx sessions and 11% less low-risk PCa diagnoses missing only 5% csPCa (80). Therefore, PSA-D may represent a good index to decide which PI-RADS 3 men should undergo a subsequent prostate biopsy. Risk stratification of PI-RADS 3 cases could further be improved by a model-based approach in which MRI-derived parameters (i.e. largest index lesion diameter) and clinical parameters (i.e. PSA-D and age) are combined in a multivariable prediction model that predicts the risk of csPCa of a PI-RADS 3 man. The discrimination of this model was 0.80 (95% CI 0.73-0.87). When compared to a biopsy all PI-RADS 3 men strategy, decision curve analysis showed a higher net benefit at threshold probabilities ≥2%. Such a model-based approach in PI-RADS 3 men, would result in 34% less TBx sessions and 23% of low-risk PCa diagnoses avoided missing no more than 5% of csPCa diagnoses.

It is evident that combining MRI-derived characteristics with clinical parameters can improve the selection of those men at high risk for aggressive disease who need a biopsy. Other studies that constructed a prediction model for csPCa detection show comparable findings, with models mainly driven by the strong predictive value of PSA-D (58, 85). Therefore, it is advisable to perform a multivariable risk stratification strategy for biopsy-decision making also after the performance of a prostate MRI, and to not let depend the biopsy decision-making on only the MRI PI-RADS score (Figure 2).

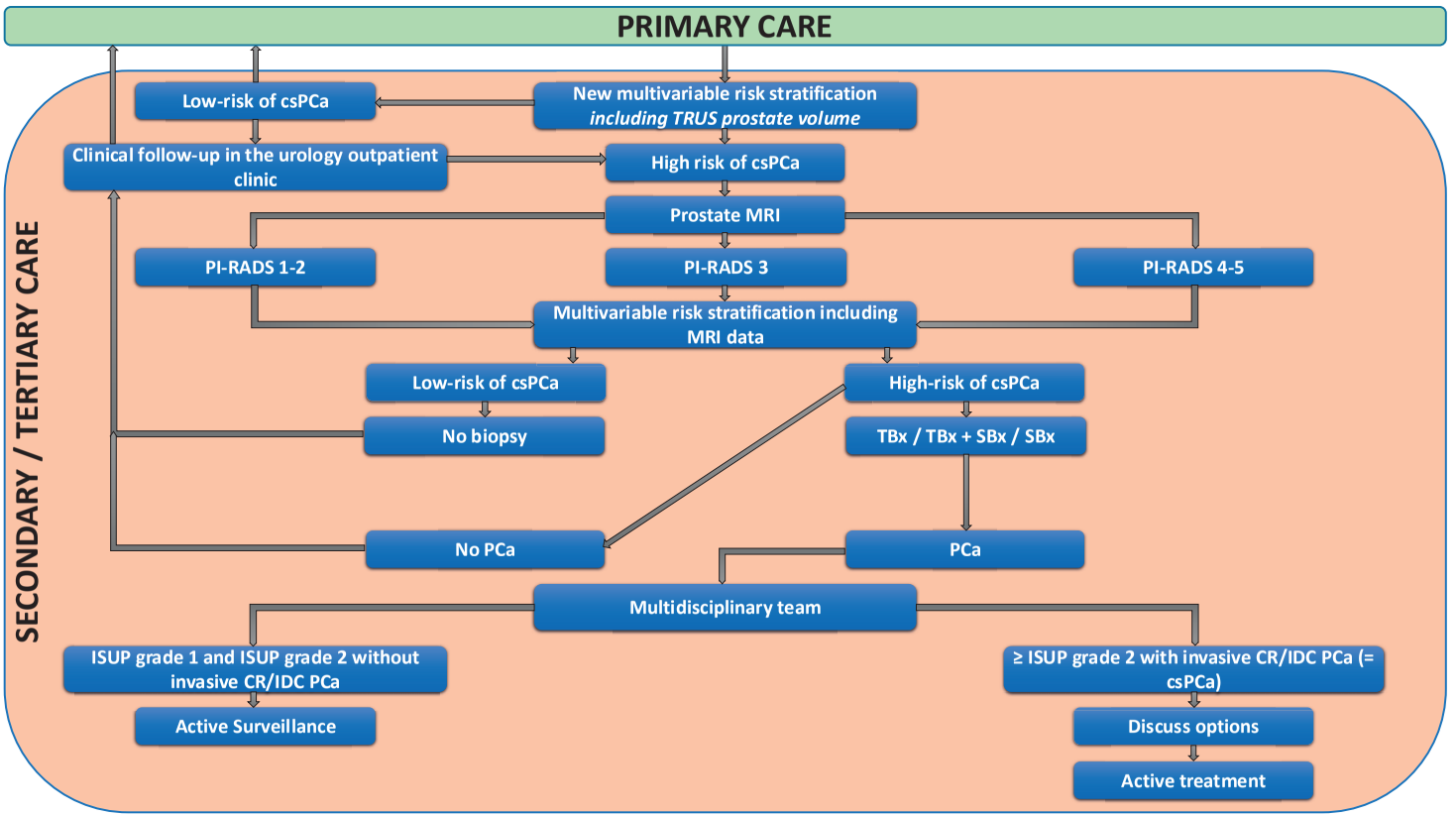

Figure 2. Proposed new prostate cancer screening and detection pathway (complete).
TRUS: transrectal ultrasound; csPCa: clinically significant prostate cancer; MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; TBx: targeted biopsy; SBx: systematic biopsy; PCa: prostate cancer; ISUP: International Society of Urological Pathology; CR: cribriform growth; IDC: intraductal carcinoma.

Conclusion

In PCa screening and detection a positive benefit-to-harm ratio is mandatory to make the disease and its diagnostic pathway acceptable to the general population and health care providers. There are indications that in the long run the harm-benefit ratio of PSA-based PCa screening could be more beneficial than reported so far. However, by following the current diagnostic protocols many men will experience short-term screening related harms, while only a selected number of men would benefit from the potentially considerable beneficial long-term effect of PSA-based PCa screening on metastatic disease and PCa-specific mortality. These short-term harms should be minimized and experienced by as few men as possible. Multivariable risk stratification and thereby a risk-based PCa diagnostic strategy in men with an elevated PSA level are the keys to a reduction of the harms of PCa diagnostics without affecting the benefit. The optimal screening and detection strategy as proposed in this general discussion (Figure 1 [= primary care part] and Figure 2 [= secondary/tertiary care part]) therefore starts with multivariable risk stratification in the primary care for patient selection for referral to the urologist. This reduces the rate of men with PSA levels ≥3.0 ng/ml unnecessarily referred to secondary care and may help the GPs to facilitate informed decision-making. The next optimization step is the performance of a second multivariable risk assessment including an accurate prostate volume estimation (e.g. by TRUS) by the urologist to select men for prostate MRI, as it significantly reduces the numbers of unnecessary prostate MRIs. The final optimization step in the proposed new screening and detection pathway is the performance of multivariable risk stratification combining clinical and radiological parameters after the performance of a prostate MRI to decide for a subsequent prostate biopsy and biopsy strategy. Such an approach can result in a reduction of unnecessary prostate biopsies, a reduction of overdiagnosis, also in men with abnormal findings on MRI.

Future perspectives

PCa has a high impact on the healthcare budget. As a result of increased life expectancy and the subsequent rise of the PCa incidence, the total estimated economic costs of PCa in Europe exceed €8,43 billion (86). In this light, the cost-effectiveness and Quality of Life (QoL) of PCa diagnostic strategies, next to their clinical performances, should be addressed. Therefore, it is even more unlikely that a purely PSA-based PCa screening and detection algorithm will be introduced for an organized population-based PCa screening program. The risk-based MRI PCa screening and detection pathway, as proposed in this thesis, has compared to a PSA-based strategy great potential to identify and treat the cancers that have impact while leaving aside the rest of the detectable cancers (24). Data and ongoing in-depth analyses from the MR PROPER study (i.e. Dutch nationwide setting) will soon provide more detailed insight in the cost-effectiveness and QoL of

such a detailed risk-based detection strategy. These results will aid in the discussion on whether, how and when a nationwide organized risk-adjusted population-based PCa screening program could be indicated in the (near) future. Furthermore, results of new, still ongoing, European risk-adjusted screening studies (e.g. PROBASE, ProScreen, The Göteborg prostate cancer screening 2 and STHLM3-MR Phase 2 trial) will lead to new insights in the field of population-based screening for PCa in the European setting in 2021 and beyond (87-90). At short notice, the study endpoints like the numbers of detected PCa, performed prostate MRIs and biopsy procedures will become available, informing us about the potential reduction in short-term PCa screening related harms by these risk-adjusted screening strategies. In the longer term, study endpoints like the number of metastatic disease and PCa-specific mortality, reflecting the potential long-term benefits of risk-adjusted PCa screening, will become clear.

Within the risk-based PCa screening and detection pathway, as proposed in figures 1 and 2 of this thesis, there is still room for improvement. The exact role and feasibility of multivariable risk stratification in the primary care needs further investigation before wide incorporation in daily clinical practice. Large-scale studies with substantial follow-up including the inclusion of GPs to actually perform the risk stratification before referral to the urologist are needed. In addition, as far as this is not yet the case there should be created awareness among GPs about their potential important contribution in improving the harm-benefit ratio of the PCa diagnostic pathway, and they should be well trained to perform the tests necessary for use of the risk prediction tools. Another option could be a population-based PCa screening program initiated by the government, i.e. outside the clinical care. This raises the question: who should then after taking a PSA test perform the first risk stratification step for referral for further diagnostic testing? Investigators involved in such a government initiated program should first get familiar with urological physical examinations for prostate volume estimation to properly assess a man's risk of PCa. This may be more time-consuming, expensive and less reliable than proper training of GPs that already have experience in medical physical examination.

There are numerous multivariable risk stratification tools available that could be used in the secondary care to select candidates for a subsequent prostate MRI, as well as numerous risk calculators including MRI data that could be used to select men for a subsequent biopsy procedure (21). However, head-to-head comparisons of these tools are necessary to determine the most optimal ones in terms of clinical performance. In addition, it is mandatory for optimal implementation that the tool is free to use, available everywhere, extensively externally validated, and calibrated for different populations.

The identification of genetic variants associated with PCa by PCa genome wide association studies (GWAS) could potentially help in targeting PCa screening and detection to men with an increased genetic risk of PCa development, which could improve the selection of men that will benefit from further invasive testing (91). This genetic information could be added to existing multivariable risk stratification tools. This shift towards more personalized medicine provides more patient-specific intervention estimates which support individualized clinical decision-making, instead of using a relative risk of intervention (92).

Key issues for the general use of prostate MRI and TBx in PCa diagnostics are reproducible standards and stable levels of high-quality imaging and interpretation, and biopsy performance (93). A systematic and robust training for MRI-technologists, radiologists, urologists/biopsy operators and pathologists, clear quality criteria for image acquisition and standardized reporting, and effective quality-assurance structures are therefore needed (94). With the increased use of MRI and TBx in daily clinical practice and the increasing supply of prostate MRI and TBx training programs, it is likely that physicians involved in PCa care will become more experienced in structured and standardized interpreting and performing MRI and TBx (95). Moreover, artificial intelligence could be used to mitigate the subjective nature of prostate MRI interpretation. There is need for mature datasets with high quality annotations to continue advancements in this field (96, 97).

To satisfy the increasing demand for prostate MRI, there is growing interest in performing prostate MRI without DCE, a so-called biparametric MRI. Performing biparametric MRI allows a higher throughput at lower costs, makes prostate MRI non-invasive and avoids potential contrast-related side-effects. However, the use of biparametric MRI requires high-standard image quality and experienced radiological interpretation (98-100). Future prospective studies, like the ongoing PRIME study, will provide important evidence whether the contrast sequences in multiparametric MRI contribute significantly to the detection of csPCa (101). Next to biparametric MRI, the diagnostic ability of prostate-specific membrane antigen (PSMA)-PET/CT in biopsy-naïve men in addition to MRI is currently determined, but is yet, too far away from becoming part of the standard diagnostic work-up (102).

Over the years questions have arisen on what prostate biopsy approach and how many biopsy cores are required to meet a sufficient diagnostic accuracy. Therefore, research in the near future should focus on the impact of upcoming in-office transperineal prostate biopsy with local anesthesia and TBx with focal saturation procedures. Recent studies have shown interesting potential for TBx with focal saturation by additional perilesional

cores to improve the csPCa detection and decrease the detection of low-risk PCa compared to the performance of TBx alone or TBx with SBx (70, 103). Philosophizing about the future, pathological verification by biopsy cores of the suspected disease on imaging may even not be necessary anymore when the imaging modalities have reached diagnostic test characteristics of 100%. Furthermore, the personalized diagnostic pathway needs to be further improved by the development of dynamic prediction models for the follow-up of men considered to be at low-risk of PCa (after the performance of a prostate MRI) or men with a negative biopsy procedure (104).

Important for future PCa research is to invest in research collaborations and sharing of relevant research data, as well as publishing study results according to standardized guidelines to easily reproduce and validate findings. A striking example of a joint effort to resolve several critical questions regarding the screening, diagnosis and treatment of PCa patients, is the EAU lead PIONEER (Prostate Cancer DIagnOsis and TreatmeNt Enhancement through the power of big data in EuRope) project (105, 106). The PIONEER project will assemble, standardize, harmonize and analyze high-quality big data from diverse European populations of PCa patients to provide evidence-based data for improving decision-making. Fortunately, there are more (inter)national initiatives to follow this idea in the years to come.

PART II: CAN RISK STRATIFICATION AT INITIATION AND DURING ACTIVE SURVEILLANCE REDUCE UNNECESSARY TESTS AND OVERTREATMENT WITHOUT MISSING CLINICALLY SIGNFICANT PROSTATE CANCER THAT COULD HARM A PATIENT IF LEFT UNTREATED?

Can we identify those men at high risk of disease upgrading who need a follow-up biopsy using magnetic resonance imaging and clinical parameters, avoiding unnecessary follow-up biopsies in men at low risk of disease upgrading?

Data from the pre-MRI era have shown that Active Surveillance (AS) is a safe strategy for carefully selected men, with a disease-specific survival at long-term follow-up ranging from 94-100% (107-110). The fear of under grading at time of diagnostic biopsy has led to the development of AS protocols with strict criteria for inclusion and monitoring. Many newly diagnosed low- and intermediate-risk PCa patients do not meet these strict eligibility criteria, although only a subgroup of these men will develop metastatic disease if their cancer is left untreated. On the other hand, many men initially considered suitable for AS experience a form of disease reclassification during follow-up and are then advised to switch to an active treatment (108). This indicates that a better selec-

tion at time of diagnosis of men who are suitable for AS and more flexible criteria for disease upgrading during follow-up are necessary (111-113). Therefore, PRIAS recently updated its protocol by recommending the performance of a prostate MRI before every (repeat) biopsy session with in case of a positive MRI the performance of TBx and SBx, using the presence of ISUP grade 2 but with invasive CR/IDC and higher grade PCa at biopsy as upgrading criterion (114). This means that men with ISUP grade 2 without invasive CR/IDC PCa are considered as candidates for AS according to the PRIAS study, and that the presence of ISUP grade 2 PCa is not necessarily a strict exclusion criterion at inclusion or during follow-up (Figure 3).

Additional testing by MRI and TBx can result in accurate patient selection for AS, but comes with an extra invasive procedure next to the already performed repeated tests (115). This could increase the burden for patients on AS, especially for men at (very) low risk of disease upgrading who will experience only little to no benefit from frequent (invasive) follow-up testing. The currently applied one size fits all approach in most AS protocols could as such result in a lot of unnecessary follow-up testing and related costs (116). Furthermore, it is known that over time compliance to AS protocols, mainly because of invasive follow-up biopsies, declines (117). The low biopsy compliance indicates that repeat biopsies are considered burdening for patients and that strategies are needed to safely reduce the number of unnecessary follow-up biopsies to increase adherence to the surveillance protocol, without missing csPCa that could harm a patient (118). Preferably, invasive follow-up testing should only be performed in men with a long life expectancy being at high risk of disease upgrading (Chapter 1). Prostate MRI could potentially help to identify these men at high risk of disease upgrading and thereby being good candidates for invasive follow-up testing, both at initiation and during AS. Refinements in the role of MRI in AS are not yet clearly established in the new PRIAS protocol (114).

In Chapter 7 and 8 refinements in conducting a surveillance policy with prostate MRI were investigated. It was shown that risk stratification based on PI-RADS score with or without PSA-density (PSA-D) could avoid follow-up biopsies in men on AS with PI-RADS score 1-2, in the majority of men with PI-RADS score 3 and even in some carefully selected men with PI-RADS score 4 on MRI. Overall, these risk-based strategies including MRI at initiation or during AS could result in avoiding approximately 60% of follow-up biopsy procedures in the studied cohorts, at the cost of missing a small number of ISUP grade 2 PCa and almost no ISUP grade 3 and higher PCa that likely will be detected within the window of curability during further follow-up (119, 120). The findings in these Chapters were done in AS cohorts where ISUP grade 1 PCa was initially detected by SBx before deciding to perform subsequent surveillance with pre-biopsy prostate

A **- If MRI is not available**

Year	1				2				3		4		5		6		7	
Month	0**	3	6	9	12	15	18	21	24	30	36	42	48	54	60	66	72	78	84
PSA-test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DRE	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Biopsy*	✓				✓								✓						✓
Evaluation	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓

* Repeat biopsy:

a) Standard after 1, 4, 7 en 10 year and subsequently every 5 years.

b) If PSA–DT is 0-10 years repeat biopsy every year is advised.

No more than 1 biopsy per year should be performed

** Time of diagnosis

B **If MRI is available and not used at inclusion**

Year	1				2				3		4		5		6		7	
Month	0***	3	6	9	12	15	18	21	24	30	36	42	48	54	60	66	72	78	84
PSA-test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DRE	✓		✓		✓				✓				✓		✓		✓		✓
Standard Biopsy*	✓				✓								✓						✓
Evaluation	✓	✓	✓		✓				✓		✓		✓		✓		✓		✓
MRI + targeted biopsies**		✓			✓								✓						✓

** MRI 3 months after diagnosis: only targeted biopsies if lesion is visible on MRI (maximum of 3 lesions (2 biopsies per lesion)), no standard TRUS guided biopsies.*

*** If PSA-doubling time <10 years: An MRI is recommended every year (only in the years no standard biopsy is taken). Additional biopsies are indicated if MRI shows progression.*

**** Time of diagnosis*

C **if MRI is available and used at inclusion**

Year	1				2				3		4		5		6		7	
Month	0**	3	6	9	12	15	18	21	24	30	36	42	48	54	60	66	72	78	84
PSA-test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DRE	✓		✓		✓				✓		✓		✓		✓		✓		✓
Standard Biopsy*	✓				✓								✓						✓
Evaluation	✓		✓		✓				✓		✓		✓		✓		✓		✓
MRI + targeted biopsies*	✓				✓								✓						✓
Evaluation	✓																		

** If PSA-doubling time <10 years: An MRI is recommended every year (only in the years no standard biopsy is taken). Additional biopsies are indicated if MRI shows PIRADS progression, more lesions or growth of currently known lesion(s).*

*** Time of diagnosis*

Figure 3. Follow-up schedule of the PRIAS study: A) traditional follow-up schedule without MRI, B) follow-up schedule if MRI is available and not used at inclusion, C) follow-up schedule if MRI is available and used at inclusion (114).
PSA: prostate-specific antigen; DRE: digital rectal examination; MRI: magnetic resonance imaging; PI-RADS: Prostate Imaging-Reporting and Data System; TRUS: transrectal ultrasound; PSA-DT: PSA-doubling time.

MRI. Incorporating prostate MRI at primary PCa diagnosis, as now is recommended by the new (inter)national PCa guidelines, will probably result in a smaller group of men with an overdiagnosis of ISUP grade 1 PCa (44-49). However, extension of the inclusion and monitoring criteria of AS protocols by allowing ISUP grade 2 without invasive CR/IDC PCa as proposed by the new PRIAS protocol means that a substantial part of the men with initially detected ISUP grade 2 PCa is also considered as a good candidate for a surveillance strategy rather than immediate active treatment (114). The group of cancers regarded as 'overdiagnosed' will become larger indicating the persistent necessity for risk-based AS strategies, also in the current MRI era (121). Incorporation of the secondary Gleason 4 growth patterns CR and IDC and thereby shifting the upgrading threshold for active treatment, opens possibilities to avoid even more follow-up biopsy procedures in men on AS since the majority of men on AS, if upgrades, upgrades from ISUP grade 1 to grade 2 without invasive CR/IDC PCa (120, 122). This new upgrading threshold as proposed by the PRIAS study could keep more men on AS and (falsely) exclude less men from AS, thereby reducing the rate of overtreatment and treatment related side-effects.

It can be concluded that risk stratification strategies based on prostate MRI with or without clinical parameters at initiation and during AS can be used to select men at high risk of disease upgrading for follow-up biopsy and avoid unnecessary biopsies in men at low risk of disease upgrading, at the cost of missing only a small amount of upgrading that likely will be detected and treated later on during follow-up. This way of using the prostate MRI, next to help for the guidance of TBx of suspicious prostate lesions, is a step towards a more personalized and refined surveillance approach rather than the current one size fits all approach in AS. It is likely that surveillance management of men on AS will incorporate results from MRI and TBx into multivariable prediction models with the emerging concept of personalized medicine (Figure 4).

Can serial magnetic resonance imaging be used to monitor low-risk prostate cancer patients during follow-up?

Patients on AS following the current updated protocols and guidelines including the performance of pre-biopsy MRI at diagnosis and during further follow-up will, when looking at these current AS protocols, at least undergo two prostate MRIs (i.e. at baseline and confirmatory biopsy). In addition, a considerable part of the patients will undergo three or more prostate MRIs during follow-up (48, 49, 114). This gives radiologists the opportunity to compare two or more MRI scans per patient and determine whether there are radiological changes (e.g. in lesion size/stage/conspicuity/PI-RADS score) visible over time. This could result in a further refinement in the role of MRI in the risk-based selection of AS participants for follow-up testing by also taking radiological

progression on serial MRI into account, although recommendations on clinical utility of such a refinement are still premature (111, 123-125). An MRI-based monitoring strategy in men on AS seems attractive to health care systems and patients, potentially avoiding follow-up biopsy procedures with its attendant morbidities in the absence of radiological progression on serial prostate MRI (126, 127).

In Chapter 8, the guidance of serial prostate MRIs with or without radiological progression (defined according to the PRECISE criteria) in the utility of repeat prostate biopsies at time of confirmatory biopsy in AS was assessed (120, 128). In serial MRI-positive men with and without radiological progression, the overall upgrading as a result of TBx and/or SBx was similar. In both groups the additional value of SBx in upgrading was substantial. These findings argue for still performing repeat biopsy procedures during surveillance in men with and without radiological progression on a positive serial MRI, while repeat SBx in serial MRI-negative men could be considered to be avoided as previously discussed.

Hence, the role of serial prostate MRIs in men on AS is challenging. Clear consensus on how to define radiological progression on serial MRI is still lacking, i.e. volume or diameter thresholds that allow to reliably distinguish between expected interscan variability and true progression are lacking (129). The PRECISE recommendations aim to facilitate a standardized and structured reporting of serial MRIs in men on AS in order to create a robust dataset to further determine the role of MRI (128). Highly experienced radiologists have shown to achieve substantial reproducibility for the PRECISE scoring system (129, 130). There are data showing a more favorable discrimination of the PRECISE scoring system for AS disqualification than shown in Chapter 8 (131). However, a not negligible amount of upgrading to high-risk PCa is still detected in men on AS with an apparent radiological stable low-risk disease on serial positive MRI (132-134). With the currently defined radiological thresholds of csPCa on serial MRI in men on AS the meaning of absence of radiological progression on positive MRI, which comprises a considerable amount of men on AS during follow-up, remains unclear. The absence of radiological progression possibly does not reflect the histopathological status of the disease. Therefore, clear consensus on how to define radiological progression (e.g. by further refined PRECISE criteria) is necessary, which subsequently needs to be validated extensively in clinical AS cohorts to define proper radiological thresholds of csPCa in men on AS. Refinements to the PRECISE criteria that can support risk assessment of patients on AS are for example the use of MRI-derived parameters as the ADC (135, 136).

In conclusion, risk-based patient selection in AS for follow-up biopsy triggered only by radiological progression on serial MRI is not (yet) possible. Currently, such an MRI-

based monitoring strategy will most likely miss a substantial number of high-risk PCa. However, prostate MRI can definitely aid in the risk-based selection for follow-up biopsy. Combining data of clinical predictors (e.g. PSA-D), MRI outcome (i.e. positive or negative) and potentially visible changes on MRI is advisable as risk stratification strategy before deciding to perform a repeat biopsy procedure in men on AS. Doing so, substantial unnecessary follow-up biopsy procedures will be avoided, while maintaining a high detection rate of upgrading to high-risk PCa that could potentially harm a patient if left untreated.

Conclusion

Most well-established AS programs have updated their follow-up protocols by recommending, if available, the performance of a prostate MRI with or without TBx at initiation and during surveillance before every repeat biopsy procedure. Prostate MRI with or without TBx in AS improves the patient selection by early identifying men who harbor higher grade disease, and on the other hand safely including men on AS with high volume low-risk disease. Additional testing by MRI and TBx comes, however, with an extra invasive procedure next to the already performed tests in men on AS. This is especially the case, when the current AS protocols and thereby the one size fits all approaches are conducted. This increases the burden for men on AS, especially for men at low risk of disease upgrading. The role of MRI in men on AS can be further refined. Prostate MRI in AS cannot only be used to help for the guidance of TBx of potential suspicious lesions, but also to better assess someone's risk of disease upgrading to improve the patient selection for invasive follow-up testing. Risk stratification strategies based on prostate MRI outcome, radiological changes on MRI and clinical parameters such as PSA-density can help to identify those men at high risk of disease upgrading who need a follow-up biopsy and safely avoid a biopsy in men at low risk of disease upgrading, both at initiation and during AS. To date, an MRI only-based monitoring strategy is not possible due to substantial added value of repeat SBx in all MRI-positive men, and because the definition of radiological progression on MRI needs to be strengthened. Furthermore, the histological secondary Gleason 4 patterns invasive cribriform growth and intraductal carcinoma are helpful in identifying men with ISUP grade 2 PCa that are suitable for AS. Incorporation of these growth patterns in risk assessment can further help to avoid follow-up biopsy procedures and keep more men safely on AS, thereby reducing overtreatment and treatment related side-effects. Extension of the inclusion and monitoring criteria of AS protocols makes a surveillance policy an interesting and safe option for a larger group of men with localized PCa, despite the new PCa guidelines that recommend the performance of a primary pre-biopsy MRI at diagnosis. The suggested improvements for AS protocols in this general discussion constitute the first

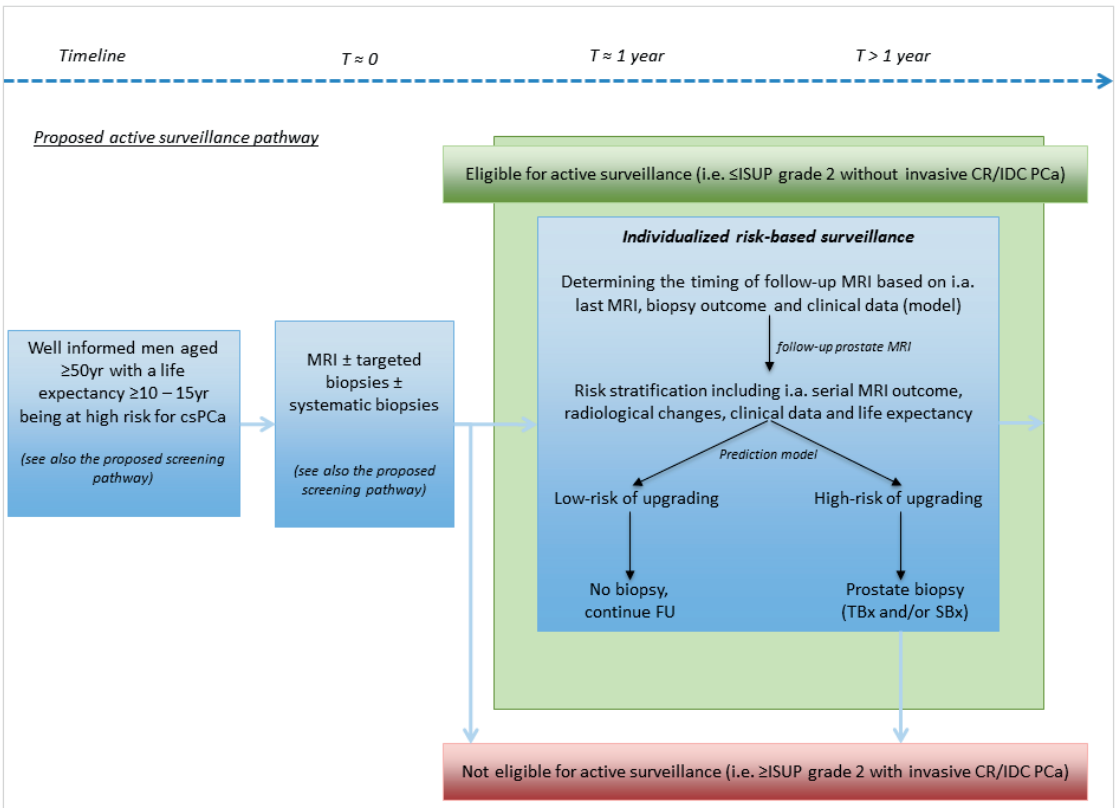

Figure 4. Proposed new active surveillance pathway.
PCa: prostate cancer; csPCa: clinically significant prostate cancer; MRI: magnetic resonance imaging; ISUP: International Society of Urological Pathology; CR: cribriform growth; IDC: intraductal carcinoma; TBx: targeted biopsy; SBx: systematic biopsy; FU: follow-up.

steps towards a more personalized AS pathway as proposed in figure 4, which could be more (cost-)effective and count on more physician's and patient's adherence.

Future perspectives

Following the course of a man's PCa with an AS protocol is most likely something that continues for many years. Developing individually tailored risk stratification strategies will be the key for (a continuous) successful implementation of AS. Similar to other stages of the PCa pathway from diagnosis to palliative care, prediction models are also being introduced in AS. The currently available models for prediction of disease upgrading perform reasonably well, but need further adaptation and external validation prior to widespread adoption in clinical practice (137-141). Figure 4 shows a proposal for an individualized risk-based AS pathway which utilizes methods for an improved prediction of a patient's risk of disease upgrading. It is likely that in the future follow-up of men on AS will be more personalized making use of dynamic risk prediction models that incorporate both repeated measurements of clinical and radiological data, as potentially newly validated risk stratification tools like novel blood and urinary (genetic) biomarkers (91, 142-148). These dynamic prediction models should also take into account the patient's comorbidity and life expectancy, and thereby his ability to receive active treatment (1, 149). The work from Tomer et al. is a step in this direction in which the choice, timing and intensity of biopsy is based on a personalized schedule weighing the number of biopsies and the delay in the detection of disease upgrading (150, 151). The next step would be the incorporation of prostate MRI data to this personalized model to improve the prediction of disease upgrading. The resulting predictions can then be used to decide the timing of the next MRI as well as to make a decision about the biopsy intensity (TBx ± SBx). Key component to reliably use prostate MRI and TBx data for proper risk assessment during AS is well trained (uro-)radiologists and urologists (152). It is likely that with the increased use of MRI and TBx in clinical practice and the increasing supply of prostate MRI and TBx training programs, physicians involved in PCa care will become more experienced in interpreting and performing MRI and TBx (94, 95). MRI reports will become more structured and standardized which will further improve the quality and value of prostate MRI in AS. In addition, the increased use of MRI will generate sufficient research data that could be used to strengthen the definition of radiological progression on follow-up MRI (130). As a result of the growth in demand for MRI, the workload for radiology departments will also increase. Introduction of a biparametric MRI protocol could be a solution for the increased workload and could potentially result in an optimized workflow while maintaining similar detection of disease upgrading compared to a multiparametric MRI scan protocol (99, 152, 153). On the other hand, the use of prostate MRI opens other new (research) possibilities. MRI does not only produce rough anatomical maps, it can also be used to get more in-depth

knowledge on functional aspects of cellular structure or information on a cellular level (154, 155). These aspects need more research in PCa and AS. MRI might also be supplemented by other new imaging modalities (e.g. prostate-specific membrane antigen [PSMA] positron-emission tomography [PET]) in AS, which could further improve risk stratification and especially the patient selection for AS at initiation (156-158). However, improvement of the quality of prostate MRIs and their radiological reports takes priority over exploring the role of PSMA-PET in AS. The risk of promising new tools like the PSMA-PET is extensively and unnecessary use in all men. In addition, it remains to be seen whether the upcoming use of in-office transperineal prostate biopsy with local anesthesia by better sampling of the prostate already can result in an improved risk stratification and selection for AS without the use of extra imaging modalities (126, 131, 159, 160). In this process of improving prediction in AS with potentially promising new risk models, biomarkers, imaging modalities and biopsy methods, the patient and his quality of life have to be at the center of it all (161). An AS strategy for low-risk PCa could be regarded as a chronic disease and therefore, although treatment related side-effects are delayed or even completely avoided, still substantially impact a patient's quality of life. The diagnosis and continuous medical checkups can cause patients experiencing a loss of control over their disease and themselves. Therefore, in the current digital era the development of innovative electronic or mobile apps that could help to guide patients through this process is meaningful. These so-called eHealth applications provide patients with the opportunity to monitor their disease, plan and manage appointments and questions for their physician (162, 163). This will encourage active participation and can have a positive effect on the quality of life of the patient. Furthermore, it can improve the quality of care as it can focus on patients' needs more specifically (i.e. personalized care). Therefore, within the PRIAS study the 'MyPSA'-app is being developed with this purpose (164). Finally, a patient's diet will play an increasing role in future PCa personalized management. Although there is no clear evidence that dietary differences may influence PCa progression, a balanced diet and regular exercise are recommended for all PCa patients because they are beneficial for overall health (165). Specifically, it is suggested that green tea polyphenols, soy isoflavones, phytoestrogens, lycopene, red wine and sunshine may have a favourable effect on PCa (23). Researchers will continue to look for foods and dietary supplements that can help in PCa patients.

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PART IV

APPENDICES

SUMMARY

Chapter 1 (General Introduction) gives an overview of the pathophysiology, epidemiology and diagnosis of prostate cancer. The concepts of screening and detection, active surveillance and risk stratification in prostate cancer care are introduced. Main objective of this thesis is to study whether the use of risk stratification strategies at time of prostate cancer detection (Part I) and at initiation and during an active surveillance strategy for low-risk prostate cancer (Part II) could safely reduce the harms of prostate cancer screening without affecting the benefit of screening, and reduce the harms of unnecessary immediate active treatment while having full cancer control. Several research questions regarding this objective are formulated in **Chapter 1**, and are answered in **Chapter 9** (General Discussion).

Part I – Screening and Detection

Chapter 2 reviews the most recent evidence for the currently available risk stratification tools in the detection of clinically significant prostate cancer (csPCa), and evaluates diagnostic strategies that combine these tools. Merging biomarkers, risk calculators and prostate MRI results in higher diagnostic performances than their use as standalone tests. In state-of-the-art clinical decision-making the patient should benefit from further testing and treatment, even when the diagnostic test is 'easy-to-perform'. The way forward in prostate cancer (PCa) diagnosis seems to be multivariable risk assessment based on blood and clinical parameters, potentially extended with information from urine samples, as a triaging test for the selection of candidates for subsequent prostate MRI and biopsy. Large prospective and comparative studies are necessary to fully assess the potentials and risks of these combined diagnostic strategies.

Reporting on the basis of long-term follow-up without PSA contamination seems crucial to get insight into the full effect of PSA-based PCa screening. In **Chapter 3** it was shown that data from the first pilot study of the European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam section (median follow-up time of 19 years, almost no PSA contamination and more than 60% of men deceased at time of analysis) suggest that there could be a more substantial reduction in metastatic disease (54%) and PCa-specific mortality (52%) in favor of PSA-based PCa screening than previously reported. Confirmation of these findings in the ongoing trials is necessary to continue the discussion and evaluation of the benefits and harms of screening for PCa.

One of the biggest challenges in PCa screening still remains to decrease its harms without affecting its benefits. Better prediction of a patient's risk of harboring csPCa and thereby better selection for referral for further testing (i.e. MRI, biopsy) could reduce

the percentage of unnecessary testing and cause a more favorable clinically significant to insignificant ratio of PCa detected. In the Dutch health care system general practitioners (GPs) play an important role since they are the first link in the chain of many diagnostic pathways. The implementation of validated PCa diagnostic risk models in the primary care could be the first optimization step in the PCa diagnostic pathway and may help the GPs to facilitate informed decision-making and improve patient selection for referral. In **Chapter 4** it was shown that the use of the ERSPC Rotterdam Prostate Cancer Risk Calculator (RPCRC) in the primary care could reduce the rate of men with a PSA level ≥3.0 ng/ml referred to the urologist with almost 50%, without missing any csPCa in men considered to be at low-risk of PCa.

The recently updated PCa guidelines recommend to perform a pre-biopsy prostate MRI in all men with a suspicion of csPCa. However, performing an MRI in all men with an elevated PSA level is a challenge due to limits in resources, capacity and availability of expertise. In addition, in a considerable proportion of patients the MRI will not show any abnormalities making it thereby potentially a redundant test. Furthermore, some patients will have false positive abnormalities on MRI resulting in unnecessary biopsies. Multivariable risk stratification could potentially help to better select upfront which men will benefit from a prostate MRI and subsequent biopsies. **Chapter 5** shows the preliminary results of a large prospective multicenter clinical effectiveness study, investigating the performances of a new risk-based PCa diagnostic strategy. The first clinical outcomes provide evidence that the ERSPC RPCRC can be used as upfront risk stratification tool for the selection of biopsy-naïve candidates for an MRI and biopsy procedure. The ERSPC RPCRC-MRI pathway resulted in men considered to be at high-risk of PCa in a csPCa and low-risk PCa detection rate of 27% and 9%, respectively. Restricting prostate MRIs and biopsies to only high-risk men could reduce 20% of MRIs and 59% of biopsies performed, at the cost of missing only 4% csPCa.

An important clinical predictor of csPCa is the PSA-density (i.e. PSA divided by prostate volume [PSA-D]). Especially in the PSA range of 4-20ng/ml, PSA-D could improve cancer risk stratification compared with PSA alone. In **Chapter 6** the added value of PSA-D in predicting csPCa in PI-RADS 3 cases is shown. Applying solely PSA-D as risk stratification tool in PI-RADS 3 men could result in 25% less targeted biopsy (TBx) sessions and 11% less low-risk PCa diagnoses, missing only 5% csPCa. Risk stratification of PI-RADS 3 cases could further be improved by a model-based approach in which MRI-derived parameters (i.e. largest index lesion diameter) and clinical parameters (i.e. PSA-D and age) are combined in a multivariable prediction model. Such a model-based approach in PI-RADS 3 men, would result in 34% less TBx sessions and 23% of low-risk PCa diagnoses avoided, missing no more than 5% of csPCa diagnoses.

Part II – Active Surveillance

The currently applied one size fits all approach in most Active Surveillance (AS) protocols could result in a lot of unnecessary follow-up testing and related costs. Strategies are needed to safely reduce the number of unnecessary follow-up biopsies to increase adherence to the surveillance protocol, without missing csPCa that could harm a patient. Prostate MRI could potentially help to identify these men at high risk of disease upgrading and thereby being good candidates for invasive follow-up testing, both at initiation and during AS. In **Chapter 7 and 8** refinements in conducting a surveillance policy with prostate MRI were investigated. It was shown that risk stratification based on PI-RADS score with or without PSA-D could avoid follow-up biopsies in men on AS with PI-RADS score 1-2, in the majority of men with PI-RADS score 3 and even in some carefully selected men with PI-RADS score 4 on prostate MRI. Overall, these risk-based strategies including MRI at initiation or during AS could result in avoiding approximately 60% of follow-up biopsy procedures in the studied cohorts, at the cost of missing a small number of International Society of Urological Pathology (ISUP) grade 2 PCa and almost no ISUP grade 3 and higher PCa that likely will be detected within the window of curability during further follow-up.

An MRI only-based monitoring strategy in men on AS seems attractive to health care systems and patients, potentially avoiding follow-up biopsy procedures with its attendant morbidities in the absence of radiological progression on serial prostate MRI. In **Chapter 8**, the guidance of serial prostate MRIs with or without radiological progression (defined according to the PRECISE criteria) in the utility of repeat prostate biopsies at time of confirmatory biopsy in AS was assessed. In serial MRI-positive men with and without radiological progression, the overall upgrading as a result of TBx and/or systematic biopsy (SBx) was similar. In both groups the additional value of SBx in upgrading to csPCa was substantial. These findings argue for still performing repeat biopsy procedures during surveillance in men with and without radiological progression on a positive serial MRI.

SAMENVATTING

In **Hoofdstuk 1** (Algemene Introductie) wordt een overzicht gegeven van de pathofysiologie, epidemiologie en diagnose van prostaatkanker. De begrippen 'screening en detectie', 'active surveillance' en 'risicostratificatie' in de prostaatkankerzorg worden geïntroduceerd. Het doel van dit proefschrift is om te bestuderen of de toepassing van risicostratificatie-strategieën op het moment van de detectie van prostaatkanker (Deel I) en op het moment van start en tijdens een active surveillance strategie voor laag-risico prostaatkanker (Deel II) veilig de nadelen van prostaatkankerscreening zou kunnen reduceren zonder het voordeel van screenen te beïnvloeden, evenals de nadelen van onnodige actieve behandeling zou kunnen reduceren zonder de controle over de prostaatkanker te verliezen. Verschillende onderzoeksvragen met betrekking tot dit doel zijn geformuleerd in **Hoofdstuk 1**, en worden beantwoord in **Hoofdstuk 9** (Algemene Discussie).

Deel I – Screening en Detectie

In **Hoofdstuk 2** wordt het meest recente bewijs voor de hedendaags beschikbare risicostratificatie hulpmiddelen in de detectie van klinisch significant prostaatkanker (csPCa) besproken, en worden diagnostische strategieën die deze hulpmiddelen combineren geëvalueerd. Het combineren van biomarkers, risicocalculatoren/predictiemodellen en prostaat MRI bevindingen resulteert in betere diagnostische prestaties dan het gebruik van deze hulpmiddelen afzonderlijk van elkaar. In de moderne klinische besliskunde moet een patiënt voordeel halen uit verdere onderzoeken en behandelingen, zelfs als de diagnostische test 'makkelijk' uitvoerbaar is. De te volgen koers in de diagnostiek naar prostaatkanker (PCa) lijkt het gebruik van multivariabele risicostratificatie gebaseerd op bloedwaardes en klinische karakteristieken, eventueel uitgebreid met data uit urine-onderzoeken, om patiënten te selecteren voor een prostaat MRI en biopten. Grote prospectieve en vergelijkende studies zijn nodig om de mogelijkheden en risico's van zulke gecombineerde diagnostische strategieën volledig in kaart te brengen.

Onderzoeken gebaseerd op lange termijn data zonder PSA contaminatie zijn cruciaal om inzicht te krijgen in het volledige effect van PSA-gebaseerde prostaatkankerscreening. In **Hoofdstuk 3** wordt gesuggereerd met data van de eerste pilot studie van de European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam sectie (mediane follow-up van 19 jaar, bijna geen PSA contaminatie en meer dan 60% van de mannen overleden op het moment van analyse) dat er een substantieel grotere reductie in gemetastaseerde ziekte (54%) en PCa-specifieke dood (52%) in het voordeel van PSA-gebaseerde prostaatkankerscreening zou kunnen zijn dan tot op heden is gerapporteerd. Een bevestiging van deze bevindingen in de lopende onderzoeken is

cruciaal om de discussie en evaluatie van de voor- en nadelen van het screenen naar PCa te kunnen continueren.

Een van de grootste uitdagingen binnen de prostaatkankerzorg blijft het verminderen van de nadelen van screening zonder de voordelen van het screenen naar PCa te beïnvloeden. Een betere voorspelling van het risico van een patiënt op csPCa en daarmee een betere selectie voor een verwijzing voor verder onderzoek (m.a.w. MRI, biopten) zou het percentage onnodige onderzoeken kunnen reduceren en een gunstigere verhouding tussen de detectie van klinisch significant en insignificant PCa kunnen bewerkstelligen. In de Nederlandse gezondheidszorg spelen huisartsen een belangrijke rol, aangezien zij de eerste schakel zijn in veel diagnostische zorgpaden. De implementatie van gevalideerde PCa diagnostische risicomodellen in de eerstelijnszorg zou de eerste optimalisatiestap in het PCa diagnostische zorgpad kunnen zijn en zou huisartsen kunnen ondersteunen in de gedeelde geïnformeerde besluitvorming en in verbetering van de patiëntenselectie voor een verwijzing naar de tweede lijn. In **Hoofdstuk 4** wordt aangetoond dat het gebruik van de ERSPC Rotterdam Prostate Cancer Risk Calculator (RPCRC) / Prostaatwijzer in de eerste lijn het percentage mannen met een PSA ≥3.0 ng/ml verwezen naar de uroloog zou kunnen reduceren met bijna 50%, zonder het missen van csPCa in de mannen die zijn beoordeeld als laag-risico op PCa.

De recent bijgewerkte PCa richtlijnen bevelen de verrichting van een pre-biopsie prostaat MRI in alle mannen met een verdenking op csPCa aan. Echter is het verrichten van een MRI in alle mannen met een verhoogde PSA waarde een uitdaging gezien de beperkingen in capaciteit en expertise. Daarnaast zal de MRI in een aanzienlijk deel van deze mannen geen afwijkingen laten zien, waardoor de MRI in deze mannen beschouwd zou kunnen worden als een overtollig onderzoek. Verder zal in een deel van de patiënten de MRI vals-positief zijn, resulterend in onnodige prostaatbiopten. Multivariabele risicostratificatie zou kunnen helpen om initieel beter te selecteren welke mannen zullen profiteren van een prostaat MRI en zo nodig biopten. In **Hoofdstuk 5** worden de eerste resultaten van een groot prospectief multicenter onderzoek, dat een nieuw risico-gebaseerd PCa diagnostisch zorgpad bestudeert, besproken. De eerste resultaten laten zien dat de ERSPC RPCRC / Prostaatwijzer gebruikt kan worden als initieel risicostratificatie hulpmiddel voor de selectie van biopsie-naïve mannen voor een MRI en bioptprocedure. Het Prostaatwijzer-MRI zorgpad resulteert in hoog-risico mannen in detectiepercentages van csPCa en laag-risico PCa van respectievelijk 27% en 9%. Het verrichten van prostaat MRI's en biopten in alleen hoog-risico mannen zou het aantal verrichtte MRI's en biopten met respectievelijk 20% en 59% kunnen reduceren, ten koste van het missen van 4% csPCa.

Een belangrijke klinische voorspeller van csPCa is de PSA-densiteit (m.a.w. het PSA gedeeld door het prostaatvolume [PSA-D]). Met name in het PSA gebied 4-20ng/ml, zou de PSA-D de risicostratificatie kunnen verbeteren in vergelijking met gebruik van alleen de PSA waarde. In **Hoofdstuk 6** wordt de toegevoegde waarde van PSA-D in de voorspelling van csPCa in PI-RADS 3 mannen bestudeerd. Het toepassen van alleen de PSA-D als risicostratificatie hulpmiddel in PI-RADS 3 mannen zou kunnen resulteren in 25% minder gerichte biopten (TBx) sessies en 11% minder laag-risico PCa diagnoses ten koste van het missen van 5% csPCa. Risicostratificatie in PI-RADS 3 mannen zou verder verbeterd kunnen worden met een op een model-gebaseerde benadering, waarin MRI-karakteristieken (m.a.w. grootste index laesiediameter) en klinische karakteristieken (m.a.w. PSA-D en leeftijd) worden gecombineerd tot een multivariabel predictiemodel. Zo een risicostratificatie strategie in PI-RADS 3 mannen zou kunnen resulteren in 34% minder TBx sessies en 23% minder laag-risico PCa diagnoses, ten koste van het missen van niet meer dan 5% csPCa diagnoses.

Deel II – Active Surveillance

De hedendaagse universele benadering in de meeste Active Surveillance (AS) protocollen zou kunnen resulteren in veel onnodige vervolgonderzoeken met daarbij komende kosten. Er zijn strategieën nodig om veilig het aantal onnodige vervolgbiopten te verminderen om op die manier de naleving van AS protocollen door patiënt en dokter te vergroten, zonder dat csPCa wordt gemist die een patiënt schade in de vorm van uitzaaiingen en/of de dood zou kunnen toebrengen. Prostaat MRI zou zowel op het moment van start als tijdens AS kunnen helpen in het beter identificeren van mannen met een verhoogd risico op meer agressieve vormen van PCa en daarmee dus zijnde goede kandidaten voor invasieve vervolgonderzoeken. In de **Hoofstukken 7 en 8** worden verfijningen in het uitvoeren van een AS beleid met prostaat MRI onderzocht. Er wordt aangetoond dat een risicostratificatie gebaseerd op de PI-RADS score met of zonder PSA-D vervolgbiopten in mannen op AS met een PI-RADS score 1-2, in de meeste mannen met een PI-RADS score 3 en zelfs in nauwkeurig geselecteerde mannen met een PI-RADS 4 score op MRI zou kunnen voorkomen. Samenvattend zouden deze risicogebaseerde strategieën op het moment van start en tijdens AS kunnen resulteren in het voorkomen van ongeveer 60% van de vervolgbiopten in de onderzochte cohorten, ten koste van het missen van een klein aantal International Society of Urological Pathology (ISUP) graad 2 PCa and bijna geen ISUP graad 3 en hoger PCa. Deze in eerste instantie gemiste hooggradige tumoren zullen vermoedelijk gedurende het verdere vervolgtraject gedetecteerd worden en dan nog steeds te genezen zijn.

Een vervolgstrategie gebaseerd op alleen MRI bevindingen in mannen op AS lijkt attractief voor gezondheidszorgsystemen en patiënten vanwege de potentie om

vervolgbiopten en de bijkomende morbiditeit achterwege te laten in mannen zonder radiologische progressie op herhaalMRI's. In **Hoofdstuk 8** wordt het nut van vervolgbiopten op het moment van verificatiebiopten in AS in mannen met herhaalMRI's met én zonder radiologische progressie (gedefinieerd volgens de PRECISE criteria) bestudeerd. In zowel mannen met een positieve MRI mét radiologische progressie als in mannen met een positieve MRI zónder radiologische progressie, was het percentage reclassificatie naar een meer agressieve vorm van PCa vergelijkbaar. In beide groepen van mannen was de toegevoegde waarde van systematische prostaatbiopten substantieel. Deze bevindingen pleiten voor het blijven verrichten van vervolgbiopten tijdens AS in mannen met én zonder radiologische progressie op een positieve herhaalMRI.

ABOUT THE AUTHOR

Daniël Fernando Osses was born in Leiderdorp on the 28th of February 1990. He completed his secondary school in 2008 at the Bonaventuracollege in Leiden. From 2008 until 2015 he studied medicine at the University of Leiden. The final year of his medical studies consisted of a dedicated year at the Urology department of the Haga Teaching Hospital in The Hague under the supervision of drs. J.D. Tijsterman, drs. F.M.J.A. Froeling and dr. H. Roshani. After obtaining his medical degree he worked as a resident (not in training) at the Urology department of the Haga Teaching Hospital. From April 2017 until December 2020 he worked on his PhD project at the departments of Urology and Radiology & Nuclear Medicine of the Erasmus University Medical Center in Rotterdam under the supervision of prof. dr. M.J. Roobol, prof. dr. G.P. Krestin and dr. I.G. Schoots. From July 2020 until March 2021 he worked as a resident (not in training) at the Urology department of the Canisius-Wilhelmina Hospital in Nijmegen under the supervision of dr. D.M. Somford. As part of his Urology traineeship, he is currently working as a resident at the General Surgery department of the Rijnstate Hospital in Arnhem under the supervision of dr. J.H.P. Lardenoije. In the future, he will continue this traineeship at the Urology departments of the Canisius-Wilhelmina Hospital (supervisor: dr. D.M. Somford) and Radboud University Medical Center (supervisors: prof. dr. J.A. Witjes and dr. B.B.M. Kortmann) in Nijmegen.

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LIST OF ABBREVIATIONS

4K	four-kallikrein
ADC	apparent diffusion coefficient
ADT	androgen deprivation therapy
Apps	mobile applications
AS	active surveillance
AUA	American Urological Association
AUC	area under the receiver operation curve
BPH	benign prostatic hyperplasia
bPSA	benign PSA
C-arm	control arm
CR	cribriform growth pattern
csPCa	clinically significant prostate cancer
CT	computed tomography
DCE	dynamic contrast enhanced
DRE	digital rectal examination
DWI	diffusion weighted imaging
EAU	European Association of Urology
EBRT	external beam radiation therapy
ERSPC	European Randomized study of Screening for Prostate Cancer
fPSA	free PSA
FU	follow-up
G	ISUP grade
GG	grade group
GP	general practitioner
GS	gleason score
GWAS	genome wide association studies
hK2	human kallikrein 2
IDC	intraductal carcinoma
iPSA	intact PSA
IQR	interquartile range
ISUP	International Society of Urological Pathology
LUTS	lower urinary tract symptoms
M+	metastatic disease
MiPS	MiProstate Score
mpMRI	multiparametric MRI
MRI	magnetic resonance imaging
MRI-TBx	MRI-targeted prostate biopsies

MRI ± TBx	MRI with or without TBx
MR PROPER	MRI PROstate with Prior Risk Assessment
mRNA	messenger RNA
ND	not determined
Non-csPCa	clinically insignificant prostate cancer
NND	number needed to diagnose
NNI	number needed to invite
NNS	number needed to screen
NPV	negative predictive value
PCa	prostate cancer
PCA3	prostate cancer antigen 3
PCPT	Prostate Cancer Prevention Trial
PET	positron-emission tomography
PHI	Prostate Health Index
PIONEER	Prostate Cancer DIagnOsis and TreatmeNt Enhancement through the power of big data in EuRope
PI-RADS	Prostate Imaging – Reporting and Data System
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PPV	positive predictive value
PRECISE	Prostate Cancer Radiological Estimation of Change in Sequential Evaluation
PRIAS	Prostate cancer Research International Active Surveillance
PROBASE	Prostate Cancer Early Detection Study Based on a "Baseline" PSA Value in Young Men
ProtecT	Prostate Testing for Cancer and Treatment trial
PSA	prostate-specific antigen
PSA-D	PSA-density
PSA-DT	PSA-density
PSMA	prostate-specific membrane antigen
PV	prostate volume
QALYs	quality-adjusted life years
QoL	quality of life
RARP	robot assisted radical prostatectomy
RC	risk calculator
RCT	randomized controlled trial
ROC	receiver-operating characteristic curve
RPCRC	Rotterdam Prostate Cancer Risk Calculator
RR	relative risk

S-arm	screening arm
S3M	Stockholm-3 model
SBx	systematic prostate biopsy
START	Standards of reporting for MRI-targeted biopsy studies
T2W	T2-weighted
TBx	targeted prostate biopsy
tPSA	total PSA
TRUS	transrectal ultrasound
TRUS-Bx	transrectal ultrasound systematic biopsy
US	ultrasound
USA	United States of America
USPSTF	United States Preventive Services Task Force

AUTHOR AFFILIATIONS

Peter Albers	University Düsseldorf, Medical Faculty, Düsseldorf, Germany *Department of Urology*
Arnout R. Alberts	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Urology*
Christian Arsov	University Düsseldorf, Medical Faculty, Düsseldorf, Germany *Department of Urology*
Chris H. Bangma	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Urology*
Gonny C.F. Bausch	STAR-SHL Medical Diagnostic Center, Rotterdam, The Netherlands *GP Laboratory*
Frank-Jan H. Drost	Erasmus University Medical Center, Rotterdam, The Netherlands *Departments of Urology AND Radiology & Nuclear Medicine*
Irene Esposito	University Düsseldorf, Medical Faculty, Düsseldorf, Germany *Department of Pathology*
Gabriel P. Krestin	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Radiology & Nuclear Medicine*
Theo van der Kwast	Toronto General Hospital, Toronto, Canada *Department of Pathology*
Geert J.L.H. van Leenders	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Pathology*
Henk B. Luiting	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Urology*
Daniël F. Osses	Erasmus University Medical Center, Rotterdam, The Netherlands *Departments of Urology AND Radiology & Nuclear Medicine*
Sebastiaan Remmers	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Urology*
Monique J. Roobol	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Urology*
Lars Schimmöller	University Düsseldorf, Medical Faculty, Düsseldorf, Germany *Department of Diagnostic and Interventional Radiology*
Ivo G. Schoots	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Radiology & Nuclear Medicine*
Fritz H. Schröder	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Urology*
Jan F.M. Verbeek	Erasmus University Medical Center, Rotterdam, The Netherlands *Department of Urology*

DANKWOORD

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De term 'Uroburo' heb ik zojuist al even laten vallen, en ik ben één van de gelukkigen geweest die deel uit mocht maken van deze mooie club. Leden van het eerste uur, Conja en Marlies, bedankt voor jullie geweldige werk voor het team en de heerlijke kletspraatjes die we gevoerd hebben. Jozien en Maaike, dank voor jullie hulp om MR PROPER tot een succes te maken in het Prostaatkankercentrum. Arnout, wat mooi dat ik jou nog 3 maanden mee heb mogen maken als onderzoeker voordat je professioneel "krasjes" bent gaan zetten. Ik hoop dat onze urologische wegen elkaar nog vaker zullen kruisen in de toekomst. Frank-Jan of gewoon FJ, mijn eerste echte onderzoeksavontuur naast MR PROPER was toch echt de befaamde Cochrane review met jou. Jouw positiviteit en doorzettingsvermogen zorgen ervoor dat wat er ook gebeurt, het altijd goed zal komen. Jan oftewel Janneman, ik heb ontzettend van je verhalen, avonturen en nutteloze 'feitjes' genoten en zal nooit je breakdancemoves uit Barcelona vergeten. Sebastiaan oftewel Sebas, veel dank voor je hulp wanneer het een en ander mijn statistische pet weer te boven ging en natuurlijk je altijd lekkere koekjes en koffie uit de corner. Henkie, bedankt voor de fantastische uurtjes CODC met veel snoep en de heerlijke frustraties rondom het biopteren. Avondje uit in Groningen moeten we maar snel herhalen nu je daar in opleiding tot uroloog gaat. Daan, thanks voor de biertjes op congres. Renée, succes met mijn 'erfenis' en jouw andere projecten, dat gaat helemaal goed komen. Ivo, veel plezier in dit team, je bent echt een bofkont. Ook Peter, Kai en Nuno, de internationale tak van het Uroburo, thanks for the pleasent cooperation. En dan tot slot, de stille kracht achter het Uroburo, Lionne! Super bedankt voor je hulp het eerste jaar van mijn promotietraject toen we nog kamergenoten waren op de 17^{e}, maar ook daarna kon ik altijd bij je terecht voor eigenlijk alles.

Heel veel dank ook aan al mijn andere collega-onderzoekers van het Erasmus MC voor de zeer prettige werkdagen, leuke feesten en partijen, skireizen, congresbezoeken en andere rariteiten zoals avondjes in Groningen of Nijmegen. Zonder jullie was het zeker een stuk minder aangenaam geweest. We waren een mooi stel bij elkaar: Toscane, Ilse, Chris, Isabel, Bodine, Lisanne, Thomas, Tess, Sophie, Rosa, Michelle, Joep, Mathijs. Wanneer weer broodje Dyna bij Dennis?

Alle andere RUAG leden, bedankt voor de gezellige tijd.

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De collega's in het Rijnstate wil ik graag bedanken voor de fijne start. Ik kijk uit naar de rest van mijn leerzame tijd bij jullie.

De collega's van het HagaZiekenhuis, bedankt dat ik bij jullie mijn eerste stapjes binnen het urologische vak heb mogen zetten. De affiniteit met het prostaatkankeronderzoek is bij jullie begonnen.

De afgelopen 4,5 jaar waren zeker een stuk minder leuk geweest zonder al mijn lieve familie en vrienden. Dank voor jullie interesse, goede zorg en bereidheid ons zo nu en dan op te zoeken in 't Beuningse.

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De mannen van A.H.C. SAP, lekker clubje met 12 unieke karakters. Ondanks dat sommigen ruim de 30 gepasseerd zijn, is men nooit te beroerd om een potje beerbasketball te spelen (de beker staat in Beuningen ;)), een weekend frituur van Snackbar Osses te eten in een Roompotje of los te gaan in de Cloos na een Whiskeyavond. Hoogtepunten van de afgelopen jaren zijn uiteraard de Lustrumreis naar Ierland én de TOPreis naar Sint Maarten geweest.

Papa Jesse, één van de 3 MooieManneee! Dank voor je gezelligheid, liefde, kerstdinertjes, gedeelde vrouwelijk 'insta' schoon en goede kampvuurgesprekken.

Verse Meul, ik zie je graag, waardeer je interesse en goede muzieksmaak, en kan ontzettend van je genieten wanneer we op een festival, Fiesta Macumba of ergens in Berlijn staan te swingen. Dank voor de zorgeloze tijd samen, alsof we ons soms op Curaçao met je bevinden. Misschien ideetje voor een nieuwe vakantie?

Het Oud Heren Dispuut oftewel OHD, als we bij elkaar komen kunnen we onze oude rollen moeiteloos vinden en is het altijd als vanouds met jullie. Koningsdag 2021 is ook zeker een dag geweest om nooit meer te vergeten!

De Linkeballen-groep, fietsende Sappers aangevuld met vuurpijl Roderick en vroege vogel BacoLen. Dank voor alle fietsavonturen in de Alpen, Vogezen of gewoon dichtbij huis. Ik hoop dat ik snel weer mijn naam als Ossedor waar kan maken.

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Hammetje, Pumba, Blaffer, Bertie, Raffie en adoptiepoes Hommeltje, soms wat frustraties maar hoofdzakelijk dank voor het lachen en de ontspanning. We zijn gek op jullie!

Lieve Javier, grote kleine broer, inmiddels opgegroeid van Dragon Ball Z animatie tot een volwassen kerel met veel talenten. Daar ben ik erg trots op. Blij ook om te zien hoe

Elzita jou en ons gezin aanvult. Het is een eer om je als één van de paranimfen achter me te hebben staan tijdens de verdediging.

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Tot slot, lieve Anouk oftewel Koekie! Niemand had kunnen voorspellen dat na onze eerste ontmoeting in De Mapo in september 2014, wij nu al ruim 6,5 jaar zeer gelukkig samen zouden zijn. Ik wil je graag bedanken voor je vrolijke karakter en altijd aanwezige lach, je onvoorwaardelijke vertrouwen en geloof in mij, jouw geduld en gave om mij te laten ontspannen en mijn autistische/neurotische trekjes even te doen vergeten, alle geweldige reizen en avonturen die we samen hebben beleefd, de manier waarop ik met jou het allerbeste kan samenwerken waardoor we het samen steeds weer zo ver schoppen in dit leven en je unieke humor die mij dagelijks aan het lachen maakt. Je maakt me heel gelukkig en ik ben daarom trots dat spoedig ons eerste kind geboren zal worden. Ik kan niet wachten op wat wij nog samen allemaal gaan beleven!

ERASMUS UNIVERSITY ROTTERDAM

PHD PORTFOLIO

Daniël Fernando Osses

Description	Organizer	EC
Required		
Prostaatkanker Overleg 2017, Rotterdam (2017)		0.30
IKNL werkgroep Urologische Tumoren 2017, Rotterdam (2017)		0.30
Courses OpenClinica, LimeSurvey and GemsTracker (2017)		1.00
Erasmus MC - Biomedical English Writing (2017)		2.00
Oral presentation at the ERSPC meeting 2017, Rotterdam (2017)		0.50
Oral presentation at Sectiedag Abdomen Radiologie 2017, Rotterdam (2017)		0.50
Erasmus MC - BROK® (Basic course Rules and Organisation for Clinical researchers) (2017)		1.50
Erasmus MC - Basic Introduction Course on SPSS (2017)		1.00
Course on coaching bachelor students (2018)		0.30
Oral presentation at Externe refereeravond urologie Erasmus MC 2018, Rotterdam (2018)		0.50
GAP3 Prostate Cancer Active Surveillance Annual Meeting 2018, Copenhagen (2018)		0.30
Presentations at EAU annual meeting 2018, Copenhagen (2018)		1.00
Oral presentation at STAR-SHL Medische Staf, Rotterdam (2018)		0.50
EAU Review 2018, Zeist (2018)		0.30
Erasmus MC - Scientific Integrity (2018)		0.30
Intervision on coaching (2018)		0.20
AUA annual meeting 2018 (2018)		1.00
Presentations at AUA annual meeting 2018, San Francisco (2018)		1.00
Poster presentation at NVU Voorjaarsvergadering 2018, Nijmegen (2018)		0.50
Erasmus MC - CPO-course: Patient Oriented Research (2018)		0.30
Oral presentation at Post EAUN meeting 2018, Amersfoort (2018)		0.50
Talentinterview training in coaching (2018)		0.20
Presentations at EAU annual meeting 2019, Barcelona (2019)		1.00
Poster presentation at AUA annual meeting 2019, Chicago (2019)		0.50
Poster presentation at ICSN conference 2019, Rotterdam (2019)		0.50
Secretary of Causes of Death Committee, ERSPC (2020)		1.00
Lid van aanbestedingsteam Datacapture Erasmus MC (2020)		1.00
Poster presentation at Virtual EAU annual meeting 2020, Amsterdam (2020)		0.50
Poster presentation at Virtual SIU annual meeting 2020, Montreal (2020)		0.50
Department Journal Club (2020)		3.00
Educational program Urology (regionale refereeravonden) (2020)		1.00
Educational evenings (RUAG) (2020)		1.00

Educational Department program (wekelijks onderwijs) (2020)	1.00
NVU biannual meetings (2020)	1.00
EAU annual meetings (2020)	1.50
Optional	
Best Poster Award (2018)	0.00
Second Prize Best Abstract by a resident (2018)	0.00
Tutoraat 1e jaars geneeskundestudenten (2019)	1.50
Best Poster Award (2019)	0.00
VO Rekenen aan prostaatkanker (2019)	1.00
Coaching bachelor students (2020)	2.00
Prostaatonderwijs OK-assistenten (2020)	0.30
Peer review (2020)	0.10
EAU Prostate Cancer Research Award 2020 (2020)	0.00
	------ +
Total EC	**32.40**