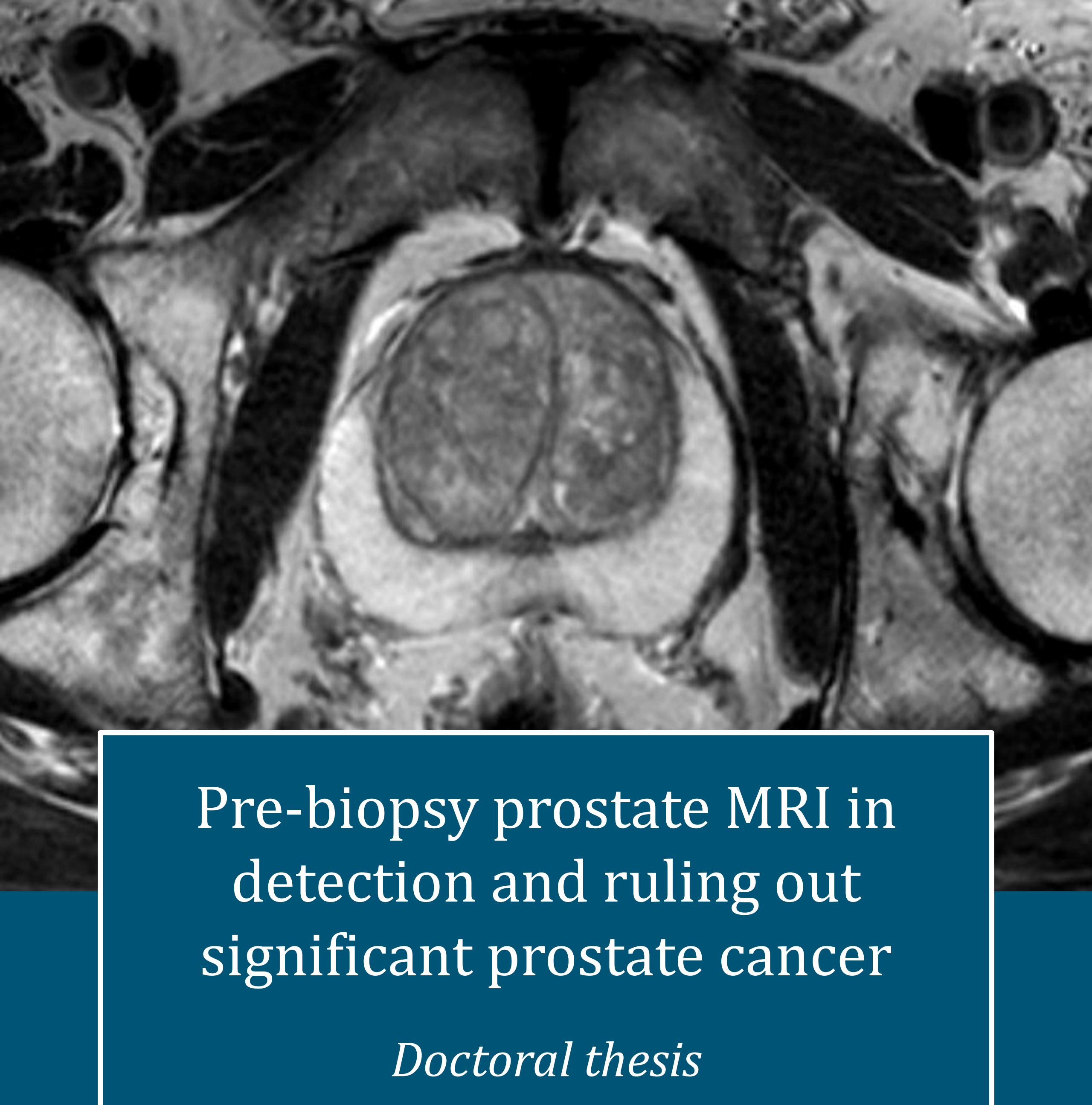

Pre-biopsy prostate MRI in detection and ruling out significant prostate cancer

Doctoral thesis

Lars Boesen, MD, PhD

Department of Urology and Urological Research

Faculty of Health Sciences,

University of Copenhagen, 2020

UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH SCIENCES

Doctoral Thesis

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2020

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Ulla Wewer
Dean and Head of Faculty

Doctoral thesis

Title:	Pre-biopsy prostate MRI in detection and ruling out significant prostate cancer
Author:	Lars Boesen, MD, PhD M: *lars.boesen@dadlnet.dk;* Tweet: *@Boesen.lars*
Department:	Department of Urology and Urological Research Herlev Gentofte University Hospital Borgmester Ib Juuls Vej 1, 2730 Herlev
Submitted:	This thesis was submitted January 6th, 2020 to the Faculty of Health and medical Sciences, University of Copenhagen

Assessment committee

Chairman:	Professor Martin Andreas Røder, MD, PhD Department of Urology, Rigshospitalet Department of Clinical Medicine, University of Copenhagen, Denmark
1. Opponent:	Professor Anders Bjartell, MD, PhD, FEBU Department of Urology, Skåne University Hospital Department of Translational Medicine, Medical Faculty, Lund University, Sweden
2. Opponent:	Professor Michael Borre, MD, PhD, DMSci Department of Urology, Århus University Hospital Institute of Clinical Medicine, University of Aarhus, Denmark
Chair of defence:	Professor Klaus Brasso, MD, PhD Department of Urology, Rigshospitalet Department of Clinical Medicine, University of Copenhagen, Denmark

Public defence

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Preface

In 2010, I applied for a position as a fellow in Urology. (Un)Fortunately, I was not offered the position, but during the interview we discussed my interest in clinical research and I was subsequently offered a follow-up meeting with the head of the Urology Department, Herlev Gentofte University Hospital. At that meeting, we discussed the basis for a new research project that originated from my early clinical experience as a young resident having met the third patient in a row in the outpatient clinic with suspicion of prostate cancer and a set of inconclusive or negative prostate biopsies. I had realized that there were limitations with the current diagnostic tools used to evaluate men suspected of prostate cancer, and prostate MRI seemed to have the potential to solve some of these limitations. However, at that time the experience and use of prostate MRI for prostate cancer management was very limited, and it was not applied in clinical practice in Denmark. Thus, in close collaboration with the Research Department of Radiology (headed by *Professor Henrik Thomsen*), we subsequently formed the basis for the clinical studies that we now have carried out over the last nine years evaluating the use of MRI for prostate cancer detection, lesion characterisation and risk stratification in a Danish setup. This doctoral thesis is the primary result of my part-time postdoc fellowship at the Department of Urology, Herlev Gentofte University Hospital from 2016 to 2019. My fellowship was generously sponsored by research grants from the Beckett Foundation and from Dr. Sofus Carl Emil Friis and Olga Doris Friis (salary) and by the Department of Radiology (MRI acquisition and reporting).

There is no doubt that this thesis could not have been possible without close involvement of a number of people that I want to thank. First and foremost, I want to thank all the patients (and their prostates), who voluntarily contributed to our studies and helped us (at least in my opinion) a step closer to better care for men suspected of prostate cancer. Thank you to all my co-authors for your important contributions to the studies in this thesis. Our studies are based on a close collaboration between individuals with different backgrounds and skills, but who all share a huge passion for their patients, profession, and the prostate. Over the years, we have collaborated closely in the clinic and through research, and our relationship has grown into valuable friendships.

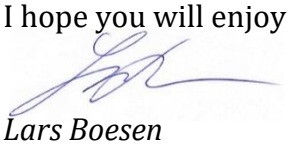
I owe a special thank you to my former PhD supervisor *Professor Henrik Thomsen* and to radiologist *Vibeke Løgager* for our numerous strategic and scientific discussions, for the constructive criticism, and for excellent guidance and support along the way. Thank you, *Vibeke,* for being *Vibeke*! You are no ordinary woman; your passion and enthusiasm for prostate MRI, your unique ability to tutor students and colleagues and most importantly, the care and interest you show for the men and their prostates, is unparalleled.

A genuine and special thank you goes to my prostate biopsy 'wingman' *Nis Nørgaard* for our professional and personal collaboration. It has been an amazing time with *Nis* establishing and implementing MRI/TRUS image fusion guided biopsies at the department. Thank you for always being ready to explore new technologies and diagnostic strategies. Likewise, to the entire prostate cancer team at Herlev Gentofte University Hospital; from the secretary and nursing staff to the highly skilled clinicians lead by chief surgeon *Henrik Jakobsen* - thank you for creating a great collegial atmosphere and a dedicated working environment.

Thank you to *Hans Stimpel* (head of Department of Urology) for providing excellent working conditions; To pathologist *Ingegerd Balslev* for her unusual engagement in our projects and her thorough and detailed histopathological evaluation of all the specimens; To *Mette Schmidt* and *Diana Lyng Christensen* for taking care of many practical issues along the way; To the Research Department of Radiology and its dedicated staff for granting the research MRIs, securing high-quality image acquisition and reporting, and for always taking good care of the patients.

Last and most importantly, I want to express my deepest gratitude to my lovely wife *Julie* and my beautiful girls *Olivia*, *Karla*, and *Vigga* for their constant love and unyielding support taking care of many of the practical family issues along the way. Without you this thesis would not have been possible. I am forever grateful.

I hope you will enjoy reading this thesis



Lars Boesen
Vedbæk, December 2019

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Manuscripts

This doctoral thesis is based on the following eight original papers, which are cited as paper I, paper II, etc. None of these papers have previously been submitted with the purpose of obtaining an academic degree, and the publications are available as appendices.

I. Boesen L, Nørgaard N, Løgager V, Thomsen HS: **Clinical Outcome Following Low Suspicion Multiparametric Prostate Magnetic Resonance Imaging or Benign Magnetic Resonance Imaging Guided Biopsy to Detect Prostate Cancer**. *Journal of Urology 2017; 198: 310–315.*

II. Boesen L, Nørgaard N, Løgager V, Balslev I, Thomsen HS: **A Prospective Comparison of Selective Multiparametric Magnetic Resonance Imaging Fusion-Targeted and Systematic Transrectal Ultrasound-Guided Biopsies for Detecting Prostate Cancer in Men Undergoing Repeated Biopsies.** *Urologia Internationalis 2017; 99: 384–391.*

III. Boesen L, Nørgaard N, Løgager V, Balslev I, Thomsen HS: **Where Do Transrectal Ultrasound- and Magnetic Resonance Imaging-guided Biopsies Miss Significant Prostate Cancer?** *Urology 2017; 110: 154–160.*

IV. Boesen L, Nørgaard N, Løgager V, Balslev I, Thomsen HS: **Multiparametric MRI in men with clinical suspicion of prostate cancer undergoing repeat biopsy: a prospective comparison with clinical findings and histopathology.** *Acta Radiologica 2018; 59: 371–380.*

V. Boesen L, Nørgaard N, Løgager V, Balslev I, Bisbjerg R, Thestrup KC, Winther MC, Jakobsen H, Thomsen HS: **Assessment of the Diagnostic Accuracy of Biparametric Magnetic Resonance Imaging for Prostate Cancer in Biopsy-Naive Men.** *JAMA Network Open 2018; 1: e180219.*

VI. Boesen L, Nørgaard N, Løgager V, Balslev I, Bisbjerg R, Thestrup KC, Jakobsen H, Thomsen HS: **Prebiopsy Biparametric Magnetic Resonance Imaging Combined with Prostate-specific Antigen Density in Detecting and Ruling out Gleason 7–10 Prostate Cancer in Biopsy-naïve Men.** *European Urology Oncology 2018; 2: 311–319.*

VII. Boesen L, Thomsen FB, Nørgaard N, Løgager V, Balslev I, Bisbjerg R, Thomsen HS, Jakobsen H: **A predictive model based on biparametric magnetic resonance imaging and clinical parameters for improved risk assessment and selection of biopsy-naïve men for prostate biopsies.** *Prostate Cancer and Prostatic Diseases 2019; 22(4): 609–616.*

VIII. Boesen L: **Magnetic resonance imaging –transrectal ultrasound image fusion guidance of prostate biopsies: current status, challenges and future perspectives.** *Scandinavian Journal of Urology 2019; 53(2–3): 89–96.*

List of abbreviations and acronyms

Name	Definition
4Kscore	Four-Kallikrein panel test
ACR	American College of Radiology
ADC	Apparent diffusion coefficient
AI	Artificial intelligence
AS	Active surveillance
AUA	American Urological Association
AUC	Area under the curve
BIDOC	Biparametric magnetic resonance imaging for detection of prostate cancer
BPH	Benign prostate hypertrophy
BpMRI	Biparametric magnetic resonance imaging
cT	Clinical tumour stage
DCE	Dynamic contrast enhanced
DRE	Digital rectal examination
DWI	Diffusion-weighted imaging
EAU	European Association of Urology
EPE	Extra prostatic extension
ERC	Endo-rectal coil
ERSPC	European randomised study of screening for prostate cancer
ESUR	European Society of Urogenital Radiology
fPSA	Free prostate-specific-antigen
GG	Gleason grade group
GP	General practitioner
GS	Gleason score
insPCa	Insignificant prostate cancer
IQR	Interquartile range
ISUP	International Society of Urological Pathology

MCCL	Maximum cancer core length
MpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
MRSI	Magnetic resonance spectroscopic imaging
NICE	The National Institute for Health and Care Excellence
NNB	Number needed to biopsy
NPV	Negative predictive value
PCa	Prostate cancer
PCA3	Prostate cancer antigen 3
PCPT	Prostate cancer prevention trial
PHI	Prostate Health Index
PI-RADS	Prostate imaging reporting and data system
PPA-coil	Pelvic-phased-array coil
PPV	Positive predictive value
PSA	Prostate-specific-antigen
PSAd	Prostate-specific-antigen density
RNA	Ribonucleic acid
RP	Radical prostatectomy
SBx	Standard biopsies
sPCa	Significant prostate cancer
START	Standards of reporting for magnetic resonance imaging -targeted biopsy studies
STHLM3	Stockholm number 3 test
T1W	T1-weighted
T2W	T2-weighted
TBx	Targeted biopsies
TPM_{bx}	Transperineal mapping biopsies
TRUS	Transrectal ultrasound
$TRUS_{bx}$	Transrectal ultrasound -guided biopsies

The list is sorted in alphabetic order; not in order of appearance in text

Motivation for this thesis – Setting the scene

The current standard diagnostic pathway for prostate cancer (PCa) differs significantly from that of other solid organ cancers in which imaging is used to rule out or identify suspicious lesions for invasive targeted biopsies. Instead, all men with suspected PCa are offered transrectal ultrasound-guided biopsies ($TRUS_{bx}$) with multiple untargeted needle-cores scattered throughout the accessible regions of the prostate gland, based on the assumption that the disease is equally likely to be found at these locations.

This non-targeted approach is used for biopsy-naive men with elevated prostate-specific-antigen (PSA) levels and/or abnormal digital rectal examination (DRE) results, men with prior negative $TRUS_{bx}$ results but where there is a persisting suspicion of missed significant PCa (sPCa), and for monitoring of men with low-risk disease undergoing active surveillance (AS).

However, three important issues are raised by the non-cancer specific causes of elevated PSA levels, the difficulties of target identification on TRUS and the wide diversity of cancers, which range from indolent to highly aggressive:

1. Men without clinically significant cancers undergo unnecessary invasive biopsies, which are associated with an increased risk of morbidities.

2. Overdiagnosis of clinically insignificant cancers can result in overtreatment or enrolment in AS, which are costly and may have negative long-term effects on patients' quality of life.

3. Underdiagnosis can result in undertreatment of clinically significant cancers due to errors in $TRUS_{bx}$ sampling and risk-stratification.

These limitations of the current PCa diagnostic pathway (*Table* 1) have highlighted the need for better pre-biopsy diagnostic tools. A simple and accurate method that improves the detection of sPCas while minimising overdetection and unnecessary biopsies by reducing the number of false-positive results is needed. Such a method may include risk calculators, biomarkers, or imaging techniques to distinguish men at increased risk of sPCa who require diagnostic biopsies and subsequent treatment from the large number of men with either a benign condition or an insignificant cancer that may be managed by monitoring. In addition, the worldwide problem of antibiotic-resistant bacteria, which may be exacerbated by prostatic-

tissue sampling, continues to grow, and the number of effective antibiotics continues to decline [1,2]. Therefore, there is a need for methods that decrease the number of unnecessary invasive tissue sampling procedures.

Limitations in PCa detection	
PSA	A threshold of 4 ng/mL may miss significant cancer at lower values
	Low specificity leading to many unnecessary biopsies
DRE	Low sensitivity as most tumours are non-palpable
$TRUS_{bx}$	Low/moderate sensitivity and specificity for PCa detection
	Risk of missing significant cancer foci
	Risk of diagnosing insignificant cancer
	Multiple non-targeted biopsies are required
	Repeat biopsy procedures are necessary
	Increased risk of infectious complications and inflammation with multiple biopsies
	Sampling errors leading to misclassification of tumour volume, extent and Gleason score
	Undersampling of the anterior region

PSA = Prostate-specific-antigen; DRE = digital rectal examination; $TRUS_{bx}$ = transrectal ultrasound-guided biopsies; PCa = prostate cancer.

Table 1: Main limitations of the current standard diagnostic tools for PCa detection.

Growing scientific evidence supports the use of magnetic resonance imaging (MRI) to resolve these issues. MRI has been shown to be the most sensitive and specific imaging tool for PCa detection, lesion characterisation and risk stratification. Its use may improve the PCa diagnostic pathway at many levels, from the initial detection of significant tumours by utilising biopsies targeted using MRI (TBx) to the evaluation and monitoring of biological aggressiveness, tumour stage and disease/treatment (*Figure 1*). Furthermore, while MRI-targeted biopsies (MRI-TBx) can improve the detection of sPCa compared with standard biopsies (SBxs) alone [3–5], a low-suspicion prostate MRI may non-invasively exclude the presence of aggressive disease [6], avoiding the need for invasive biopsies. Accordingly, MRI could potentially be used as a triage test to improve risk stratification and minimise overdiagnoses and unnecessary biopsies.

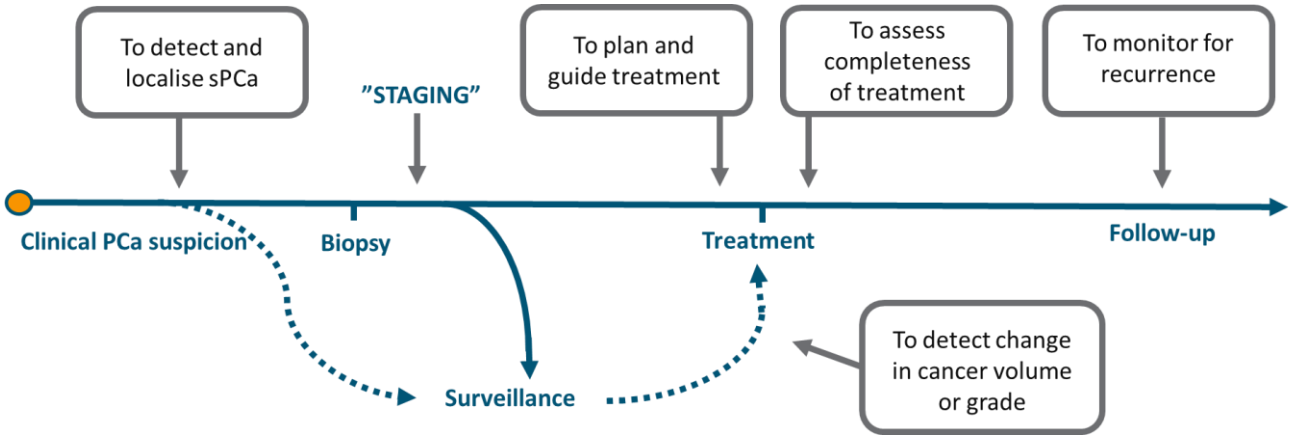

Figure 1: Prostate magnetic resonance imaging (MRI) may be beneficial throughout the PCa diagnostic pathway. *Abbreviations*: PCa = prostate cancer; sPCa = significant PCa.

In Denmark, the implementation of prostate MRI technology was initially hampered by discouraging clinical results [7,8]. However, in 2011, a PhD study by our research group systematically evaluated the improved performance of prostate MRI in the detection and staging of PCa in a Danish setup [9]. We re-evaluated the use of 'modern' mpMRI in the diagnostic work-up of PCa based on improvements in MRI equipment and sequences combined with publication of clinical prostate MRI guidelines [10] that included a structured uniform scoring system to standardise mpMRI readings and a guide to obtaining high-quality images. Overall, our studies showed that mpMRI improved the detection of sPCas that had previously been missed by $TRUS_{bx}$ and provided valuable information regarding cancer histopathological aggressiveness and tumour stage in the pre-therapeutic setting.

However, the role of MRI in PCa diagnosis is rapidly evolving. Since our early experiences of using MRI for PCa detection during the PhD studies, the focus has changed from identifying men with missed sPCas on prior $TRUS_{bx}$ to assessing the value of using MRI as a triage test in biopsy-naïve men that improves the detection of sPCas, increases the precision of targeting for biopsy cores and avoids unnecessary biopsies. Therefore, the studies included in the present doctoral thesis were carried out to further assess the diagnostic accuracy of pre-biopsy prostate MRI in improving risk stratification and optimising detection of sPCa, decreasing detection of insignificant (ins)PCa and avoiding unnecessary biopsies in both biopsy-naïve men and those with prior negative biopsies, who are suspected of having missed sPCa.

Chapter 1: Introduction

The normal prostate is a walnut-sized gland located in front of the rectum between the male bladder and the urogenital pelvic floor surrounding the urethra. Its purpose is to secrete fluid that nourishes and protects sperm cells. Because there is a risk of abnormal growth of the prostatic epithelial cells, prostate cancer (PCa) may develop with age as single or multiple tumours, which have the potential to metastasise, primarily to the lymph nodes and bone, causing metastatic morbidity and potentially leading to death. PCa is a major health concern in the western world. It is responsible for the second highest number of cancer-related deaths and is the most common malignant disease among men in the Nordic countries. More than 4,400 Danish men are diagnosed with PCa each year, and approximately 1,100 of these men die from the disease, accounting for 4–5% of all male deaths [11]. The known risk factors for a PCa diagnosis include older age and familial, genetic and/or ethnic disposition. The majority of men diagnosed with PCa are between 65 and 75 years of age; PCa is rarely detected in men who are younger than 50 years. For aggressive PCa, early detection is essential for a good prognosis and effective treatment. However, subclinical PCas may be present in 30–70% of men older than 60 years, constituting a large reservoir of potentially detectable PCas [12]. The extent to which this large disease reservoir exceeds the considerably lower lifetime risk of mortality due to PCa provides a crude estimate of the potential for overdiagnoses, because most men with PCa never develop clinically significant symptoms that cause morbidity or mortality. In itself, the existence of a disease reservoir of detectable PCas does not lead to overdiagnoses. However, since PSA testing was introduced several decades ago for PCa detection, the incidence rate of newly diagnosed PCas has more than doubled. PCa is now detected earlier, resulting in stage-migration and a dramatic increase in disease prevalence. However, although the earlier detection of localised PCa has resulted in a 5-year survival rate of greater than 90%, the PCa mortality rate in Scandinavia has remained virtually unchanged and is among the highest in the world.

The heterogeneity in clinical PCa manifestation, which ranges from the more common indolent tumours (i.e., clinically insignificant cancers) that do not cause mortality or morbidity to the fewer aggressive tumours (i.e., clinically significant cancers) that can lead to death if left untreated, challenges the clinicians' much hailed quest to help the sick by its propensity to harm the healthy. Thus, the ability to discriminate between life-threatening and insignificant cancers is critical and makes diagnoses and subsequent treatment planning challenging. Currently,

there is no consensus on the best treatment option for men with localised PCa. Initial therapies may include surgery (radical prostatectomy [RP]) or radiation therapy (brachytherapy or external beam radiation), which are associated with significant morbidity risks (e.g., impotence, incontinence and/or radiation damage to the bladder or rectum), or observational strategies, such as AS [13]. Thus, to select the optimal treatment and clinical management strategies, it is essential to determine the precise location, stage and level of aggression for each tumour.

Standard diagnostic pathway

The current standard pathway for diagnosing PCa has remained unchanged for decades and includes PSA testing and DRE followed by $TRUS_{bx}$.

Prostate-specific-antigen (PSA)

Prostate-specific antigen, also known as human kallikrein 3, is a glycoprotein that is produced almost exclusively by the prostatic epithelial cells. Its function is to liquefy the semen and thereby improve the motility of sperm cells. Small quantities of PSA can be measured in the serum of men with normal prostate glands. However, PSA levels are often elevated in men with PCa due to increased production of PSA by the cancerous cells and its leakage into the blood-vessels. PSA is the most frequently used blood-based biomarker for early detection and risk stratification of PCa. Elevated PSA levels can often be detected before cancer-related symptoms, which often first occur when the cancer has already metastasised and are directly correlated with a higher risk of having PCa, higher tumour grades and stages, and a higher risk of metastasis [14]. However, PSA is not PCa-specific, and its levels can be altered by many benign conditions such as age-induced benign prostatic hyperplasia (BPH), infections, inflammation/prostatitis, surgical procedures affecting the urinary tract, or medication (e.g., 5-alpha reductase inhibitors). A PSA level of ≥4 ng/mL has traditionally been established as a PCa-suspicion threshold that triggers diagnostic prostate biopsies ($TRUS_{bx}$), although this biopsy-threshold may be adjusted to take the patient's age and race into account [15]. Nevertheless, only one in three men with PSA levels above this threshold has PCa that is detected by the diagnostic biopsies. Conversely, men with PSA levels that are below this threshold (i.e., have "normal" PSA levels) can still harbour aggressive disease [16–20], and there is no absolute value below which PSA can be used to rule out PCa [16]. Thus, a specified PSA cut-off level cannot be used to accurately distinguish between men with and without PCa nor between men

with insPCa and sPCa [21]. Therefore, all PSA levels should rather be considered as part of a continuum of risk for PCa. PSA level is also included in predictive and prognostic nomograms and used as a biomarker for PCa risk stratification and for monitoring treatment response [22].

PSA screening

Because using PSA testing to screen for PCa is associated with a high false-positive rate, this approach is controversial and generates continuous debate within the medical and urological communities [23]. PCa mortality rates vary widely among different countries, and the reduced mortality rate observed in the United States of America over the past few decades has been partly attributed to aggressive PSA screening policies [24]. At present, the United States Preventive Service Task Force recommends that PSA screening should be based upon shared decision making and should focus on men aged from 55 to 69 years [25]. However, opponents of screening argue that the test has no net benefit and that the harms (e.g., high false-positive rate, overdetection of insPCa, and biopsy complications) outweigh the benefits demonstrated in randomised trials [26–28]. Furthermore, there are uncertainties regarding the age at which to initiate and discontinue screening and the optimal frequency of testing which further challenges the practical considerations of screening strategies. However, as data from the large ERSPC (European Randomised Study of Screening for Prostate Cancer) screening trial [26] accumulates, the reduction in mortality rates resulting from PSA screening remains unchanged (21%), whereas the numbers needed to screen and treat have decreased. Nevertheless, many men who do not have PCa undergo unnecessary biopsies because elevated PSA levels are not cancer specific, and insignificant cancers are detected by the random untargeted $TRUS_{bx}$ sampling, potentially leading to overdetection and overtreatment [29]. The potential side effects of treatment can have a severe impact on urinary, bowel and sexual function, reducing patients' quality of life. An increased emphasis on MRI and prediction models to guide individualised risk-based patient selection for prostate biopsies may reduce the number of unnecessary biopsies and overdiagnoses of insPCa and the increased adoption of AS strategies could counteract the problem of overtreatment. These MRI-based strategies are discussed later in this thesis and could lead to a more favourable balance between the net benefits and potential harms of PCa screening that may encourage its more widespread implementation.

PSA - refinements and derivatives for early detection of PCa

Refinements have been proposed to address the sensitivity and specificity limitations of using PSA testing to detect PCa. These include calculating free PSA (fPSA) levels and the percentage of fPSA (free to total PSA ratio), PSA kinetics covering PSA velocity (annual increase in PSA level) and PSA doubling time (exponential increase in PSA level over time), as well as PSA density (PSAd; PSA level divided by prostate volume). Although these PSA-derived refinements may be related to cancer risk and growth rates, none are tissue- or cancer-specific and none have been shown to add any incremental value in clinical decision making as stand-alone tests [30]. However, while PSAd measurements alone provide limited assistance when making biopsy decisions and require an accurate assessment of prostate volume using imaging, predictive values for detecting and ruling out sPCas appear to improve significantly when PSAd is combined with MRI-derived suspicion scores [31–33].

Furthermore, additional PSA-derived serum and urinary biomarkers are now commercially available. These include the Prostate Health Index (PHI) test, which is a diagnostic blood test that combines free and total PSA and the pro-PSA isoform; the Four-Kallikrein panel (4Kscore) test, which measures a panel of kallikreins in serum; and the Prostate Cancer Antigen 3 (PCA3) score, which reflects the ratio of PCA3/PSA RNA (ribonucleic acid) molecules detected in a urinary specimen following a DRE. These additional tests have been developed to improve risk assessment, distinguish between benign and malignant prostatic conditions, and avoid biopsies in PSA-tested men. However, although the PHI and 4Kscore perform equally well when compared head-to-head [34] and all tests seem to improve sPCa prediction and reduce the number of unnecessary biopsies compared to PSA alone [35–37], their implementation in routine clinical practice has been limited.

Digital rectal examination (DRE)

The location of the prostate gland, directly in front of the rectum, allows for transrectal digital palpation and examination (DRE), which is a fundamental part of the basic clinical examination for evaluating men suspected of having PCa. In total, 70–75% of PCas are located in the peripheral zone of the prostate, and these may be identified by DRE as hard and irregular lesions if the tumour is large enough [9]. However, many PCas with much smaller tumour volumes are now detected at earlier stages, and much fewer cancers are detected by DREs. Furthermore, because not all cancers grow into hard, solid lesions and ~25% of PCas are

located in the transitional zone and cannot be identified by DRE, the examination has limited sensitivity and specificity [38–41] for PCa detection. Thus, a normal DRE cannot be used to rule out PCa. However, an abnormal DRE is a good predictor of pathologically aggressive disease [42,43] and is a strong indicator for performing prostate biopsies because it may identify as much as 18% of those men who have PCa, irrespective of their PSA levels [43]. Furthermore, DREs are traditionally used for clinical tumour staging (i.e., assigning a cT category) and for risk stratification, and DRE findings are incorporated into predictive and prognostic nomograms.

Transrectal ultrasound and biopsies

Transrectal ultrasound (TRUS) is the standard imaging modality for prostate evaluation. TRUS is ideal for measuring the prostate volume and for guiding biopsies, but lacks sensitivity and specificity in detecting and staging PCa [44,45]. Although PCa may appear as a hypoechoic lesion on TRUS, more than 40–50% of the cancerous lesions are isoechoic [44,46] and cannot be identified. Furthermore, the transitional zone can appear heterogeneous due to BPH, making it particularly difficult to detect tumours located in the anterior part of the prostate. As a result, all men who are suspected of having PCa undergo biopsies regardless of TRUS findings, although more than half of men with elevated PSA levels harbour a benign condition or insPCa that can be managed by monitoring.

Prostate biopsies can be performed either transrectally ($TRUS_{bx}$) or transperineally. Although these two approaches have comparable PCa detection rates, transperineal biopsies may be associated with a lower risk of infection. However, due to the anatomical location of the prostate and the feasibility of the procedure in clinical practice, $TRUS_{bx}$ has been the standard-of-care for confirming or excluding the presence of PCa since it was introduced nearly 30 years ago [47]. During the $TRUS_{bx}$ procedure, 10–12 SBx needle-cores are obtained systematically from predefined anatomical regions of the peripheral zone of the prostate. The biopsy cores are then analysed by the uro-pathologist for the presence of PCas. The immediate side-effects of $TRUS_{bx}$ include pain/discomfort, bleeding (haematuria, haematospermia and haematochezia), and severe infection (affecting approximately 3–5% of patients) despite antibiotic prophylaxis. Due to the poor PCa target identification associated with TRUS and the short length of the biopsy needles, SBxs are prone to sampling errors. Consequently, sPCas may be missed [48], cancer aggressiveness may be misclassified [22,44] and insPCas may be detected

unintentionally by the random untargeted sampling procedure (*Figure 2*), potentially leading to overdetection and overtreatment [29].

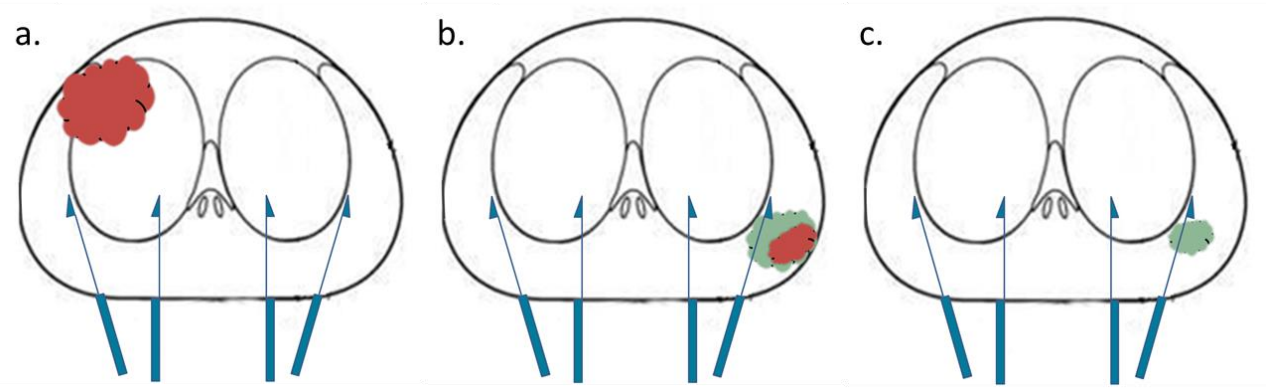

Figure 2: Poor PCa target identification and limited length of standard transrectal ultrasound-guided biopsy ($TRUS_{bx}$) cores often leads to a) missed significant cancer (red area); b) risk of missing the most aggressive part of the tumour, causing cancer undergrading; and c) overdiagnosis of insignificant cancer (green area), potentially leading to overtreatment.

Men with benign $TRUS_{bx}$ findings but who are still suspected of having PCa constitute a clinical dilemma [49]. $TRUS_{bx}$ has limited diagnostic accuracy, with high false-negative rates of up to 20–30% [48]. Therefore, evaluating men with negative $TRUS_{bx}$ results remains a problem for clinicians because the indication for repeating biopsies (i.e., re-biopsies) may be a rise in a non-specific PSA measurement [49]. As a result, men considered at risk of having PCa remain under long-term PSA-surveillance with prolonged check-ups and possibly multiple biopsies that increase costs, as well as patient anxiety and morbidity. Furthermore, although the PCa detection rate declines as the number of $TRUS_{bx}$ procedures increases [50], there is no consensus on when to stop [18] and the repeated sampling often leads to an increased risk of detecting insPCas. In addition, the worldwide prevalence of antibiotic-resistant bacteria is increasing, whereas the number of effective antibiotics is declining [1,2], emphasising the need to reduce unnecessary tissue sampling.

The limitations of TRUS mean there is a great need for an improved imaging modality that can improve target identification and guide prostate biopsies towards suspicious lesions that are likely to be clinically sPCas, while minimising unnecessary biopsies and overdetection of small insPCas that are below the detection threshold of imaging.

Risk prediction models

Risk prediction models that combine clinical parameters (e.g., age, PSA levels, DRE results, and TRUS findings) may be used for pre-biopsy risk assessments to separate men at high risk of PCa who require invasive diagnostic biopsies from men who are likely to have benign conditions or insPCa and might safely avoid biopsies, allowing each group to be counselled accordingly [51,52]. The online ERSPC [51] and PCPT (Prostate Cancer Prevention Trial) [52] risk calculators are among the most frequently used models, and these predict the probability of detecting PCa on confirmatory diagnostic $TRUS_{bx}$. However, although these risk calculators are superior to PSA testing alone, the models show limited discriminatory power in detecting and ruling out sPCa (area under the curve [AUC], 0.69–0.74) [53]. Nevertheless, novel risk prediction models based on additional blood or urine tests for genetic and protein biomarkers (e.g., the 4Kscore [35], the Stockholm, Number 3 (STHLM3) test [54], the PHI [36], and the PCA3 scores [37]) have been developed to improve diagnostic accuracy in detecting and ruling out sPCa.

While the 4Kscore and the STHLM3 test both include clinical variables to produce diagnostic test results, the PHI and PCA3 scores can be combined with clinical parameters in nomograms to further improve their diagnostic accuracies [37,55]. However, although these risk models predict the likelihood of having sPCa, they do not determine the location or size of intra-prostatic tumours, and they are often based solely on results from $TRUS_{bx}$, with its inherent limitations and potential for sampling errors [48,56,57].

Despite its shortcomings, PSA is still the first-line biomarker used for early detection and screening of PCa because it remains the single most reliable biomarker for identifying men at increased risk. However, guidelines recommend that only men above 50–55 years of age with good performance status and long life-expectancy may undergo PSA testing for screening and early detection of PCa, and only after these patients have been informed of the potential risks and benefits of the procedure and have participated in shared decision making [13,25,58]. The Danish Urological Society does not recommend PSA testing/screening asymptomatic men who do not have a genetic predisposition towards PCa, or a family history of the disease.

Grading prostate cancer

The histopathological aggressiveness of PCa is classified by the Gleason grading system [59,60] for prostatic adenocarcinomas. Although carcinomas other than adenocarcinomas exist (e.g.,

small cell carcinomas), they are exceptionally rare and account for less than 0.5% of prostatic tumours. The Gleason system grades prostatic tissue on a scale of 1–5, according to the histopathological arrangement and appearance of the cells (*Figure 3*).

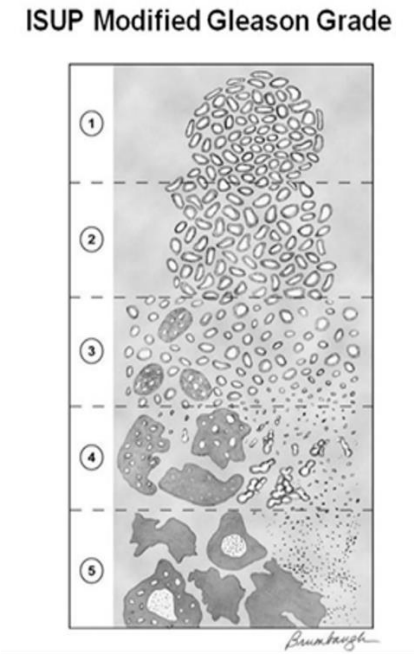

Figure 3: The modified Gleason grading system currently used in our department for histopathological grading. For low Gleason grades (e.g., 1 and 2), the cancerous tissue closely resembles normal prostatic tissue; the disparity increases at higher Gleason grades (reprinted with permission from the publisher).

Abbreviation: ISUP = International Society of Urological Pathology.

Whereas Gleason grades 1 and 2 indicate normal prostatic tissue, grades 3–5 represent cancerous tissue, with grade 5 tissue being the most abnormal and malignant. These cancers are often heterogeneous, with more than one Gleason grade being present in a tumour. Therefore, a composite Gleason score (GS) is assigned, which evaluates the surface area of a tumour in terms of a 'primary' (predominant growth pattern) and a 'secondary' (second most prevalent growth pattern) grade. The GSs assigned after needle biopsies can differ because these include the sum of the primary Gleason grade and the highest grade. If no secondary Gleason grade exists, the primary grade is doubled to assign a GS. Although the GS ranges from 2–10, a GS ≥6 is the cellular growth pattern most often used to define PCa.

The GS is strongly related to the clinical behaviour and prognosis of a cancer and it is an important parameter that is used in nomograms and risk calculators to guide individual treatment decisions. A higher GS indicates a more aggressive tumour, a greater risk of the cancer spreading, and a poorer prognosis [61–63]. However, because GSs of 2–5 are no longer used and the lowest GS assigned for a cancer is 6, patients may assume incorrectly that their

cancer is moderately aggressive. To address some of the ambiguities associated with using the GS system, GS scores may be separated into five prognostic Gleason grade groups (GG 1–5) to simplify prognoses and patient management [64–66]. This simplified grading system correlates strongly with disease survival as well as the risk of progression [66,67] and was adopted at the International Society of Urological Pathology (ISUP) 2014 consensus conference [65]. This system was also accepted by the World Health Organisation in 2016 and is now endorsed by the major uro-oncology journals where it should be reported in conjunction with the GS, until it becomes widely accepted [68].

As high Gleason grades are strongly associated with aggressive tumours and a poor disease prognosis, accurate assessments of tumour aggressiveness are essential for planning treatment for each patient. However, GSs are upgraded following RP in one-third of patients [69]. Therefore, the GS obtained using $TRUS_{bx}$ may be inaccurate due to sampling errors. If an incorrect GS is assigned at biopsy, this may lead to incorrect risk stratification and over- or undertreatment. To improve the correlation between biopsy and RP specimen GSs and enhance patient stratification to predict clinical outcomes more accurately, GS reporting has changed over time and the Gleason grade 4 criteria have been expanded [70]. This alteration has led to an upgrade of several GS 7 (3 + 4) tumours previously interpreted as GS 6, which makes it difficult to compare histopathological data over time. As a result, some patients with low-volume Gleason grade 4 disease should not be automatically excluded from surveillance regimens, such as AS [71,72]. Furthermore, patients with GS 7 (4 + 3) PCa have a poorer prognosis (i.e., increased risk of biochemical recurrence and rate of positive lymph nodes following RP) than patients with GS 7 (3 + 4) PCa [73–80]. In addition, recent results have shown that needle biopsies containing low-volume Gleason grade 4 samples were associated with low-risk PCa in RP specimens [81]. Therefore, the difference between GS 7 (3 + 4) and GS 7 (4 + 3) results is clinically important. The newly adopted GG system takes this difference into account.

Chapter 2: MRI of the prostate

The use of prostate MRI for PCa detection and staging is not new. It dates back to the 1980s [82] when image interpretation relied solely on morphological imaging and, therefore, suffered from poor diagnostic accuracy. One of the first diagnostic studies was published in 1983 by *Hricak et al.* [83] and included 25 patients; it reported that the greatest potential of pelvic MRI seemed to be its ability to detect pathology confined to the prostate gland. However, it was unclear whether a neoplastic nodule could be differentiated from chronic prostatitis. Since then, there have been significant improvements in both MRI hardware and software, and the addition of functional imaging in a standard multiparametric approach (mpMRI) has meant that mpMRI has emerged as a powerful and accurate imaging modality for tumour detection, lesion characterisation and staging that can change the management of PCa [84].

MRI of the prostate gland is performed using either a 1.5 or 3.0 Tesla (T) MRI scanner combined with a pelvic-phased-array (PPA) coil placed over the pelvis with or without an endorectal coil (ERC). The main advantage of the 3.0 T over the 1.5 T scanner is the improved signal-to-noise ratio, which can improve image resolution or reduce the image acquisition time. Although no large scale studies have directly compared PCa detection, lesion characterisation and staging using 1.5 T and 3.0 T scanners, it is generally acknowledged that 3.0 T scanners improve PCa staging accuracy [85], especially for diffusion-weighted imaging (DWI) imaging [86]. In addition, an ERC may enhance image quality [87,88] on 1.5 T scans and improve detection of peripheral zone tumours [89]. However, a lower detection rate of anterior/transition zone tumours has been reported, and other disadvantages that include increased scan times, costs, image artefacts close to the coil and reduced patient compliance, combined with the better spatial resolution that can be achieved using 3.0 T MRI scans, have meant that the ERC method is not used frequently in current clinical practice. Furthermore, MRI quality also relies on patient preparation. Patient movement and metallic implants in the lower back/hip can produce image artefacts that may hamper diagnostic accuracy. The administration of an enema prior to the examination and the use of intestinal spasmolytics may decrease rectal peristaltic motion and reduce intra-luminal air and faeces that may generate MRI artefacts.

State-of-the-art multiparametric MRI (mpMRI)

State-of-the-art prostate MRI can provide detailed information on morphological, biological and vascular changes in the prostate gland and characterise tissue cellularity that may be associated with aggressive tumours [90,91]. It includes high-resolution anatomical T2-weighted (T2W) images combined with one or more functional MRI techniques, such as DWI or dynamic contrast enhanced (DCE) imaging [10], in an mpMRI approach. Proton MR-spectroscopic imaging (MRSI) was previously used in addition to the other MRI sequences and to measure changes in tissue metabolism that typically occur in PCas. However, because MRSI is technically challenging and requires significant expertise and long scan times, it is no longer recommended as part of the standard protocol.

Image sequences

High-resolution *T2W imaging* is the cornerstone of prostate MRI and generates detailed anatomical assessments of the prostatic zonal anatomy (i.e., the peripheral, transitional and central zones as well as the anterior fibromuscular stroma); it is used for PCa detection, localisation and staging, including identifying extra-prostatic tumour extension (EPE). Whereas the normal peripheral zone often shows high signal intensity due to its high glandular tissue content, the transitional and central zones often show lower or mixed signal intensities due to BPH nodules, and this may hamper image interpretation (*Figure 4*).

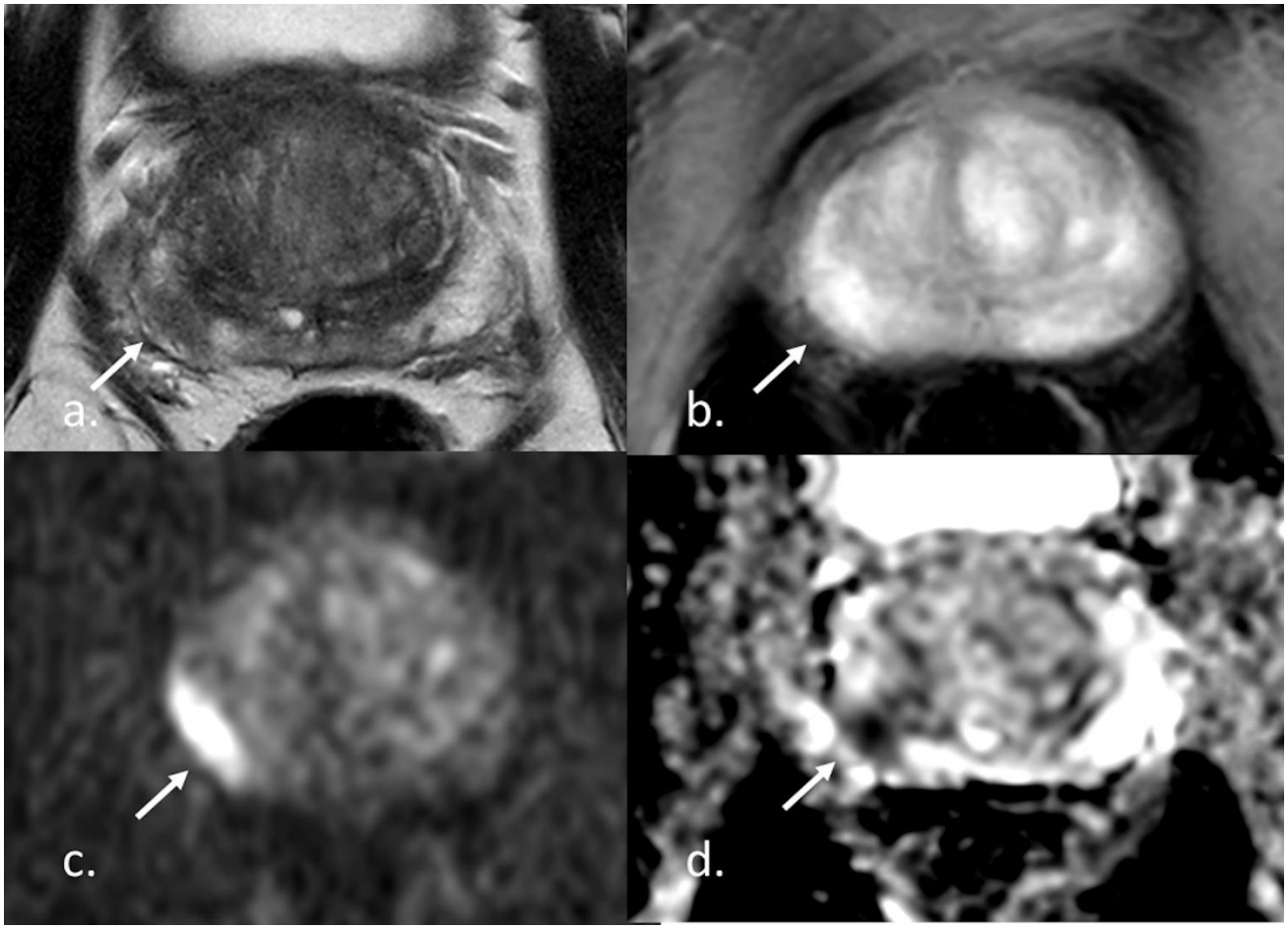

Figure 4: Multiparametric MRI of the prostate gland. The T2-weighted (T2W) image (a) shows a suspicious lesion (white arrow) in the right peripheral zone, which corresponds to high signal intensity (bright) on high *b*-value diffusion-weighted imaging (DWI) (c) and a dark area on the corresponding apparent diffusion coefficient (ADC) map (d). The suspicious lesion shows early focal enhancement when dynamic contrast enhancement (DCE) is applied (b).

PCas often appear as hypo-intense lesions in the normally homogeneous benign peripheral zone of the prostate gland [92,93] (*Figure 4*). However, image interpretation is not always straightforward because not all PCas are hypo-intense on T2W imaging, and "sparse" tumours containing large amounts of intermixed benign prostatic tissue appear more similar to "normal" peripheral zone tissue than do dense tumours [94]. Moreover, several benign conditions such as prostatitis, fibrosis, atrophy, BPH, calcifications and post-biopsy haemorrhages can also appear on T2W images as areas of low signal intensity, potentially producing false-positive readings [92,95]. Because post-biopsy haemorrhages can mimic PCas on T2W imaging, a period of up to 6 weeks is often recommended between biopsies and MRI, although there is no general consensus established for diagnostic purposes. However, on T1-weighted (T1W) images, haemorrhages appear as areas of high signal intensity, and these can

be used to rule out false-positive results on T2W images that are caused by haemorrhages [96]. Due to moderate sensitivity (0.57–0.62) and specificity (0.74–0.78) in PCa detection and localisation [97], T2W imaging is combined with additional functional MRI sequences to increase its diagnostic performance and accuracy.

Diffusion-weighted imaging (DWI) is a non-invasive functional MRI technique that assesses changes in the diffusion of water molecules (i.e., Brownian motion) that are due to microscopic structural tissue changes. PCas often disrupt normal prostate gland structures and contain tightly packed cells that restrict diffusion, limiting the Brownian motion of water molecules within tumours. These changes in diffusion are reflected in changes in signal intensity on DWI. Qualitative assessment of areas with high signal intensity on high *b*-value DWI shows restricted diffusion due to tightly packed cells. Apparent diffusion coefficients (ADCs) are calculated using signal intensity changes from at least two *b*-values. Restricted diffusion decreases the measured ADC values and is visible as dark areas on the ADC map [98,99].
Greater cellular density and restricted rates of diffusion compared to surrounding normal tissue are typical characteristics of PCa tumour tissue. Consequently, PCa tumours often appear as bright areas on high *b*-value DWI and dark areas with low ADC_{tumour} values on an ADC map [99–102]. Although the spatial resolution of DWI is low, DWI may be used to identify areas of restricted diffusion where cell density is high, and thereby differentiate between malignant and benign prostatic tissue. When used in clinical practice, DWI has improved sensitivity and, in particular, specificity compared to T2W imaging alone [97,103] (*Figure 4*). Several studies have reported a significant negative correlation between ADC_{tumour} values and GSs from biopsies and RP specimens [91,104–108]. However, although ADC_{tumour} values may be used as non-invasive indicators of tumour aggression, there is considerable overlap between ADC values from malignant and benign tissue [109,110] and significant variation, depending on the zonal origin [111,112]. Furthermore, studies are needed to standardise ADC measurements and values across different MRI vendors. Therefore, no consensus on ADC_{tumour} cut-off values that correspond to different GSs has been established.

Dynamic-contrast enhanced (DCE) imaging generates a series of fast high-temporal T1W images before, during and after intravenous injection of a gadolinium-based contrast media. DCE imaging is based on the premise that the vasculature of malignant and benign prostatic tissues

differs. PCa often stimulates angiogenesis and increased vascular permeability [113,114], which produces a large early contrast enhancement peak (i.e., increased positive enhancement) followed by a rapid contrast washout on DCE imaging [115–118]. DCE-MRI seems to improve PCa detection sensitivity [119–121] but not specificity because benign conditions, such as hyper-vascularised BPH nodules and prostatitis, can mimic pathological enhancement patterns [117,122]. Thus, DCE-MRI should be combined with T2W and DWI imaging in an mpMRI approach to balance sensitivity and specificity for PCa detection. However, supplementing T2W and DWI with DCE-MRI requires contrast media, lengthens image acquisition times and is costly [123]. Furthermore, recent guidelines suggest that DCE-MRI should play less of a role in PCa detection, questioning the added value of applying this procedure in men suspected of having PCa [124–127]. However, although DCE-MRI may only add limited sensitivity to overall mpMRI performance in a detection setting, it is essential when assessing patients for local recurrence of PCa [128–132].

MRI interpretation with Prostate Imaging Reporting and Data System (PI-RADS)

The purpose of prostate MRI is to identify or rule out abnormal lesions and grade them using PCa suspicion scores. However, due to differences in study protocols, MRI equipment, expertise, and MRI scoring systems, the diagnostic accuracy of published studies varies [3,5,133,134]. Furthermore, prostate MRI interpretation is challenging, requires expertise and involves a long learning curve. Experienced readers are significantly more accurate than non-experienced readers [135–137]. As a result, a consensus-based clinical guideline was developed and published by the European Society of Urogenital Radiology (ESUR) in 2012. This guideline included recommendations for clinical indications for prostate MRI, minimal and optimal imaging acquisition protocols, and a structured uniform Prostate Imaging Reporting and Data System (PI-RADS v1) to standardise and promulgate high-quality prostate MRI data acquisition and evaluation [10]. Several studies evaluated this initial PI-RADS v1 classification and validated its diagnostic accuracy for sPCa detection in a clinical setting [133,138,139]. A review by *Hamoen et al*. [133] reported pooled sensitivity and specificity of 78% (95% confidence interval [CI], 72–89%) and 79% (95% CI, 68–86%) for detecting sPCa using PI-RADS v1, respectively, and demonstrated an improved risk stratification and enhanced diagnostic ratio of sPCa vs. insPCa detection.

Overall, the PI-RADS classification is a lesion-based scoring system that was developed to reduce variation among observers and interpretations, to provide a framework for communication among clinicians, and to facilitate quality assurance and research that will improve patient outcomes. In PI-RADS, lesions are independently scored on each image sequence (T2W, DWI and DCE) using a 5-point scale (i.e., 1 – highly unlikely, 2 – unlikely, 3 – equivocal, 4 – likely, and 5 – highly likely) according to their likelihood of being sPCa. In addition, because not all sequences are unanimous in their scoring, an overall final PI-RADS score assessment category is also provided. However, although the initial PI-RADS v1 guideline provided explicit criteria for grading lesions, how the individual scores should be combined in an overall PI-RADS assessment category was not clearly defined. This was a major limitation, and it meant there could be variations in how PI-RADS v1 was applied [133]. Furthermore, the interpretation of the DCE-MRI score in PI-RADS v1 relied on perfusion curve characteristics, which inherently entail a vast heterogeneity and overlap between benign and malignant lesions. Thus, including DCE-MRI scores equally in the summation of the individual scores led to higher scores for benign lesions and increased the number of false-positive readings. Since the publication of PI-RADS v1, DWI has reportedly been the most effective sequence for detecting lesions in the peripheral zone of the prostate gland [140], whereas T2W imaging has proved optimal for detecting lesions in the transitional zone [141]. As a result, *Vaché et al.* [142] suggested refining sequence weighting depending on the location of each lesion and proposed providing a final score that included the individual scores but was driven by the dominant sequence to improve the diagnostic performance of mpMRI. Due to the limitations of PI-RADS v1 described above, a joint steering committee with representatives from the ESUR, the American College of Radiology (ACR) and the AdMeTech Foundation was established to further develop, improve and simplify PI-RADS scoring based on research and expert knowledge. A new PI-RADS v2 was released online in December 2014 [143] in an effort to make the PI-RADS scoring more globally acceptable. Although PI-RADS v1 and v2 appeared to be equally effective in detecting PCa [144], PI-RADS v2 showed slightly better inter-observer agreement and reduced scoring times, suggesting that v2 is more suitable for clinical practice. Furthermore, to allow better comparisons to be made among different studies, the reporting of MRI-biopsy studies should be standardized as proposed by the START (Standards of reporting for MRI-targeted biopsy studies) consensus group [145].

Overall, the PI-RADS is intended as a "living" document that evolves as clinical experience and scientific validation accrue [146]. As a result, a modified PI-RADS v2.1 [147] was recently published to further improve inter-reader variability and simplify PI-RADS assessment of prostate MRI. However, although PI-RADS was developed to standardise prostate MRI, reduce inter-reader variability, and objectively improve the detection and localisation of sPCa, some clinicians consider it too prescriptive compared to the less prescriptive, non-objective Likert scoring method. Whereas the PI-RADS is a lesion scoring system based on formal anatomical and functional criteria, the Likert scale allows the reporting physician a more subjective assessment when assigning suspicion scores based on personal experience and individual weighting of different factors. However, neither scoring system has proved consistently superior to the other when comparisons have been made using either biopsies [139,148] or RP specimens [142,149]. Despite the absence of a direct head-to-head comparison between the Likert and PI-RADS v2 (now PI-RADS v2.1) methods, the PI-RADS scoring method has received broad international acceptance and is widely used in clinical practice [150]. Nevertheless, improvements are still being made to all scoring systems, and in expert hands they have all been effective in diagnosing PCa.

Chapter 3: Objectives and hypotheses

The main objectives of this doctoral thesis are to assess the diagnostic accuracy of pre-biopsy prostate MRI in detecting and ruling out sPCa in men undergoing prostate biopsies and evaluate whether MRI can be used to

- *Maximise detection of clinically significant PCa*

- *Minimise detection of clinically insignificant PCa*

and

- *Minimise the number of men needing invasive prostate biopsies*

The secondary aims are to 1) assess the use and requirements of prostate MRI from a clinical perspective, 2) compare an MRI-guided diagnostic pathway with the current standard diagnostic approach – systematic $TRUS_{bx}$ for all men suspected of having PCa, and 3) compare the diagnostic accuracy and limitations of targeted and systematic biopsies. Furthermore, state-of-the art mpMRI utilising various scanning parameters and the benefits of a simpler, more rapid biparametric (bp)MRI approach will be discussed.

<u>This doctoral thesis is based on the following three main hypotheses:</u>

1. Prostate MRI can improve detection of clinically significant PCa by guiding MRI-TBx towards suspicious lesions in both biopsy-naïve men and in men with prior negative $TRUS_{bx}$ findings but where there is a persisting suspicion of PCa.

2. Prostate MRI has a high negative predictive value (NPV) for sPCa and may non-invasively exclude the presence of aggressive disease, thereby avoiding the need for invasive biopsies.

3. Pre-biopsy prostate MRI may be used as a triage test to improve risk stratification and identify men at high risk of having sPCa, who require diagnostic biopsies and subsequent treatment, from the large number of men with either a benign condition or an insPCa that can be managed by monitoring.

Although it can be useful at many levels of the PCa diagnostic pathway (*Figure 1*), the use of prostate MRI to detect and localise PCa lesions is the focus of this doctoral thesis. The use of prostate MRI for PCa staging, treatment planning and disease monitoring, including detection of metastasis (e.g., in lymph nodes or bone) and recurrence, fall outside the scope of this thesis.

Thesis components

This doctoral thesis is based on seven original papers and one review article that assess the diagnostic accuracy of pre-biopsy MRI (multi- or biparametric) with or without targeted biopsies in detecting and ruling out sPCa in biopsy-naïve men and in men undergoing repeat biopsies. Each paper aims to provide new insight regarding a specific objective. These specific objectives are:

- To assess the future risk of detecting sPCa following either a low-suspicion MRI or a benign MRI-TBx result regarding a suspicious lesion in men with prior negative biopsies over a period of at least 3 years. (***Paper I***)

- To compare the PCa detection rate of systematic $TRUS_{bx}$ and mpMRI-targeted biopsies in a repeat biopsy setting and evaluate the clinical significance of following an "MRI-targeted-only" approach. (***Paper II***)

- To identify the locations of sPCa lesions missed by $TRUS_{bx}$ and mpMRI-targeted biopsies in men undergoing repeat biopsies. (***Paper III***)

- To compare mpMRI score subgroups and mpMRI-targeted biopsies to repeat systematic $TRUS_{bx}$ and PSA-based findings for detecting clinically sPCa in men undergoing repeat biopsies. (***Paper IV***)

- To assess the diagnostic accuracy and NPV of a novel bpMRI method applied in biopsy-naïve men in detecting and ruling out sPCa in confirmatory biopsies. (***Paper V***)

- To assess the diagnostic accuracy, predictive values, and best biopsy strategy for combining bpMRI and PSAd in detecting and ruling out sPCa (GS 7–10). (***Paper VI***)

- To develop a predictive model for sPCa in biopsy-naive men based on bpMRI findings and clinical parameters. (***Paper VII***)

- To assess the current status, challenges and future perspectives of prostate MRI/TRUS image fusion biopsies. (**review; *Paper VIII***)

Chapter 4: General methodology

In this section, the general methodology of the included studies will be specified. More detailed specifications of the materials and methods, including study population, image acquisition and analysis, biopsy methods, histopathological evaluation, and definition of sPCa from each study are included in the papers, which can be found in the appendix.

Materials & methods

All clinical studies (*papers I–VII*) were conducted as original single-centre studies at Herlev Gentofte University Hospital in a collaboration involving the Departments of Urology, Radiology, Pathology, and the Urological Research Unit. Two prospective databases were constructed and approved by the Local Committee for Health Research Ethics (H-12011066 and H-15009341) and the Danish Data Protection Agency for use in these studies.

The databases were registered at www.*clinicaltrials.gov* (NCT01640262 and NCT02584179), and patient data were selectively culled from the databases to meet the specific objectives of each individual study. All studies conformed to the START consortium criteria for MRI biopsy studies [145], and all patients provided written informed consent.

Study population

We used patient data from two separate patient cohorts derived from an ethnically homogeneous, non-PSA screened Scandinavian population. However, the two cohorts were from different time periods, were evaluated using different pre-biopsy MRI scanning approaches (mpMRI or bpMRI), and had different biopsy status:

a. *Men with prior negative $TRUS_{bx}$ undergoing repeat biopsy (repeat biopsy men)*

   This patient cohort (*patient cohort 1*) included 302 men who were prospectively enrolled between September 2011 and September 2013. A total of 13 men were excluded due to claustrophobia or technical problems with the MRI procedure. Therefore, the final study population included 289 men with a median age of 64 years (interquartile range [IQR], 59–67) and median PSA level of 12.8 ng/mL (IQR, 8.3–19.1). The inclusion criteria required all men to have a history of at least one negative $TRUS_{bx}$ session (i.e., 10–12 biopsy cores) but there had to be a persisting suspicion of PCa (i.e., a persistently elevated/rising PSA level, an abnormal DRE or a prior abnormal TRUS image) that warranted a repeat biopsy. The

exclusion criteria were: a prior PCa diagnosis, a prior prostate MRI examination, or general contra-indications for MRI (e.g., severe claustrophobia, a pacemaker, or metallic implant). Patient data were selectively culled from this *patient cohort 1* to meet the specific objectives for *papers I–IV*.

b. *Men with no prior biopsies (biopsy-naïve men)*

This patient cohort (*patient cohort 2*) included 1,063 men who were prospectively enrolled in the BIparametric MRI for Detection Of prostate Cancer (BIDOC) database between November 2015 and June 2017. A total of 43 men were excluded for various reasons (see *Figure 1* in *paper V*). Therefore, the final study population included 1,020 men with a median age of 67 years (IQR, 61–71) and median PSA level of 8.0 ng/mL (IQR, 5.7–13.0). The inclusion criteria required clinical suspicion of PCa (PSA ≥4 ng/mL and/or an abnormal DRE result) that warranted a diagnostic biopsy. The exclusion criteria were: prior prostate biopsies, a prior prostate MRI examination, or general contra-indications for MRI (e.g., severe claustrophobia, a pacemaker, or metallic implant). Patient data were selectively culled from this *patient cohort 2* to meet the specific objectives for *papers V–VII*.

MRI parameters and acquisition

MRI was performed in all men prior to biopsies. The men enrolled in *patient cohort 1* (i.e., the repeat biopsy group) underwent mpMRI using one of two 3.0 T MRI scanners (Achieva/Ingenia; Philips Healthcare, Best, the Netherlands) with a PPA coil (Philips Healthcare) positioned over the pelvis. A minimum interval of at least 3 weeks between the latest $TRUS_{bx}$ and mpMRI was mandatory to reduce biopsy-related haemorrhagic artefacts. If tolerated, a 1 mg intramuscular glucagon (Glucagen®; Novo Nordisk, Bagsvaerd, Denmark) injection combined with a 1 mg intravenous hyoscine butylbromide (Buscopan®; Boehringer Ingelheim, Ingelheim am Rhein, Germany) injection was administered to reduce peristaltic motion. Tri-planar T2W images from below the prostatic apex to above the seminal vesicles were obtained. In addition, axial DWI was performed, including four *b*-values (b0, b100, b800 and b1400) along with reconstruction of the corresponding ADC map (*b*-values 100 and 800), together with DCE imaging before, during and after intravenous administration of 15 mL gadoterate meglumine (Dotarem 279.3 mg/mL; Guerbet, Villepinte, France). The contrast agent was administered using a power injector (MedRad, Warrendale, PA, USA) followed by a 20 mL saline flush

injection at a flow rate of 2.5 mL/s. The mpMRI image acquisition time was approximately 45 min. The imaging parameters are listed in *Table* 2.

MpMRI sequence parameters

Sequences	Pulse sequence	TR (ms)	TE (ms)	FA (°)	FOV (cm)	ACQ matrix	Number of slices	Thickness (mm)
DWI axial, s/mm² b = 0, 100, 800, 1400	SE-EPI	4697 / 4916	81 / 76	90	18×18	116×118 / 116×118	18 / 25	4
T2W axial	SE-TSE	3129 / 4228	90	90	16×16 / 18×18	248×239 / 248×239	20 / 31	3
T2W sagittal	SE-TSE	3083 / 4223	90	90	16×16 / 16×20	248×242 / 268×326	20 / 31	3
T2W coronal	SE-TSE	3361 / 4510	90	90	19×19	252×249 / 424×423	20	3
T1W coronal	SE-TSE	675 / 714	20 / 15	90	40×48 / 44×30	540×589 / 408×280	36 / 41	3.6 / 6
3d DCE axial	FFE-3d-TFE	5.7 / 10	2.8 / 5	12	18×16	128×111 / 256×221	18	4 / 4.5

DWI = Diffusion-weighted imaging; DCE = dynamic contrast enhanced; T1W = T1-weighted imaging; T2W = T2-weighted imaging; SE = spin echo; EPI = echo planar imaging; TSE = turbo spin echo; TFE = turbo field echo; FFE = fast field echo; TR = repetition time; TE = echo time; FA = flip angle; FOV = field of view; ACQ matrix = acquisition matrix.

Table 2: Sequence parameters for 3.0 Tesla Achieva / Ingenia multiparametric MRI with pelvic-phased-array coil.

The men enrolled in *patient cohort 2* (i.e., the biopsy-naive group) underwent bpMRI using the same 3.0 T MRI scanner (Ingenia; Philips Healthcare) with a PPA coil (Philips Healthcare) positioned over the pelvis. The bpMRI protocol included axial T2W imaging and DWI (*b*-values: 0, 100, 800 and 2,000) and reconstruction of the corresponding ADC maps. A sagittal T2W luxury scout image was obtained to support the axial sequences for MRI/TRUS image fusion. The overall bpMRI image acquisition time was approximately 15 min. The imaging parameters are listed in *Table* 3.

BpMRI sequence parameters

Sequences	Pulse sequence	TR (ms)	TE (ms)	NEX	FOV (cm)	ACQ voxel	Number of slices	Thickness (mm)
DWI axial, s/mm² b = 0, 100, 800, 2000	SE-EPI	9983	71	2	18×18×10	2.1×2.2×4	26	4
T2W axial	SE-TSE	3745	90	1	18×18×10	0.45×0.45×3	30	3
T2W sagittal (luxury scout)	SE-TSE	3.3	1.65	2	27×27×5.5	1. 5×1.5×3	14	3

DWI = Diffusion-weighted imaging; T2W = T2-weighted imaging; SE = spin echo; EPI = echo planar imaging; TSE = turbo spin echo; TR = repetition time; TE = echo time; NEX = number of excitations/average signals; FOV = field of view; ACQ = acquisition matrix.

Table 3: Sequence parameters for 3.0 Tesla Ingenia biparametric MRI with pelvic-phased-array coil.

Image analysis

All MRI data underwent evaluation by the same prostate MRI physician who was blinded to the clinical findings. Any suspicious lesion was registered on a regional prostate scheme (e.g., see *Figure 2* in *paper III*) and scored on a 5-point scale according to its likelihood of being a sPCa (1–highly unlikely, 2–unlikely, 3–equivocal, 4–likely, and 5–highly likely), using PI-RADS v1 or v2 criteria. The men who underwent mpMRI (i.e., *repeat biopsy patient cohort 1*) were scored using PI-RADS v1 criteria because PI-RADS v2 was not published at the time of patient inclusion. The men who underwent bpMRI (i.e., *biopsy-naive patient cohort 2*) were scored using PI-RADS v2 criteria. However, because the bpMRI protocol does not include DCE imaging, scoring of lesions in the peripheral zone relied solely on DWI findings, and equivocal PI-RADS score 3 lesions may not have been upgraded to scores of 4 due to the absence of positive contrast enhancement. Thus, the PI-RADS v2 scoring criteria for bpMRI negative (PI-RADS score 1–2) and PI-RADS score 5 lesions remained unchanged, but the distribution of PI-RADS score 3 and 4 lesions was potentially affected by this modified PI-RADS v2 score (PI_{mod}), which was used to assess all bpMRI scans. In some of the papers (*papers I, VI and VII*), the MRI scores were stratified into three suspicion groups: low suspicion/negative MRI result (score 1–2), equivocal MRI result (score 3), and high suspicion/positive MRI result (score 4–5). Men with no identified lesions were assigned an overall score of 1.

Prostate biopsies: $TRUS_{bx}$ and MRI TBx

Initially, all patients underwent $TRUS_{bx}$ according to international guidelines [30]. In our institution, we use a SBx template of 10 SBx cores from separate prostatic regions (i.e., six lateral and four medial cores from the base, middle and apex on both the left and right sides). The SBx cores were obtained systematically, using a procedure that was blind to any MRI findings, and marked separately for each location/region. Suspicious lesions identified by TRUS were sampled by taking the SBx core for the corresponding region. The operator then reviewed the patient's MRI data on a dedicated workstation in the biopsy room, and additional MRI-TBx (1–2 cores/lesion) were targeted towards any suspicious lesion using either cognitive or software-based (Hitachi HI-RVS [Hitachi Medical Systems, Wellingborough, UK] or Invivo Uro-Nav [Philips Healthcare]) MRI-TRUS image fusion. All prostate biopsies were obtained by one of two experienced operators using the end-fire biopsy technique and potted separately. For a detailed description of MRI-TRUS image fusion biopsies see review *paper VIII*.

Histopathological evaluation and prostate cancer significance

All biopsy samples and RP specimens underwent histopathological evaluation by the same genitourinary pathologist. The location, the GS based on the ISUP 2005 consensus [59], and the percentage of cancerous tissue were determined for each PCa positive biopsy core. In addition, patients evaluated in *papers II and V–VII* were allocated ISUP 2014 GGs [65] based on the GS scoring criteria [59]. Furthermore, all cancerous foci including tumour volumes, the overall GS, the pathological stage (pT; TNM classification [151]), and the presence and location of any EPE for patients diagnosed with PCa who subsequently underwent RP (see *paper IV*) were recorded by the pathologist.

The histopathological findings were used to define sPCa. Although this definition varied slightly across the studies, the primary definition always included the GS/GG. Tumour volume was included in the definition of sPCa in *papers I and III–IV* (*Table* 4). Moreover, secondary definitions of sPCa were additionally assessed in *paper V*. The definition of sPCa in the RP specimens described in *paper IV* was: 1) GS ≥ 3 + 4; 2) locally advanced disease (≥pT3a); or 3) a tumour volume of >0.5 cc.

Primary definition of significant prostate cancer

Paper	Gleason score (GS)		Tumour volume
V. *JAMA Netw Open* 2018 [124]*	GS ≥ 4 + 3	or	any biopsy core ≥ 50% GS 3 + 4
I. *J Urology* 2017 [152] III. *Urology* 2017 [153] IV. *Acta Radiol* 2018 [154]	GS ≥ 3 + 4	or	MCCL ≥ 50% SBx ≥ 3 positive cores
II. *Urol Int* 2017 [155] VI. *Eur Urol Onc* 2019 [156] VII. *PCAN* 2019 [157]	GS ≥ 3 + 4		

*More than one definition was assessed in this paper
GS = Gleason score; MCCL = maximum cancer core length; SBx = standard biopsy.

Table 4: The primary definition of significant prostate cancer used in the studies included in this doctoral thesis.

Chapter 5: Discussion of main study findings and comparisons with the current knowledge

This doctoral thesis evaluates the use of pre-biopsy MRI in the detection and risk assessment of sPCa in a Danish setup. In this section, the main study results will be discussed and compared with those of previous studies in relation to the existing knowledge in the field, with a focus on clinical practice. More detailed discussions of the results from each study, including limitations, are included in the papers, which can be found in the appendix.

Definition of significant prostate cancer (sPCa)

Clinically sPCa can be defined as PCa that is deemed to cause/will cause cancer-related symptoms or death. However, throughout history, physicians have struggled with a clear consensus on what clinical findings define sPCa and how these may be translated into measurements that can be used in clinical practice. Importantly, the definition of sPCa varies slightly across the studies included in this doctoral thesis (*Table* 4), and this may hamper direct comparisons of outcome parameters for a particular test with the findings from each study and with previous studies. However, there is no globally accepted definition of sPCa either at biopsy or after RP, and our definitions reflect the most common definitions that have been used in previous studies. The large reservoir of potentially detectable indolent PCas in adult men [12], which substantially exceeds the lifetime risk of PCa-related morbidity or death (i.e., the ultimate definition of sPCa), challenges the clinician to distinguish future life-threatening sPCas from insPCas in the initial diagnosis and in subsequent treatment planning. Urologists have traditionally relied on PSA testing, DREs and $TRUS_{bx}$ findings to stratify patients into risk groups, as suggested by D'Amico [158,159], and have estimated the likelihood of EPE, seminal vesicle invasion, lymph node involvement and/or recurrence after treatment using nomograms or Partin tables [160–162]. However, these models are based on statistical predictions that integrate the known intrinsic sampling errors of $TRUS_{bx}$, the limited diagnostic accuracy of DREs and the uncertain relationship between PSA levels and tumour stage. Thus, the definition of sPCa has evolved over time, and different institutions have suggested and used various definitions [163]. Nonetheless, although the GS system was introduced more than 50 years ago, it remains one of the strongest predictors of PCa aggressiveness and is the most widely used grading system worldwide. The GS system has been modified to simplify and improve its

clinical and prognostic performance and many clinicians consider it the most important predictor of significant and insignificant PCas [57,164]. As a result, many published research studies investigating PCa diagnoses, including many of the papers in this doctoral thesis, rely primarily on histopathological findings to define insPCa as GG 1 and sPCa as GG 2 or above. In addition, MRI shows significantly greater sensitivity in detecting GG ≥2 compared with GG 1 cancers due to the lower hypo-intensity and restricted diffusion on T2W imaging and DWI of higher grade cancers [165]. Moreover, cancer visibility on MRI is influenced by tumour volume [166], with larger tumours being easier to detect than GG 1 cancers <0.5 cc in size (*Table* 5). Therefore, MRI can be used for sPCa detection and for improving the diagnostic ratio of sPCa vs. insPCa, as discussed in the following sections.

Prostate cancer detection rates

Gleason score (GS) & ISUP grade group (GG)	Tumour volume (cc)		
	< 0.5	0.5–2	> 2
GS 6 or GG 1	21–29%	43–54%	67–75%
GS 7 or GG 2–3	63%	82–88%	97%
GS 8–10 or GG 4–5	80%	93%	100%

GS = Gleason score; GG = grade group; ISUP = International Society of Urological Pathology.

Table 5: Multiparametric MRI prostate cancer detection rates (%) stratified by tumour volume and Gleason score/grade group of radical prostatectomy specimens. Modified from *Bratan et al.* [165].

Aims of pre-biopsy MRI

Pre-biopsy MRI primarily addresses the three main limitations of the current diagnostic pathway: a) many men with benign conditions or clinically insPCa undergo unnecessary biopsies, which are associated with morbidity; b) overdiagnosis of insPCa leading to possible overtreatments; and c) underdiagnosis of sPCa due to $TRUS_{bx}$ sampling errors. However, pre-biopsy MRI may be used as a triage test to minimise the number of men requiring a biopsy, minimise detection of insPCas, potentially minimise the number of cores required to confirm a diagnosis and plan treatment, and to maximise detection of sPCa. This translates into two major benefits: 1) avoiding unnecessary biopsies, and 2) improving sPCa detection.

Avoiding prostate biopsies

Using pre-biopsy MRI to avoid biopsies addresses two major limitations with our current diagnostics. First, because PSA is not cancer-specific, many men with benign reasons for elevated PSA levels undergo unnecessary biopsies. Second, MRI does not detect all PCas and its poor sensitivity for low volume, low grade (GG 1) tumours can be beneficial because these tumours rarely harm the patient. Because these tumours are below the detection threshold of MRI and therefore "missed", the use of MRI as a triage test to decide whether to biopsy may address the issue of overdiagnosis and overtreatment of insignificant disease. Avoiding or delaying a biopsy if the MRI result is negative (i.e., a PI-RADS score of 1 or 2) would reduce the number of men requiring biopsies and decrease the detection of insPCas. However, if MRI is to be used in clinical practice to guide biopsy decisions, it must not miss sPCas. Therefore, negative MRI results must have a high NPV.

In *papers V and I*, we report that the NPV of MRI was 97% (*paper V*; bpMRI) and 95% (*paper I*; mpMRI) for excluding the presence of sPCa in biopsy-naïve men and men undergoing repeat biopsy, respectively. The purpose of *paper V* was to assess the diagnostic accuracy of bpMRI in biopsy-naïve men and compare the diagnostic performance of SBx in all men against SBx plus TBx restricted to men with suspicious bpMRI findings using combined biopsy results from all men as a reference standard. Overall, we found that restricting biopsies to men with suspicious bpMRIs meant 30% (305/1,020 men; $p < 0.001$) could avoid biopsies, insPCa diagnoses were reduced by 40% (173 vs. 288 men; $p < 0.001$), and sPCa diagnoses were improved by 11% (396 vs. 351 men; $p < 0.001$) compared with our current diagnostic standard – $TRUS_{bx}$ alone for all men. The purpose of *paper I* was, however, slightly different. The main objective of this study was to assess the future risk of being diagnosed with any PCa and sPCa following either a low-suspicion mpMRI or a benign TBx result for a suspicious lesion in men with a prior negative $TRUS_{bx}$ result. The NPV for ruling out sPCa was 95% over a follow-up period of at least 3 years (median, 47 months). However, most of the sPCas missed by MRI-TBx were detected by repeat $TRUS_{bx}$ in men with a positive MRI result suggesting that these results had not been misinterpreted but that TBx had missed the sPCas due to targeting errors. Our findings in *paper I* are similar to those of *Panebianco et al.* [167], who reported a "sPCa-diagnosis free survival" of 95–96% at >2 years of follow-up following a negative MRI result. In that study, all missed sPCas were detected within the first 2 years of follow-up and all were organ confined. Similarly, *Venderink et al.* [168] reported that more than half of patients (mixture of biopsy-naïve and

prior biopsy-negative men) having mpMRI of the prostate avoided biopsies (PI-RADS ≤2), and in those patients, sPCa detection-free-survival was 99.6% after 3 years. The overall conclusions from our two studies (*papers V and I*) are that a low-suspicion MRI result has a high NPV in ruling out sPCa in biopsy-naïve men at initial biopsy and over a longer term in men with prior negative $TRUS_{bx}$ results. Therefore, MRI could potentially be used as a triage test to exclude aggressive disease and avoid unnecessary biopsies. However, the definition of sPCa used in *paper V* was any core with GG ≥3 or maximum cancer-core length ≥50% of GG 2 PCa. The more conservative sPCa definition of any cancer core with GG ≥2 (a tertiary definition in the study), proposed by other institutions, yielded slightly different diagnostic accuracies and a decrease in NPV from 97% to 93%. This may partly be explained by the influence of the observed increase in sPCa prevalence from 404 (39.6%) cases to 475 (46.5%) cases in the 1,020 men. NPV often decreases as disease prevalence increases. For example, *Moldavan et al.* [6] analysed 48 studies (9,613 patients) and found a median NPV of 88% for mpMRI in ruling out sPCa (i.e., GG ≥2) but also reported that predictive values were strongly influenced by disease prevalence in the population studied.

Reference standard test

A key challenge in many diagnostic studies assessing the accuracy of MRI in ruling out sPCa has been the lack of a robust gold standard to which the MRI and biopsy results can be compared. Multiple studies [3,169,170], including those described in this doctoral thesis, have used SBx, TBx or combined biopsy results as reference standards. This is problematic because MRI-negative regions of the prostate gland are not sampled by TBx, and $TRUS_{bx}$ is flawed, with SBx missing up to 30–40% of sPCas [48,56]. Thus, sPCa lesions may have been missed by biopsies and the true frequency of false-negative readings cannot be assessed to calculate a "true" NPV. On the other hand, using results from different biopsy techniques for comparisons reflects clinical practice. Another way to assess the diagnostic accuracy of MRI results is to compare them with histopathological assessments of RP specimens. Although this patient group is affected by selection bias because none of the patients will have negative histological results, many previous studies have shown a strong association between mpMRI findings and RP specimens [88,171]. In *paper IV*, we analysed a subgroup of 64 patients diagnosed with PCa who subsequently underwent RP and showed that increased PI-RADS scores were strongly associated with more aggressive cancer and advanced stages of the disease. TBx were

significantly (p = 0.019) better than SBx at predicting the postoperative presence of sPCa, as TBx and SBx correctly identified 47/60 (78%) and 35/60 (58%) of patients with a sPCa in their RP specimen, respectively. However, some sPCas were missed by TBx, and mpMRI reportedly fails to detect sPCa lesions in 5–28% of cases [172–174] when RP specimens are used as a reference standard. Similarly, a meta-analysis by *Rooij et al.* [175] showed that 1.5T mpMRI had moderate diagnostic accuracy for local staging with a pooled sensitivity and specificity in detecting EPE of 57% and 97%, respectively. Thus, although using 3T MRI and functional imaging significantly improves diagnostic accuracy [175], there is still an unknown proportion of sPCas that are difficult to detect on MRI.

One of the most accurate and reliable reference tests for comparing MRI results may be 5-mm transperineal mapping biopsies (TPM_{bx}), which reportedly detect cancers with volumes of 0.2 cc or greater with 95% accuracy [176]. Results from two prospective level 1 evidence trials from the United Kingdom have been published that compare the diagnostic accuracy of mpMRI in biopsy-naïve men (*PROMIS* [177]) and in men with prior negative biopsies (*PICTURE* [178]) using TPM_{bx} as the reference standard. The *PROMIS* study was a multicentre paired-confirmatory cohort study that included 576 biopsy-naïve men and compared mpMRI to $TRUS_{bx}$ using TPM_{bx} as the reference standard. The *PROMIS* study results suggested that if mpMRIs were used as a triage test, one in four men could safely avoid prostate biopsies and the diagnostic ratio of sPCa vs. insPCa could be improved. The definition of sPCa was GG ≥3 or maximum cancer-core length ≥6 mm, which was almost identical to the definition we used in the *BIDOC* study [124] (*paper V*). However, if sPCa was defined as any cancer core with GG ≥2 (a tertiary definition in the *PROMIS and BIDOC* studies), then the NPV decreased from 89% to 76%, missing 12% of sPCas. Nevertheless, no GG ≥3 PCas were missed. The *PICTURE* study [178] was a single-centre diagnostic validation cohort study that assessed the NPV of mpMRI in ruling out sPCa (same definition as that used in the *PROMIS* study) in 249 men requiring a repeat biopsy. When an mpMRI Likert ≥3 suspicion score biopsy threshold was applied, 14% of these men could avoid a biopsy and the NPV was 91%. The results using the definition of sPCa as any cancer core with GG ≥2 PCa was not reported in the *PICTURE* study.

Although TPM_{bx} are highly accurate [179] and may correctly assess the risk of PCa [180], the procedure often requires general anaesthesia, is associated with a high degree of morbidity (as assessed during the *PICTURE* study), and has a high risk of overdetecting insPCas. Thus, TPM_{bx} is much more cumbersome, time consuming and costly than $TRUS_{bx}$ or TBx, which makes it less

feasible for clinical practice. Furthermore, TBx of suspicious mpMRI lesions were not performed as part of the *PROMIS* and *PICTURE* studies. It was assumed that TBx would achieve the same diagnostic accuracy as TPM_{bx}, which is unrealistic due to TBx targeting errors. However, in 2018, results from the multicentre, randomised non-inferiority *PRECISION* trial were published by *Kasivisvanathan et al.* [181]. A total of 500 biopsy-naïve men suspected of having PCa were randomised to either an MRI-diagnostic pathway with or without TBx, or to standard $TRUS_{bx}$ for all men. Using mpMRI as a triage test improved PCa risk stratification and decreased the number of men needing biopsies by 28%. It also decreased the diagnoses of insPCas by 13%, and improved sPCa diagnoses (defined as any core with GG ≥2 PCa) by 12% compared with $TRUS_{bx}$ for all men. Because no biopsies were performed on MRI-negative men, the NPV could not be assessed. However, similar results were reported by the *4M* [170] and *MRI-first* [169] studies that included standard $TRUS_{bx}$ for MRI-negative men. A comparison of these studies with our *BIDOC* study findings (*paper V*) is shown in *Table* 6 to assess the benefits of using an MRI-guided diagnostic pathway over standard $TRUS_{bx}$ in biopsy-naïve men. This comparison shows that ≥21% of men consistently avoided biopsies across these studies.

Study	PRECISION [181], *NEJM 2018*	MRI first [169], *Lancet Onc 2018*	4M [170], *Eur Urol 2018*	BIDOC [124], *JAMA Open 2018*
Design & population	MC RCT, *N* = 500, median age 64 yrs.; PSA 6.6 ng/mL; abnormal DRE 15%	MC paired validation, *N* = 251, median age 64 yrs.; PSA 6.5 ng/mL; abnormal DRE 31%	MC paired validation, *N* = 626, median age 65 yrs.; PSA 6.4 ng/mL; abnormal DRE 28%	SC paired validation, *N* = 1,020, median age 67 yrs.; PSA 8.0 ng/mL; abnormal DRE 37%
MRI & scoring	1.5 T & 3.0 T PI-RADS	1.5 T & 3.0 T Likert > PI-RADS	3.0 T PI-RADS	3.0 T bpMRI PI-RADS compliant
Reference test	TBx only**	Combined Bx	Combined Bx	Combined Bx
sPCa prevalence	38%	37%	30%	47%
sPCa detection rate				
TBx*	38%	32%	25%	45%***
SBx	26%	30%	23%	43%
InsPCa detection rate				
TBx*	9%	6%	14%	11%***
SBx	22%	20%	25%	19%
Benefits of MRI over $TRUS_{bx}$				
Men avoiding biopsy	28%	21%	49%	30%
Cores per MRI ROI	4	3	2–4 (in-bore)	1–2
sPCa yields	+12%	+2%	+2%	+2%
InsPCa yields	–13%	–14%	–11%	–8%

*TBx restricted to MRI-positive men
**TBx only in MRI arm – no biopsies on MRI-negative men
***TBx performed as targeted + standard

MRI = magnetic resonance imaging; bpMRI = biparametric MRI; MC = multicentre; SC = single centre; RCT = randomised controlled trial; PCa = prostate cancer; sPCa = significant (GG ≥2) PCa; insPCa = insignificant (GG 1) PCa; GG = Gleason grade group; DRE = digital rectal examination; PSA = prostate-specific-antigen; PI-RADS = prostate imaging reporting and data system; ROI = region of interest; TBx = targeted biopsy; SBx = standard biopsy; $TRUS_{bx}$ = transrectal ultrasound-guided biopsy; combined bx = targeted + standard biopsies.

Table 6: Comparison of recently published level 1 studies showing the benefits of an MRI-guided diagnostic approach over standard $TRUS_{bx}$ in biopsy-naïve men

In April 2019, a large *Cochrane review* by *Drost et al.* [182] assessed the diagnostic accuracy of prostate MRI with or without MRI-TBx against SBx for detecting PCa. The overall conclusion from this review was that if biopsies were restricted to men with suspicious MRI results, one in three men (33% of biopsy-naïve men and 30% of those with a prior negative biopsy result) could avoid invasive biopsies and there would be a significant reduction in insPCa diagnoses (a 37% reduction in biopsy-naïve men and a 38% reduction in those with prior negative biopsy

results). However, it also showed that an MRI-guided diagnostic pathway will miss some men with clinically sPCas and, therefore, further research in this area is important. Nevertheless, because prostate biopsies are associated with patient anxiety and morbidity as well as overdetection of insPCas and can lead to overtreatment or enrolment in AS with long-term costs and negative effects on quality of life, omitting biopsies in MRI-negative men seems reasonable in selected cases. As shown in *Table* 7, the median SBx detection rate of GG ≥2 PCas in MRI-negative men is approximately 6%, and the majority of these PCas are GG 2 cancers. Therefore, $TRUS_{bx}$ should be performed in approximately 20 MRI-negative men to find one sPCa at the expense of a significant increase in insPCa diagnoses. Consequently, although it is difficult to weigh the relative risks and benefits of an optimal biopsy strategy for each individual patient, these findings emphasise that additional predictors, such as PSAd measurements, risk calculators or a safety net based on clinical and biochemical monitoring to detect missed/growing sPCas after a negative MRI result are reasonable alternatives to $TRUS_{bx}$ for all MRI-negative men. Thus, while men with a high a-priori risk of PCa should undergo biopsies regardless of MRI findings, MRI-negative men with a low clinical risk of sPCa may avoid biopsies based on shared decision making [13]. This strategy will be discussed later in the thesis.

Reference	Included patients (*n*)	Negative (–ve) MRIs, % (*n*)	PCa in –ve MRIs, % (*n*)	sPCa in –ve MRIs, % (*n*)	HG PCa in –ve MRIs, % (*n*)
Multiparametric MRI					
Itatani [183]; 2014	621	31% (193)	13% (25)	4%	3%
Pokorny [184]; 2014	223	36% (81)	31% (25)	11%	4%
Panebiancho [185]; 2014	570	23% (130)	0% (0)	0% (0)	0% (0)
Porpiglia [186]; 2017	107	24% (26)	19% (5)	0% (0)	0% (0)
MRIfirst [169]; 2018	251	21% (53)	29% (13)	11% (5)	2% (1)
4M study [170]; 2018	626	49% (309)	23% (71)	3% (10)	0.3% (1)
Bryant [187]; 2018	792	35% (278)	27% (76)	15% (42)	2% (6)
Biparametric MRI					
Multi-IMPROD [188]; 2019	338	22% (75)	15% (11)	5% (4)	0% (0)
BIDOC [124]; 2018	1,020	30% (305)	28% (86)	7% (21)	2% (7)

MRI = magnetic resonance imaging; PCa = prostate cancer; –ve MRI = negative MRI (PI-RADS/Likert score 1–2); sPCa = significant PCa (GG ≥2); HG PCa = high grade PCa (GG ≥3).

Table 7: Comparison of $TRUS_{bx}$ PCa detection rates in men with negative MRI results. Note: this list of currently available data is not complete.

Improving sPCa detection

Multiple studies have shown that the MRI suspicion score categories (i.e., PI-RADS and/or Likert) are strongly associated with PCa detection rates and that the diagnostic yield of sPCas (GG ≥2) increases with rising MRI suspicion scores [4,182]. Furthermore, because mpMRI is highly sensitive for detecting aggressive tumours (i.e., volume >0.5 cc and/or GS >6), it correctly identifies the location of the index lesion in 92–95% of patients [165,189–191]. Because MRI is so effective in identifying highly suspicious lesions, TBx are increasingly being used to improve detection of sPCa. A review by *Stabile et al.* [192], which assessed 34 papers published within the last 5 years (14 biopsy-naïve, 10 prior-negative biopsy, and 10 prior-positive biopsy studies), showed that MRI-TBx consistently resulted in the detection of more sPCas and fewer insPCas than SBx across all three patient cohorts. The relative sensitivity of TBx compared to SBx was 1.15 for biopsy-naïve men and 1.45 for men with prior negative

biopsies. Thus, the effect was most prominent in men with prior negative biopsies. These results are consistent with our findings, described in *paper V* (biopsy-naïve men) and *papers II and IV* (prior biopsy-negative men). However, we only found a limited 1.3% (i.e., non-significant) increase in the detection of GG ≥2 PCas in the *BIDOC* study (*paper V*, biopsy-naïve men; relative sensitivity ratio, 1.03), which is similar to the findings of the *MRI-first* (ratio, 1.08) [169] and *4M* (ratio, 1.09) [170] studies. In addition, the *Cochrane review* showed only a limited pooled relative sensitivity of 1.05 favouring MRI-TBx for the detection of GG ≥2 PCas in biopsy-naïve men, but a much higher ratio of 1.44 in men with prior negative biopsies, which are similar to the ratios of 1.52 and 1.32 reported in *papers II and IV*, respectively. This confirms that MRI followed by TBx significantly outperforms SBx in detecting sPCa (GG ≥2) in men with prior negative biopsies, but has a more limited value in biopsy-naïve men [3]. However, none of the studies demonstrated non-inferiority of an MRI-TBx approach, and the randomised controlled *PRECISION* trial did show a significant 12% (relative sensitivity ratio, 1.46) increase in sPCa detection when using the MRI-diagnostic pathway. Interestingly, the reported sPCa detection rates and sensitivity ratios in the *PRECISION* (1.42), *MRI-first* (1.08) and *4M* (1.09) studies relied on an "MRI-targeted only" approach. This was different from our *BIDOC* study, which used combined (i.e., targeted plus standard) biopsies for MRI-positive men. This difference will be discussed in the following sections.

Targeted biopsies

In general, MRI-guided TBx uses MRI images to identify suspicious lesions and guide prostate biopsy sampling. Several MRI-guided biopsy techniques have been established to selectively sample MRI-positive lesions by TBx, but none of these has proved to be clinically superior to the others. These techniques include MRI/TRUS image fusion biopsies (cognitive or software-based) and in-bore biopsies. Direct in-bore TBx is considered the gold standard for MRI-guided TBx because it can accurately sample lesions of interest and visually confirm needle deployment at the target site. However, this method is expensive, has limited availability and does not allow concurrent systematic sampling. Conversely, fusing MRI data with TRUS (i.e., MRI/TRUS fusion) combines the superior imaging of MRI with the easy-to-use ultrasound guidance, which allows skilled operators to perform TBx in real time in an outpatient clinic, saving time and costs but retaining targeting accuracy [5,193,194]. Furthermore, TBx can be

combined with systematic biopsies, which are still recommended by the European Association of Urology (EAU) guideline [13].

All TBx described in the studies included in this doctoral thesis were performed as cognitive or software-based MRI/TRUS image fusion biopsies. MRI/TRUS image fusion was implemented in our department in 2011 with the introduction of prostate MRI into clinical practice. MRI-TBx were initially performed using cognitive fusion, but this technique was quickly replaced by a software-based fusion procedure to improve targeting accuracy. With the anticipated increase in the use of pre-biopsy MRI, a more widespread implementation of MRI/TRUS image fusion software platforms is expected in clinical practice. As a result, the objective of the review included in this doctoral thesis (*paper VIII*) was to assess the current status, challenges and future perspectives associated with performing MRI/TRUS image fusion prostate biopsies. Previous studies have not shown that a particular biopsy technique (e.g., in-bore, software-based or cognitive image fusion) or MRI/TRUS fusion platform is superior to others. Costs, local preferences and ease of use will inform choices regarding biopsy techniques and/or fusion platforms.

Targeted vs. standard vs. combined biopsies

There is an ongoing debate regarding whether TBx should be used in addition to SBx in a "combined approach" or relied upon in a "targeted-only" approach to detect clinically sPCas. The prospective cohort study by *Siddiqui et al.* [5] that included 1,003 (primarily prior biopsy-negative) men undergoing both SBx and TBx favoured a "targeted-only" strategy compared with SBx or combined biopsies because this option increased the diagnostic yield of sPCas, while reducing insPCa detection. Conversely, *Filson et al.* [195] did not find that a "targeted-only" strategy enhanced sPCa detection in 1,042 men from an equally mixed cohort of biopsy-naïve, prior biopsy-negative and prior biopsy-positive men, and they recommended a combined approach for all patients. In our *BIDOC* study (*paper V*), we found that restricting combined biopsies to men with suspicious MRI results (a "partially combined" approach) was the preferred strategy for achieving a high sPCa and low insPCa detection yield. These findings highlight three general biopsy strategies: 1) a "combined" strategy, in which all men undergo SBx plus TBx of any suspicious lesion identified by MRI; 2) a "partially combined" strategy, in which SBx plus TBx are restricted to MRI-positive men, and MRI-negative men avoid biopsies; and 3) a "targeted-only" strategy, in which TBx are restricted to men with positive MRI results

and SBx is omitted completely. Several studies, including *paper V* for biopsy-naïve men and *paper II* for prior biopsy-negative men, have tried to evaluate the efficacy of these different biopsy strategies. Because all men underwent a "combined" procedure, the additional value of TBx and SBx over the other can be assessed. The "combined" strategy, which is often used as the reference standard, yields the highest sensitivity for detection of sPCas, but this comes at the cost of overdetecting insPCas. Because our *BIDOC* study (*paper V*) was not initially designed to evaluate a "targeted-only" strategy, but instead to compare a "partially combined" strategy (restricting SBx plus TBx to MRI-positive men) with either SBx or combined biopsies in all men, we did not assess the added value of SBx in MRI-positive men separately. However, we found that adding SBx to all MRI-negative men, thereby transforming a "partially combined" strategy into a "combined" strategy, detected 4.4% (21 of 475 cases) more GG ≥2 PCas (a tertiary definition of sPCa) and 2.0% (8 of 404 cases) more sPCas. Unfortunately, this was at the expense of a 56% (179 vs. 115 cases) increase in GG1 PCa diagnoses. Nevertheless, both strategies improved sPCa detection and reduced the number of men diagnosed with insPCa compared with the current standard procedure - $TRUS_{bx}$ for all men.

In *paper II*, we assessed a "targeted-only" strategy compared with standard repeat $TRUS_{bx}$ and combined biopsies for all men with prior negative biopsy results. We found that a "targeted-only" strategy missed 5.7% of GG ≥2 PCas (3 of 53 cases) that were detected by SBx in a "combined" strategy (i.e., the value of adding SBx to TBx). However, the value of adding TBx (i.e., the percentage of patients diagnosed by adding TBx to SBx in MRI-positive men) was significantly higher than the value of adding SBx to TBx in both MRI-positive and -negative patients (37.7% vs. 5.7%; $p < 0.001$).

Overall, the number needed to biopsy (NNB) to find one additional man with GG ≥2 PCa was 15 for *paper V* (adding SBx to MRI-negative men; biopsy-naive men) and 69 for *paper II* (adding SBx to both MRI-positive and -negative men; men with prior negative biopsy results) at the expense of an additional 3 and 7 men diagnosed with insignificant GG1 PCas, respectively. *Note: the NNB reported in paper II should be corrected to 69 because disease prevalence of sPCa (26%) and insPCa (18%) using combined biopsy results are now being taken into account.*

To assess the accuracy and reproducibility of an MRI-TBx-guided biopsy strategy, it is important to recognise that not all cancers are visible on MRI [172]. Images may be misinterpreted and TBx may miss or undersample sPCa lesions due to targeting errors. Pooled

sensitivity results from the *Cochrane review* [182] showed that MRI (12 studies and 3,091 patients from mixed cohorts), TBx (MRI-positive men; 8 studies and 1,553 patients) and SBx (4 studies and 3,421 patients) miss 9%, 20% and 37% of GG ≥2 PCas (29% prevalence) using template-guided biopsies as a reference standard, respectively. This means that 10–20% of GG ≥2 PCas are missed in an MRI "targeted-only" biopsy strategy, which is one of the reasons why a "combined" strategy seems appropriate for biopsy-naïve men. However, as previously reported, performing SBx in MRI-negative biopsy-naïve patients yields an average detection rate of only ~6% for GG ≥2 PCas (*Table* 7), with the majority being GG 2 cancers. Therefore, the EUA guidelines [13] currently recommend a "combined" biopsy strategy for MRI-positive biopsy-naïve men, while SBx may be omitted in men with negative MRI results and low clinical suspicion of having PCa based on shared decision making. For men with prior negative biopsy results, a "targeted-only" strategy is recommended for MRI-positive men and SBx only for MRI-negative men with high clinical suspicion of having PCa. These recommendations are partly based on the conclusions from the *Cochrane review* [182], which suggested that to detect GG ≥2 PCas, the added value of an MRI-guided diagnostic pathway with TBx restricted to men with positive MRI results in a "targeted-only" approach was higher than the added value of performing SBx in all men. This was the case for both biopsy-naïve men (6.3% vs. 4.3%) and for men with prior negative biopsy results (9.6% vs. 2.3%). Sub-stratifying MRI-positive and -negative men also helps to understand the added value of SBx. For MRI-positive and -negative biopsy-naïve patients, the added value of SBx was 4.9% (NNB, 20) and 8.1% (NNB, 13), and for men with prior negative biopsy results the values were 2.7% (NNB, 37) and 5.3% (NNB, 19), respectively. These findings are consistent with our results, described in *papers V and II*.

Clearly, omitting SBx in an MRI-guided diagnostic pathway leads to missed sPCas. The proportion of missed sPCas reportedly ranges from 2–28% [172–174,182,192], depending on the definition of sPCa and the reference standard (e.g., TPMbx, SBx only, combined biopsies or RP specimens). However, the value of adding SBx to a TBx approach appears to be limited, especially for men undergoing repeat biopsies. Furthermore, the majority of sPCas missed by MRI appear to be low volume, apical or postero-lateral organ-confined GG 2 cancers [153,196,197]. Whether missing 4–6% of sPCas in a "targeted-only" approach is acceptable is a matter of risk assessment and individual preference, but it compares favourably with the 5% prevalence of GG ≥2 PCas among men with benign DRE and PSA levels of 2.1–4 ng/mL in the placebo-arm of the Prostate Cancer Prevention Trial [16].

Decreasing insignificant PCa diagnoses

Clearly, the addition of SBx to a TBx approach comes at a cost of overdetecting insPCas. The sensitivity of MRI for GG1 PCas is low. Therefore, these cancers are often missed by TBx. However, if SBx is applied to MRI-negative men and/or as an adjunct to TBx in MRI-positive men, the detection rate of insPCas increases significantly [192]. The results from *paper V* showed that diagnoses of insPCas (i.e., primary definition) and GG1 PCas decreased by 31% (173 vs. 250 cases; absolute, –8%) and 33% (115 vs. 172 cases; absolute, –6%), respectively, when combined biopsies were restricted to MRI-positive men (i.e., "partially combined" biopsy strategy) compared with performing combined biopsies in all men. Compared to current standard treatment (i.e., SBx alone for all men), diagnoses of insPCas (i.e., primary definition) and GG1 PCas decreased by 40% (173 vs. 288 cases; absolute, –11%) and 42% (198 vs. 115 cases; absolute, –8%), respectively. The results from *paper II* showed that utilising a "targeted-only" approach for men with prior negative biopsies, produced even greater decreases in GG1 PCa diagnoses (14 vs. 33 cases; relative/absolute risk reduction, –66%/–13%). Our findings are consistent with previously published studies (*Table* 6) and results reported in a systematic review of 16 studies (1,926 patients) performed by *Schoots et al.* [3], which showed that omitting SBx would almost halve the detection rate of insPCas (relative sensitivity, 0.56).

Location of missed sPCas and optimal TBx number

In *paper III*, we assessed the location of sPCa lesions missed by repeat $TRUS_{bx}$ and TBx in men with prior negative biopsy results. Overall, we found that both SBx and TBx miss sPCa lesions in specific segments of the prostate gland in men undergoing repeat biopsies. The missed sPCa lesions were primarily anterior for SBx (84%) and postero-lateral mid-prostatic for TBx (60%). *Schouten et al.* [196] showed that the same problem occurs in biopsy-naïve men and that both techniques had difficulty detecting apical lesions.

Multiple factors can influence the diagnostic performance of MRI and TBx and result in sPCas being missed. These factors include MRI quality, reader oversight/experience, the presence of MRI-invisible cancers, poor biopsy technique, and intra-lesion Gleason grade heterogeneity [198]. Furthermore, apical lesions can be difficult to detect on MRI because this region is often small and close to the prostatic margin/sphincter, as well as adjacent anatomical structures [199]. Similarly, lesions may be missed in the postero-lateral segment due to small sub-

capsulated or infiltrative tumours [199]. However, *paper III* reported that most patients with missed sPCas were MRI positive (i.e., had PI-RADS 3–5 lesions), suggesting that these lesions were missed due to mpMRI/TRUS image fusion sampling errors rather than mpMRI misinterpretation. Still, there is always a risk of mis-registration, which hampers the accuracy of TBx when combining two image modalities for image fusion. Furthermore, sampling errors can occur due to prostate deformation and movement during the biopsy session, and it is difficult to confirm accurate biopsy-needle deployment at the target site using MRI-TRUS image fusion [200]. Performing in-bore TBx may improve sampling accuracy because in this procedure, needle deployment at the region of interest can be confirmed. However, in-bore TBx is time consuming and occupies the MRI-suite twice. Furthermore, it cannot be combined with SBx, which is recommended for MRI-positive men by standard guidelines [30,201]. However, as reported in *paper III* and in the study by *Schouten et al.* [196], adding additional systematic cores to TBx only in the postero-lateral mid-prostatic and apical segments of the prostate gland may be enough to improve detection of missed sPCas without the need to sample all prostatic regions using 10–12 standard SBx cores.

Another way to reduce sampling errors may be to obtain more targeted cores per lesion (i.e., focal lesion saturation/sampling of penumbra) as recently proposed by *Giannarini et al.* [202] and by the PI-RADS steering committee [203]. However, in our studies we only obtained 1–2 cores per lesion, which may be inadequate, as highlighted in the study by *Lu et al.* [204] where a two-core approach missed 16% (biopsy-naïve men) and 27% (prior biopsy-negative men) of sPCas. However, increasing the number of cores may simultaneously increase the risk of biopsy-related adverse events [205]. In the *BIDOC* study (*paper V*), we found that most men with benign TBx of suspicious lesions detected by MRI (n = 237), confirmed as false negatives by positive SBx cores from the corresponding region, were insPCas (84%). This problem of benign TBx associated with suspicious lesions detected by MRI was investigated by *Chelluri et al*. [206] who found that if a PCa was detected in a subsequent targeted re-biopsy, it was rarely a sPCa. Furthermore, multiple studies have recently shown that missed sPCas in MRI-positive men are generally due to sampling errors rather than MRI misinterpretation [170,207–211]. Increasing the number of cores targeting suspicious lesions enhances sPCa yields because sPCas are often detected in adjacent sextants to MRI targets. Moreover, systematic sampling of apparently normal, non-adjacent sectors does not seem to alter risk stratification in the majority of cases [207,208]. In addition, multiple cores obtained from the index lesion (focal

saturation TBx) apparently provide a better assessment of pathology (GS) than a single targeted core from the centre of the lesion (non-saturation TBx), when RP is used as the reference standard [212]. If this is not due to biopsy targeting errors caused by fusion biopsy mis-registration and needle deflection, it may be explained by intra-tumour GS heterogeneity (i.e., some foci being more aggressive than others in the same tumour) or the fact that cancer volumes are often underestimated on MRI [213], making the ideal target region difficult to determine. However, although focal saturation in and around a suspicious lesion detected by MRI enhances sPCa yields and improves pre-therapeutic risk assessment, there is no consensus of opinion on the optimal number of cores to have per lesion.

Thus, if an unexpected biopsy result occurs, it is important to re-evaluate each step of the process from quality control of MRI acquisition, interpretation and reporting, to the actual biopsy procedure itself to identify potential sources of error.

Biparametric vs. multiparametric MRI

At present, the ESUR recommends a full mpMRI prostate examination, including DCE-MRI with intravenous contrast media, for all patients suspected of having PCa. However, the role and importance of DCE-MRI in PCa diagnosis has changed over time from a five-point score in the PI-RADS v1 classification to a binary (positive/negative) score, secondary to DWI and T2W imaging in the updated PI-RADS v2 and v2.1. Thus, DCE-MRI now plays a minor role in detection of PCa. It is essentially only used to upgrade PI-RADS 3 lesions in the peripheral zone of the prostate to a score of 4 if the lesions are DCE-positive (i.e., show focal enhancement) and it has no role in transition zone lesion assessment. Nonetheless, DCE reportedly improves DWI scores in some instances [120] and many physicians consider it a “safety net” sequence that is useful if, for example, the T2W or DWI sequence is degraded by artefacts or insufficient signal-to-noise ratio [147]. Furthermore, DCE may be useful in validating and characterising lesions identified by less experienced readers. However, the caveats include prolonged scan times and the use of an intravenous gadolinium-based contrast medium. Furthermore, DCE imaging often does not seem to improve the overall clinical picture for detecting and localising sPCas in biopsy-naïve men or men with prior negative biopsy results [125,126,214–216]. Consequently, the possibility of performing prostate MRI without DCE as an abbreviated bpMRI procedure has attracted growing interest. The benefits of bpMRI include decreased image acquisition and interpretation times, reduced overall costs, and avoiding the following procedures: 1)

glomerular filtration rate measurements; 2) screening for prior contrast reactions; 3) facilitating intravenous access; and 4) using gadolinium contrast media, which may be associated with adverse effects. Furthermore, reducing scan times from ~40 min to ~15 min (the durations of our mpMRI and bpMRI scans, respectively) may lessen patient anxiety and increase compliance, which can reduce motion artefacts and improve image quality. This less expensive, more rapid bpMRI approach could significantly improve patient access and facilitate more widespread clinical implementation of prostate MRI prior to biopsies, especially in the large patient populations throughout the western world where PCa prevalence is high. However, although a recent meta-analysis by *Niu et al.* [216] suggested that bpMRI has a high diagnostic accuracy in sPCa detection (sensitivity, 0.85), the pooled sensitivity of mpMRI for detecting any PCa was significantly higher (bpMRI 0.80 vs. mpMRI 0.85; $p = 0.01$). Nevertheless, a head-to-head comparison of sPCa detection rates was not presented and the authors reported that the studies were highly heterogeneous. Thus, the results of this meta-analysis should be applied cautiously. A large study by *van der Leest et al.* [217] showed that a fast bpMRI and an mpMRI approach had equivalent sPCa detection rates (both 95%), but that the bpMRI approach had slightly lower specificity (65% vs. 69%). Thus, no sPCas were missed using the fast technique, but 2% more men needed biopsies resulting in a 1% increase in insPCa detection. Interestingly, although the bpMRI scans were read by experts in this study, the number of indeterminate PI-RADS 3 cases increased significantly. Therefore, bpMRI requires expert readers, as demonstrated by *Gatti et al.* [218] who found that less experienced readers needed DCE-MRI to enhance sensitivity and lesion detection. This study indicated that the threshold for reliable interpretation using bpMRI was approximately 700–800 cases.

At present, the PI-RADS steering committee supports continued research to assess the performance of bpMRI and acknowledges the potential benefits of the procedure for various clinical scenarios in the recently published PI-RADS version 2.1 guidelines. However, the steering committee has justified concerns regarding the use of bpMRI in inexperienced hands. In addition, there are clinical situations in which mpMRI should be preferred over bpMRI. For detailed descriptions of these clinical situations, please see the PI-RADS v2.1 guidelines [147]. With the anticipated increase in the use of bpMRI in clinical practice, the lack of DCE-MRI will probably change the proportion of men with PI-RADS assessment category 3 and 4 cancers, and this will have an impact on the likelihood of sPCa in these categories. Therefore, diagnostic pathway and biopsy strategy modifications will be needed for both biopsy-naïve men and men

with prior negative biopsy results. The problem of indeterminate PI-RADS 3 cases will be discussed later in the thesis.

Risk stratification using biparametric MRI and clinical parameters

In *papers V–VII*, we evaluated the diagnostic accuracy of bpMRI used alone [124], combined with PSAd measurements [156], and included in a predictive model with clinical parameters [157] for detecting and ruling out sPCa in biopsy-naive men. Furthermore, we evaluated whether bpMRI alone or combined with additional clinical predictors could be used as a triage test to improve the diagnosis of sPCa and identify patients who could safely avoid unnecessary biopsies.

Summary of BIDOC study

In *paper V*, we prospectively assessed the diagnostic accuracy and NPV of bpMRI for detecting and ruling out sPCa in biopsy-naive men with clinical suspicion of having PCa that warranted a diagnostic biopsy (i.e., PSA ≥4 ng/mL and/or abnormal DRE results). We compared the diagnostic performance of the following biopsy strategies: (1) SBxs in all men; (2) standard plus targeted biopsies restricted to men with suspicious bpMRI results (i.e., partially combined biopsy strategy); and (3) combined biopsies in all men, which served as a reference standard. The final study population consisted of 1,020 patients with a median age of 65 years and median PSA level of 6.9 ng/mL. Overall, combined biopsies (TBx plus SBx) detected sPCa in 404 of 1,020 (i.e., 40%) men. We found that bpMRI suspicion scores were strongly associated with PCa detection rates and that low suspicion bpMRI results had a very high NPV (97%) in ruling out sPCa in confirmatory biopsies. If only men with suspicious bpMRI results underwent combined biopsies, 30% (305/1,020; $p < 0.001$) of men avoided primary biopsies, the diagnoses of insPCa decreased by 40% (173 vs. 288; $p < 0.001$) and the diagnoses of sPCa increased by 11% (396 vs. 351; $p < 0.001$) using fewer biopsy cores, compared with our current diagnostic standard – SBx alone for all men (*Figure 5*).

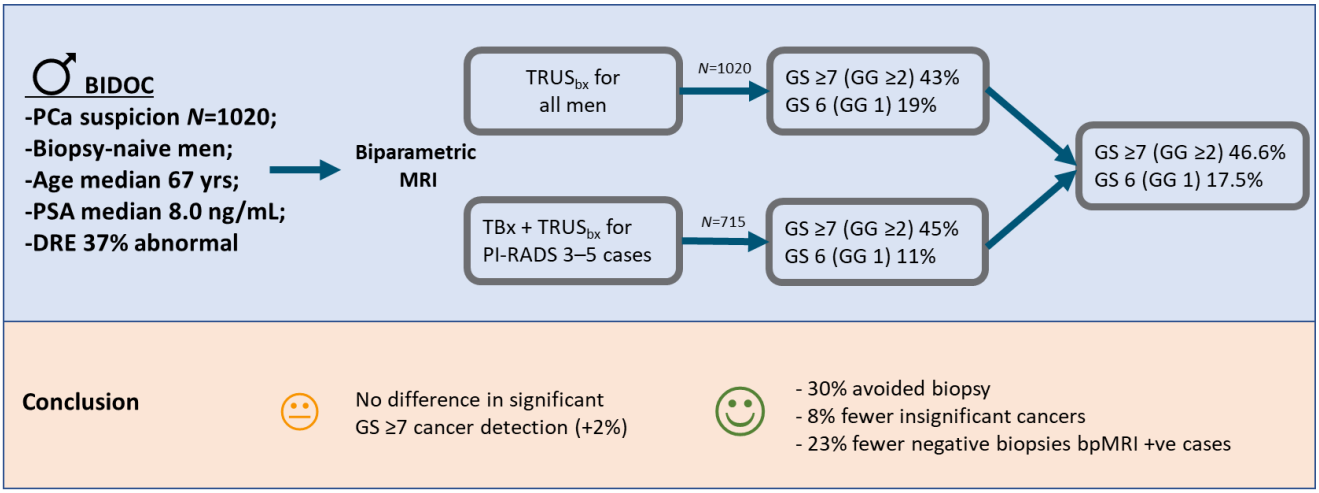

Figure 5: Infographic showing the main results of the *BIDOC* study.

Abbreviations: BIDOC = Biparametric MRI for Detection of Prostate Cancer; PSA = prostate-specific-antigen; DRE = digital rectal examination; TBx = biopsies targeted using MRI; PI-RADS = prostate imaging reporting and data system; GS = Gleason score; GG = Gleason grade group.

Therefore, our results suggest that a simple and rapid bpMRI scan can be used as a triage test to improve PCa risk stratification, exclude the presence of aggressive disease, and allow 30% of men who are clinically suspected of having PCa to safely avoid or delay invasive prostate biopsies with its inherent complications. The implications of avoiding biopsies, reducing insPCa diagnoses, and improving sPCa diagnoses have been addressed previously. However, we also evaluated various definitions of sPCa and found that the NPV of low suspicion bpMRI results decreased from 97% to 93% when we changed the definition of sPCa to that most frequently used – i.e., any GG ≥2 PCa. This led us to further analyse our data and evaluate the diagnostic performance of bpMRI relative to patient clinical parameters. These results are described in *papers VI and VII*.

Summary of bpMRI combined with PSAd study

In *paper VI*, we used patient data from the *BIDOC* database to assess whether combining PSAd measurements with bpMRI scores could improve the diagnostic accuracy and predictive values for detecting and ruling out GG ≥2 PCa. In addition, we determined the best biopsy strategy and the proportion of men who could safely avoid biopsies based on bpMRI scores and PSAd thresholds. For this analysis, we selected patients from the database who were clinically suspected of having localised disease (PSA <20 ng/mL and DRE <cT3) and thus excluded patients who were suspected of having more advanced disease before biopsies were

performed. We did this because in clinical practice, men with high risk features (PSA ≥20 ng/mL and DRE ≥cT3a) before a biopsy was performed would probably undergo biopsies regardless of the PSAd and MRI findings. A total of 808 patients met the inclusion criteria. The median age of these patients was 65 years and the median PSA level was 6.9 ng/mL. Overall, sPCa was detected in 283 of 808 men, and we found that PSAd significantly influenced the positive predictive values (PPVs) and NPVs of bpMRI in detecting and ruling out sPCa. Interestingly, the NPV increased significantly from 83% to 95% (p = 0.002) for bpMRI scores of 1–2 (i.e., low suspicion MRI results) and from 53% to 93% (p < 0.001) for bpMRI scores of 3 (i.e., equivocal suspicion MRI results) when the PSAd was <0.15 ng/mL/cc. The best biopsy strategy, based on decision curve analysis of benefits and risks for biopsy thresholds ranging from 7.5% to 15%, was restricting biopsies to men with suspicious bpMRI results (i.e., scores of ≥4) or a PSAd ≥0.15 ng/mL/cc. This strategy decreased the number of men requiring biopsies by 41% (329/808) and decreased overdiagnoses of insPCas by 45% (79/177), while missing only 6% (17/289) of men with sPCas (the majority being GG2 PCas). The NPV of this strategy was high (95%), but the PPV was moderate (56%). In addition, although this strategy was apparently effective in ruling out sPCas, it was less effective at confirming the presence of sPCas, because 44% of men who tested positive would still undergo unnecessary biopsies.

Few retrospective studies, with a limited number of patients, have tried to assess the diagnostic accuracy of combining bpMRI and PSAd [219–221], as highlighted in *paper VI*. However, although limited bpMRI study data are available at present, the impact of PSAd on mpMRI suspicion scores for detecting GG ≥2 PCas has been assessed in larger cohorts [31–33]. In a study of 1,040 men, *Distler et al.* [31] reported that the NPV of low suspicion mpMRI results increased from 79% to 89% when the PSAd was ≤0.15 ng/mL/cc. Similarly, in a study of 514 men undergoing repeat biopsies, *Hansen et al.* [32] reported that for GG ≥2 PCas in men with PSAds of ≤0.2 ng/mL/cc, the NPV of a negative mpMRI (Likert 1–2) was 91% and the PPV of an equivocal mpMRI was 9%. This suggests that these men could be spared immediate repeat prostate biopsies. However, these studies differed from ours because they analysed mpMRI data recorded using different MRI scoring systems and included men who had previously undergone prostate biopsies. In a similar study to ours, *Washimo et al*. included 288 biopsy-naïve men and found no GG ≥2 PCas in men with low or equivocal suspicion mpMRI results (PI-

RADSv2 score <4) and a PSAd <0.15 ng/mL/cc, when using 14-core systematic transperineal biopsies and cognitively targeted biopsies of suspicious mpMRI lesions as a reference standard. Thus, our study is consistent with previous research and confirms that MRI combined with PSAd improves the diagnostic accuracy and predictive values for detecting and ruling out GG ≥2 PCa. It also validates the efficacy of using a simple and rapid bpMRI protocol and defines an optimal biopsy strategy. In an accompanying commentary to this study (*paper VI*), *Morote et al.* [222] call for a multivariate analysis to detect independent predictors besides bpMRI and PSAd, and encourage the authors to generate a nomogram and risk calculator. This is what we did in the following *paper VII*.

Summary of bpMRI combined with clinical parameters in a prediction model study

Paper VII describes how we tried to develop a predictive nomogram, based on bpMRI scores and multiple clinical variables, to improve risk assessment and selection of men for prostate biopsies. PCa risk prediction models that combine clinical parameters with genetic and protein biomarkers in the blood and/or urine can improve individualised pre-biopsy risk assessments but have limited discriminatory power in detecting and ruling out significant disease. However, although these risk models can estimate the likelihood of having sPCa, they do not determine the location or size of intra-prostatic tumours, and they are often based solely on results from $TRUS_{bx}$, which can be affected by sampling errors [48,56,57]. The use of MRI also enhances sPCa detection and risk assessments when combined with clinical parameters [223,224] and can improve the accuracy of risk calculators, such as the ERSPC risk calculator [225,226]. MRI not only estimates the risk of sPCa but also provides information on cancer location and volume for targeted biopsies. However, because MRI can miss significant GG ≥2 PCas, additional clinical predictors are often needed to supplement MRI as a triage test. In addition, it was unclear how risk models and bpMRI perform when combined. Therefore, the objective of this study (*paper VII*) was to develop a novel predictive model based on bpMRI findings and clinical parameters to detect and rule out sPCa in biopsy-naïve men, using results from advanced biopsy techniques (SBx plus TBx) as the reference standard.

For this study, we used patient data from the *BIDOC* database and included 876 patients who were clinically suspected of having PCa (PSA ≥4 ng/mL and/or abnormal DRE results). We chose to exclude men with very high PSA levels (PSA ≥50 ng/mL) and those aged ≥75 years. These 876 men had a median age of 65 years and PSA levels of 7.3 ng/mL. We created four

multivariable prediction models based on bpMRI scores and clinical parameters (i.e., age, tumour stage, PSA level, prostate volume, and PSAd) that estimated the risk of sPCa at biopsy (any biopsy core with GG ≥2 PCa). We compared these risk models by analysing the areas under the curves and decision curves. As previously, because many men with high PSA levels or suspicious DRE findings would undergo prostate biopsies regardless of the MRI results and/or risk calculator analyses, we performed a subgroup analysis of men with non-palpable tumours (cTx–T1c) and PSA levels <20 ng/mL.

Overall, sPCa was detected in 350 of 876 (40%) men. The model defined by bpMRI scores, age, tumour stage, and PSAd measurements (i.e., the advanced imaging model) had the highest discriminatory power (AUC, 0.89), showed good calibration on internal bootstrap validation, and resulted in the greatest net benefit on decision curve analysis for a clinically relevant biopsy threshold of >5%. We also found that the advanced imaging model was superior in a sub-group analysis of 592 men with normal DREs (cTx–T1c) and PSA levels of <20 ng/mL.

Our findings are consistent with comparable studies that used mpMRI-derived data for risk assessments, as reported in the review by *Schoots et al.* [227]. These researchers explored the performance of new mpMRI risk models and showed that multivariable imaging models that combine mpMRI findings with clinical parameters into a risk prediction nomogram improve the diagnostic accuracy for detecting and ruling out sPCa. However, our study (*paper VII*) presents the first risk prediction nomogram that combines a prospectively derived bpMRI score with easily obtainable clinical parameters and uses results from advanced biopsy techniques (i.e., SBx plus TBx) as a reference standard. Similar to the comparative studies that analysed mpMRI data, we found that the bpMRI-derived score was the strongest single explanatory predictor of sPCa (≥GG2) and that discriminatory accuracy was significantly enhanced when this was combined with clinical parameters. In our study, we chose to include only the PSAd in the advanced models to avoid multicollinearity because PSAd was strongly associated with PSA levels and prostate volume on Pearson's correlation matrix, and PSAd was the most reliable predictor among these three variables.

Overall, our model provides individualised probability estimates for identifying a GG ≥2 PCa after a prostate biopsy is performed and may be used to counsel men considering whether to have an invasive biopsy. However, this risk model was developed at a single institution using one set of data and lacks external validation in other cohorts, which is an important step before a model can be applied and recommended for widespread use in clinical practice.

Decision curve analysis

In *papers V–VII*, we used net benefit and decision curve analyses to assess the utility of different risk models and biopsy strategies for decision making by comparing net benefits at a range of clinically reasonable risk thresholds. Many decisions in medicine involve trade-offs between diagnosing a patient with a disease that requires treatment versus unnecessary additional testing for those who are healthy or do not benefit from further examinations. In general, many risk prediction models recommend a treatment threshold that maximises the sum of the true-positive and true-negative disease discovery rates and assume that sensitivity and specificity are equally important. For patients who are suspected of having PCa, the clinician often relies on risk models that estimate the risk of sPCa and the likelihood of benefitting from prostate biopsies. However, missing a sPCa (i.e., a false negative result) is not the same as a benign biopsy (i.e., a false positive) result. Therefore, the implications of these different outcomes need to be taken into account to determine an optimal biopsy threshold for clinical practice. Net benefit analysis incorporates clinical considerations for decision making and includes benefits (i.e., true positive results - detecting sPCa) and harms (i.e., false positive results - performing unnecessary biopsies) on a single scale by allocating a net benefit score/number. It incorporates an "exchange rate" that is based on clinical judgement and weighs benefits against potential harms. This "harms-to-benefits" ratio reflects the maximum number of men a physician would recommend for biopsy (i.e., the acceptable number of unnecessary biopsies) to find one man with sPCa. Thus, a risk threshold above which biopsies are recommended can be specified. For instance, risk thresholds of 5% and 20% are equivalent to performing biopsies in 20 men for the 5% threshold and in five men for the 20% threshold to find one man with sPCa. However, because this decision may be subjective, the net benefits of various clinically relevant thresholds may be plotted using decision curve analysis. Thus, various biopsy strategies can be compared with the default strategies – biopsy all or biopsy none – and the strategy with the highest net benefit at a specific risk threshold is deemed to have the greatest clinical value.

The decision curve analysis described in *paper VI* compared various biopsy strategies by combining bpMRI scores with PSAd measurements. It showed that restricting biopsies to men with bpMRI scores of ≥4 or PSAd measurements of ≥0.15 ng/mL/cc produced the greatest net benefits for biopsy thresholds ranging from 7.5% to 15%. These bpMRI and PSAd thresholds were also the suggested single parameter cut-offs for recommending biopsies determined by

the Youden's J index to balance sensitivity and specificity. For a simple clinical approach, we chose to report only one threshold for bpMRI and one for PSAd in this study. However, by retrospectively assessing the diagnostic yields of sPCas and altering the PSAd thresholds for biopsies according to bpMRI findings, we determined that the best strategy was restricting biopsies to men with positive bpMRI results or PSAd ≥0.15 ng/mL/cc for equivocal bpMRI results and PSAd ≥0.20 ng/mL/cc for negative bpMRI results for biopsy risk-thresholds ranging from 10–30% (*Figure 6*) [228].

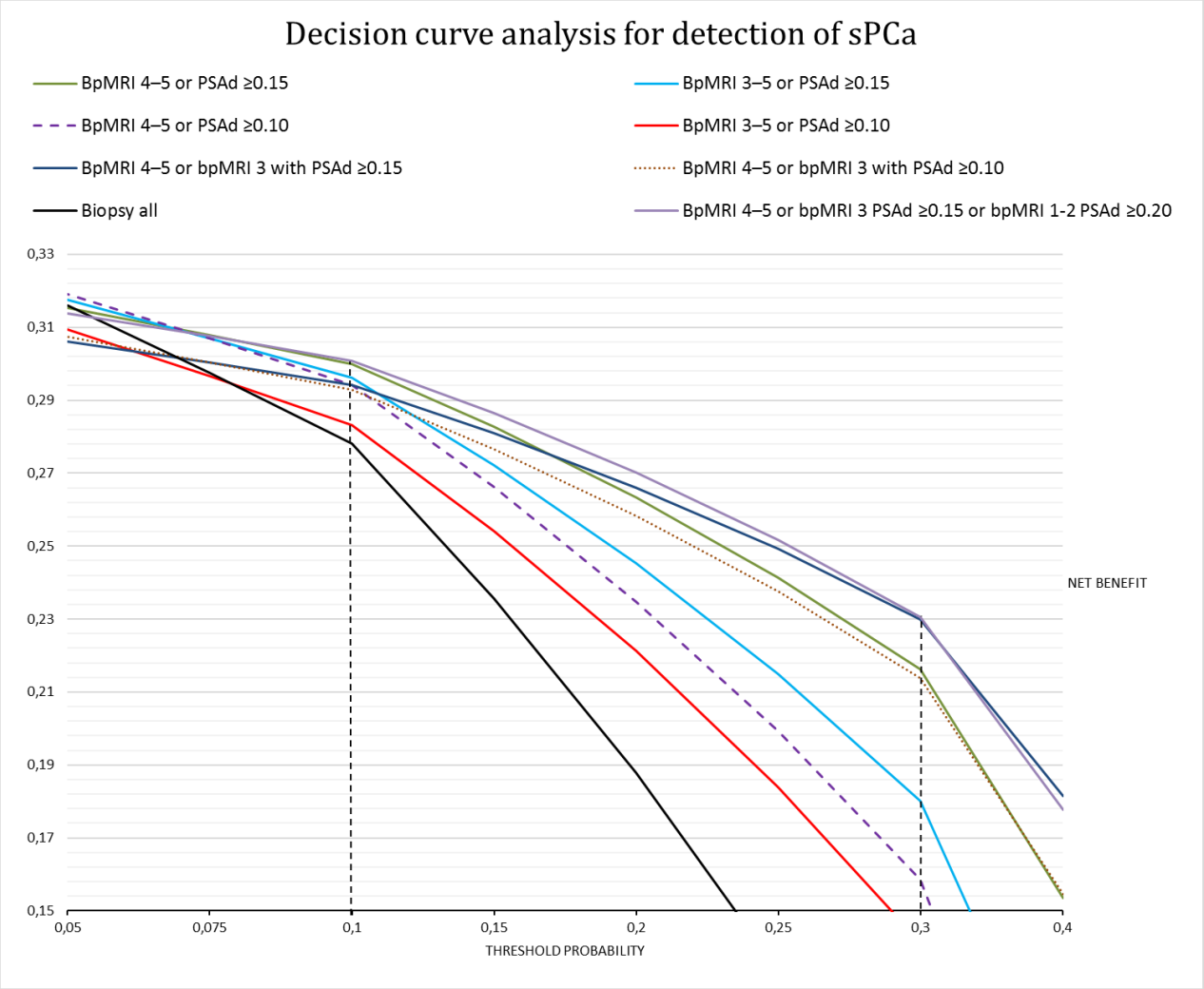

Figure 6: Decision curve analysis of the study results in *paper VI* [156] when the PSAd thresholds for biopsy were altered according to bpMRI findings. The best strategy was restricting biopsies to men with positive bpMRIs or PSAd ≥0.15 ng/mL/cc for equivocal bpMRIs and ≥0.20 ng/mL/cc for negative bpMRIs for biopsy risk-thresholds ranging from 10–30% (dotted lines). *NB the axes are truncated.*

Abbreviations: bpMRI = biparametric MRI; PSAd = PSA density.

Compared with the PSAd threshold of ≥0.15 ng/mL/cc for all men suggested in *paper VI*, this strategy further reduced the number of men requiring a biopsy to 45% (vs. 41%), missed 7% of sPCas (vs. 6%), and yielded sensitivity, specificity, PPV and NPV estimates of 93% (vs. 94%), 66% (vs. 59%), 60% (vs. 56%) and 95% (95%), respectively (*Table* 8).

Comparison of biopsy strategies

Restrict biopsies to men with	Biopsies avoided *n* (%)[a]	InsPCa avoided *n* (%)[b]	sPCa, *n* (%) Missed[c]	sPCa, *n* (%) NPV
BpMRI ≥ 3–5	300 (37%)	65 (37%)	21 (7%)	93%
BpMRI ≥ 4–5 or PSAd ≥ 0.15	329 (41%)	79 (45%)	17 (6%)	95%
BpMRI ≥ 4–5 or bpMRI 3 and PSAd ≥ 0.15 or bpMRI ≥ 1–2 and PSAd ≥ 0.20	363 (45%)	90 (51%)	20 (7%)	95%

[a] Number of patients below the biopsy threshold (% of total number; *N* = 808)
[b] Number of patients with insPCa who were below the biopsy threshold (% of total number; *n* = 177)
[c] Number of patients with sPCa who were below the biopsy threshold (% of total number; *n* = 283)
BpMRI = biparametric magnetic resonance imaging; insPCa = insignificant prostate cancer; sPCa = significant prostate cancer; PSAd = prostate-specific-antigen density (ng/mL/cc); NPV = negative predictive value.

Table 8: Results of different biopsy strategies based on bpMRI combined with PSA density.

In *paper VII*, we used decision curve analysis to compare the clinical performance of various risk models and showed that the advanced imaging model (combining age, DRE, PSAd and bpMRI scores) was superior (i.e., resulted in the greatest net benefit) to the other models for all clinically relevant biopsy thresholds >5%. Thus, using this model apparently improves patient outcomes irrespective of physician or patient preferences. However, according to the review by *Schoots et al.* [227], a net benefit was obtained at a risk threshold of >10% sPCa detection in most of the MRI risk prediction models that were assessed in this review.

In general, whether a patient and/or physician finds a certain risk threshold acceptable is a matter of personal preference and risk assessment. For instance, an older man with comorbidities may be prepared to accept a higher risk of missing or delaying diagnosis of sPCa (e.g., accepting a risk threshold >15–20%) than a younger, healthier man (e.g., 5–10%). For a urologist, a "10% threshold probability" may be a reasonable answer to the question: "How many biopsies would you, as a urologist, perform to find one sPCa that might be present in a

group of patients?" Conversely, from a patient's perspective, a "20–40% threshold probability" may be a more sensible to answer the question: "How many negative biopsy sessions would you, as a patient, accept to find a sPCa that you might have?" However, there is no doubt that clinical diagnostic tools that can enable patients to reach informed conclusions about their healthcare preferences are needed in this era of shared clinical decision making.

Indeterminate PI-RADS 3 cases

Management of indeterminate PI-RADS 3 cases constitutes a clinical dilemma, specifically: whether to biopsy these cases or not. A PI-RADS score of 3 is assigned by the prostate MRI reader when the probability of sPCa is uncertain. The prevalence of PI-RADS 3 index-lesions reportedly ranges from one in three (32%) to one in five (22%) men [229], depending on the patient cohort and prior biopsy status. SPCas (GG ≥2) are detected in 16–22% of these PI-RADS 3 lesions. Thus, an MRI-guided diagnostic pathway requires a management strategy for these uncertain scans, which involve a significant number of sPCas. Although the EAU guidelines recommend biopsies for all PI-RADS 3 cases, a follow-up strategy may be an acceptable alternative for patients with a low *a priori* risk of sPCa [203,229] because this would minimise the number of unnecessary biopsies. Recently, *Maggi et al.* [230] performed a meta-analysis of 28 studies assessing PI-RADS 3 cases (total number of PI-RADS 3 cases, 1,759; range in each study, 20–187) and reported a prevalence of 17% for PI-RADS 3 cases (range, 6–46%). The detection rates of any PCa and sPCa in this meta-analysis were 36% (range, 10–56%) and 19% (range, 3–47%), respectively. There were no significant differences between TBx and SBx detection rates and no decisive data suggesting different results when biopsy-naïve men were compared with prior biopsy-negative men. However, performing combined biopsies (TBx plus SBx) yielded the highest sPCa detection rate, and a PSAd of ≥0.15 ng/mL/cc was reported as a potentially suitable threshold for deciding to perform a biopsy on a PI-RADS 3 case.

Although we did not perform a direct analysis of PI-RADS 3 cases in our studies, subgroup analyses described in *paper IV* (*patient cohort 1*; 289 prior biopsy-negative men), using PI-RADS v1 scoring for mpMRI, and in *paper V* (*patient cohort 2*; 1,020 biopsy-naïve men), using a modified PI-RADS v2 score for bpMRI, showed that the prevalence of PI-RADS 3 cases was 34% (97/289 cases) and 13% (130/1,020 cases), respectively. Among these, sPCas were detected in 5% (5/97) and 13% (17/130) of cases when each study's primary definition of a sPCa was used. Thus, the number of PI-RADS 3 cases needed to biopsy to find one sPCa ranged from 20 men in

paper IV to 8 men in *paper V*. A possible alternative clinical approach to reducing the number of false-positive scans and balancing sensitivity and specificity would be to use PI-RADS ≥4 instead of PI-RADS ≥3 cases as a threshold to select men for biopsies. However, although this approach would reduce the number of men requiring biopsies, the number of missed sPCas would increase, and data from studies that have used contemporary definitions of sPCa do not suggest that this is likely to be a good strategy [149,229]. Nonetheless, adapting the PI-RADS ≥4 threshold in combination with other clinical parameters, such as the PSAd, may help to balance the risk of missing sPCas and avoiding unnecessary biopsies. The results described in *paper VI* show that the PSAd significantly influenced the diagnostic yield of sPCas stratified according to suspicious bpMRI results and that the optimal threshold for recommending biopsies in equivocal indeterminate PI-RADS 3 cases (15%; 124/808 cases) was a PSAd of ≥0.15 ng/mL/cc. The NPV increased from 53% to 93% (p < 0.001) when the PSAd was <0.15 ng/mL/cc, and the PPV increased from 7% to 47% (p = 0.002) when the PSAd was ≥0.15 ng/mL/cc. Using this threshold to determine whether to perform biopsies on men with PI-RADS 3 findings reduced the proportion of avoided prostate biopsies by 71% (88/124 cases) while missing 5% (6/124 cases) of men with GG ≥2 PCas. Our studies indirectly showed that the proportion of PI-RADS 3 cases decreased as prostate MRI reader experience increased in parallel with the inclusion period of patients for *papers IV and V* (i.e., there were fewer PI-RADS 3 cases when the modified PI-RADS v2 was used for bpMRI in biopsy-naïve men than when PI-RADS v1 was used for mpMRI in repeat-biopsy men). Because experts are often more eager to minimise the number of PI-RADS 3 readings than non-experts, the rate of PI-RADS 3 cases might serve as an indicator of prostate MRI expertise, as suggested by *Greer et al.* [149] who showed that specialists (>2000 MRI reads) produced fewer PI-RADS 3 diagnoses than non-specialists (300–500 MRI reads). This conclusion is supported by a recent study at the prostate MRI centre of excellence in Nijmegen, which showed that very few PI-RADS 3 cases were diagnosed (6%) when MRI scan results were read by experts [170]. However, a post-hoc sub-group analysis of these data [217] showed that when the diagnostic performance of mpMRI and a fast bpMRI approach were compared, there was a significant relative increase of 75% (from 6% to 11%) in PI-RADS 3 cases. Thus, although the number of PI-RADS 3 cases remained low (11%), bpMRI increases uncertainty even among experts and should only be performed at centres that have a low rate of mpMRI PI-RADS 3 diagnoses.

Overall, although there is no general consensus on how to manage indeterminate PI-RADS 3 cases, an evaluation of clinical sPCa risk factors is an important aspect of the decision process regarding biopsies. One approach would be to restrict combined biopsies (TBx plus SBx) to PI-RADS 3 cases with a high pre-biopsy risk of sPCa (e.g., PSAd ≥0.15 ng/mL/cc), while following-up low-risk men with PSA- and MRI-based surveillance.

Cost-effectiveness of an MRI-guided diagnostic strategy

It is important to assess the costs and benefits of an MRI-guided diagnostic pathway before implementing this strategy in clinical practice. We did not assess the costs and benefits of our diagnostic strategy directly in any of the studies included in this doctoral thesis, but other studies have included such an analysis in comparison with standard $TRUS_{bx}$ in biopsy-naïve men [231–235]. A study by de *Rooij et al.* [231] reported that the total costs of an MRI-guided strategy are equal to those of a standard $TRUS_{bx}$-based strategy but that the reduction in overdiagnoses and subsequent overtreatment of insPCa in the MRI strategy leads to improvements in quality of life. In a similar study, *Cerantola et al.* [232] analysed the medical costs associated with diagnosis and treatment of PCa at 5, 10, 15 and 20 years after initial diagnosis and concluded that an MRI-TBx strategy was cost-effective. However, both of these studies assumed that men with negative MRI results do not undergo biopsies or have any further tests, regardless of whether they had any pre-biopsy high-risk features (e.g., high PSA levels/PSAd measurements, family history of PCa, elevated risk based on risk models). In clinical practice, additional predictors are often used to supplement MRI and lower the false-negative rate, in accordance with current guidelines [13,203,236] as previously discussed. Thus, not all men with negative MRI results avoid standard $TRUS_{bx}$, and many of these cost-effectiveness analyses did not take this into account. *Faria et al.* [233] analysed patient outcome data from the *PROMIS* study and reported that mpMRI followed by up to two MRI-targeted $TRUS_{bx}$ sessions is a superior strategy to the current clinical standard ($TRUS_{bx}$ for all men) and is "good value for money". This analysis assessed multiple combinations of mpMRI, $TRUS_{bx}$, and TPM_{bx} used in various scenarios. However, no MRI-TBx were performed in the *PROMIS* study and the authors assume that MRI-guided $TRUS_{bx}$ would achieve the same diagnostic accuracy as TPM_{bx}. This is not a realistic assumption due to the misregistration and targeting errors associated with MRI-TRUS image fusion, as previously discussed. *Venderink et al.* [234] compared the cost-effectiveness of different biopsy strategies ($TRUS_{bx}$ vs. MRI-TRUS image

fusion vs. in-bore biopsies) and found that TBx using MRI-TRUS image fusion was more cost-effective than $TRUS_{bx}$. These researchers also showed that in-bore biopsies were only the best strategy if the sensitivity for sPCa diagnosis was at least 12% more than for MRI-TRUS image fusion biopsies and was ≥89%. However, the recent multicentre, randomised *FUTURE trial* [237] by *Wegelin et al.* did not find any significant differences in PCa detection rates among the three MRI-based TBx techniques, as previously addressed and discussed in *paper VIII*.
Overall, an MRI-guided diagnostic pathway seems cost-effective compared to standard $TRUS_{bx}$ in biopsy-naïve men, even in a PSA-screened cohort [235] and in men undergoing repeat biopsies [238]. However, the cost-effectiveness of a biopsy strategy depends on the local costs and quality of each individual treatment/biopsy procedure and the *willingness-to-pay* threshold per health-related quality-adjusted life year, which will vary by health institution and country. Furthermore, MRI and biopsy data are often derived from studies and opinions from specialist centres. Thus, it is difficult to extrapolate findings from one institution and healthcare centre to others. This hampers the generalisability of study findings among different countries. For example, if the *willingness-to-pay* threshold from The National Institute for Health and Care Excellence (NICE) was applied in the study by *Venderink et al.* [234], the sensitivity for sPCa diagnosis for in-bore biopsies should be ≥99% to be at its most cost-effective.

Future studies that are based on solid evidence from long-term real-world outcomes (as distinct from model estimates) and include both patients who have been correctly diagnosed and treated and those who have been misclassified and/or followed-up are needed to evaluate the true cost-effectiveness of an MRI-guided diagnostic pathway. Furthermore, if such a strategy was introduced in general community hospitals and not only in specialist centres, from which most of the data for the cost-effectiveness analyses were derived, it is uncertain how often inadequate/poor-quality MRI scans would need to be repeated. This factor could also change the results of the costs–benefits analyses. Thus, varying MRI quality and interpretation, as well as MRI-TBx reproducibility described by previous studies must be taken into account before an MRI-guided diagnostic strategy can safely be applied in the general population [239].

Chapter 6: Current recommendations, limitations and the MRI-guided diagnostic pathway from a urologist's clinical perspective

The use of pre-biopsy MRI for PCa diagnosis has been studied extensively in recent years and there is no doubt that this has led to improvements in detection, localisation and risk stratification of sPCa compared to our current diagnostic pathway – performing $TRUS_{bx}$ in all men who are clinically suspected of having PCa. The discussion has now moved on from whether MRI is useful for PCa detection to how and when to use it to maximise detection of sPCas, while avoiding unnecessary biopsies and diagnosis of insPCas. In 2015, the EAU recommended that prostate MRI scans should be performed on all men with prior negative $TRUS_{bx}$ results who remain under suspicion of having PCa. Since then, multiple studies have been published supporting the use of pre-biopsy MRI as a triage test in biopsy-naïve men to improve the selection of those who should have invasive prostate biopsies. These studies have led the EAU to update their guidelines again in March 2019 [13] to recommend pre-biopsy prostate MRI for all biopsy-naïve men. Similarly, the United Kingdom's NICE [236] updated their guidelines in May 2019 to recommend pre-biopsy prostate MRI for all biopsy-naïve men who are clinically suspected of having localised PCa and who are suitable for radical treatment if sPCa is detected. Whereas the EAU guidelines recommend combined prostate biopsies (i.e., TBx plus SBx) for MRI-positive men, the NICE guidelines recommend MRI-guided prostate biopsies but do not specify whether this should involve TBx alone or combined with SBx. Both guidelines recommend omitting biopsies when the MRI results are negative and the clinical risk of PCa appears to be low, after discussing potential risks and benefits with the patient. Likewise, an updated version of the American Urological Association (AUA) standard operating procedure policy statement on the use of mpMRI in the diagnosis, staging and management of PCa was published in October 2019, and the AUA now also supports the use of pre-biopsy MRI for biopsy-naïve men at risk of harbouring PCa, as well as for prior biopsy-negative men undergoing re-biopsy [240]. Thus, international guidelines are increasingly recommending an MRI-guided diagnostic pathway, including the PI-RADS steering committee [203,241] guidelines, which also suggest altering the MRI-directed biopsy and surveillance strategies according to PI-RADS assessment categories and patient populations (i.e., biopsy-naïve or prior biopsy-negative men) (*Table* 9).

Population and MRI-directed biopsy strategy	PI-RADS Category 1–2	PI-RADS Category 3	PI-RADS Category 4–5
Biopsy-naive men			
Recommendation	SBx if the patient is at high risk	MRI-TBx with or without SBx	MRI-TBx and SBx
Optional	If the patient is not at high risk, no immediate biopsy – safety net monitoring	No biopsy in carefully chosen patients if they are not at high risk – safety net monitoring	MRI-TBx focal saturation
Men with prior negative standard $TRUS_{bx}$ at persistent risk			
Recommendation	If the patient is not at high risk, no immediate biopsy – safety net monitoring	MRI-TBx with or without SBx	MRI-TBx with or without SBx
Optional	Whole-prostate mapping biopsies if the patient is at high risk or as part of a clinical trial	Whole-prostate mapping biopsies	MRI-TBx focal saturation or MRI-TBx and mapping biopsies

MRI = magnetic resonance imaging; PI-RADS = prostate imaging reporting and data system; SBx = standard transrectal ultrasound-guided biopsies ($TRUS_{bx}$); MRI-TBx = MRI-targeted biopsies.

Table 9: The PI-RADS steering committee's suggested biopsy strategies, depending on the patient population and the PI-RADS assessment category. Modified from *Padhani et al.* [241]

Interestingly, the primary focus of prostate MRI studies has shifted from identification of any PCa towards detection and localisation of GG ≥2 PCas only, which are deemed to be clinically significant disease. Conversely, GG1 cancers are now considered to be indolent disease (i.e., insPCa) that can often be managed by monitoring and do not require treatment. Thus, the ideal biopsy strategy for men who are suspected of having PCa would detect all sPCas but avoid subjecting those with benign conditions or insPCas to biopsies because these men may be overtreated or given an unnecessary cancer diagnosis. An MRI-guided diagnostic pathway is therefore an appealing strategy because it offers some advantages over $TRUS_{bx}$, despite the shortcomings described previously. Our studies showed that an MRI-guided diagnostic pathway detected more sPCas than $TRUS_{bx}$, but that the beneficial effect was most prominent in men with prior negative biopsy results. However, the MRI-strategy performed better in avoiding insignificant GG1 PCa diagnoses by almost two-fold for biopsy-naïve men (*paper V*,

relative risk 1/0.58 = 1.72) and three-fold for prior biopsy-negative men (*paper II*, relative risk 1/0.34 = 2.92). In addition, between one-third and half of men avoided invasive biopsies. Because the MRI-diagnostic pathway showed only a limited improvement in GG ≥2 PCa diagnoses for biopsy-naïve men, standard $TRUS_{bx}$ performed by our expert may be adequate to confirm a sPCa diagnosis at our institution in this specific patient cohort. Whether the additional time and costs associated with an MRI-guided diagnostic pathway in biopsy-naïve men is offset by the significant reduction in men needing biopsies, concomitant reduction in biopsy-related morbidities, and a halving of insPCa diagnoses is a matter for debate that must take local preferences, capacity, expertise, and costs–benefits analyses into account.

For men with prior negative biopsies, it is evident that an MRI-guided diagnostic pathway is superior to repeat $TRUS_{bx}$ for GG ≥2 PCa detection, as demonstrated by the relative sensitivities reported in *papers II* (1.52) *and IV* (1.32). The fact that MRI-TBx detects more sPCas than SBx in this patient cohort is reasonable because SBx has previously failed to detect cancer in these men, who usually present with increasing PSA levels that warrant a repeat biopsy. These men are therefore likely to benefit from MRI and TBx *a priori*.

PCa management within the ageing population constitutes a major economic burden. Because PCa is a heterogeneous disease that most frequently occurs in elderly men, often along with comorbidities, improved risk stratification and patient-specific treatment planning are needed to maximise sPCa detection while minimising biopsy- and treatment-related morbidities. As previously discussed, the use of PSA measurements for screening purposes is controversial and an area of continuous debate within the medical and urological communities [23]. Whereas the US Preventive Service Task Force recommends PSA screening based upon shared decision making and patient preferences for men aged from 55 to 69 years, the associated risks (i.e., high false-positive rate for PSA measurements, overdetection of insPCas, and biopsy complications) have led the Danish Urology Society to recommend not using PSA-testing/screening in any asymptomatic man who has no family history of, or genetic predisposition towards PCa. However, using MRI as a secondary triage test after PSA testing could potentially minimise uncertainties and improve the balance between risks and benefits. Although MRI is significantly better than $TRUS_{bx}$ for detecting and ruling out aggressive high-grade PCas, some moderate-risk cancers will be missed if all MRI-negative men choose not to have biopsies. Thus, even though the implementation of pre-biopsy MRI is changing rapidly in clinical practice, patients

and physicians must realise that MRI alone is not a flawless test and additional predictors/biomarkers are needed in certain clinical scenarios. Furthermore, the overall diagnostic role of MRI as a triage test must be defined before deciding on an optimal biopsy strategy. For example, if the overall diagnostic strategy is to reduce the heavy unnecessary biopsy burden and reduce insPCa diagnoses, while maintaining a high diagnostic accuracy of sPCa, then an MRI-guided diagnostic pathway (i.e., omitting biopsies in MRI-negative men with low clinical risk) prevails. However, if the strategy is to maximise detection of any potential PCa, then a combined biopsy strategy including SBx for MRI-negative men should be preferred. Nevertheless, this latter strategy may still miss some sPCas and one could argue that a 5-mm TPM_{bx} approach, which would be cumbersome, time consuming and costly, may be an even better strategy for detecting all sPCas than TBx plus SBx, despite its lower feasibility for clinical practice.

From a urologist's clinical perspective, there is no doubt that MRI is rapidly changing the future management of PCa. At present, a paradigm shift in the PCa diagnostic pathway is taking place across countries and institutions. This involves the increased use of upfront pre-biopsy MRI to stratify biopsy-naïve men according to their MRI-determined risk of having sPCa. As discussed previously, MRI can overcome many of the limitations of the current diagnostic pathway, which relies on flawed PSA, DRE and $TRUS_{bx}$ findings. Furthermore, as the worldwide prevalence of antibiotic-resistant bacteria, which may be exacerbated by prostatic-tissue sampling, continues to increase, so does the value of a non-invasive triage method that improves the diagnostic ratio of clinically sPCa vs. insPCa and reduces unnecessary biopsies. However, the inter-reader variability across studies and radiologists, the learning curve for operators, MRI costs and availability, as well as concern regarding missed sPCa diagnoses due to omitting biopsies in MRI-negative men have all been highlighted by sceptics as reasons not to recommend a more widespread adoption of an MRI-guided diagnostic pathway. Although the sceptics have a right to question whether high-quality diagnostic MRI acquisition and reporting can be delivered across healthcare centres, these reservations about the widespread implementation of prostate MRI in clinical practice should not detract from the results of numerous studies that have shown the superiority of an MRI-guided diagnostic pathway in comparison with $TRUS_{bx}$ in both biopsy-naïve men and in men with prior negative biopsies. A well-conducted MRI procedure can allow approximately 25–50% of men who are suspected of having PCa to consider avoiding invasive

biopsies, decreases overdiagnoses of insPCas by approximately 50%, and improves the detection of sPCas regardless of the definition of clinical significance. However, there is no doubt that there are limitations and caveats that need to be addressed before widespread adoption of prostate MRI as a triage test for all men who are suspected of having PCa is recommended for general clinical practice, outside specialist centres.

First, there are numerous factors that can affect biopsy outcomes in an MRI-guided diagnostic pathway, as shown in *Figure 7.*

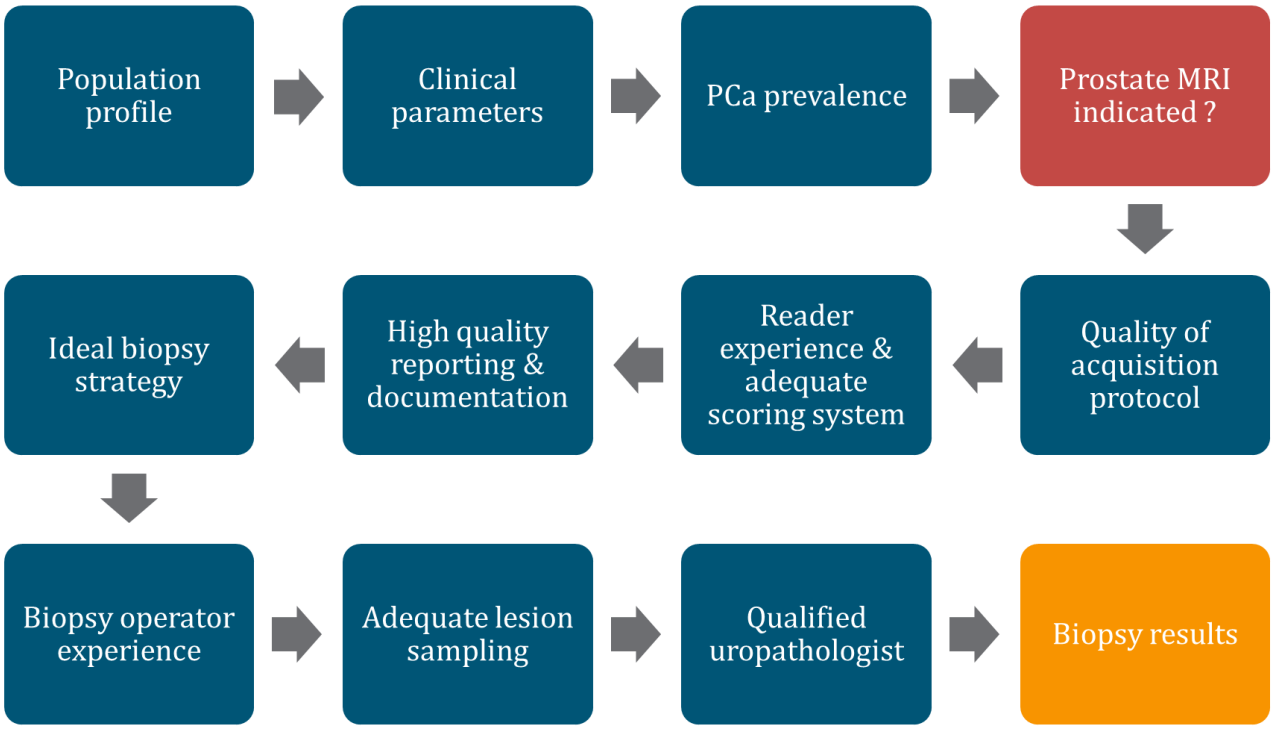

Figure 7: Factors that can influence the biopsy outcome of an MRI-guided diagnostic pathway.

The benefits of an MRI-guided diagnostic pathway primarily depend on: 1) high-quality, well-conducted MRI procedures optimised for PCa detection; 2) experienced radiologists; and 3) skilled urologists or radiologists to carry out TBx based on MRI guidance. The chain is only as strong as its weakest link [242]. There is a need for quality standards and quality control procedures to ensure high quality throughout the entire diagnostic pathway. This includes double-readings of MRI scans - especially equivocal cases, feedback from pathologists in a multidisciplinary team setting, and training that includes performance measures for the

radiologists and urologists who read the MRI scans and perform the TBx. *Padhani et al.* recently published a review [203] on behalf of the PI-RADS steering committee that provides a status update on prostate MRI and assesses the performance characteristics of PI-RADS v2 assessment categories for PCa detection. This review highlights the current strengths and limitations of the MRI-guided diagnostic approach and addresses several of the issues that need to be improved. One problem is how to decrease the large inter-reader variability among radiologists. Despite the efforts of the PI-RADS steering committee to standardise and promulgate high-quality prostate MRI acquisition and reading procedures, there is still significant variation in PI-RADS scores and sPCa yields across studies [243] and readers [244,245]. For example, in a study comparing the diagnostic accuracy of mpMRI for sPCa detection across nine radiologists with varying expertise, *Sonn et al.* [245] showed that the per-lesion correlation between PI-RADS scores and the presence of sPCa (GG ≥2) varied significantly across readers, and that the proportion of false negatives (i.e., where sPCas were detected in MRI-negative [PI-RADS ≤2] men) ranged from 13% to 60%. For instance, the sPCa yield of PI-RADS 2 and PI-RADS 5 lesions obtained by different readers ranged from 13% to 34% and from 40% to 80%, respectively. This means that a PI-RADS 5 lesion identified by one radiologist was associated with almost the same risk of sPCa (40%) as a PI-RADS 2 lesion identified by another reader (34%). Thus, this study shows that significant variations in interpretation can be found among attending radiologists with varying prostate MRI experience performing routine clinical care in which MRI scan results were read according to standard workflow procedures. It highlights real-world differences in interpretation by radiologists and demonstrates that the standardisation of acquisition and interpretation procedures, the systematic training of readers, and quality assurance are pivotal points in the diagnostic pathway. Hopefully, the problem of inter-reader variability will be decreased when the newly released PI-RADS v2.1 guidelines are applied [147].

Moreover, comprehensive and accurate information must be transferred between MRI readers and the operators performing the biopsies (e.g., urologists) using a standardised report format. The urologists responsible for treating patients must consider the strengths and limitations of MRI and be able to place the information from the MRI scans in the correct clinical context for each patient. Thus, a dedicated prostate MRI education program, which covers both technical and interpretative aspects, is needed to support MRI readers, technologists and urologists in clinical practice to produce acceptable diagnostic results. Whether this should involve

accreditation and certification of institutions or patient management at a few specialist reference centres in a multidisciplinary setting should be decided by radiological and urological professional organisations and authorities at the national and international levels. The keys to success are high-quality imaging, reporting, and biopsies by radiologists and urologists working together in multidisciplinary teams. Thus, clinicians should be cautious and know their own institution's performance statistics before making clinical decisions based on MRI findings.

Second, it remains unclear whether MRI-TBx should be used alone in a "targeted-only" strategy or in combination with SBx to maximise the diagnostic yield of sPCas. We know from previous studies (*Cochrane review* and *Table* 7) that the added value of SBx for detecting GG ≥2 PCa in biopsy-naïve men with negative MRI results is 4–6% for a disease prevalence of 28–38%. Whether this added value is high enough to recommend SBx for all MRI-negative men is a matter of opinion and debate. However, for repeat biopsy men, the added value of SBx is much lower, favouring a TBx-only approach. The NPV of a negative MRI result relies on disease prevalence, and this should be taken into account when deciding whether SBx should be performed on MRI-negative men. For instance, a biopsy-naïve man with a low *a priori* risk of sPCa (e.g., a slightly elevated PSA level, low PSAd, and no family history of PCa) and a negative MRI result could probably safely avoid SBx, whereas a man with a high *a priori* risk of sPCa could not. Similarly, a repeat biopsy man with a high *a priori* risk of sPCa missed by prior $TRUS_{bx}$ (e.g., rising/high PSA levels, no inflammation in prior biopsies, presence of high-grade prostatic intraepithelial neoplasia in multiple cores, or a family history of PCa) may well require SBx, despite negative MRI findings. Thus, an individualised risk assessment based on MRI findings and clinical variables, such as PSAd or a more advanced risk model, is essential before deciding which men can safely avoid biopsies.

Third, while the benefits of prostate MRI, after PSA assessment, as a triage test in a selected patient group (i.e., men who are clinically suspected of having PCa) have been extensively validated in large level 1 evidence studies, its use as a first line screening tool in the general population is relatively untested. In one of the first published MRI screening studies, *Nam et al.* [246] assessed the value of mpMRI as an initial PCa screening test. These researchers recruited 47 unselected men from the general population and found that mpMRI significantly outperformed PSA measurements (AUC, 0.81 vs. 0.67) in predicting the presence of PCa and

that it was the only significant predictor of clinically significant GG ≥2 disease (adjusted odds ratio, 3.5; 95% CI, 1.5–8.3). However, the sensitivity of mpMRI was not reported and a clear biopsy threshold was not determined. In a similar pilot study that included 124 men, *Bergdahl et al.* [247] compared PSA plus MRI with conventional PSA screening during the 10th round of screening of the Gothenburg randomised screening trial and found that a screening strategy which lowered the PSA cut-off to ≥1.8 ng/mL followed by TBx in MRI-positive men increased sPCa detection while improving specificity. Although the results of these two studies are interesting, few patients were involved and larger studies, such as the *MVP* (MRI versus PSA in Prostate Cancer Screening; *www.clinicaltrials.gov* NCT02799303) or the ReIMAGINE (NCT04063566) studies, are needed to confirm their findings.

In general, a high sensitivity is one of the most important aspects of a PCa screening tool. Most of the recently published studies have reported that prostate MRI has a high sensitivity and can reliably identify men with sPCa. However, in a clinical setting, the NPV is at least as important, to ensure that screening can reliably rule out sPCa in MRI-negative men. Because previous studies have focused on men who are suspected of having PCa based on first-line PSA and/or DRE assessments, we do not know how MRI will perform as a screening tool in the general population, and we cannot directly apply the sensitivities and NPVs of previous studies on this cohort. Nonetheless, as previously described, the NPV of mpMRI was highest among populations with the lowest incidence of cancer. Therefore, the NPV is likely to be even higher in men who are not pre-screened using PSA measurements. However, there will be some men with normal PSA levels who show abnormalities on MRI scans. These cases will be difficult to assess, especially for non-experts, due to the moderate specificity of MRI. Therefore, the number of false-positive readings in this population, which has a low *a priori* risk of disease, could increase and the number of men undergoing unnecessary biopsies could escalate. Hence, although MRI may have a role in future screening strategies, avoiding unnecessary biopsies will remain a challenge. Moreover, the question of "whether MRI screening alone or combined with PSA" leads to a significant reduction in PCa mortality and/or morbidity, proposed by *Bergdahl et al.*, remains unanswered. Therefore, at present, pre-biopsy prostate MRI should not be used for men who do not have a clinical indication for biopsy.

Fourth, a clear consensus definition of sPCa is needed for MRI biopsy studies to allow direct interstudy comparisons and, more importantly, to develop redefined risk calculators that

include biopsy results from TBx because most of the nomograms that currently predict outcomes are based on SBx results with their inherent limitations. Because TBx are MRI-guided towards the most aggressive part of a lesion, the highest tumour-grade component will often be sampled. Thus, TBx will often generate a higher disease-grade assessment than $TRUS_{bx}$. Although this may mean that TBx results will show a better correlation with the final pathological assessment after RP than $TRUS_{bx}$ findings [248,249], it could also lead to risk-category inflation [250,251]. For example, *Mesko et al.* [250] found that adding TBx to SBx reduced the number of low-risk patients substantially (30% to 4%) and doubled the number of high-risk patients (21% to 42%). While most studies have focused on cancer detection rates, less attention has been given to the impact of MRI-TBx on treatment decisions. Whether a man with high-risk PCa detected by TBx will have the same prognosis and should be treated in the same way as a man with high-risk PCa detected solely by SBx remains uncertain. Furthermore, due to intra-tumour GS heterogeneity, it may be necessary to obtain multiple biopsy cores from each lesion to accurately assess disease pathology. *Mesko et al.* [250] demonstrated that more than half of their MRI-targeted lesions had different GS among the individual biopsy cores sampled from the same lesion, including a non-negligible number (21%) of GG 1 to GG 4–5 differences. Thus, although this study had a small sample size (i.e., 51 foci with two or more positive cores) and lacked histopathological correlation with RP specimens, it indicates that the number of biopsy cores obtained per lesion may affect the overall prognostic risk-group allocation. However, the optimal number of cores that should be obtained per lesion was not specified. Future studies are needed to determine the minimum number of cores needed to accurately confirm a diagnosis and enable treatment planning depending on lesion location and size, as well as prostate gland volume estimates, all of which may be affected by operator experience.

Fifth, because of the anatomical location of the prostate gland and the feasibility of the procedure, transrectal biopsy has been the standard and most frequently used approach for decades. The biopsy-needle must pass through the rectal wall multiple times, and there is a risk of inoculating the prostate gland with rectal bacteria. Therefore, transrectal biopsies require prophylactic antibiotics. However, because the worldwide prevalence of antibiotic-resistant bacteria in the rectal flora is increasing and the number of effective antibiotics is declining [1,2], a transperineal biopsy route has been proposed. In transperineal biopsies all cores are obtained

by puncturing the disinfected perineal skin. The procedure is guided robotically, using a brachy-grid or performed freehand. Because neither the rectal wall nor the urinary tract is penetrated, this is considered to be an aseptic procedure with only limited use of antibiotics. Consequently, the use of transperineal prostate biopsies has become more widely accepted. However, there is an increased risk of urinary retention and most procedures are still performed under general anaesthesia, although some centres/experts advocate performing transperineal biopsies under local anaesthesia in selected cases. This makes the procedure less suitable for routine clinical practice. Thus, there should be more emphasis in the future on strategies for preventing sepsis following transrectal prostate biopsies. In addition to converting to a transperineal approach, these strategies may include identifying men at higher risk of sepsis, targeted antibiotic prophylaxis, and the use of rectal swabs/disinfection, based on local resistance profiles.

Finally, an MRI-guided diagnostic pathway will result in earlier detection of some sPCas and delayed/missed detection of others due to MRI-negative men being able to avoid biopsies. However, it is uncertain how this will affect PCa survival rates over the long term. As described above, it is extremely important to achieve a clear consensus definition of sPCa in terms of a cancer that requires early diagnosis and treatment, given the possibility of PCa risk-category inflation with MRI-TBx. However, because the definition of sPCa tends towards more aggressive cancers, the future role of MRI may be of greater value due to its high sensitivity for high-grade (GG ≥3) cancers.

Chapter 7: Future perspectives

Because MRI is now recommended as a first line triage tool for men who are suspected of having PCa, there are new questions to consider for the future. MRI is very sensitive for high-grade PCas and has a high NPV, especially when combined with clinical parameters such as PSAd measurements. Therefore, many centres are now working on clinical programmes that include MRI and reduce the use of $TRUS_{bx}$. Furthermore, although the ESUR still recommends the use of DCE-MRI as part of an mpMRI approach for all indications, this procedure is time consuming and would place a significant financial and resource burden on any healthcare system if used in all men prior to biopsies. It is anticipated that in the future a rapid bpMRI method that reduces scan times and costs, while maintaining a high diagnostic accuracy as shown in our studies, will be used increasingly in clinical practice for biopsy-naïve men. As a result of our studies, in March 2019 our department implemented a policy of pre-biopsy MRI scans for all men who are candidates for curative treatment if they are diagnosed with sPCa. Men with prior negative biopsies undergo mpMRI followed by TBx if a positive MRI result is obtained (i.e., 3–4 cores per lesion in a "targeted-only" approach) and occasionally SBx in MRI-negative men if there is a high *a priori* risk of sPCa. However, biopsy-naïve men are stratified to bpMRI or mpMRI according to pre-biopsy clinical risk factors (*Figure 8*). Men considered to be at high risk of sPCa (i.e., those with PSA levels ≥20 ng/mL or DRE ≥T2c) undergo pre-biopsy mpMRI followed by SBx plus TBx regardless of mpMRI findings (men with mpMRI-negative results only undergo SBx). Because these men have a high pre-biopsy risk of sPCa, mpMRI-TBx will often do little to change the overall diagnosis but can significantly improve the quality of treatment decisions. This is because the scan can be used for local cancer staging. Performing staging mpMRI prior to biopsies is highly advantageous because post-biopsy haemorrhage may cause artefacts that hamper staging mpMRI accuracy. Men with a low to intermediate clinical risk of sPCa (i.e., those with PSA levels <20 ng/mL or DRE <T2c) undergo pre-biopsy bpMRI, which is analysed according to the modified PI-RADS scoring criteria (i.e., no DCE sequences) and the PSAd is calculated. The bpMRI suspicion score and PSAd measurement determine whether a man is recommended for prostate biopsies. This strategy is primarily based on the findings we describe in *paper VI*. Biopsies are recommended for men with suspicious bpMRI results (score ≥4), PSAd ≥0.15 ng/mL/cc or additional high-risk factors such as family history of PCa, a high score on a risk-calculator or known germline mutations (e.g., BRCA-2). For men undergoing biopsies, the strategies are SBx plus TBx (i.e., 3–4 cores per lesion) for bpMRI-positive men and

SBx for bpMRI-negative men. Men with low to equivocal suspicion bpMRI results (i.e., scores of ≤3), PSAd <0.15 ng/mL/cc and no additional high-risk factors can avoid immediate biopsies and undergo surveillance. Men with equivocal bpMRI findings who are undergoing surveillance are followed-up in our department by measuring PSA levels and a control mpMRI scan after 6 months. Men with low-suspicion bpMRI results and PSAd <0.15 ng/mL/cc are discharged to the care of their General Practitioner (GP) for PSA and DRE surveillance with specific instructions regarding patient referral back to our department for further diagnostic evaluation. This new diagnostic strategy is a paradigm shift for our department, and all men are asked for written informed consent to use their anonymised data for research, quality assurance, and follow-up (particularly those who are not biopsied) over the long-term.

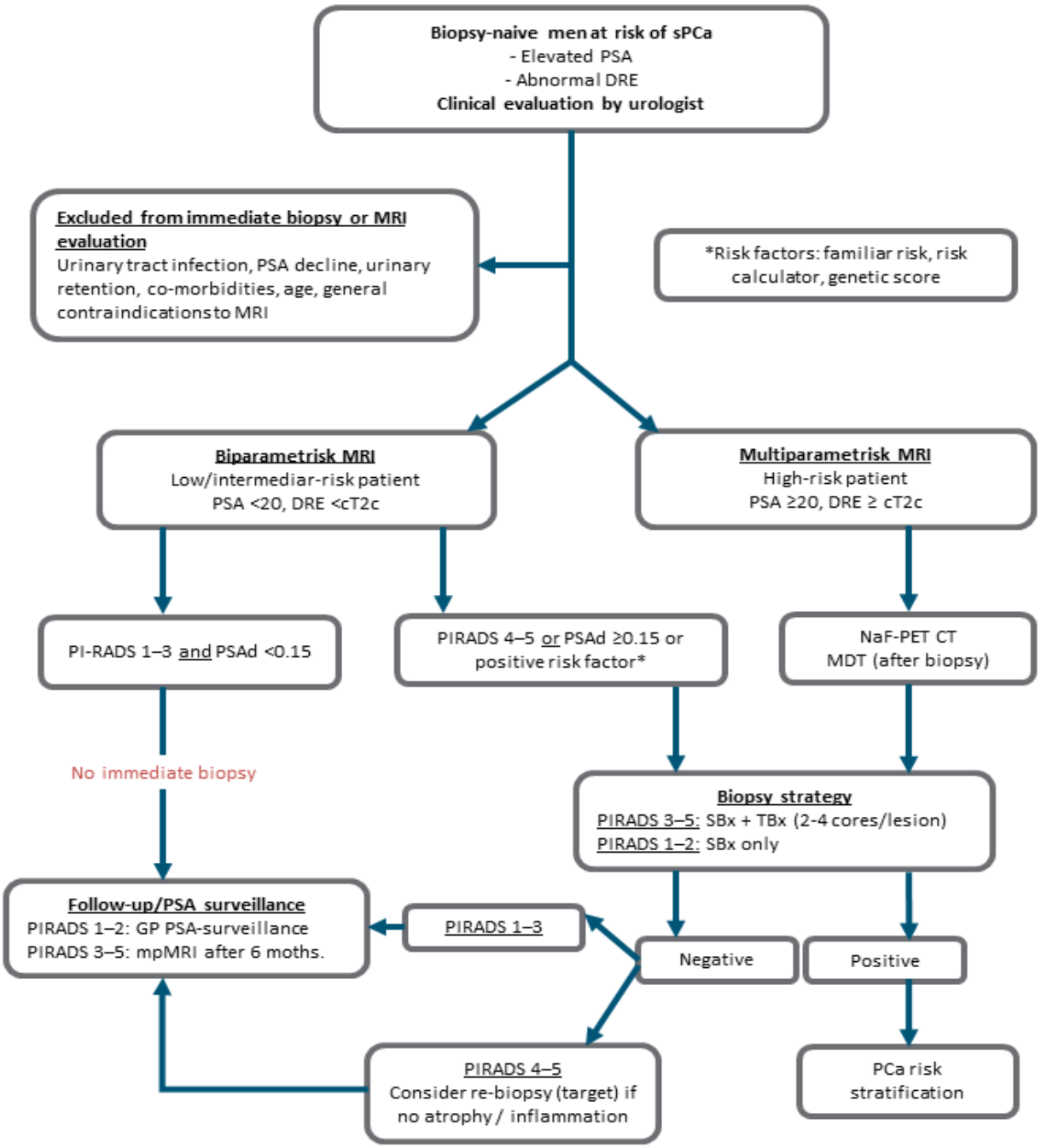

Figure 8: Flow chart showing the MRI-guided diagnostic strategy for biopsy-naïve men who may have PCa that is currently used at the Department of Urology, Herlev Gentofte University Hospital, Herlev, Denmark in 2019.
Abbreviations: cT = clinical tumour staging category; NaF-PET CT = sodium fluoride positron emission tomography-computed tomography; MDT = multidisciplinary team; SBx = standard biopsy; GP = general practitioner.

In parallel, it is anticipated that future developments in MRI/TRUS image fusion platforms will continue to evolve and may include automatic prostate image segmentation, deformable co-registration with real-time motion correction, and improved ultrasound resolution with or without additional use of ultrasound contrast, elastography or micro-ultrasound to enhance biopsy allocation and improve targeting accuracy. Moreover, in the future, biopsy needles may be replaced with catheters for focal treatment. In addition, improvements in MRI/TRUS image fusion platforms may allow focal treatments to be performed under local anaesthetic outside the MRI/operating suite. However, as described previously, although prostate MRI detects most index-lesions, even high-grade non-index sPCa lesions may be missed. This may have important consequences for focal therapies and/or AS cohorts if diagnoses are based solely on TBx findings, as clinicians continue to rely less on $TRUS_{bx}$ procedures.

Additionally, novel tools based on clinical variables and extended blood and/or urine tests for genetic and protein biomarkers have been developed to predict the presence of sPCas, such as the 4Kscore [35], the STHLM3 test [54], the PHI [36], and the PCA3 scores [37]. However, although these risk models predict the likelihood of having sPCa, they do not determine intra-prostatic tumour location or size and they are often based solely on results from SBx. The use of MRI provides an anatomical guide to cancer location and volume for TBx, and the results can be used to improve risk stratification. Future studies will determine how MRI and risk models perform together in clinical practice. On the other hand, a simple blood/urine-based clinical biomarker or risk calculator with a high sensitivity and NPV for sPCa would be extremely valuable as a test to select men who would benefit from MRI to avoid the anticipated tsunami of MRIs that could overwhelm limited financial and logistic constraints. Such a strategy could potentially be applied by the GP in the primary sector and act as a triage test before referral to the secondary sector for MRI, potentially reducing the need for MRI scans. Although novel biomarkers and risk calculators have been tested in a few studies on both biopsy-naïve men and men undergoing biopsies, as reported in the review by *Osses et al.* [252], larger prospective and comparative studies will be needed to fully assess the potential and risks of these combined strategies. Thus, the new challenge for the future might be to avoid MRIs, as proposed by *Alberts et al.* [253] who reported that approximately 50% of mpMRI procedures for cases where there was persistent clinical suspicion of PCa and prior negative biopsies could have been avoided by using a multivariable risk calculator based on clinical parameters and prior $TRUS_{bx}$ findings.

Another emerging research field involves the use of artificial intelligence (AI) in diagnostic medicine, including its applications in radiological and pathological characterisation of PCa [254]. For instance, one prostate MRI examination that combines multiple anatomical and functional MR sequences may include more than 300 image slides that can be used to detect and characterise PCas. The growing speed of data generation, the anticipated future increase in imaging data volume, and the multiple stages involved in the diagnostic and prognostic PCa pathways (e.g., diagnostic MRI, image- and robotic-guided interventions, providing tissue for histopathological evaluation and advanced genomic sequencing) have led to an increased interest in AI and machine learning to assist in PCa detection, lesion characterisation, and prognostication. Because the radiological assessment of MRI scans using the PI-RADS scoring system and the pathological GS assessment of biopsies and RP specimens are subjective, limited by the qualitative or semi-quantitative interpretation criteria, and highly dependent on expertise, most studies have shown large inter-reader variability across radiologists and pathologists, especially in the assessment of intermediate GG 2–3 PCas [245,255–257]. Thus, computer-aided diagnoses based on radiomics, advanced pattern recognition algorithms, and image processing software developed from high-quality training sets and deep-learning may be used to analyse large datasets, extract the relevant information to locate and assess tumours, and recognise complex patterns with increasing confidence [258]. Therefore, in the future, AI and machine learning may improve the diagnostic accuracy of radiological and pathological analyses, decrease human resource costs and improve clinical workflow and treatment choices. Thus, although AI is not quite ready yet for clinical application, its future potential seems very promising.

Chapter 8: Conclusions

This doctoral thesis analysed the diagnostic accuracy of pre-biopsy MRI (multi- or biparametric) with or without MRI-TBx for detecting and ruling out sPCa in biopsy-naïve men and in men with prior negative biopsies. Overall, convincing results obtained using an MRI-guided diagnostic pathway support using pre-biopsy MRI as a triage test for all men who are suspected of having PCa, where a biopsy is clinically indicated, and MRI findings may have a clinical impact on diagnosis and treatment management. A well-conducted MRI procedure can allow approximately 25–50% of these men to consider avoiding invasive biopsies, decreases overdiagnoses of insPCas by approximately 50%, and improves the detection of sPCas regardless of the definition of clinical significance. However, the superiority of such a pathway compared to the current strategy – $TRUS_{bx}$ for all men – depends on the patient population and relies on high-quality MRI procedures that are optimised for PCa detection, as well as experienced radiologists and skilled physicians who can carry out TBx based on MRI guidance.

Summary in English

Prostate cancer (PCa) is responsible for the second highest number of cancer-related deaths and is the most frequently diagnosed malignant disease among men in the Nordic countries. PCas range from indolent tumours (i.e., clinically insignificant cancers), that have no impact on mortality or morbidity if left untreated, to aggressive disease (i.e., clinically significant prostate cancers [sPCas]) that must be detected early to ensure a good prognosis and to provide effective treatment. This heterogeneity in the clinical manifestation of PCa makes diagnoses and subsequent treatment planning challenging. The current diagnostic pathway for PCa includes prostate-specific-antigen (PSA) testing and digital rectal examination followed by transrectal ultrasound-guided biopsies ($TRUS_{bx}$). However, limitations in the sensitivity and specificity of this approach have resulted in overdiagnoses and subsequent overtreatment of indolent cancers as well as underdiagnoses and delayed diagnoses of significant cancers. The limitations of the current diagnostic pathway have highlighted the need for better tools (e.g., risk calculators, biomarkers and imaging techniques) to distinguish men who are at higher risk of sPCa and require diagnostic biopsies as well as subsequent treatment from those with either a benign condition or insignificant (ins)PCas that may be managed by monitoring. In addition, the worldwide prevalence of antibiotic-resistant bacteria is increasing, whereas the number of effective antibiotics is declining, emphasising the need to reduce unnecessary tissue sampling.

Growing evidence suggests that magnetic resonance imaging (MRI) may be able to resolve some of these issues. Studies have shown that MRI is the most sensitive and specific imaging tool for PCa detection, lesion characterisation and risk stratification. Lesions identified by MRI may be stratified by suspicion and potentially aggressive regions targeted using MRI-guided biopsies (TBx) to enhance the detection of sPCas. Conversely, low-suspicion MRI results may non-invasively exclude the presence of aggressive disease, thereby avoiding the need for biopsies. Therefore, MRI could potentially be used as a triage test to improve risk stratification and minimise overdiagnoses and unnecessary biopsies.

The overall aim of this doctoral thesis was to assess the diagnostic accuracy of pre-biopsy MRI (multi- or biparametric) with or without targeted biopsies for detecting and ruling out sPCas in men undergoing prostate biopsies. The thesis is based on seven original papers and one review article that each aim to provide new insight regarding a specific objective. Patient data from two separate cohorts were used: biopsy-naïve men and men with prior negative $TRUS_{bx}$ results. All the men originated from an ethnically homogeneous, non-PSA screened Scandinavian

population. However, the two cohorts were from different time periods, were evaluated using different pre-biopsy MRI scanning approaches (multiparametric [mp] or biparametric [bp]MRI), and had different biopsy status. The results of each paper are discussed in a clinical context, including discussion of current recommendations, limitations, and future perspectives on a MRI-guided diagnostic pathway from a urologist's perspective.

Papers I–IV assessed the diagnostic accuracy of mpMRI +/– TBx for detecting and ruling out sPCas in men undergoing repeat biopsies. Overall, these studies showed that mpMRI followed by TBx improved the detection of sPCas compared to $TRUS_{bx}$ and had a high negative predictive value (NPV) in ruling out longer term significant disease. MpMRI suspicion scores were strongly associated with biopsy and radical prostatectomy results at both the patient and lesion levels, and a TBx-only approach (i.e., no systematic biopsies) may be preferred for MRI-positive men undergoing repeat biopsies. Furthermore, we found that $TRUS_{bx}$ and TBx cores missed sPCas in particular regions of the prostate gland and knowing these locations may improve future repeat biopsy procedures.

Since mpMRI can improve diagnostic outcomes for men with prior negative $TRUS_{bx}$ results but who remain under suspicion of having sPCa, our focus has recently shifted to utilising pre-biopsy prostate MRI as a triage test for biopsy-naïve men. The purpose of this strategy is to distinguish men with either benign conditions or clinically indolent cancers, who can avoid or delay invasive biopsies, from men at higher risk of having sPCa who do require diagnostic biopsies. However, performing mpMRI in all men who are suspected of having PCa may be time consuming and would place a major financial burden on any healthcare system. Experience has shown that the contrast-enhanced imaging sequences in the mpMRI approach often do little to improve the overall clinical picture in detecting and localising sPCas. This has led to a growing interest in performing prostate MRI without contrast-enhancement as an abbreviated bpMRI procedure. This less expensive, more rapid MRI approach may significantly improve patient access and facilitate more widespread clinical implementation of prostate MRI prior to biopsies, especially in the large patient populations in the western world where PCa prevalence is high.

Therefore, the objective of *papers V–VII* was to assess the diagnostic accuracy of bpMRI for detecting and ruling out sPCa in biopsy-naive men. Overall, the studies showed that bpMRI used alone, combined with PSA density measurements, or included in a predictive model with clinical parameters improved risk stratification and detection of sPCas and had a high NPV in ruling out sPCas on confirmatory biopsies. An optimal biopsy threshold and approach was

suggested based on a decision curve analysis that weighed benefits (i.e., detecting sPCas) and harms (i.e., performing unnecessary biopsies).

An MRI/TRUS image fusion biopsy approach was used in all of these clinical papers (*papers I–VII*) to selectively sample lesions using TBx. Therefore, a review article (*paper VIII*) was also included in the thesis to assess the current status, challenges and future perspectives linked to this approach.

Based on the results from *papers I–VII*, the overall conclusion of this doctoral thesis is that a well-conducted MRI procedure can allow approximately 25–50% of men who are suspected of having PCa to consider avoiding invasive biopsies, decreases overdiagnoses of insPCas by approximately 50%, and improves the detection of sPCas regardless of the definition of clinical significance. Convincing results obtained using an MRI-guided diagnostic pathway support using pre-biopsy MRI as a triage test for all men who are suspected of having PCa, where a biopsy is clinically indicated, and MRI findings may have a clinical impact on diagnosis and treatment management.

Summary in Danish

Prostatacancer (PCa) er den hyppigste kræftsygdom blandt mænd i Norden og ansvarlig for det næsthøjeste antal kræftrelaterede dødsfald. Sygdommen spænder fra mange helt fredelige tilfælde (in-signifikante cancere [insPCa]), der ikke kræver behandling over til aggressive former (signifikante cancere [sPCa]), der kan forårsage sygelighed og død for mange mænd. Det er disse aggressive tilfælde, der har gavn af tidlig diagnostik og behandling.

De metoder, vi har brugt i årevis til at vurdere om en mand har aggressiv cancer indebærer prostata-specifikt-antigen [PSA] blodprøve, digital rektal eksploration [DRE] og transrektale ultralydsvejledte prostata biopsier [$TRUS_{bx}$], er desværre ikke særligt præcise. Formålet med biopsierne er at bestemme om PCa er til stede, og at bestemme tumorens histologiske aggressivitet (Gleason scoren). Da mange mænd med godartede lidelser i prostata har falsk forhøjede PSA-målinger, og da over halvdelen af cancerforandringerne ikke kan ses på ultralydsscanning, får alle mænd, der er under mistanke for PCa, foretaget screenings-biopsier (10-12 stk. spredt i prostata) selvom kun ca. halvdelen har cancer og endnu færre har aggressiv behandlingskrævende sygdom. En stor gruppe mænd biopteres derfor unødigt med risiko for svær infektion og blødning. Screenings-biopsierne indebærer desuden en betydelig risiko for enten fejlskud (en aggressiv cancer overses) eller overdiagnostik af insPCa, der enten kan føre til overbehandling med tilhørende bivirkninger eller kræver langvarig kontrol. Denne usikkerhed gør også at mænd med negative biopsier ofte følges i langvarige forløb, der indebærer PSA blodprøve-kontrol og gentagne (invasive) biopsier, hvilket forsinker diagnostikken og udgør betydelige omkostninger for de enkelte urologiske afdelinger.

Der er således brug for mere effektive og præcise metoder til at skelne mellem mænd med aggressiv behandlingskrævende sygdom og mænd uden cancer eller med fredelig sygdom, der blot kan observeres. Meget tyder på at MR-skanning af prostata kan løse nogle af de diagnostiske udfordringer. Undersøgelser har vist, at MR-skanning mere nøjagtigt viser hvor en eventuel aggressiv kræftknude sidder og kan vejlede en biopsi-nål mod kræftknudens mest aggressive sted for derved at opnå en mere præcis diagnose med få biopsi-indstik. Omvendt kan en normal MR-skanning betyde, at nogle mænd helt kan undgå biopsier, hvilket er tiltagende nødvendigt grundet det stigende antal antibiotika-resistente bakterie infektioner, der ses efter $TRUS_{bx}$. Derfor kan MR-skanning potentielt bruges som triagerings-test til at

forbedre risikovurderingen af mænd under mistanke for PCa og minimere antallet af overdiagnoser (reducere diagnostikken af insPCa) og unødvendige biopsier.

Det overordnede mål med denne doktorafhandling er derfor at analysere den diagnostiske nøjagtighed af en pre-bioptisk MR-skanning af prostata (multi- eller biparametrisk) med eller uden målrettede biopsier (TBx) til at påvise eller udelukke sPCa hos mænd, der er under mistanke for PCa. Afhandlingen er baseret på syv originale artikler og en oversigtsartikel (review), der hver især har til formål at give ny indsigt i et specifikt formål. Der er brugt patientdata fra to separate kohorter: biopsi-naive mænd og mænd med tidligere negative $TRUS_{bx}$, men med persisterende mistanke om PCa. Alle inkluderede mænd er fra en etnisk homogen, ikke-PSA-screenet skandinavisk befolkning. Imidlertid stammer de to kohorter fra forskellige tidsperioder, de blev undersøgt med forskellige pre-bioptiske MR-skannings metoder (multi- og biparametrisk MR-skanning), og de havde forskellig biopsi status (biopsi-naive og tidligere negativ $TRUS_{bx}$). De overordnede resultater fra hver artikel diskuteres i en klinisk kontekst, herunder drøftelse af aktuelle anbefalinger, begrænsninger og fremtidsperspektiver for en MR-vejledt diagnostisk strategi.

Artiklerne I – IV analyserer den diagnostiske nøjagtighed af en multiparametrisk MR-skanning +/– TBx til påvisning eller udelukkelse af sPCa hos mænd, der gennemgår gentagne biopsier (re-biopsi). Samlet set viste studierne, at multiparametrisk MR-skanning efterfulgt af TBx forbedrede diagnostikken af sPCa sammenlignet med $TRUS_{bx}$ og havde en høj negativ prædiktiv værdi (NPV) til at udelukke signifikant sygdom på længere sigt. MR-skannings fundne var stærkt korreleret til de histologiske resultater efter både biopsi og radikal prostatektomi på patient- og læsions niveau. En "TBx-only" strategi (dvs. udelukkende TBx af suspekte MR-fund uden supplerende systematiske biopsier) anbefales for MR-positive mænd, der gennemgår re-biopsi. Desuden fandt vi, at både $TRUS_{bx}$ og MR-vejledte TBx var behæftet med fejlskud og "overså" sPCa i bestemte regioner i prostata, og ved at kende placeringen af disse regioner kan man forbedre den fremtidige diagnostiske re-biopsi strategi.

Efter vi viste at multiparametrisk MR-skanning af prostata forbedrede diagnostikken af mænd med tidligere negative $TRUS_{bx}$, men persisterende mistanke om sPCa, er vores fokus for nylig rettet mod at bruge pre-bioptisk prostata MR-skanning, som triagerings-test også for biopsi-naive mænd. Formålet med denne strategi er at bruge MR-skanning til at skelne mænd med enten godartede tilstande eller klinisk fredelige kræftforandringer, som kan undgå eller

udskyde invasive biopsier, fra mænd med højere risiko for at have sPCa, der kræver diagnostiske biopsier. Imidlertid kan det være tidskrævende at udføre multiparametrisk MR-skanning på alle mænd, der mistænkes for at have PCa, og det vil være en stor økonomisk og ressourcekrævende byrde for sundhedsvæsenet. Erfaringen har vist, at de kontrastforstærkede billedsekvenser ved en multiparametrisk MR-skanning ofte kun ændrer marginalt ved den overordnede kliniske vurdering når tegn på sPCa skal be- eller afkræftes. Dette har ført til en voksende interesse for at udføre prostata MR-skanning uden kontrastforstærkede billeder, som en forkortet biparametrisk MR-procedure. Denne metode er både billigere og hurtigere og kunne derfor potentielt resultere i en mere udbredt klinisk implementering af prostata MR-skanning til alle mænd før stillingtagen til biopsier; især i de store patientpopulationer i den vestlige verden, hvor prævalensen af PCa er høj.

Derfor var formålet med *artiklerne V – VII* at vurdere den diagnostiske nøjagtighed af biparametrisk MR-skanning til påvisning og udelukkelse af sPCa hos biopsi-naive mænd under mistanke for PCa. Generelt viste undersøgelserne, at biparametrisk MR-skanning anvendt enten alene, kombineret med PSA-densitetsmålinger, eller inkluderet i et nomogram sammen med kliniske parametre (alder, DRE og PSA-densitet) forbedrede risikovurderingen af om en mand havde sPCa og omvendt havde en høj NPV til at udelukke sPCa, så invasive biopsier potentielt kunne undgås. Baseret på beslutningskurve-analyse, der afvejede fordele (påvisning af sPCa) og ulemper (udførelse af unødvendige biopsier) blev en optimal biopsitærskel og fremgangsmåde foreslået.

I alle de kliniske artikler (*artikel I – VII*) anvendte vi en MR / TRUS-billedfusionsbiopsi-teknik til selektivt at målrette biopsierne (TBx) mod de suspekte MR-læsioner. Derfor er en oversigtsartikel (*review artikel VIII*) også inkluderet i denne afhandling for at beskrive status, udfordringer og fremtidige perspektiver tilknyttet denne biopsimetode.

Den samlede konklusion af denne doktorafhandling baseret på resultaterne fra *artiklerne I – VII* er, at en veludført MR-skanning af prostata kan 1) reducere antallet af mænd, der kræver invasive biopsier grundet mistanke om PCa med 25–50%, 2) mindske overdiagnostikken af insPCa med ca. 50%, og 3) forbedre diagnostikken af sPCa uanset hvilken definition af aggressiv sygdom der benyttes. Resultaterne understøtter således brugen af en MR-vejledt diagnostisk strategi for alle mænd, der mistænkes for at have PCa, hvor biopsier er klinisk indiceret, og hvor MR-skannings fund vurderes at have indflydelse på behandlingsstrategien.

References

[1] Bennett HY, Roberts MJ, Doi S a R, et al. The global burden of major infectious complications following prostate biopsy. Epidemiol Infect 2015;144:1–8.

[2] Batura D. Editorial commentary: Fluoroquinolone-resistant intestinal organisms and infections after prostate biopsy: Shifting sands of the prevention narrative. Clin Infect Dis 2015;60:988–9.

[3] Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic Resonance Imaging-targeted Biopsy May Enhance the Diagnostic Accuracy of Significant Prostate Cancer Detection Compared to Standard Transrectal Ultrasound-guided Biopsy: A Systematic Review and Meta-analysis. Eur Urol 2015;68:438–50.

[4] Fütterer JJ, Briganti A, De Visschere P, et al. Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature. Eur Urol 2015;68:1045–53.

[5] Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/Ultrasound Fusion–Guided Biopsy With Ultrasound-Guided Biopsy for the Diagnosis of Prostate Cancer. JAMA 2015;313:390–7.

[6] Moldovan PC, Van den Broeck T, Sylvester R, et al. What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. Eur Urol 2017;72:250–66.

[7] Borre M, Lundorf E, Marcussen N, et al. Phased array magnetic resonance imaging for staging clinically localised prostrate cancer. Acta Oncol 2005;44:589–92.

[8] Chabanova E, Balslev I, Logager V, et al. Prostate cancer: 1.5 T endo-coil dynamic contrast-enhanced MRI and MR spectroscopy--correlation with prostate biopsy and prostatectomy histopathological data. Eur J Radiol 2011;80:292–6.

[9] Boesen L. Multiparametric MRI in detection and staging of prostate cancer. Dan Med J 2017;64.

[10] Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. Eur Radiol 2012;22:746–57.

[11] Engholm G, Ferlay J, Christensen N, et al. NORDCAN--a Nordic tool for cancer information, planning, quality control and research. Acta Oncol 2010;49:725–36.

[12] Welch HG, Black WC. Overdiagnosis in Cancer. JNCI J Natl Cancer Inst 2010;102:605–13.

[13] Mottet N, van den Bergh R, Briers E, et al. EAU - EANM - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. Eur Assoc Urol Guidel 2019 2019;53:1–161.

[14] Antenor J V., Han M, Roehl KA, et al. Relationship between initial prostate specific antigen level and subsequent prostate cancer detection in a longitudinal screening study. J Urol 2004;172:90–3.

[15] Oesterling JE. Age-Specific Reference Ranges for Serum PSA. N Engl J Med 1996;335:345–6.

[16] Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤4.0 ng per milliliter. N Engl J Med 2004;350:2239–46.

[17] Catalona WJ, Hudson MA, Scardino PT, et al. Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: receiver operating characteristic curves. J Urol 1994;152:2037–42.

[18] Djavan B, Ravery V, Zlotta A, et al. Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop? J Urol 2001;166:1679–83.

[19] Obort AS, Ajadi MB, Akinloye O. Prostate-specific antigen: any successor in sight? Rev Urol 2013;15:97–107.
[20] Parekh DJ, Ankerst DP, Troyer D, et al. Biomarkers for Prostate Cancer Detection. J Urol 2007;178:2252–9.
[21] Hernández J, Thompson IM. Prostate-specific antigen: a review of the validation of the most commonly used cancer biomarker. Cancer 2004;101:894–904.
[22] Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014;65:124–37.
[23] Eggener SE, Cifu AS, Nabhan C. Prostate Cancer Screening. JAMA 2015;314:825–6.
[24] Etzioni R, Gulati R, Cooperberg MR, et al. Limitations of basing screening policies on screening trials: The US Preventive Services Task Force and Prostate Cancer Screening. Med Care 2013;51:295–300.
[25] Grossman DC, Curry SJ, Owens DK, et al. Screening for Prostate Cancer. JAMA 2018;319:1901.
[26] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014;384:2027–35.
[27] Andriole GL, Crawford ED, Grubb RL, et al. Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up. JNCI J Natl Cancer Inst 2012;104:125–32.
[28] Tsodikov A, Gulati R, Heijnsdijk EAM, et al. Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials. Ann Intern Med 2017;167:449–55.
[29] Gandaglia G, Briganti A, Fossati N, et al. The Problem Is Not What to Do with Indolent and Harmless Prostate Cancer—The Problem Is How to Avoid Finding These Cancers. Eur Urol 2016;70:547–8.
[30] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2017;71:618–29.
[31] Distler FA, Radtke JP, Bonekamp D, et al. The Value of PSA Density in Combination with PI-RADS™ for the Accuracy of Prostate Cancer Prediction. J Urol 2017;198:575–82.
[32] Hansen NL, Barrett T, Koo B, et al. The influence of prostate-specific antigen density on positive and negative predictive values of multiparametric magnetic resonance imaging to detect Gleason score 7–10 prostate cancer in a repeat biopsy setting. BJU Int 2017;119:724–30.
[33] Washino S, Okochi T, Saito K, et al. Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy naïve patients. BJU Int 2017;119:225–33.
[34] Nordström T, Vickers A, Assel M, et al. Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer. Eur Urol 2015;68:139–46.
[35] Parekh DJ, Punnen S, Sjoberg DD, et al. A Multi-institutional Prospective Trial in the USA Confirms that the 4Kscore Accurately Identifies Men with High-grade Prostate Cancer. Eur Urol 2015;68:464–70.
[36] Loeb S, Sanda MG, Broyles DL, et al. The Prostate Health Index Selectively Identifies Clinically Significant Prostate Cancer. J Urol 2015;193:1163–9.
[37] Wei JT, Feng Z, Partin AW, et al. Can Urinary PCA3 Supplement PSA in the Early Detection

of Prostate Cancer? J Clin Oncol 2014;32:4066–72.
[38] Varenhorst E, Berglund K, Löfman O, et al. Inter-observer variation in assessment of the prostate by digital rectal examination. Br J Urol 1993;72:173–6.
[39] Chodak GW. Early detection and screening for prostatic cancer. Urology 1989;34:10–2; discussion 46-56.
[40] Pedersen K, Carlsson P, Varenhorst E, et al. Screening for carcinoma of the prostate by digital rectal examination in a randomly selected population. BMJ 1990;300:1041–4.
[41] Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol 1994;151:1283–90.
[42] Gosselaar C, Roobol MJ, Roemeling S, et al. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. Eur Urol 2008;54:581–8.
[43] Okotie OT, Roehl KA, Han M, et al. Characteristics of prostate cancer detected by digital rectal examination only. Urology 2007;70:1117–20.
[44] Harvey CJ, Pilcher J, Richenberg J, et al. Applications of transrectal ultrasound in prostate cancer. Br J Radiol 2012;85:S3-17.
[45] Heidenreich A, Bolla M, Joniau S, et al. Guidelines on Prostate Cancer 2009.
[46] Spajic B, Eupic H, Tomas D, et al. The incidence of hyperechoic prostate cancer in transrectal ultrasound-guided biopsy specimens. Urology 2007;70:734–7.
[47] Hodge KK, McNeal JE, Terris MK, et al. Random Systematic Versus Directed Ultrasound Guided Transrectal Core Biopsies of the Prostate. J Urol 1989;142:71–4.
[48] Shariat SF, Roehrborn CG. Using biopsy to detect prostate cancer. Rev Urol 2008;10:262–80.
[49] Puppo P. Repeated Negative Prostate Biopsies with Persistently Elevated or Rising PSA: A Modern Urologic Dilemma. Eur Urol 2007;52:639–41.
[50] Roehl KA, Antenor J V., Catalona WJ. Serial biopsy results in prostate cancer screening study. J Urol 2002;167:2435–9.
[51] Roobol MJ, Van Vugt HA, Loeb S, et al. Prediction of prostate cancer risk: The role of prostate volume and digital rectal examination in the ERSPC risk calculators. Eur Urol 2012;61:577–83.
[52] Thompson IM, Ankerst DP, Chi C, et al. Assessing Prostate Cancer Risk: Results from the Prostate Cancer Prevention Trial. JNCI J Natl Cancer Inst 2006;98:529–34.
[53] Foley RW, Maweni RM, Gorman L, et al. European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators significantly outperform the Prostate Cancer Prevention Trial (PCPT) 2.0 in the prediction of prostate cancer: a multi-institutional study. BJU Int 2016;118:706–13.
[54] Grönberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): A prospective population-based diagnostic study. Lancet Oncol 2015;16:1667–76.
[55] Loeb S, Shin SS, Broyles DL, et al. Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer. BJU Int 2017;120:61–8.
[56] Ukimura O, Coleman JA, de la Taille A, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol 2013;63:214–30.
[57] Van Der Kwast TH, Roobol MJ. Defining the threshold for significant versus insignificant prostate cancer. Nat Rev Urol 2013;10:473–82.

[58] Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol 2018;199:683–90.
[59] Epstein JI, Allsbrook WC, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2005;29:1228–42.
[60] Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol 1974;111:58–64.
[61] Egevad L, Granfors T, Karlberg L, et al. Prognostic value of the Gleason score in prostate cancer. BJU Int 2002;89:538–42.
[62] Rusthoven CG, Carlson JA, Waxweiler T V, et al. The prognostic significance of Gleason scores in metastatic prostate cancer. Urol Oncol 2014;32:707–13.
[63] Brimo F, Montironi R, Egevad L, et al. Contemporary grading for prostate cancer: implications for patient care. Eur Urol 2013;63:892–901.
[64] Pierorazio PM, Walsh PC, Partin AW, et al. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int 2013;111:753–60.
[65] Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016;40:244–52.
[66] Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. Eur Urol 2016;69:428–35.
[67] Berney DM, Beltran L, Fisher G, et al. Validation of a contemporary prostate cancer grading system using prostate cancer death as outcome. Br J Cancer 2016;114:1078–83.
[68] Zietman A, Smith J, Klein E, et al. Consensus Guidelines for Reporting Prostate Cancer Gleason Grade. Urology 2016;93:1.
[69] Epstein JI, Feng Z, Trock BJ, et al. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol 2012;61:1019–24.
[70] Delahunt B, Miller RJ, Srigley JR, et al. Gleason grading: past, present and future. Histopathology 2012;60:75–86.
[71] Bangma CH, Bul M, van der Kwast TH, et al. Active surveillance for low-risk prostate cancer. Crit Rev Oncol Hematol 2013;85:295–302.
[72] Park HJ, Ha YS, Park SY, et al. Incidence of upgrading and upstaging in patients with low-volume Gleason score 3+4 prostate cancers at biopsy: finding a new group eligible for active surveillance. Urol Int 2013;90:301–5.
[73] Pierorazio PM, Walsh PC, Partin AW, et al. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int 2013;111:753–60.
[74] Eggener SE, Scardino PT, Walsh PC, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J Urol 2011;185:869–75.
[75] Chan TY, Partin AW, Walsh PC, et al. Prognostic significance of Gleason score 3+4 versus Gleason score 4+3 tumor at radical prostatectomy. Urology 2000;56:823–7.
[76] Stephenson AJ, Scardino PT, Eastham JA, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2005;23:7005–12.
[77] Rasiah KK, Stricker PD, Haynes A-M, et al. Prognostic significance of Gleason pattern in patients with Gleason score 7 prostate carcinoma. Cancer 2003;98:2560–5.

[78] Herman CM, Kattan MW, Ohori M, et al. Primary Gleason pattern as a predictor of disease progression in gleason score 7 prostate cancer: a multivariate analysis of 823 men treated with radical prostatectomy. Am J Surg Pathol 2001;25:657–60.
[79] Stark JR, Perner S, Stampfer MJ, et al. Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3? J Clin Oncol 2009;27:3459–64.
[80] Amin A, Partin A, Epstein JI. Gleason score 7 prostate cancer on needle biopsy: relation of primary pattern 3 or 4 to pathological stage and progression after radical prostatectomy. J Urol 2011;186:1286–90.
[81] Huang CC, Kong MX, Zhou M, et al. Gleason Score 3 + 4=7 Prostate Cancer With Minimal Quantity of Gleason Pattern 4 on Needle Biopsy Is Associated With Low-risk Tumor in Radical Prostatectomy Specimen. Am J Surg Pathol 2014;38(8):1096–101.
[82] Steyn JH, Smith FW. Nuclear magnetic resonance imaging of the prostate. Br J Urol 1982;54:726–8.
[83] Hricak H, Williams R, Spring D, et al. Anatomy and pathology of the male pelvis by magnetic resonance imaging. Am J Roentgenol 1983;141:1101–10.
[84] Sciarra A, Barentsz J, Bjartell A, et al. Advances in magnetic resonance imaging: how they are changing the management of prostate cancer. Eur Urol 2011;59:962–77.
[85] Hoeks CMA, Barentsz JO, Hambrock T, et al. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. Radiology 2011;261:46–66.
[86] Ullrich T, Quentin M, Oelers C, et al. Magnetic resonance imaging of the prostate at 1.5 versus 3.0T: A prospective comparison study of image quality. Eur J Radiol 2017;90:192–7.
[87] Heijmink SWTPJ, Fütterer JJ, Hambrock T, et al. Prostate cancer: body-array versus endorectal coil MR imaging at 3 T--comparison of image quality, localization, and staging performance. Radiology 2007;244:184–95.
[88] Turkbey B, Merino MJ, Gallardo EC, et al. Comparison of endorectal coil and nonendorectal coil T2W and diffusion-weighted MRI at 3 Tesla for localizing prostate cancer: correlation with whole-mount histopathology. J Magn Reson Imaging 2014;39:1443–8.
[89] Mirak SA, Shakeri S, Bajgiran AM, et al. Three Tesla Multiparametric Magnetic Resonance Imaging: Comparison of Performance with and without Endorectal Coil for Prostate Cancer Detection, PI-RADS™ version 2 Category and Staging with Whole Mount Histopathology Correlation. J Urol 2019;201:496–502.
[90] Hambrock T, Hoeks C, Hulsbergen-van de Kaa C, et al. Prospective assessment of prostate cancer aggressiveness using 3-T diffusion-weighted magnetic resonance imaging-guided biopsies versus a systematic 10-core transrectal ultrasound prostate biopsy cohort. Eur Urol 2012;61:177–84.
[91] Turkbey B, Shah VP, Pang Y, et al. Is apparent diffusion coefficient associated with clinical risk scores for prostate cancers that are visible on 3-T MR images? Radiology 2011;258:488–95.
[92] Cruz M, Tsuda K, Narumi Y, et al. Characterization of low-intensity lesions in the peripheral zone of prostate on pre-biopsy endorectal coil MR imaging. Eur Radiol 2002;12:357–65.
[93] Turkbey B, Albert PS, Kurdziel K, et al. Imaging localized prostate cancer: current approaches and new developments. AJR Am J Roentgenol 2009;192:1471–80.
[94] Langer DL, van der Kwast TH, Evans AJ, et al. Intermixed normal tissue within prostate cancer: effect on MR imaging measurements of apparent diffusion coefficient and T2--

sparse versus dense cancers. Radiology 2008;249:900–8.
[95] Tamada T, Sone T, Jo Y, et al. Prostate cancer: relationships between postbiopsy hemorrhage and tumor detectability at MR diagnosis. Radiology 2008;248:531–9.
[96] White S, Hricak H, Forstner R, et al. Prostate cancer: effect of postbiopsy hemorrhage on interpretation of MR images. Radiology 1995;195:385–90.
[97] Tan CH, Wei W, Johnson V, et al. Diffusion-weighted MRI in the detection of prostate cancer: meta-analysis. AJR Am J Roentgenol 2012;199:822–9.
[98] Qayyum A. Diffusion-weighted imaging in the abdomen and pelvis: concepts and applications. Radiographics 2009;29:1797–810.
[99] Kim CK, Park BK, Kim B. Diffusion-weighted MRI at 3 T for the evaluation of prostate cancer. AJR Am J Roentgenol 2010;194:1461–9.
[100] Somford DM, Fütterer JJ, Hambrock T, et al. Diffusion and perfusion MR imaging of the prostate. Magn Reson Imaging Clin N Am 2008;16:685–95.
[101] Zelhof B, Pickles M, Liney G, et al. Correlation of diffusion-weighted magnetic resonance data with cellularity in prostate cancer. BJU Int 2009;103:883–8.
[102] Gibbs P, Pickles MD, Turnbull LW. Diffusion imaging of the prostate at 3.0 tesla. Invest Radiol 2006;41:185–8.
[103] Wu L-M, Xu J-R, Ye Y-Q, et al. The clinical value of diffusion-weighted imaging in combination with T2-weighted imaging in diagnosing prostate carcinoma: a systematic review and meta-analysis. AJR Am J Roentgenol 2012;199:103–10.
[104] Verma S, Rajesh A, Morales H, et al. Assessment of aggressiveness of prostate cancer: correlation of apparent diffusion coefficient with histologic grade after radical prostatectomy. AJR Am J Roentgenol 2011;196:374–81.
[105] Hambrock T, Somford DM, Huisman HJ, et al. Relationship between apparent diffusion coefficients at 3.0-T MR imaging and Gleason grade in peripheral zone prostate cancer. Radiology 2011;259:453–61.
[106] Vargas HA, Akin O, Franiel T, et al. Diffusion-weighted endorectal MR imaging at 3 T for prostate cancer: tumor detection and assessment of aggressiveness. Radiology 2011;259:775–84.
[107] Jung S Il, Donati OF, Vargas HA, et al. Transition zone prostate cancer: incremental value of diffusion-weighted endorectal MR imaging in tumor detection and assessment of aggressiveness. Radiology 2013;269:493–503.
[108] van As NJ, de Souza NM, Riches SF, et al. A study of diffusion-weighted magnetic resonance imaging in men with untreated localised prostate cancer on active surveillance. Eur Urol 2009;56:981–7.
[109] Oto A, Kayhan A, Jiang Y, et al. Prostate cancer: differentiation of central gland cancer from benign prostatic hyperplasia by using diffusion-weighted and dynamic contrast-enhanced MR imaging. Radiology 2010;257:715–23.
[110] Litjens GJS, Hambrock T, Hulsbergen-van de Kaa C, et al. Interpatient variation in normal peripheral zone apparent diffusion coefficient: effect on the prediction of prostate cancer aggressiveness. Radiology 2012;265:260–6.
[111] Kim JH, Kim JK, Park B-W, et al. Apparent diffusion coefficient: prostate cancer versus noncancerous tissue according to anatomical region. J Magn Reson Imaging 2008;28:1173–9.
[112] Tamada T, Sone T, Jo Y, et al. Apparent diffusion coefficient values in peripheral and transition zones of the prostate: comparison between normal and malignant prostatic tissues and correlation with histologic grade. J Magn Reson Imaging 2008;28:720–6.

[113] Brawer MK, Deering RE, Brown M, et al. Predictors of pathologic stage in prostatic carcinoma. The role of neovascularity. Cancer 1994;73:678–87.
[114] Bigler SA, Deering RE, Brawer MK. Comparison of microscopic vascularity in benign and malignant prostate tissue. Hum Pathol 1993;24:220–6.
[115] Noworolski SM, Henry RG, Vigneron DB, et al. Dynamic contrast-enhanced MRI in normal and abnormal prostate tissues as defined by biopsy, MRI, and 3D MRSI. Magn Reson Med 2005;53:249–55.
[116] Choi YJ, Kim JK, Kim N, et al. Functional MR imaging of prostate cancer. Radiographics 2007;27:63–75.
[117] Verma S, Turkbey B, Muradyan N, et al. Overview of dynamic contrast-enhanced MRI in prostate cancer diagnosis and management. AJR Am J Roentgenol 2012;198:1277–88.
[118] Ocak I, Bernardo M, Metzger G, et al. Dynamic contrast-enhanced MRI of prostate cancer at 3 T: a study of pharmacokinetic parameters. AJR Am J Roentgenol 2007;189:849.
[119] Turkbey B, Pinto PA, Mani H, et al. Prostate cancer: value of multiparametric MR imaging at 3 T for detection--histopathologic correlation. Radiology 2010;255:89–99.
[120] Greer MD, Shih JH, Lay N, et al. Validation of the Dominant Sequence Paradigm and Role of Dynamic Contrast-enhanced Imaging in PI-RADS Version 2. Radiology 2017;285:859–69.
[121] Tamada T, Sone T, Higashi H, et al. Prostate cancer detection in patients with total serum prostate-specific antigen levels of 4-10 ng/mL: diagnostic efficacy of diffusion-weighted imaging, dynamic contrast-enhanced MRI, and T2-weighted imaging. AJR Am J Roentgenol 2011;197:664–70.
[122] Engelbrecht MR, Huisman HJ, Laheij RJF, et al. Discrimination of prostate cancer from normal peripheral zone and central gland tissue by using dynamic contrast-enhanced MR imaging. Radiology 2003;229:248–54.
[123] Pahwa S, Schiltz NK, Ponsky LE, et al. Cost-effectiveness of MR Imaging–guided Strategies for Detection of Prostate Cancer in Biopsy-Naive Men. Radiology 2017;285:157–66.
[124] Boesen L, Nørgaard N, Løgager V, et al. Assessment of the Diagnostic Accuracy of Biparametric Magnetic Resonance Imaging for Prostate Cancer in Biopsy-Naive Men. JAMA Netw Open 2018;1:e180219.
[125] Sherrer RL, Glaser ZA, Gordetsky JB, et al. Comparison of biparametric MRI to full multiparametric MRI for detection of clinically significant prostate cancer. Prostate Cancer Prostatic Dis 2019;22:331–6.
[126] Jambor I, Boström PJ, Taimen P, et al. Novel biparametric MRI and targeted biopsy improves risk stratification in men with a clinical suspicion of prostate cancer (IMPROD Trial). J Magn Reson Imaging 2017;46:1089–95.
[127] Vargas HA, Hötker AM, Goldman DA, et al. Updated prostate imaging reporting and data system (PIRADS v2) recommendations for the detection of clinically significant prostate cancer using multiparametric MRI: critical evaluation using whole-mount pathology as standard of reference. Eur Radiol 2016;26:1606–12.
[128] Cirillo S, Petracchini M, Scotti L, et al. Endorectal magnetic resonance imaging at 1.5 Tesla to assess local recurrence following radical prostatectomy using T2-weighted and contrast-enhanced imaging. Eur Radiol 2009;19:761–9.
[129] Haider MA, Chung P, Sweet J, et al. Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:425–30.
[130] Yakar D, Hambrock T, Huisman H, et al. Feasibility of 3T dynamic contrast-enhanced

magnetic resonance-guided biopsy in localizing local recurrence of prostate cancer after external beam radiation therapy. Invest Radiol 2010;45:121–5.
[131] Wu LM, Xu J-R, Gu HY, et al. Role of magnetic resonance imaging in the detection of local prostate cancer recurrence after external beam radiotherapy and radical prostatectomy. Clin Oncol (R Coll Radiol) 2013;25:252–64.
[132] Panebianco V, Barchetti F, Sciarra A, et al. Prostate cancer recurrence after radical prostatectomy: the role of 3-T diffusion imaging in multi-parametric magnetic resonance imaging. Eur Radiol 2013;23:1745–52.
[133] Hamoen EHJ, de Rooij M, Witjes JA, et al. Use of the Prostate Imaging Reporting and Data System (PI-RADS) for Prostate Cancer Detection with Multiparametric Magnetic Resonance Imaging: A Diagnostic Meta-analysis. Eur Urol 2015;67:1112–21.
[134] Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol 2013;63:125–40.
[135] Mullerad M, Hricak H, Wang L, et al. Prostate cancer: detection of extracapsular extension by genitourinary and general body radiologists at MR imaging. Radiology 2004;232:140–6.
[136] Fütterer JJ, Engelbrecht MR, Huisman HJ, et al. Staging prostate cancer with dynamic contrast-enhanced endorectal MR imaging prior to radical prostatectomy: experienced versus less experienced readers. Radiology 2005;237:541–9.
[137] Wassberg C, Akin O, Vargas HA, et al. The incremental value of contrast-enhanced MRI in the detection of biopsy-proven local recurrence of prostate cancer after radical prostatectomy: effect of reader experience. AJR Am J Roentgenol 2012;199:360–6.
[138] Schimmöller L, Quentin M, Arsov C, et al. Inter-reader agreement of the ESUR score for prostate MRI using in-bore MRI-guided biopsies as the reference standard. Eur Radiol 2013;23:3185–90.
[139] Roethke MC, Kuru TH, Schultze S, et al. Evaluation of the ESUR PI-RADS scoring system for multiparametric MRI of the prostate with targeted MR/TRUS fusion-guided biopsy at 3.0 Tesla. Eur Radiol 2014;24:344–52.
[140] Langer DL, van der Kwast TH, Evans AJ, et al. Prostate cancer detection with multi-parametric MRI: logistic regression analysis of quantitative T2, diffusion-weighted imaging, and dynamic contrast-enhanced MRI. J Magn Reson Imaging 2009;30:327–34.
[141] Hoeks CMA, Hambrock T, Yakar D, et al. Transition zone prostate cancer: detection and localization with 3-T multiparametric MR imaging. Radiology 2013;266:207–17.
[142] Vaché T, Bratan F, Mège-Lechevallier F, et al. Characterization of Prostate Lesions as Benign or Malignant at Multiparametric MR Imaging: Comparison of Three Scoring Systems in Patients Treated with Radical Prostatectomy. Radiology 2014;272:446–55.
[143] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol 2016;69:16–40.
[144] Tewes S, Mokov N, Hartung D, et al. Standardized Reporting of Prostate MRI: Comparison of the Prostate Imaging Reporting and Data System (PI-RADS) Version 1 and Version 2. PLoS One 2016;11:e0162879.
[145] Moore CM, Kasivisvanathan V, Eggener S, et al. Prostate Cancer Standards of Reporting for MRI-targeted Biopsy Studies (START) of the Prostate : Recommendations from an International Working Group. Eur Urol 2013;64:544–52.
[146] Barentsz JO, Weinreb JC, Verma S, et al. Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use.

Eur Urol 2016;69:41–9.
[147] Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. Eur Urol 2019;76:340–51.
[148] Renard-Penna R, Mozer P, Cornud F, et al. Prostate Imaging Reporting and Data System and Likert Scoring System: Multiparametric MR Imaging Validation Study to Screen Patients for Initial Biopsy. Radiology 2015;275:458–68.
[149] Greer MD, Brown AM, Shih JH, et al. Accuracy and agreement of PIRADSv2 for prostate cancer mpMRI: A multireader study. J Magn Reson Imaging 2017;45:579–85.
[150] Spilseth B, Ghai S, Patel NU, et al. A Comparison of Radiologists' and Urologists' Opinions Regarding Prostate MRI Reporting: Results From a Survey of Specialty Societies. Am J Roentgenol 2018;210:101–7.
[151] Sobin L, Gospodarowicz M WC. TNM Classification of Malignant Tumours . Urological Tumours. Seventh edition, International Union Against Cancer. 7 th. Hoboken, NJ: Wiley-Blackwell; 2009.
[152] Boesen L, Nørgaard N, Løgager V, et al. Clinical Outcome Following Low Suspicion Multiparametric Prostate Magnetic Resonance Imaging or Benign Magnetic Resonance Imaging Guided Biopsy to Detect Prostate Cancer. J Urol 2017;198:310–5.
[153] Boesen L, Nørgaard N, Løgager V, et al. Where Do Transrectal Ultrasound- and Magnetic Resonance Imaging-guided Biopsies Miss Significant Prostate Cancer? Urology 2017;110:154–60.
[154] Boesen L, Nørgaard N, Løgager V, et al. Multiparametric MRI in men with clinical suspicion of prostate cancer undergoing repeat biopsy: a prospective comparison with clinical findings and histopathology. Acta Radiol 2018;59:371–80.
[155] Boesen L, Nørgaard N, Løgager V, et al. A Prospective Comparison of Selective Multiparametric Magnetic Resonance Imaging Fusion-Targeted and Systematic Transrectal Ultrasound-Guided Biopsies for Detecting Prostate Cancer in Men Undergoing Repeated Biopsies. Urol Int 2017;99:384–91.
[156] Boesen L, Nørgaard N, Løgager V, et al. Prebiopsy Biparametric Magnetic Resonance Imaging Combined with Prostate-specific Antigen Density in Detecting and Ruling out Gleason 7–10 Prostate Cancer in Biopsy-naïve Men. Eur Urol Oncol 2019;2:311–9.
[157] Boesen L, Thomsen FB, Nørgaard N, et al. A predictive model based on biparametric magnetic resonance imaging and clinical parameters for improved risk assessment and selection of biopsy-naïve men for prostate biopsies. Prostate Cancer Prostatic Dis 2019;22:609–16.
[158] D'Amico A V, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969–74.
[159] D'Amico A V, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localized prostate carcinoma in the prostate specific antigen era. Cancer 2002;95:281–6.
[160] Wang L, Hricak H, Kattan MW, et al. Prediction of organ-confined prostate cancer: incremental value of MR imaging and MR spectroscopic imaging to staging nomograms. Radiology 2006;238:597–603.
[161] Ohori M, Kattan MW, Koh H, et al. Predicting the presence and side of extracapsular extension: A nomogram for staging prostate cancer. J Urol 2004;171:1844–9.
[162] Eifler JB, Feng Z, Lin BM, et al. An updated prostate cancer staging nomogram (Partin

tables) based on cases from 2006 to 2011. BJU Int 2013;111:22–9.
[163] Kryvenko ON, Epstein JI. Improving the evaluation and diagnosis of clinically significant prostate cancer. Curr Opin Urol 2017;27:191–7.
[164] Matoso A, Epstein JI. Defining clinically significant prostate cancer on the basis of pathological findings. Histopathology 2019;74:135–45.
[165] Bratan F, Niaf E, Melodelima C, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. Eur Radiol 2013;23:2019–29.
[166] Le JD, Tan N, Shkolyar E, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: Correlation with whole-mount histopathology. Eur Urol 2015;67:569–76.
[167] Panebianco V, Barchetti G, Simone G, et al. Negative Multiparametric Magnetic Resonance Imaging for Prostate Cancer: What's Next? Eur Urol 2018;74:48–54.
[168] Venderink W, van Luijtelaar A, van der Leest M, et al. Multiparametric magnetic resonance imaging and follow-up to avoid prostate biopsy in 4259 men. BJU Int 2019;124:775–84.
[169] Rouvière O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019;20:100–9.
[170] van der Leest M, Cornel E, Israël B, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Mu. Eur Urol 2019;75:570–8.
[171] Delongchamps NB, Lefèvre A, Bouazza N, et al. Detection of significant prostate cancer with magnetic resonance targeted biopsies--should transrectal ultrasound-magnetic resonance imaging fusion guided biopsies alone be a standard of care? J Urol 2015;193:1198–204.
[172] Tan N, Margolis DJ, Lu DY, et al. Characteristics of detected and missed prostate cancer foci on 3-T multiparametric MRI using an endorectal coil correlated with whole-mount thin-section histopathology. Am J Roentgenol 2015;205:W87–92.
[173] Thompson JE, van Leeuwen PJ, Moses D, et al. The Diagnostic Performance of Multiparametric Magnetic Resonance Imaging to Detect Significant Prostate Cancer. J Urol 2016;195:1428–35.
[174] Russo F, Regge D, Armando E, et al. Detection of prostate cancer index lesions with multiparametric magnetic resonance imaging (mp-MRI) using whole-mount histological sections as the reference standard. BJU Int 2016;118:84–94.
[175] de Rooij M, Hamoen EHJ, Witjes JA, et al. Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. Eur Urol 2016;70:233–45.
[176] Hu Y, Ahmed HU, Carter T, et al. A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy strategies compared with template prostate mapping biopsies in patients who have undergone radical prostatectomy. BJU Int 2012;110:812–20.
[177] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.
[178] Simmons LAM, Kanthabalan A, Arya M, et al. The PICTURE study: diagnostic accuracy of multiparametric MRI in men requiring a repeat prostate biopsy. Br J Cancer

2017;116:1159.
[179] Crawford ED, Rove KO, Barqawi AB, et al. Clinical-pathologic correlation between transperineal mapping biopsies of the prostate and three-dimensional reconstruction of prostatectomy specimens. Prostate 2013;73:778–87.
[180] Valerio M, Anele C, Bott SRJ, et al. The Prevalence of Clinically Significant Prostate Cancer According to Commonly Used Histological Thresholds in Men Undergoing Template Prostate Mapping Biopsies. J Urol 2016;195:1403–8.
[181] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med 2018;378:1767–77.
[182] Drost F-JH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev 2019.
[183] Itatani R, Namimoto T, Atsuji S, et al. Negative predictive value of multiparametric MRI for prostate cancer detection: Outcome of 5-year follow-up in men with negative findings on initial MRI studies. Eur J Radiol 2014;83:1740–5.
[184] Pokorny MR, de Rooij M, Duncan E, et al. Prospective Study of Diagnostic Accuracy Comparing Prostate Cancer Detection by Transrectal Ultrasound–Guided Biopsy Versus Magnetic Resonance (MR) Imaging with Subsequent MR-guided Biopsy in Men Without Previous Prostate Biopsies. Eur Urol 2014;66:22–9.
[185] Panebianco V, Barchetti F, Sciarra A, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: A randomized study. Urol Oncol Semin Orig Investig 2015;33:17.e1-17.e7.
[186] Porpiglia F, Manfredi M, Mele F, et al. Diagnostic Pathway with Multiparametric Magnetic Resonance Imaging Versus Standard Pathway: Results from a Randomized Prospective Study in Biopsy-naïve Patients with Suspected Prostate Cancer. Eur Urol 2017;72:282–8.
[187] Bryant RJ, Hobbs CP, Eyre KS, et al. Comparison of Prostate Biopsy with or without Prebiopsy Multiparametric Magnetic Resonance Imaging for Prostate Cancer Detection: An Observational Cohort Study. J Urol 2019;201:510–9.
[188] Jambor I, Verho J, Ettala O, et al. Validation of IMPROD biparametric MRI in men with clinically suspected prostate cancer: A prospective multi-institutional trial. PLOS Med 2019;16:e1002813.
[189] Baco E, Ukimura O, Rud E, et al. Magnetic Resonance Imaging–Transectal Ultrasound Image-fusion Biopsies Accurately Characterize the Index Tumor: Correlation with Step-sectioned Radical Prostatectomy Specimens in 135 Patients. Eur Urol 2015;67:787–94.
[190] Radtke JP, Schwab C, Wolf MB, et al. Multiparametric Magnetic Resonance Imaging (MRI) and MRI-Transrectal Ultrasound Fusion Biopsy for Index Tumor Detection: Correlation with Radical Prostatectomy Specimen. Eur Urol 2016;70:846–53.
[191] Rud E, Klotz D, Rennesund K, et al. Detection of the Index Tumor and Tumor Volume in Prostate Cancer using T2w and DW MRI alone. BJU Int 2014.
[192] Stabile A, Giganti F, Emberton M, et al. MRI in prostate cancer diagnosis: do we need to add standard sampling? A review of the last 5 years. Prostate Cancer Prostatic Dis 2018;21:473–87.
[193] Sonn GA, Natarajan S, Margolis DJA, et al. Targeted biopsy in the detection of prostate cancer using an office based magnetic resonance ultrasound fusion device. J Urol 2013;189:86–91.
[194] Valerio M, Donaldson I, Emberton M, et al. Detection of Clinically Significant Prostate Cancer Using Magnetic Resonance Imaging-Ultrasound Fusion Targeted Biopsy: A Systematic Review. Eur Urol 2015;68:8–19.

[195] Filson CP, Natarajan S, Margolis DJA, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: The role of systematic and targeted biopsies. Cancer 2016;122:884–92.
[196] Schouten MG, van der Leest M, Pokorny M, et al. Why and Where do We Miss Significant Prostate Cancer with Multi-parametric Magnetic Resonance Imaging followed by Magnetic Resonance-guided and Transrectal Ultrasound-guided Biopsy in Biopsy-naïve Men? Eur Urol 2017;71:896–903.
[197] De Visschere PJL, Naesens L, Libbrecht L, et al. What kind of prostate cancers do we miss on multiparametric magnetic resonance imaging? Eur Radiol 2016;26:1098–107.
[198] Muthigi A, George AK, Sidana A, et al. Missing the Mark: Prostate Cancer Upgrading by Systematic Biopsy over Magnetic Resonance Imaging/Transrectal Ultrasound Fusion Biopsy. J Urol 2017;197:327–34.
[199] Rosenkrantz AB, Verma S, Turkbey B. Prostate Cancer: Top Places Where Tumors Hide on Multiparametric MRI. Am J Roentgenol 2015;204:W449–56.
[200] Boesen L. Magnetic resonance imaging—transrectal ultrasound image fusion guidance of prostate biopsies: current status, challenges and future perspectives. Scand J Urol 2019;53:89–96.
[201] Rosenkrantz AB, Verma S, Choyke P, et al. Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR. J Urol 2016;196:1613–8.
[202] Giannarini G, Crestani A, Rossanese M, et al. Multiparametric Magnetic Resonance Imaging-targeted Prostate Biopsy: A Plea for a Change in Terminology, and Beyond. Eur Urol Oncol 2020;3:395–6.
[203] Padhani AR, Weinreb J, Rosenkrantz AB, et al. Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 Status Update and Future Directions. Eur Urol 2019;75:385–96.
[204] Lu AJ, Syed JS, Ghabili K, et al. Role of Core Number and Location in Targeted Magnetic Resonance Imaging-Ultrasound Fusion Prostate Biopsy. Eur Urol 2019;76:14–7.
[205] Wegelin O, Exterkate L, van der Leest M, et al. Complications and Adverse Events of Three Magnetic Resonance Imaging–based Target Biopsy Techniques in the Diagnosis of Prostate Cancer Among Men with Prior Negative Biopsies: Results from the FUTURE Trial, a Multicentre Randomised Controlled Trial. Eur Urol Oncol 2019;2:617–24.
[206] Chelluri R, Kilchevsky A, George AK, et al. Prostate Cancer Diagnosis on Repeat Magnetic Resonance Imaging-Transrectal Ultrasound Fusion Biopsy of Benign Lesions: Recommendations for Repeat Sampling. J Urol 2016;196:62–7.
[207] Bryk DJ, Llukani E, Taneja SS, et al. The Role of Ipsilateral and Contralateral Transrectal Ultrasound-guided Systematic Prostate Biopsy in Men With Unilateral Magnetic Resonance Imaging Lesion Undergoing Magnetic Resonance Imaging-ultrasound Fusion-targeted Prostate Biopsy. Urology 2017;102:178–82.
[208] Miah S, Servian P, Patel A, et al. A prospective analysis of robotic targeted MRI-US fusion prostate biopsy using the centroid targeting approach. J Robot Surg 2020;14:69–74.
[209] Zhang M, Milot L, Khalvati F, et al. Value of Increasing Biopsy Cores per Target with Cognitive MRI-targeted Transrectal US Prostate Biopsy. Radiology 2019;291:83–9.
[210] Hamid S, Donaldson IA, Hu Y, et al. The SmartTarget Biopsy Trial: A Prospective, Within-person Randomised, Blinded Trial Comparing the Accuracy of Visual-registration and Magnetic Resonance Imaging/Ultrasound Image-fusion Targeted Biopsies for Prostate Cancer Risk Stratification. Eur Urol 2019;75:733–40.

[211] Simmons LAM, Kanthabalan A, Arya M, et al. Accuracy of Transperineal Targeted Prostate Biopsies, Visual Estimation and Image Fusion in Men Needing Repeat Biopsy in the PICTURE Trial. J Urol 2018;200:1227–34.
[212] Calio BP, Sidana A, Sugano D, et al. Risk of Upgrading from Prostate Biopsy to Radical Prostatectomy Pathology—Does Saturation Biopsy of Index Lesion during Multiparametric Magnetic Resonance Imaging-Transrectal Ultrasound Fusion Biopsy Help? J Urol 2018;199:976–82.
[213] Priester A, Natarajan S, Khoshnoodi P, et al. Magnetic Resonance Imaging Underestimation of Prostate Cancer Geometry: Use of Patient Specific Molds to Correlate Images with Whole Mount Pathology. J Urol 2017;197:320–6.
[214] Kuhl CK, Bruhn R, Krämer N, et al. Abbreviated Biparametric Prostate MR Imaging in Men with Elevated Prostate-specific Antigen. Radiology 2017;285:493–505.
[215] De Visschere P, Lumen N, Ost P, et al. Dynamic contrast-enhanced imaging has limited added value over T2-weighted imaging and diffusion-weighted imaging when using PI-RADSv2 for diagnosis of clinically significant prostate cancer in patients with elevated PSA. Clin Radiol 2017;72:23–32.
[216] Niu X ke, Chen X hui, Chen Z fan, et al. Diagnostic performance of biparametric MRI for detection of prostate cancer: A systematic review and meta-analysis. Am J Roentgenol 2018;211:369–78.
[217] van der Leest M, Israël B, Cornel EB, et al. High Diagnostic Performance of Short Magnetic Resonance Imaging Protocols for Prostate Cancer Detection in Biopsy-naïve Men: The Next Step in Magnetic Resonance Imaging Accessibility. Eur Urol 2019;76:574–81.
[218] Gatti M, Faletti R, Calleris G, et al. Prostate cancer detection with biparametric magnetic resonance imaging (bpMRI) by readers with different experience: performance and comparison with multiparametric (mpMRI). Abdom Radiol 1934;44:1883–93.
[219] Rais-Bahrami S, Siddiqui MM, Vourganti S, et al. Diagnostic value of biparametric magnetic resonance imaging (MRI) as an adjunct to prostate-specific antigen (PSA)-based detection of prostate cancer in men without prior biopsies. BJU Int 2015;115:381–8.
[220] Fascelli M, Rais-Bahrami S, Sankineni S, et al. Combined Biparametric Prostate Magnetic Resonance Imaging and Prostate-specific Antigen in the Detection of Prostate Cancer: A Validation Study in a Biopsy-naive Patient Population. Urology 2016;88:125–34.
[221] Lee S, Oh YT, Jung DC, et al. Combined analysis of biparametric MRI and prostate-specific antigen density: Role in the prebiopsy diagnosis of gleason score 7 or greater prostate cancer. Am J Roentgenol 2018;211:W166–72.
[222] Morote J, Celma A, Planas J. Re: Lars Boesen, Nis Nørgaard, Vibeke Løgager, et al. Prebiopsy Biparametric Magnetic Resonance Imaging Combined with Prostate-specific Antigen Density in Detecting and Ruling out Gleason 7-10 Prostate Cancer in Biopsy-naïve Men. Eur Urol Oncol 2020;3:392–3.
[223] van Leeuwen PJ, Hayen A, Thompson JE, et al. A multiparametric magnetic resonance imaging-based risk model to determine the risk of significant prostate cancer prior to biopsy. BJU Int 2017;120:774–81.
[224] Mehralivand S, Shih JH, Rais-Bahrami S, et al. A Magnetic Resonance Imaging–Based Prediction Model for Prostate Biopsy Risk Stratification. JAMA Oncol 2018;4:678.
[225] Radtke JP, Wiesenfarth M, Kesch C, et al. Combined Clinical Parameters and Multiparametric Magnetic Resonance Imaging for Advanced Risk Modeling of Prostate Cancer—Patient-tailored Risk Stratification Can Reduce Unnecessary Biopsies. Eur Urol

2017;72:888–96.
[226] Alberts AR, Roobol MJ, Verbeek JFM, et al. Prediction of High-grade Prostate Cancer Following Multiparametric Magnetic Resonance Imaging: Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculators. Eur Urol 2019;75:310–8.
[227] Schoots IG, Roobol MJ. Multivariate risk prediction tools including MRI for individualized biopsy decision in prostate cancer diagnosis: current status and future directions. World J Urol 2020;38:517–29.
[228] Boesen L, Løgager V, Nørgaard N, et al. Assessment of diagnostic yields of significant prostate cancer by altering the prostate-specific antigen density thresholds for biopsy according to MRI findings. ECR 2019:B-0442.
[229] Schoots IG. MRI in early prostate cancer detection: how to manage indeterminate or equivocal PI-RADS 3 lesions? Transl Androl Urol 2018;7:70–82.
[230] Maggi M, Panebianco V, Mosca A, et al. Prostate Imaging Reporting and Data System 3 Category Cases at Multiparametric Magnetic Resonance for Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus 2020;6:463–78.
[231] de Rooij M, Crienen S, Witjes JA, et al. Cost-effectiveness of Magnetic Resonance (MR) Imaging and MR-guided Targeted Biopsy Versus Systematic Transrectal Ultrasound-Guided Biopsy in Diagnosing Prostate Cancer: A Modelling Study from a Health Care Perspective. Eur Urol 2013;66:430–6.
[232] Cerantola Y, Dragomir A, Tanguay S, et al. Cost-effectiveness of multiparametric magnetic resonance imaging and targeted biopsy in diagnosing prostate cancer. Urol Oncol Semin Orig Investig 2016;34:119.e1-9.
[233] Faria R, Soares MO, Spackman E, et al. Platinum Priority-Prostate Cancer Optimising the Diagnosis of Prostate Cancer in the Era of Multiparametric Magnetic Resonance Imaging: A Cost-effectiveness Analysis Based on the Prostate MR Imaging Study (PROMIS). Eur Urol 2018;73:23–30.
[234] Venderink W, Govers TM, De Rooij M, et al. Cost-effectiveness comparison of imaging-guided prostate biopsy techniques: Systematic transrectal ultrasound, direct in-bore MRI, and image fusion. Am J Roentgenol 2017;208:1058–63.
[235] Barnett CL, Davenport MS, Montgomery JS, et al. Cost-effectiveness of magnetic resonance imaging and targeted fusion biopsy for early detection of prostate cancer. BJU Int 2018;122:50–8.
[236] The National Institute for Health and Care Excellence (NICE) (2019) guideline for Prostate cancer: diagnosis and management (NG131). NICE; 2019.
[237] Wegelin O, Exterkate L, van der Leest M, et al. The FUTURE Trial: A Multicenter Randomised Controlled Trial on Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies. Eur Urol 2019;75:582–90.
[238] Pepe P, Pepe G, Pepe L, et al. Cost-effectiveness of Multiparametric MRI in 800 Men Submitted to Repeat Prostate Biopsy: Results of a Public Health Model. Anticancer Res 2018;38:2395–8.
[239] Walz J. Platinum Priority-Editorial What Needs To Be Done Before Prostate Magnetic Resonance Imaging Can Safely Be Applied in the General Population. Eur Urol 2019;75:397–8.
[240] Bjurlin MA, Carroll PR, Eggener S, et al. Update of the Standard Operating Procedure on the Use of Multiparametric Magnetic Resonance Imaging for the Diagnosis, Staging and

Management of Prostate Cancer. J Urol 2020;203:706–12.
[241] Padhani AR, Barentsz J, Villeirs G, et al. PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway. Radiology 2019;292:464–74.
[242] Rouvière O, Schoots IG, Mottet N. Multiparametric Magnetic Resonance Imaging Before Prostate Biopsy: A Chain is Only as Strong as its Weakest Link. Eur Urol 2019;75:889–90.
[243] Richenberg J, Løgager V, Panebianco V, et al. The primacy of multiparametric MRI in men with suspected prostate cancer. Eur Radiol 2019;29:6940–52.
[244] Hansen NL, Koo BC, Gallagher FA, et al. Comparison of initial and tertiary centre second opinion reads of multiparametric magnetic resonance imaging of the prostate prior to repeat biopsy. Eur Radiol 2017;27:2259–66.
[245] Sonn GA, Fan RE, Ghanouni P, et al. Prostate Magnetic Resonance Imaging Interpretation Varies Substantially Across Radiologists. Eur Urol Focus 2019;5:592–9.
[246] Nam RK, Wallis CJD, Stojcic-Bendavid J, et al. A Pilot Study to Evaluate the Role of Magnetic Resonance Imaging for Prostate Cancer Screening in the General Population. J Urol 2016;196:361–6.
[247] Grenabo Bergdahl A, Wilderäng U, Aus G, et al. Role of Magnetic Resonance Imaging in Prostate Cancer Screening: A Pilot Study Within the Göteborg Randomised Screening Trial. Eur Urol 2016;70:566–73.
[248] Le JD, Stephenson S, Brugger M, et al. Magnetic resonance imaging-ultrasound fusion biopsy for prediction of final prostate pathology. J Urol 2014;192:1367–73.
[249] Arora H, Nyame YA, El-Shafei A, et al. Prediction of pathological outcome at radical prostatectomy for MRI-ultrasound fusion prostate biopsy versus standard transrectal ultrasound guided prostate biopsy. J Clin Oncol 2017;35:73–73.
[250] Mesko S, Marks L, Ragab O, et al. Targeted Prostate Biopsy Gleason Score Heterogeneity and Implications for Risk Stratification. Am J Clin Oncol 2018;41:497–501.
[251] Robertson NL, Hu Y, Ahmed HU, et al. Prostate cancer risk inflation as a consequence of image-targeted biopsy of the prostate: A computer simulation study. Eur Urol 2014;65:628–34.
[252] Osses D, Roobol M, Schoots I, et al. Prediction Medicine: Biomarkers, Risk Calculators and Magnetic Resonance Imaging as Risk Stratification Tools in Prostate Cancer Diagnosis. Int J Mol Sci 2019;20:1637.
[253] Alberts AR, Schoots IG, Bokhorst LP, et al. Risk-based Patient Selection for Magnetic Resonance Imaging-targeted Prostate Biopsy after Negative Transrectal Ultrasound-guided Random Biopsy Avoids Unnecessary Magnetic Resonance Imaging Scans. Eur Urol 2016;69:1129–34.
[254] Goldenberg SL, Nir G, Salcudean SE. A new era: artificial intelligence and machine learning in prostate cancer. Nat Rev Urol 2019;16:391–403.
[255] Rosenkrantz AB, Ginocchio LA, Cornfeld D, et al. Interobserver Reproducibility of the PI-RADS Version 2 Lexicon: A Multicenter Study of Six Experienced Prostate Radiologists. Radiology 2016;280:793–804.
[256] Egevad L, Ahmad AS, Algaba F, et al. Standardization of Gleason grading among 337 European pathologists. Histopathology 2013;62:247–56.
[257] Berney DM, Algaba F, Camparo P, et al. The reasons behind variation in Gleason grading of prostatic biopsies: areas of agreement and misconception among 266 European pathologists. Histopathology 2014;64:405–11.
[258] Harmon SA, Tuncer S, Sanford T, et al. Artificial intelligence at the intersection of pathology and radiology in prostate cancer. Diagn Interv Radiol 2019;25:183–8.

Appendices – Original papers

I. Boesen L, Nørgaard N, Løgager V, Thomsen HS: **Clinical Outcome Following Low Suspicion Multiparametric Prostate Magnetic Resonance Imaging or Benign Magnetic Resonance Imaging Guided Biopsy to Detect Prostate Cancer**. *Journal of Urology 2017; 198: 310–315.*

II. Boesen L, Nørgaard N, Løgager V, Balslev I, Thomsen HS: **A Prospective Comparison of Selective Multiparametric Magnetic Resonance Imaging Fusion-Targeted and Systematic Transrectal Ultrasound-Guided Biopsies for Detecting Prostate Cancer in Men Undergoing Repeated Biopsies.** *Urologia Internationalis 2017; 99: 384–391.*

III. Boesen L, Nørgaard N, Løgager V, Balslev I, Thomsen HS: **Where Do Transrectal Ultrasound- and Magnetic Resonance Imaging-guided Biopsies Miss Significant Prostate Cancer?** *Urology 2017; 110: 154–160.*

IV. Boesen L, Nørgaard N, Løgager V, Balslev I, Thomsen HS: **Multiparametric MRI in men with clinical suspicion of prostate cancer undergoing repeat biopsy: a prospective comparison with clinical findings and histopathology.** *Acta Radiologica 2018; 59: 371–380.*

V. Boesen L, Nørgaard N, Løgager V, Balslev I, Bisbjerg R, Thestrup KC, Winther MC, Jakobsen H, Thomsen HS: **Assessment of the Diagnostic Accuracy of Biparametric Magnetic Resonance Imaging for Prostate Cancer in Biopsy-Naive Men.** *JAMA Network Open 2018; 1: e180219.*

VI. Boesen L, Nørgaard N, Løgager V, Balslev I, Bisbjerg R, Thestrup KC, Jakobsen H, Thomsen HS: **Prebiopsy Biparametric Magnetic Resonance Imaging Combined with Prostate-specific Antigen Density in Detecting and Ruling out Gleason 7–10 Prostate Cancer in Biopsy-naïve Men.** *European Urology Oncology 2018; 2: 311–319.*

VII. Boesen L, Thomsen FB, Nørgaard N, Løgager V, Balslev I, Bisbjerg R, Thomsen HS, Jakobsen H: **A predictive model based on biparametric magnetic resonance imaging and clinical parameters for improved risk assessment and selection of biopsy-naïve men for prostate biopsies.** *Prostate Cancer and Prostatic Diseases 2019; 22(4): 609–616.*

VIII. Boesen L: **Magnetic resonance imaging –transrectal ultrasound image fusion guidance of prostate biopsies: current status, challenges and future perspectives.** *Scandinavian Journal of Urology 2019; 53(2–3): 89–96*

Original papers

Boesen L, Nørgaard N, Løgager V, Thomsen HS: **Clinical Outcome Following Low Suspicion Multiparametric Prostate Magnetic Resonance Imaging or Benign Magnetic Resonance Imaging Guided Biopsy to Detect Prostate Cancer**.
Journal of Urology 2017; 198: 310–315.

Clinical Outcome Following Low Suspicion Multiparametric Prostate Magnetic Resonance Imaging or Benign Magnetic Resonance Imaging Guided Biopsy to Detect Prostate Cancer

Lars Boesen,* Nis Nørgaard, Vibeke Løgager and Henrik S. Thomsen

From the Department of Urology (LB, NN) and Department of Radiology (VL, HST), Herlev Gentofte University, Hospital Herlev Ringvej, Herlev, Denmark

Abbreviations and Acronyms

GS = Gleason score

LUTS = lower urinary tract symptoms

mp-MRI = multiparametric magnetic resonance imaging

MRI = magnetic resonance imaging

NPV = negative predictive value

PCa = prostate cancer

PI-RADS = Prostate Imaging Reporting and Data System

PSA = prostate specific antigen

sPCa = significant prostate cancer

TB_{MRI} = mp-MRI targeted biopsy

TRUS-bx = transrectal ultrasound guided biopsy

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* Correspondence: Telephone: +45 38681041; FAX: +45 38684657; e-mail: lars.boesen@dadlnet.dk.

Purpose: We assessed the risk of significant prostate cancer being detected after low suspicion magnetic resonance imaging or suspicious magnetic resonance imaging with benign magnetic resonance imaging guided biopsies in men with prior negative systematic biopsies.

Materials and Methods: Overall 289 prospectively enrolled men underwent magnetic resonance imaging followed by repeat systematic and targeted biopsies of any suspicious lesions at baseline. A total of 194 patients with low suspicion magnetic resonance imaging or benign target biopsies were suitable for this study. Those who were negative for prostate cancer at baseline were followed for at least 3 years. We calculated the negative predictive values of magnetic resonance imaging in ruling out any prostate cancer and significant prostate cancer, defined as any core with Gleason score greater than 6, or more than 2 positive cores/cancerous core 50% or greater.

Results: Prostate cancer was detected in 38 of 194 (20%) patients during the median study period of 47 months (IQR 43–52). The overall negative predictive value of magnetic resonance imaging in ruling out any and significant prostate cancer was 80% (156 of 194) and 95% (184 of 194), respectively. No patient with low suspicion magnetic resonance imaging had intermediate/high grade cancer (Gleason score greater than 6). The majority of patients with no cancer during followup (132 of 156, 85%) had a decreasing prostate specific antigen and could be monitored in primary care.

Conclusions: Low suspicion magnetic resonance imaging in men with prior negative systematic biopsies has a high negative predictive value in ruling out longer term, significant cancer. Therefore, immediate repeat biopsies are of limited clinical value and could be avoided even if prostate specific antigen is persistently increased.

Key Words: diagnostic imaging, magnetic resonance imaging, outcome assessment, biopsy, prostatic neoplasms

TRANSRECTAL ultrasound guided biopsies for detecting prostate cancer are prone to sampling errors due to difficulties in target identification.[1,2] Therefore, concerns about the possibility of missing significant prostate cancer lead to men with negative TRUS-bx results frequently undergoing repeat biopsies, resulting in increased medical costs, patient anxiety and morbidity. However, although the detection rate of sPCa

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decreases as the number of TRUS-bx procedures increases,[3] there is no actual consensus on when to stop.[4]

Multiparametric MRI has become increasingly important in PCa diagnosis[5–8] and mp-MRI is now recommended for all men with prior negative TRUS-bx if there is a continued suspicion of sPCa.[9,10] Suspicious lesions on mp-MRI can be targeted using mp-MRI guided biopsies of the most aggressive part of a tumor, enhancing the detection of sPCa.[5,11,12] Conversely, a normal mp-MRI may noninvasively exclude the possibility of aggressive disease, avoiding the need for biopsies.[7] Therefore, the application of mp-MRI in everyday clinical decision making has the potential to change the management of PCa.

However, not all cancers are visible using mp-MRI and less suspicious lesions may be misinterpreted. In addition, TB_{MRI} can be inaccurate. To our knowledge there are no current guidelines on performing repeat biopsies in men with a previous negative TRUS-bx and low risk mp-MRI or benign TB_{MRI} results for a suspicious lesion. Numerous studies have described the advantages of using TB_{MRI} to detect sPCa and conversely attempted to validate the importance of a negative mp-MRI by reporting high negative predictive values.[12–14] However, few studies have retrospectively evaluated clinical outcomes in the long term.[15,16] Therefore, we prospectively assessed the risk of being diagnosed with PCa after low suspicion mp-MRI or a benign TB_{MRI} of a suspicious lesion in cases with a previous negative TRUS-bx result but persistent clinical suspicion of sPCa during a followup of at least 3 years.

MATERIAL AND METHODS

Patient Selection

Subjects were selected from a prospective, single institutional trial (Clinical Trial Registration NCT01640262, www.clinicaltrials.gov) assessing the diagnostic accuracy of TB_{MRI} in men with a previous negative TRUS-bx result but for whom persistent clinical suspicions of sPCa warranted repeat biopsy. The study was approved by the institutional review board, and all patients provided written informed consent, and were enrolled between September 2011 and September 2013. All patients underwent mp-MRI followed by a combination of systematic re-TRUS-bx and TB_{MRI} for any suspicious lesions at baseline. A total of 194 men with low suspicion mp-MRI (126) or a benign TB_{MRI} of a suspicious lesion (68) at baseline were included in this analysis (see figure).

Outcome Measures

The primary end point was the detection of sPCa. Secondary end points included overall PCa detection, detection rates stratified by mp-MRI based suspicion and clinical outcome during followup.

Mp-MRI and Prostate Biopsies

Multiparametric MRI included tri-planar T2-weighted, dynamic contrast enhanced and diffusion weighted images along with reconstructions of the corresponding apparent diffusion coefficient map using a 3.0 T magnet (Philips Healthcare, Best, the Netherlands) with a pelvic phased array coil positioned over the pelvis, as recommended by the ESUR (European Society of Urogenital Radiology)[6] and as previously described.[17] For imaging parameters see the supplementary table (http://jurology.com/). Suspicious lesions were registered and scored according to PI-RADS version 1 classification from the ESUR.[6] All cases were classified on a scale of 1 to 5 according to the likelihood of sPCa (1—highly unlikely, 2—unlikely, 3—equivocal, 4—likely and 5—highly likely), and separated into the 3 mp-MRI based suspicion groups of high (PI-RADS 4 or greater), moderate (PI-RADS 3) and low (PI-RADS 2 or less). All patients then underwent a systematic 10-core repeat TRUS-bx procedure (extended sextant biopsy scheme) from both sides of the lateral (base, mid, apex) and medial (base, apex) prostate by the same urologist, who was blinded to the mp-MRI findings. As is standard procedure for a repeat biopsy, the medial cores were targeted anteriorly to sample a greater proportion of the anterior segment and transitional zone, where undetected tumors often reside. Additional TB_{MRI} was subsequently targeted toward any suspicious lesion (PI-RADS 3 or greater) using cognitive fusion (52) or fusion based software (142) (Hitachi HI-RVS system, Hitachi Ltd., Tokyo, Japan).

Histopathological Evaluation

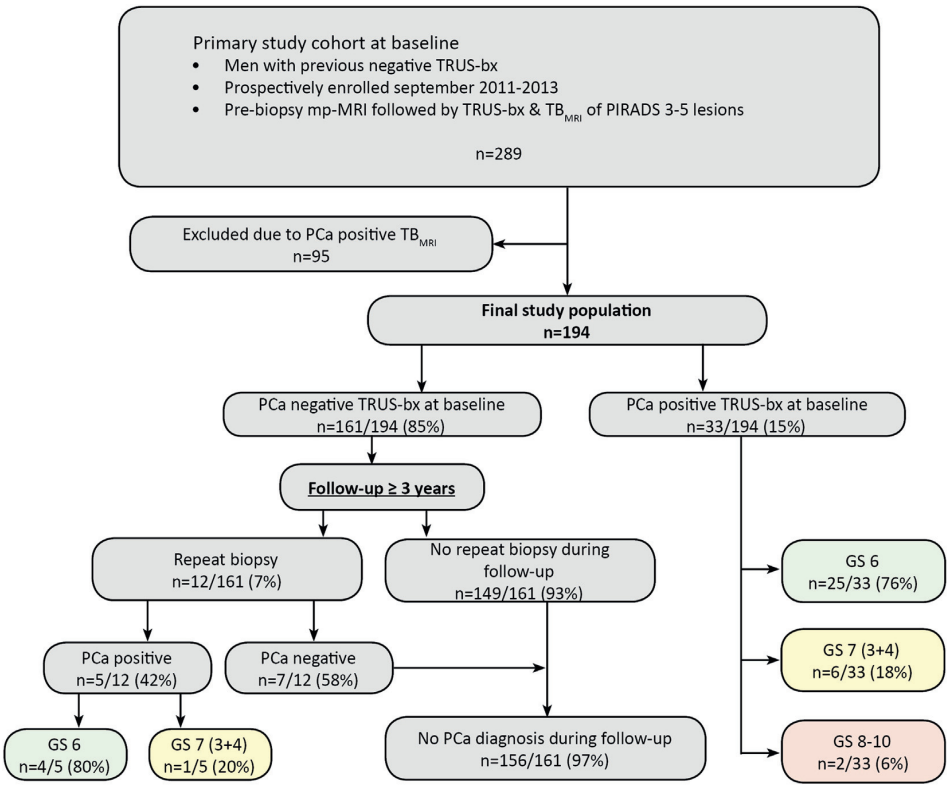
All biopsy samples were reviewed by the same genitourinary pathologist. For each PCa positive biopsy core its precise location, Gleason score based on the 2005 International Society of Urological Pathology Consensus and percentage of cancerous tissue were determined.[18] The biopsy GS was separated into the 3 categories of low (GS 6), intermediate (GS 7) and high (GS 8 or greater).

Clinical Significance

Cancer significance (ie sPCa) was defined using histopathological assessments of the biopsies to include tumor grade and volume, as any core with GS greater than 6, or more than 2 PCa cores/cancerous core 50% or greater.[19]

Clinical Evaluation

The initial false-negative rate and NPV of mp-MRI and TB_{MRI} in ruling out prostate cancer and significant prostate cancer were assessed immediately in patients with PCa detected by TRUS-bx at baseline. The clinical followup routine of the remaining (followup) patients with benign biopsies was applied at the discretion of the treating urologist, and included PSA measurements, digital rectal examination or treatment (eg surgery or medication) of accompanying LUTS. Only men with persistent clinical suspicion of missed sPCa (primarily unexplainable increasing PSA) underwent repeat biopsy during followup. Patients were followed for at least 3 years (followup data obtained December 1, 2016) and all



Flowchart of study population showing inclusion and exclusion criteria. Initially 289 men were included and then 95 with PCa positive TB_{MRI} at baseline were excluded to form subgroup of 194 men (study population) with low suspicion mp-MRI or benign TB_{MRI} of suspicious lesion. There were 33 men with PCa detected at baseline and another 5 with PCa detected during followup. Overall 9 patients had intermediate/high grade cancer (Gleason score greater than 6) but none of these had low suspicion lesions on mp-MRI.

relevant data were recorded to assess clinical outcome, including those with repeat biopsies and a subsequent PCa diagnosis.

Statistical Analysis

Patient characteristics were stratified by biopsy results and assessed using descriptive statistics. Continuous variables including age, PSA, PSA density (PSA/$TRUS_{volume}$), prior negative biopsies, number of mp-MRI lesions and TB_{MRI} were compared using the Wilcoxon rank sum test to determine differences between patients with positive and negative biopsies. The NPVs of mp-MRI and TB_{MRI} in ruling out PCa and sPCa were calculated. The analyses were performed using SPSS® version 22.0 and $p < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical characteristics are summarized in table 1. Overall 126 patients had low suspicion mp-MRI and another 68 had benign TB_{MRI} of moderate (56) or highly suspicious (12) lesions. In total, PCa was detected in 38 of 194 (20%) patients at baseline and during followup (see figure, table 1). There was no significant difference between the number of prior negative TRUS-bx sessions and the detection of PCa ($p = 0.280$, table 2). In most patients PCa was detected at baseline (33 of 38), with 15, 10 and 8 men having low, intermediate and highly suspicious lesions on mp-MRI, respectively. In addition, 25, 6 and 2 of

Table 1. *Demographic data*

	PCa Neg	PCa Pos	p Value	Overall
Median pt age (IQR)	62 (57–66)	66 (61–68)	0.064	63 (58–67)
Median prior biopsy (IQR)	2 (1–3)	2 (1–3)	0.28	2 (1–3)
Median ng/ml PSA (IQR)	11.0 (7.9–17)	12.0 (8.0–17.5)	0.841	11.0 (7.9–17)
Median cc TRUS vol (IQR)	73 (52–94)	73 (51–94)	0.999	73 (51–93)
Median ng/ml/cc PSA density (IQR)	0.16 (0.13–0.23)	0.17 (0.13–0.22)	0.557	0.16 (0.13–0.23)

Table 2. *Relationship between the number of prior negative TRUS-bx sessions and detection of PCa during followup*

	PCa Neg	PCa Pos	Totals
No. prior neg TRUS-bx sessions			
1	44	11	55
2	59	10	69
3	37	9	46
4	11	6	17
5	3	2	5
6	2	0	2
Totals	156	38	194

these patients had low, intermediate and high GS cancer, respectively (table 3). No patient with low suspicion mp-MRI had intermediate or high grade PCa. Including the volume of cancerous tissue in addition to GS in assessing cancer significance did not change the overall detection of sPCa at baseline because all 25 patients with low grade disease had fewer than 3 positive PCa cores/cancer tissue per core less than 50% on repeat TRUS-bx. The negative predictive value of mp-MRI followed by TB_{MRI} in ruling out PCa and sPCa at baseline was 83% (161 of 194) and 96% (186 of 194), respectively.

The remaining 161 patients had a benign condition (148, 75 with inflammation), high grade prostatic intraepithelial neoplasia (8) or an adenocarcinoma suspicious lesion (5) in the baseline biopsy. Of these 161 patients 12 (7%) underwent repeat biopsy and 5 of the 12 had PCa detected during a median followup of 47 months (IQR 43–52). Median time to repeat biopsy was 13 months (IQR 8–31) and only 1 detected tumor was not low grade (4 GS 6, 1 GS 7). However, 1 case of low grade PCa was categorized as sPCa because of 4 positive TRUS-bx cores.

Overall 10 of 194 patients (5%) had sPCa detected during the study period and, therefore, the NPV of mp-MRI followed by TB_{MRI} in ruling out prostate cancer and significant prostate cancer was 80% (156 of 194) and 95% (184 of 194), respectively. No PCa was detected in 156 patients during the followup period. These patients had a significantly decreased PSA (median 8.9 ng/ml, IQR 5.4–13) at the end of followup compared with baseline (median 11 ng/ml, IQR 7.9–17) ($p < 0.001$) and the majority (132 of 156, 85%) with stable clinical features were returned to primary care monitoring (table 4). A large proportion (44 of 156, 28%) were treated for LUTS, including 16 (10%) who underwent transurethral prostate resection during followup.

Table 3. *Relationship between mp-MRI suspicion groups and GS in patients diagnosed with PCa at baseline*

	PCa at Baseline			
	GS 6	GS 7	GS 8–10	Totals
mp-MRI suspicion:				
Low	15	0	0	15
Moderate	6	3	1	10
High	4	3	1	8
Totals	25	6	2	33

DISCUSSION

Clinicians are increasingly faced with the problem of patients with prior negative TRUS-bx but persistently increased PSA and low suspicion mp-MRI or benign TB_{MRI} of suspicious lesions. Here we followed patients with these characteristics to assess the clinical value and NPV of low suspicion mp-MRI or benign TB_{MRI} during a median of 47 months. Overall we found a high NPV (95%) in ruling out sPCa and no patient with low suspicion mp-MRI had intermediate or high grade cancer. Therefore, in men with a prior negative TRUS-bx and low suspicion lesions on mp-MRI, immediate repeat biopsies may be unnecessary because at worst, these patients are likely to have low grade disease qualifying for surveillance after 3 years.

Overall 38 of 194 (20%) patients were diagnosed with PCa. However, 87% of cases were detected at baseline by repeat TRUS-bx with 76% having low grade disease. All 8 men with sPCa at baseline had intermediate or highly suspicious mp-MRI lesions targeted by TB_{MRI} which had proven histologically benign. This is most likely due to targeting errors rather than mp-MRI misinterpretation, because with TB_{MRI} image fusion there is a risk of misregistration when the image modalities are combined using anatomical landmarks. Chelluri et al evaluated this problem of benign TB_{MRI} associated with suspicious mp-MRI lesions, and reported that if PCa was detected in a targeted repeat biopsy, this was usually in a low risk tumor.[20]

While low suspicion mp-MRI cannot unequivocally rule out PCa, the key clinical concern is to detect significant disease. Our findings confirm that

Table 4. *Treatment and followup records*

	PCa Neg	PCa Pos	Totals
PSA surveillance primary care	132	0	132
PSA surveillance in-house	24	0	24
Active surveillance	0	20	20
Radical prostatectomy	0	12	12
External beam radiation	0	2	2
Hormonal treatment	0	1	1
Watchful waiting	0	3	3
Totals	156	38	194

Five patients with benign biopsy at baseline had PCa detected at repeat biopsy during followup. Of these patients 4 were put on active surveillance and 1 underwent radical prostatectomy.

PCa which remains undetected on mp-MRI and TB_{MRI} is primarily low grade. In 125 men with only low suspicion lesions on mp-MRI Yerram et al found that 92% had no cancer or low grade (GS 6) disease.[21] Using radical prostatectomy specimens as a reference standard De Visschere et al retrospectively demonstrated that low suspicion mp-MRI had a NPV of 90% in ruling out GS 7 or greater prostate cancer in 391 patients in a 2-year period.[22] They concluded that the majority of undetected tumors had a low GS, and were small or confined within the organ.

Including the volume of cancerous tissue in the sPCa assessment did not alter the NPV because only 1 additional patient with low grade cancer had more than 2 positive TRUS-bx cores at repeat biopsy. Low grade PCa was presumably below the detection limit of mp-MRI and only detected randomly using untargeted systematic TRUS-bx. Furthermore, a large proportion of patients with no PCa detected had apparent benign causes (eg inflammation, LUTS) of increased PSA at inclusion and presented a significantly decreasing PSA during followup.

Debate is ongoing whether TB_{MRI} should be accompanied by systematic biopsy or used in isolation.[23,24] However, the quality and the interpretation of the pre-biopsy mp-MRI are uncertain but essential factors which, combined with the risk of TB_{MRI} sampling errors, could result in significant tumors remaining undetected in a "targeted only" approach. Therefore, the European Association of Urology guidelines recommend that systematic TRUS-bx should supplement TB_{MRI}.[9] In our study TB_{MRI} failed to detect GS 7 or greater cancers in the baseline biopsies of 8 patients, presumably due to sampling errors. Delongchamps et al analyzed 125 radical prostatectomy specimens in which TB_{MRI} failed to detect 4% of the significant cancers.[25] Cash et al concluded that the main reason for false-negative TB_{MRI} results was sampling error, but this can be rectified with a positive TRUS-bx core from the targeted lesion.[26] False-negative TB_{MRI} results can also arise from misleadingly high mp-MRI suspicion scores.

This study not only reinforces previous work and suggests low suspicion mp-MRI has a high NPV in ruling out significant prostate cancer at baseline, it also validates its efficacy in the long term. It supports deferring additional biopsies in TRUS-bx negative cases with low suspicion mp-MRI, potentially reducing the number of unnecessary repeat biopsies.

One limitation of our study is that our cohort is not homogeneous, as we included patients with varying numbers of previous negative biopsies and excluded those with PCa detected by TB_{MRI} at baseline. Therefore, the selected patients were likely to have a low disease burden. However, similar to the study by Sonn et al we found no relationship between the number of previous biopsies and the detection of sPCa.[12] Another study limitation is that we do not know whether PCa detected by repeat TRUS-bx during followup was undetected at baseline or emerged by tissue transformation. In addition, not all patients underwent repeat biopsy during followup. This could generate selection bias because the decision to refer patients for repeat biopsy was made at the discretion of the treating urologist. Moreover, there could be undetected PCa foci resulting from our use of repeat TRUS-bx as the reference standard. Therefore, the true rate of false-negative readings cannot be accurately assessed even though followup exceeded 3 years.

However, it is reasonable to assume that patients who did not undergo repeat biopsy during followup had a lower risk of sPCa because their overall condition aroused less clinical suspicion. Previous studies have demonstrated a good correlation between mp-MRI results and radical prostatectomy specimens,[24,27] although some report that mp-MRI failed to detect significant tumors in 5% to 28% of cases.[28–30] Therefore, an uncertain proportion of sPCa foci are difficult to detect using mp-MRI, often due to low tumor volume. Nonetheless, our results suggest that cancers that are not detected by mp-MRI are unlikely to be significant prostate cancers that are subsequently detected using TRUS-bx. Therefore, repeat TRUS-bx is of limited clinical value in men with a prior negative TRUS-bx and subsequent low suspicion mp-MRI.

Finally, our TB_{MRI} does not have a needle tracking system capable of identifying targeting errors, although now there are software fusion systems that can retrospectively assess biopsy performance. Our patient sample size is limited and PCa often develops slowly. Therefore, these results should be verified in a larger prospective study with a longer followup to assess clinical end points including disease progression, cancer specific mortality and associated costs.

Despite these limitations our data provide additional evidence of the reliability of low suspicion mp-MRI as a noninvasive diagnostic tool capable of ruling out more aggressive PCa and suggesting that immediate biopsies are unnecessary in patients with prior negative TRUS-bx.

CONCLUSION

Low suspicion mp-MRI in men with a prior negative TRUS-bx has a high negative predictive value in ruling out sPCa in the longer term. Therefore,

repeat biopsies are likely to be of limited clinical value and could be avoided, even in men with a persistently increased PSA. Conversely, repeat TRUS-bx should be considered in addition to fusion targeted biopsies in men with suspicious lesions on mp-MRI because of the risk of targeting errors.

REFERENCES

1. Ukimura O, Coleman JA, de la Taille A et al: Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol 2013; **63:** 214.
2. Shariat SF and Roehrborn CG: Using biopsy to detect prostate cancer. Rev Urol 2008; **10:** 262.
3. Roehl KA, Antenor JA and Catalona WJ: Serial biopsy results in prostate cancer screening study. J Urol 2002; **167:** 2435.
4. Djavan B, Ravery V, Zlotta A et al: Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop? J Urol 2001; **166:** 1679.
5. Schoots IG, Roobol MJ, Nieboer D et al: Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol 2015; **68:** 438.
6. Barentsz JO, Richenberg J, Clements R et al: ESUR prostate MR guidelines 2012. Eur Radiol 2012; **22:** 746.
7. Fütterer JJ, Briganti A, De Visschere P et al: Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol 2015; **68:** 1045.
8. Gupta RT, Polascik TJ, Taneja SS et al: Recent developments in multiparametric prostate MR imaging. Curr Radiol Rep 2014; **2:** 74.
9. Mottet N, Bellmunt J, Bolla M et al: EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2017; **71:** 618.
10. Rosenkrantz AB, Verma S, Choyke P et al: Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR. J Urol 2016; **196:** 1613.
11. Moore CM, Robertson NL, Arsanious N et al: Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol 2013; **63:** 125.
12. Sonn GA, Chang E, Natarajan S et al: Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol 2014; **65:** 809.
13. Pokorny MR, de Rooij M, Duncan E et al: Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. Eur Urol 2014; **66:** 22.
14. Siddiqui MM, Rais-Bahrami S, Turkbey B et al: Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015; **313:** 390.
15. Hong CW, Walton-Diaz A, Rais-Bahrami S et al: Imaging and pathology findings after an initial negative MRI-US fusion-guided and 12-core extended sextant prostate biopsy session. Diagn Interv Radiol 2014; **20:** 234.
16. Itatani R, Namimoto T, Atsuji S et al: Negative predictive value of multiparametric MRI for prostate cancer detection: outcome of 5-year follow-up in men with negative findings on initial MRI studies. Eur J Radiol 2014; **83:** 1740.
17. Boesen L, Noergaard N, Chabanova E et al: Early experience with multiparametric magnetic resonance imaging-targeted biopsies under visual transrectal ultrasound guidance in patients suspicious for prostate cancer undergoing repeated biopsy. Scand J Urol 2015; **49:** 25.
18. Epstein JI, Allsbrook WC, Amin MB et al: The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2005; **29:** 1228.
19. Epstein JI, Walsh PC, Carmichael M et al: Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994; **271:** 368.
20. Chelluri R, Kilchevsky A, George AK et al: Prostate cancer diagnosis on repeat magnetic resonance imaging-transrectal ultrasound fusion biopsy of benign lesions: recommendations for repeat sampling. J Urol 2016; **196:** 62.
21. Yerram NK, Volkin D, Turkbey B et al: Low suspicion lesions on multiparametric magnetic resonance imaging predict for the absence of high-risk prostate cancer. BJU Int 2012; **110:** E783.
22. De Visschere PJ, Naesens L, Libbrecht L et al: What kind of prostate cancers do we miss on multiparametric magnetic resonance imaging? Eur Radiol 2016; **26:** 1098.
23. Schoots IG: Omission of systematic transrectal ultrasound guided biopsy from the MRI targeted approach in men with previous negative prostate biopsy might still be premature. Ann Transl Med 2016; **4:** 205.
24. Salami SS, Ben-Levi E, Yaskiv O et al: In patients with a previous negative prostate biopsy and a suspicious lesion on magnetic resonance imaging, is a 12-core biopsy still necessary in addition to a targeted biopsy? BJU Int 2015; **115:** 562.
25. Delongchamps NB, Lefèvre A, Bouazza N et al: Detection of significant prostate cancer with magnetic resonance targeted biopsies—should transrectal ultrasound-magnetic resonance imaging fusion guided biopsies alone be a standard of care? J Urol 2015; **193:** 1198.
26. Cash H, Günzel K, Maxeiner A et al: Prostate cancer detection on transrectal ultrasonography-guided random biopsy despite negative real-time magnetic resonance imaging/ultrasonography fusion-guided targeted biopsy: reasons for targeted biopsy failure. BJU Int 2015; **118:** 35.
27. Turkbey B, Merino MJ, Gallardo EC et al: Comparison of endorectal coil and nonendorectal coil T2W and diffusion-weighted MRI at 3 Tesla for localizing prostate cancer: correlation with whole-mount histopathology. J Magn Reson Imaging 2014; **39:** 1443.
28. Tan N, Margolis DJ, Lu DY et al: Characteristics of detected and missed prostate cancer foci on 3-T multiparametric MRI using an endorectal coil correlated with whole-mount thin-section histopathology. AJR Am J Roentgenol 2015; **205:** W87.
29. Thompson JE, van Leeuwen PJ, Moses D et al: The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol 2016; **195:** 1428.
30. Russo F, Regge D, Armando E et al: Detection of prostate cancer index lesions with multiparametric magnetic resonance imaging (mp-MRI) using whole-mount histological sections as the reference standard. BJU Int 2016; **118:** 84.

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A Prospective Comparison of Selective Multiparametric Magnetic Resonance Imaging Fusion-Targeted and Systematic Transrectal Ultrasound-Guided Biopsies for Detecting Prostate Cancer in Men Undergoing Repeated Biopsies

Lars Boesen[a] Nis Nørgaard[a] Vibeke Løgager[b] Ingegerd Balslev[c] Henrik S. Thomsen[b]

[a]Department of Urology, [b]Department of Radiology and [c]Department of Pathology, Herlev Gentofte University Hospital, Herlev, Denmark

Keywords
Prostate cancer · Biopsy · Magnetic resonance imaging · Ultrasonography · Outcome

Abstract
Introduction: The aim of the study was to compare the prostate cancer (PCa) detection rate of systematic transrectal ultrasound-guided biopsies (TRUS-bx) and multiparametric-MRI targeted biopsies (mp-MRI-bx) in a repeat biopsy setting and evaluate the clinical significance following an "MRI-targeted-only" approach. ***Materials and Methods:*** Patients with prior negative biopsies underwent prostatic multiparametric-MRI that was scored using the Prostate Imaging Reporting and Data System (PI-RADS) classification. All underwent both repeated TRUS-bx and mp-MRI-bx using image fusion of any PI-RADS ≥3 lesion. Biopsy results from TRUS-bx, mp-MRI-bx, and the combination were compared. ***Results:*** PCa was detected in 89 out of 206 (43%) patients. Of these, 64 (31%) and 74 (36%) patients were detected using mp-MRI-bx and TRUS-bx, respectively. Overall, mp-MRI-bx detected fewer patients with low-grade (Gleason score [GS] 3 + 3) cancers (14/64 vs. 41/74) and more patients with intermediate/high-grade cancers (GS ≥3 + 4) (50/64 vs. 33/74) using fewer biopsy cores compared with TRUS-bx ($p < 0.001$). Using an "MRI-targeted-only" approach in men with PI-RADS ≥3 lesions reduced the number of men requiring repeated biopsies by 50%, decreased low-grade cancer diagnoses by 66%, and increased intermediate/high-grade cancer diagnoses by 52%. ***Conclusions:*** MRI-targeted biopsies have a high detection rate for significant PCa in patients with prior negative transrectal ultrasound-guided biopsies and preferentially detect intermediate/high-grade compared with low-grade tumors.

Introduction

Transrectal ultrasound-guided biopsies (TRUS-bx) have limited diagnostic accuracy in detecting prostate cancer (PCa) and often fail to diagnose significant cancers [1]. To overcome this problem, patients with negative TRUS-bx regularly undergo repeated biopsy procedures with some urologists recommending increasing the number of cores [2], while others suggest saturation biopsy tech-

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Lars Boesen, MD, PhD
Department of Urology
Herlev Gentofte University Hospital
Herlev Ringvej 75, DK–2730 Herlev (Denmark)
E-Mail lars.boesen@dadlnet.dk

niques [3]. These approaches often lead to an increased PCa detection rate, but also increase the diagnosis of insignificant low-grade tumors potentially leading to unnecessary treatment plans [4–6]. PCa is evaluated using the Gleason score (GS), which is strongly related to tumor aggressiveness and prognosis. Pre-therapeutic risk assessments based on the GS from TRUS-bx can be inaccurate due to sampling errors. This is confirmed by an upgraded GS in one third of patients following radical prostatectomy (RP) [7]. Inaccurate GS at biopsy may lead to incorrect risk stratification and possibly to over- or under-treatment.

The limitations of TRUS-bx have highlighted the need for improved diagnostic tools, such as biomarkers, or imaging techniques that might enhance the identification of significant PCa without increasing the detection of insignificant tumors. Better techniques could possibly decrease the number of unnecessary biopsy sessions and cores.

Multiparametric MRI (mp-MRI) and targeted biopsies can improve the detection of significant PCa [8–12] and lead to more accurate GS grading [13–15]. Fusion software combining mp-MRI data and real-time TRUS imaging has been developed to increase the accuracy of targeted biopsies and can now be used in outpatient clinics. There is an ongoing debate question whether targeted biopsies should be used in isolation or in combination with systematic biopsies to increase the diagnostic yield of significant high-grade cancers while excluding lower-grade tumors. In this prospective study, we address this dilemma by comparing the detection rate of PCa by mp-MRI/TRUS fusion-targeted biopsies (mp-MRI-bx) with the detection rate of systematic TRUS-bx in the same patient cohort, which had prior negative TRUS-bx results. In addition, we evaluated the significance of the detected cancers and compared the results of an "mp-MRI-targeted-only" and a systematic TRUS-bx approach.

Materials and Methods

This prospective trial was approved by the Local Committee for Health Research Ethics (No. H-1-2011–066) and the data protection agency. It was registered at Clinicaltrials.gov (No. NCT01640262). All patients were prospectively enrolled between September 2012 and September 2013 after they gave written informed consent. Inclusion criteria required that all had at least one prior negative TRUS-bx session (10–12 cores) and a persistent clinical suspicion of PCa (elevated PSA, an abnormal digital rectal examination, or a previous abnormal TRUS image) that warranted a repeat biopsy (rebiopsy). The exclusion criteria were a prior PCa diagnosis, prior prostate mp-MRI, or presence of general contraindications for MRI.

Multiparametric MRI

Mp-MRI was performed prior to rebiopsy using a 3.0 T MRI magnet (Ingenia, Philips Healthcare, Best, The Netherlands) with a pelvic-phased-array coil (Philips Healthcare) positioned over the pelvis. Tri-planar T2-weighted-, diffusion-weighted-, and dynamic contrast-enhanced images according to the European Society of Urogenital Radiology [9] recommendation and as previously described [15].

All mp-MRI images were reviewed by the same dedicated mp-MRI physician with 2 years of experience in prostate interpretation and all suspicious lesions were registered on an 18-region modified prostate diagram provided by the European Consensus Meeting [16]. All patients were overall classified by the Prostate Imaging Reporting and Data System (PI-RADS) version 1 classification [9] on a 5-point PI-RADS scale (1–highly unlikely, 2–unlikely, 3–equivocal, 4–likely, and 5–highly likely) based on their likelihood of having clinically significant PCa. Patients with no suspicious lesions were classified as PI-RADS score 1. The newly published PI-RADS version 2 [17] was not available during the timeframe of this study.

Biopsy: TRUS-bx and mp-MRI-bx

Initially, all patients underwent systematic repeated TRUS-bx blinded to mp-MRI findings. This included a 10-core extended sextant re-biopsy-scheme from the lateral and medial part of the prostate (base, mid, apex) on both the left and right sides. Abnormalities on TRUS-bx were sampled using the standard core for the relevant segment. TRUS-bx was immediately followed by targeted mp-MRI-bx of any identified lesion using the HI-RVS-system (Hitachi Ltd., Tokyo, Japan). This system uses a small electromagnetic field generator placed in close proximity to the patient and tracks the spatial location of the TRUS probe using a small attached sensor. Patient mp-MRI data were loaded into the system after TRUS-bx and fused and synchronized with the corresponding TRUS images using zonal anatomy and tissue landmarks. Mp-MRI-bx was targeted toward mp-MRI-identified lesions (1–2 cores/lesion) using T2-weighted-imaging superimposed on the real-time TRUS images. All prostate biopsies (TRUS-bx and mp-MRI-bx) were taken in the axial plane using an end-fire TRUS probe and were performed by the same operator who had extensive experience in TRUS-bx (>20 years) but less experience in software-based image fusion (1 year).

Histopathological Evaluation

All biopsy samples were described by the same genitourinary pathologist with >11 years of dedicated experience. The location on the prostate diagram, the GS based on the International Society of Urological Pathology 2005 consensus [18], and the quantity of cancerous tissue per core (%) were all determined for each PCa-positive biopsy core. The patients GS scores were divided into 3 categories: low (GS ≤6), intermediate (GS = 7), and high (GS ≥8) grade PCa. In addition, patients were allocated to International Society of Urological Pathology 2014 Gleason grade groups [19] based on the GS scoring criteria [18]. Cancer significance was defined as (1) insignificant low-grade PCa (GS 6) and (2) significant intermediate/high-grade PCa (GS ≥7).

Statistical Analysis

Patient characteristics were stratified by biopsy results and assessed using descriptive statistics. Continuous variables including age, PSA, PSA-d, prior biopsy procedures, number of mp-MRI lesions, and number of mp-MRI-bx were compared using the Wil-

Table 1. Patient characteristics

	Total (n = 206)	PCa negative (n = 117)	PCa positive (n = 89)	p value
Age, years, median (IQR)	65 (58–68)	63 (47–67)	66 (61–99)	0.304
PSA, ng/mL, median (IQR)	12.8 (8.9–19.6)	11.0 (7.9–17.1)	14.0 (9.7–21.7)	0.032
PSA density, ng/mL/mL, median (IQR)	0.20 (0.13–0.29)	0.16 (0.12–0.23)	0.26 (0.17–0.45)	0.001
Prior biopsy, median (IQR)	2 (2–3)	2 (2–3)	2 (1–3)	0.124
$Time_{mp\text{-}MRI}$ to biopsy, days	7 (1–14)	7 (1–15)	2 (0–14)	0.527
cT_{DRE} category, n (%)				
Nonpalpable lesions (cT1)	188 (91)	110 (94)	78 (88)	0.137
Palpable lesions (cT2–T3)	18 (9)	7 (6)	11 (12)	
cT_{TRUS} category, n (%)				
Nonvisual lesions (cT1)	141	89	52	
Visual lesions (cT2–T3)	65	28	37	0.010
Mp-MRI included lesions, n	302	209	93	
Lesion/patient, mean (range)	1.5 (1–4)			
Zone of origin, n (%)				
Peripheral zone	155 (51)	116	38	
Transitional zone/anterior location	147 (49)	93	55	0.025

PCa, prostate cancer; TRUS, transrectal ultrasound; mp-MRI, multiparametric MRI; IQR, interquartile range.

coxon Rank sum test. Fisher's exact test was used to compare the tumor stage determined by digital rectal examination (cT_{DRE}) and TRUS (cT_{TRUS}) pooled in non-palpable/palpable and nonvisual/visual tumor groups including the zone of lesion origin. Pre-biopsy mp-MRI PI-RADS scores were compared with biopsy results using a chi-square analysis to determine the correlation between suspicion on mp-MRI and positive biopsies. PCa-detection rates using mp-MRI-bx and systematic TRUS-bx were compared using the McNemar test. The highest GS from systematic TRUS-bx and mp-MRI-bx from each patient were compared and examined using a paired t test and further evaluated for accuracy using weighted kappa-statistics. A p value below 0.05 was considered significant. Statistical analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic data are displayed in Table 1. Of 213 prospectively enrolled patients, 7 were excluded because of mp-MRI technical problems or because they were claustrophobic. PCa was detected in 89 out of 206 (43%) patients and the remaining (57%) had a benign condition (n = 107), HGPIN (n = 2), or cellular changes indicating adenocarcinoma (n = 8).

TRUS-bx

Abnormal TRUS image results were observed in 65 (32%) patients and TRUS-bx-detected PCa in 74 (36%) of the 206 patients. Of these, 41 (55), 28 (38), and 5 (7%) had had low- (GS ≤6), intermediate- (GS = 7), and high-grade (GS ≥8) PCa, respectively. Most patients (86%) had predominantly GS grade 3 (3 + 3 or 3 + 4) corresponding to Gleason grade groups 1 or 2.

Mp-MRI-bx

Mp-MRI-bx was performed in 189 out of 206 (92%) patients with PI-RADS scores 2–5 and detected PCa in 64 out of 206 (31%). Of these, 14 (22), 36 (56), and 14 (22%) had low-, intermediate-, and high-grade PCa, respectively. The proportion of intermediate/high-grade PCa was significantly higher using mp-MRI-bx (Table 2, $p < 0.001$) and there was a lower PCa detection rate in patients with PI-RADS 1–2 compared with PI-RADS 4–5 (20 vs. 75%, $p < 0.001$; Fig. 1). Mp-MRI were without lesions in 17 out of 206 patients who did not have mp-MRI-bx. TRUS-bx-detected PCa in 4 of these patients and all had 1 out of 10 positive cores with GS 6 (3 + 3) in 5–10% of the biopsy length.

Mp-MRI-bx vs. TRUS-bx

Of the 89 patients with PCa, 25 patients were detected only using TRUS-bx, 15 patients were detected only using mp-MRI-bx, and 49 patients were detected using both methods. Although TRUS-bx detected more patients with PCa, the difference was not statistically significant (McNemar, p = 0.155). Mp-MRI-bx cores had a greater mean cancerous core length (43.3 vs. 22.4%, $p < 0.001$)

Table 2. Comparison of the GS and grade for patients between mp-MRI-bx and systematic TRUS-bx

	TRUS-bx						
	no PCa	GS 6 grade 1	GS 7 (3 + 4) grade 2	GS 7 (4 + 3) grade 3	GS 8 grade 4	GS 9–10 grade 5	total
Mp-MRI-bx							
No PCa	0	23	2	0	0	0	25
GS 6 grade 1	4	9	1	0	0	0	14
GS 7 (3 + 4) grade 2	5	6	14	1	0	0	26
GS 7 (4 + 3) grade 3	2	2	4	2	0	0	10
GS 8 grade 4	3	1	2	2	2	0	10
GS 9–10 grade 5	1	0	0	0	1	2	4
Total	15	41	23	5	3	2	89

GS, Gleason score; TRUS-bx, transrectal ultrasound-guided biopsies; mp-MRI-bx, multiparametric MRI-guided biopsies.

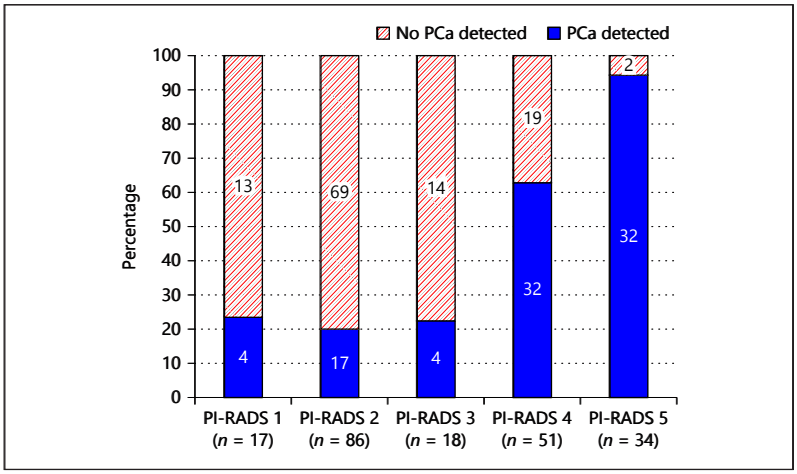

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Fig. 1. Patients diagnosed with prostate cancer (PCa) stratified by multiparametric MRI suspicion score (PI-RADS).

and a greater PCa detection yield per core (28% of 421 targeted cores vs. 7.4% of 2,060 systematic cores, $p < 0.001$) compared to TRUS-bx cores.

Overall, mp-MRI-bx detected 14 out of 89 (16%) and TRUS-bx 41 out of 89 (46%) patients with low-grade PCa ($p < 0.001$; Fig. 2). Conversely, mp-MRI detected intermediate/high-grade PCa in 20 out of 89 (22%) patients who were either missed ($n = 11$) or misclassified as low grade ($n = 9$) on TRUS-bx (Table 2). Equally, TRUS-bx detected significant cancer in 3 patients who were missed ($n = 2$) or misclassified as low grade ($n = 1$) on mp-MRI-bx. Of the 15 patients (17%) diagnosed with PCa only by mp-MRI-bx, 11 out of 15 (73%) had significant intermediate/high-grade cancer. In PCa patients diagnosed both on TRUS-bx and mp-MRI-bx, 18 out of 49 (37%) had an overall GS upgrade and 9 of these patients (50%) were reclassified from low-grade (GS 6) to significant intermediate/high-grade cancer based on the additional mp-MRI-bx. The number of men requiring a repeat biopsy was reduced by 50%, low-grade cancer diagnoses were decreased by 66%, and intermediate/high-grade cancer diagnoses were increased by 52% if only patients with equivocal/highly suspicious lesions (PI-RADS ≥3) followed an mp-MRI-'targeted only' approach without additional repeated TRUS-bx (Table 3).

Discussion

In this prospective study, we compared outcomes of mp-MRI fusion-targeted and systematic transrectal ultrasound-guided biopsies to detect PCa in men undergo-

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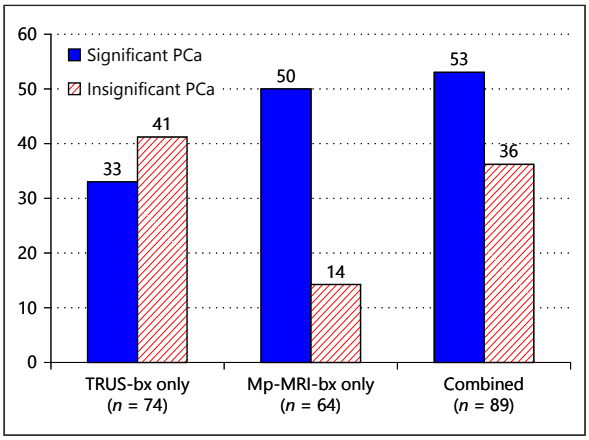

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Fig. 2. Patients diagnosed with significant (Gleason score ≥3 + 4) and insignificant (Gleason score 3 + 3) prostate cancer (PCa) stratified by biopsy technique (transrectal ultrasound-guided biopsies [TRUS-bx], multiparametric MRI-guided biopsies [mp-MRI-bx], and the combined approach).

Table 3. Per patient analysis of biopsy results comparing TRUS-bx and mp-MRI-bx for patients with PI-RADS score ≥3

	TRUS-bx	Mp-MRI-bx	Difference, %
Biopsy patients, *n*	206	103	–50
Low-grade PCa	41	14	–66
Intermediate/high-grade PCa	33	50	52
Biopsy cores, *n*	2,060	209	–90

PCa, prostate cancer; TRUS-bx, transrectal ultrasound-guided biopsies; mp-MRI-bx, multiparametric MRI-guided biopsies; Low-grade PCa, Gleason score 6; intermediate/high-grade PCa, Gleason score ≥7.

ing repeated biopsies and found an overall PCa detection rate of 43% (89/206) with 60% (53/89) harboring significant (GS ≥7) cancers. We found that TRUS-bx detected more patients with PCa than mp-MRI-bx (36 vs. 31%), although the difference was not statistically significant (p = 0.155). However, the proportion of intermediate/high-grade PCa detected was significantly higher using mp-MRI-bx, fewer biopsy cores were required, and these had a greater mean cancerous core-length. In addition, more than half of the patients with PCa detected using TRUS-bx had low-grade disease. The poor PCa target identification of TRUS means clinicians are repeatedly faced with a dilemma in patients with negative TRUS-bx because a nonspecific rise in PSA is regarded as an indication for repeated prostate biopsies. Men considered at risk remain under PSA-surveillance for lengthy periods that involve repeated check-ups and possibly multiple biopsy sessions that can cause severe infections, bleeding, and anxiety. There is the additional problem of detecting insignificant low-grade PCa leading to possible overtreatment. Our findings are consistent with previous studies confirming that mp-MRI and mp-MRI/TRUS-fusion biopsies can be used in this challenging patient group to identify undetected high-grade cancers in patients with prior negative TRUS-bx sessions [12, 14, 20]. Sonn et al. [12] demonstrated that office-based fusion biopsies can be performed in an outpatient clinic, thereby improving the detection of significant PCa in 105 patients, and Vourganti et al. [20] reported that only PSA density and mp-MRI-based suspicion were good indicators of significant cancer at repeat biopsy, whereas the number of previous biopsy sessions was not. We found a statistically significant correlation between the suspicion grade on mp-MRI and detection of PCa on confirmatory biopsy (p < 0.001). Mp-MRI-bx also identified 20 additional patients with intermediate/high-grade PCa that were either not detected or misclassified as low grade using TRUS-bx. Thus, pre-biopsy mp-MRI can increase the detection rate of significant PCa previously missed by TRUS-bx and stratify patients and lesions according to suspicion on mp-MRI.

In a targeted biopsy setting, the operator has to choose to either add the mp-MRI-bx to the systematic TRUS-bx scheme or rely on an mp-MRI-bx "targeted only" approach. Using mp-MRI-bx as an adjunct to TRUS-bx led to a GS upgrade in 37% of cases compared with TRUS-bx alone. Among these, 88% of patients (29/33) harbored intermediate/high-grade PCa and 38% (n = 11) would not have been diagnosed with PCa if this had been based solely on TRUS-bx. Conversely, TRUS-bx identified PCa that were not detected using mp-MRI-bx, resulting in a 30% overall GS upgrade. However, the vast majority of these (23/27 [85%]) were upgraded from no cancer on mp-MRI-bx to GS 6 PCa on TRUS-bx. Therefore, mp-MRI-bx increases the diagnoses of intermediate/high-grade cancers without increasing the diagnoses of low-grade disease.

Recent concerns have grown regarding the overdetection and subsequent overtreatment of men with insignificant low-grade PCa. The high diagnostic rate of low-grade disease using TRUS-bx demonstrated in this study may add to these concerns and could favor a "targeted-only" strategy. Combining mp-MRI-bx with systematic TRUS-bx in our setting meant that 30 patients had to be

biopsied to identify one additional man with GS 7(3 + 4) at the expense of 8 additional men with GS 6 (3 + 3). Therefore, the combined strategy seems to be of limited clinical value in a repeated biopsy setting because the majority of patients with GS ≥7 PCa were detected using mp-MRI-bx, while TRUS-bx contributed a substantial number of patients with only low-grade disease. Overall, our results indicate that the diagnostic yield of intermediate/high-grade vs. low-grade cancers can be improved using fewer biopsy cores if an mp-MRI "targeted-only" approach is applied. By only targeting patients with PI-RADS ≥3 lesions, the number of men requiring biopsies and the diagnosis of low-grade PCa was reduced by 50 and 66%, respectively. In addition, the detection of intermediate/high-grade cancers increased by 52% compared with TRUS-bx. These results are consistent with a recent large study (1,003 patients) by Siddiqui et al. [21], which found that 200 patients had to be biopsied by TRUS-bx in addition to mp-MRI-bx to diagnose one additional patient with a high-risk tumor (GS 7 [4 + 3]), at the expense of 17 additional patients with low-risk tumors. However, that study included a mixed cohort of patients (biopsy-naive and men with prior negative TRUS-bx), excluded men with no abnormalities detected using mp-MRI, and defined low-volume GS 7(3 + 4) tumors as low-risk cancers. Moreover, the prospective study by Filson et al. [22] reported results that were contradicting to ours and found that the combined approach (mp-MRI-bx plus TRUS-bx) yielded the highest detection rate of significant cancer and result only in 1 additional low-risk PCa case detected per intermediate/high-risk PCa case. However, this study also included a mixed cohort of patients (biopsy-naive, prior negative, and prior positive biopsies) and the number of missed significant cancers following an mp-MRI "targeted-only" approach was significantly lower when considering only men with prior negative biopsies, as compared to our study. Nonetheless, the European Association of Urology guidelines [23] recommend a combined approach for all men with prior negative biopsies.

There are several limitations to this study. TRUS-bx and mp-MRI results were interpreted by one highly experienced TRUS-operator and one dedicated mp-MRI physician. Less experienced operators might not achieve the same diagnostic yield. Our TRUS-bx technique for patients with prior negative TRUS-bx is modified to target the medial cores more anteriorly to sample a greater proportion of the anterior prostate, where tumors undetected by initial biopsies often reside. However, our repeated TRUS-bx scheme comprises the same prostatic sextant zones used in the initial biopsy setting and does not include extended cores (>10–12 samples) or saturation-biopsies. Routinely increasing the number of cores might have improved the diagnostic rates at repeat TRUS-bx. However, it would not change the utility of mp-MRI-bx and insignificant PCa would still be detected.

The patients in this study were also selected as good candidates for targeted biopsies because many presented with rising PSA levels and clinical suspicion warranting a repeat biopsy. Therefore, these results may not be directly applicable to biopsy-naïve men, who constitute a different patient population. As a result, future studies in biopsy-naïve men such as the PRECISION trial (www.clinicaltrials.gov, NCT02380027) are evolving to clarify the implications of mp-MRI-bx and a "targeted-only" approach in the initial biopsy setting.

Additionally, because biopsy results were used comparatively in this study, the true rate of false negative readings cannot be assessed for patients with negative biopsies. A further analysis of patients who subsequently underwent RP following diagnosis might identify some cases, although this is a selected patient group. Using biopsy results as comparing reference allowed the comparison of 2 biopsy approaches in a repeat biopsy setting. Furthermore, previous studies have shown a good correlation between mp-MRI and the RP specimen [24, 25], even though some report that mp-MRI failed to detect significant tumors in 5–28% of cases [26–28]. Thus, there is an unknown proportion of significant cancers that are difficult to detect using mp-MRI. In addition, prostate biopsies are still necessary to confirm the presence of PCa in a suspicious lesion, as mp-MRI findings are not cancer-specific. Furthermore, targeted mp-MRI-bx cannot always be accurate due to misregistration using image-fusion and PCa lesions may therefore be missed. Conversely, unnecessary targeted biopsies may be conducted due to false-positive mp-MRI readings. Moreover, the cost effectiveness of a diagnostic mp-MRI and the additional use of mp-MRI-bx have not been fully explored. Thus, cautions should be made about recommending "targeted-only" biopsies over a systematic approach. Nevertheless, our results indicate that cancers that are not detected by mp-MRI followed by mp-MRI-bx in a repeat biopsy setting are unlikely to be significant higher-grade tumors that are detected using systematic repeated TRUS-bx cores.

Finally, the criterion for significant PCa was based solely on the GS from histopathological assessment of the biopsies and we chose not to include patient-specific static risk factors such as age, PSA, or number of visible MRI lesions, as they do not change between biopsy modalities.

A number of definitions of insignificant and significant PCa including clinical findings, GS, and tumor volume (number of positive cores and maximum cancerous core length) have been proposed [29, 30]. Including these parameters might have changed our results. However, there is still no clear consensus on the definition of significant PCa in targeted biopsies, although incorporating the maximum cancerous core length has been recommended for risk stratification [30]. Including only GS findings in the definition of significant PCa led to a more strict comparison between the 2 biopsy modalities.

In conclusion, mp-MRI/TRUS fusion biopsies have a high detection rate for significant PCa in patients with prior negative TRUS-bx and preferentially detect intermediate/high-grade compared with low-grade tumors. In patients with prior negative TRUS-bx and moderate to highly suspicious lesions on mp-MRI, an mp-MRI "targeted-only" biopsy strategy may be most beneficial. However, more comprehensive, multicenter studies will be required before recommending an mp-MRI "targeted-only" biopsy strategy for widespread adoption.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Shariat SF, Roehrborn CG: Using biopsy to detect prostate cancer. Rev Urol 2008;10:262–280.
2 Ploussard G, Nicolaiew N, Marchand C, Terry S, Vacherot F, Vordos D, et al: Prospective evaluation of an extended 21-core biopsy scheme as initial prostate cancer diagnostic strategy. Eur Urol 2014;65:154–161.
3 Maccagnano C, Gallina A, Roscigno M, Raber M, Capitanio U, Saccà A, et al: Prostate saturation biopsy following a first negative biopsy: state of the art. Urol Int 2012;89:126–135.
4 Ukimura O, Coleman JA, de la Taille A, Emberton M, Epstein JI, Freedland SJ, et al: Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol 2013;63:214–230.
5 Zaytoun OM, Moussa AS, Gao T, Fareed K, Jones JS: Office based transrectal saturation biopsy improves prostate cancer detection compared to extended biopsy in the repeat biopsy population. J Urol 2011;186:850–854.
6 Boccon-Gibod LM, Dumonceau O, Toublanc M, Ravery V, Boccon-Gibod LA: Micro-focal prostate cancer: a comparison of biopsy and radical prostatectomy specimen features. Eur Urol 2005;48:895–859.
7 Epstein JI, Feng Z, Trock BJ, Pierorazio PM: Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol 2012;61:1019–1024.
8 Sciarra A, Barentsz J, Bjartell A, Eastham J, Hricak H, Panebianco V, et al: Advances in magnetic resonance imaging: how they are changing the management of prostate cancer. Eur Urol 2011;59:962–977.
9 Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al: ESUR prostate MR guidelines 2012. Eur Radiol 2012;22:746–757.
10 Moore CM, Robertson NL, Arsanious N, Middleton T, Villers A, Klotz L, et al: Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol 2013;63:125–140.
11 Delongchamps NB, Peyromaure M, Schull A, Beuvon F, Bouazza N, Flam T, et al: Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. J Urol 2013;189:493–499.
12 Sonn GA, Chang E, Natarajan S, Margolis DJ, Macairan M, Lieu P, et al: Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol 2014;65:809–815.
13 Hambrock T, Hoeks C, Hulsbergen-van de Kaa C, Scheenen T, Fütterer J, Bouwense S, et al: Prospective assessment of prostate cancer aggressiveness using 3-T diffusion-weighted magnetic resonance imaging-guided biopsies versus a systematic 10-core transrectal ultrasound prostate biopsy cohort. Eur Urol 2012;61:177–184.
14 Siddiqui MM, Rais-Bahrami S, Truong H, Stamatakis L, Vourganti S, Nix J, et al: Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol 2013;64:713–719.
15 Boesen L, Noergaard N, Chabanova E, Logager V, Balslev I, Mikines K, et al: Early experience with multiparametric magnetic resonance imaging-targeted biopsies under visual transrectal ultrasound guidance in patients suspicious for prostate cancer undergoing repeated biopsy. Scand J Urol 2015;49:25–34.
16 Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, et al: Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol 2011;59:477–494.
17 Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al: PI-RADS prostate imaging – reporting and data system: 2015, Version 2. Eur Urol 2016;69:16–40.
18 Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL: The 2005 international society of urological pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma. Am J Surg Pathol 2005;29:1228–1242.
19 Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al: The 2014 international society of urological pathology (ISUP) consensus conference on gleason grading of prostatic Carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244–252.
20 Vourganti S, Rastinehad A, Yerram NK, Nix J, Volkin D, Hoang A, et al: Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies. J Urol 2012;188:2152–2157.
21 Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al: Comparison of MR/ultrasound fusion – guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390.
22 Filson CP, Natarajan S, Margolis DJ, Huang J, Lieu P, Dorey FJ, et al: Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. Cancer 2016;122:884–892.
23 Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al: EAU–ESTRO–SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618–629.
24 Delongchamps NB, Lefèvre A, Bouazza N, Beuvon F, Legman P, Cornud F: Detection of significant prostate cancer with magnetic resonance targeted biopsies – should transrectal ultrasound-magnetic resonance imaging fusion guided biopsies alone be a standard of care? J Urol 2015;193:1198–1204.

25 Turkbey B, Merino MJ, Gallardo EC, Shah V, Aras O, Bernardo M, et al: Comparison of endorectal coil and nonendorectal coil T2W and diffusion-weighted MRI at 3 Tesla for localizing prostate cancer: correlation with whole-mount histopathology. J Magn Reson Imaging 2014;39:1443–1448.
26 Tan N, Margolis DJ, Lu DY, King KG, Huang J, Reiter RE, et al: Characteristics of detected and missed prostate cancer foci on 3-T multiparametric MRI using an endorectal coil correlated with whole-mount thin-section histopathology. AJR Am J Roentgenol 2015;205:W87–W92.
27 Thompson JE, van Leeuwen PJ, Moses D, Shnier R, Brenner P, Delprado W, et al: The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol 2016;195:1428–1435.
28 Russo F, Regge D, Armando E, Giannini V, Vignati A, Mazzetti S, et al: Detection of prostate cancer index lesions with multiparametric magnetic resonance imaging (mp-MRI) using whole-mount histological sections as the reference standard. BJU Int 2016;118:84–94.
29 Ploussard G, Epstein JI, Montironi R, Carroll PR, Wirth M, Grimm MO, et al: The contemporary concept of significant versus insignificant prostate cancer. Eur Urol 2011;60:291–303.
30 Moore CM, Kasivisvanathan V, Eggener S, Emberton M, Fütterer JJ, Gill IS, Grubb RL, et al: Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an International Working Group. Eur Urol 2013;64:544–552.

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Where Do Transrectal Ultrasound- and Magnetic Resonance Imaging-guided Biopsies Miss Significant Prostate Cancer?

Lars Boesen, Nis Nørgaard, Vibeke Løgager, Ingegerd Balslev, and Henrik S. Thomsen

OBJECTIVE To identify the location of missed significant prostate cancer (sPCa) lesions by transrectal ultrasound-guided biopsy ($TRUS_{bx}$) and multiparametric magnetic resonance imaging-guided biopsy ($mpMRI_{bx}$) in men undergoing repeat biopsies.

MATERIALS AND METHODS A total of 289 men with prior negative $TRUS_{bx}$ underwent multiparametric magnetic resonance imaging. The location of any suspicious lesion was registered and scored using Prostate Imaging Reporting and Data System version 1 classification according to the likelihood of being sPCa. All patients underwent repeat transrectal ultrasound-guided biopsy ($reTRUS_{bx}$) and targeted $mpMRI_{bx}$ (image fusion) of any suspicious lesion. Biopsy results were compared and the locations of missed sPCa lesions were registered. Cancer significance was defined as (1) any core with a Gleason score of >6, (2) cancer core involvement of ≥50% and for $reTRUS_{bx}$ on patient level, and (3) the presence of ≥3 positive cores.

RESULTS Of the 289 patients, prostate cancer was detected in 128 (44%) with 88 (30%) having sPCa. Overall, 165 separate prostate cancer lesions were detected with 100 being sPCa. Of these, $mpMRI_{bx}$ and $reTRUS_{bx}$ detected 90% (90/100) and 68% (68/100), respectively. The majority of sPCa lesions (78%) missed by primary $TRUS_{bx}$ were located either anteriorly or in the apical region. Missed sPCa lesions at repeat biopsy were primarily located anteriorly (84%) for $reTRUS_{bx}$ (n = 27/32) and posterolateral midprostatic (60%) for $mpMRI_{bx}$ (n = 6/10).

CONCLUSION Both $TRUS_{bx}$ and $mpMRI_{bx}$ missed sPCa lesions in specific segments of the prostate. Missed sPCa lesions at repeat biopsy were primarily located anteriorly for $TRUS_{bx}$ and posterolateral midprostatic for $mpMRI_{bx}$. Localization of these segments may improve biopsy techniques in men undergoing repeat biopsies. UROLOGY 110: 154–160, 2017. © 2017 Elsevier Inc.

Patients with benign transrectal ultrasound-guided biopsy ($TRUS_{bx}$) for prostate cancer (PCa) detection constitute a clinical dilemma.[1] As $TRUS_{bx}$ has limited diagnostic accuracy because of poor PCa target identification, a significant number of cancers are missed[2] and the issue of possible Gleason score (GS) undergrading is evident.[3,4] Clinicians are therefore repeatedly challenged in men with negative prostate biopsies, as the indication for repeated biopsies (rebiopsy) often is driven by a rise in a nonspecific prostate-specific antigen (PSA) measure. A minimum of 10-12 systematic $TRUS_{bx}$ cores, sampling the posterior peripheral zone of the prostate, is recommended in biopsy-naive men.[5] However, the number of cores, the biopsy technique, and the sampling sites in men undergoing rebiopsies are debatable. Recommendations have been made to either increase the number of cores,[6] include sampling of the transitional zone (TZ) by directing rebiopsy cores more anteriorly[7] or moving toward saturation biopsy techniques.[8] However, these approaches often lead to an unfavorable increased detection of insignificant prostate cancers (insPCa's) potentially leading to unnecessary treatments.[7,9,10]

There is a need for an improved target identification of significant prostate cancer (sPCa) without a concurrent increase of insPCa. Prostate multiparametric magnetic resonance imaging (mpMRI) has emerged as an accurate imaging modality for this purpose.[11,12] Suspicious lesions identified on mpMRI can be targeted by selective multiparametric magnetic resonance imaging-guided biopsy ($mpMRI_{bx}$) and can improve detection of missed sPCa[13,14] at rebiopsy. However, not all cancers are visible on mpMRI and lesions may be misinterpreted.[15,16]

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From the Department of Urology, Herlev Gentofte University Hospital, Herlev, Denmark; the Department of Radiology, Herlev Gentofte University Hospital, Herlev, Denmark; and the Department of Pathology, Herlev Gentofte University Hospital, Herlev, Denmark

Address correspondence to: Lars Boesen, M.D., Ph.D., Department of Urology, Herlev Gentofte University Hospital, Herlev Ringvej 75, Herlev, Denmark 2730. E-mail: lars.boesen@dadlnet.dk

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Furthermore, $mpMRI_{bx}$ can be inaccurate because of lesion targeting errors and far from all institutions have the setup and experience in mpMRI diagnostics. Thus, numerous urologists still rely on systematic $TRUS_{bx}$ for rebiopsy sessions. Therefore, awareness of the location of missed sPCa foci by $TRUS_{bx}$ and $mpMRI_{bx}$ may improve rebiopsy techniques. The objective of the present study was to identify the location of sPCa lesions missed by transrectal ultrasound (TRUS) and $mpMRI_{bx}$ in men undergoing rebiopsy.

MATERIALS AND METHODS

Patients

This is a retrospective analysis of patient data from a study database approved by the Local Committee for Health Research Ethics (No.H-1-2011-066) and the Danish Data Protection Agency. All patients were prospectively enrolled from September 2011 to September 2013 and provided written informed consent. The study was registered at Clinicaltrials.gov (No.NCT01640262). Inclusion required all patients to have a history of negative $TRUS_{bx}$ findings and a clinical suspicion of missed sPCa (persistent elevated PSA, an abnormal digital rectal examination, or a previous abnormal TRUS image) that warranted a rebiopsy. The exclusion criteria were patients previously diagnosed with PCa or who had a general contraindication to mpMRI. All prior $TRUS_{bx}$ sessions included a systematic extended biopsy scheme (10-12 cores). No patient had prior mpMRIs. Parts of the patient data were included in a prior study, but no data on the location of missed sPCa were included.

mpMRI. mpMRI was performed before rebiopsy using a 3.0-T magnetic resonance imaging scanner (Philips Healthcare, Best, The Netherlands) with a pelvic–phased-array coil (Philips Healthcare) positioned over the pelvis according to the European Society of Urogenital Radiology guidelines[17] and as previously published.[18] All identified mpMRI lesions were registered and scored on a modified 18-region prostate diagram[19] by the same physician using the Prostate Imaging Reporting and Data System (PIRADS) version 1 classification.[17] Lesions were scored from 1 to 5 according to the probability of being sPCa (1, very low; 2, low; 3, intermediate; 4, high; and 5, very high). Patients with no suspicious lesions were not scored by PIRADS.

Biopsies. All patients underwent both systematic repeat transrectal ultrasound-guided biopsy ($reTRUS_{bx}$) and $mpMRI_{bx}$ in the same biopsy session. Ten systematic $reTRUS_{bx}$ cores from 10 prostatic regions (6 lateral and 4 medial from the base, middle, and apex from both left and right sides) were obtained by the operator blinded to any mpMRI findings and marked separately. Suspicious lesions seen on TRUS were sampled using the core for the corresponding region. The operator then subsequently reviewed the patients' mpMRI data on a dedicated workstation in the biopsy room and additional $mpMRI_{bx}$ (1-2cores per lesion) were targeted toward any PIRADS 2-5 lesion using mpMRI-TRUS image fusion either cognitive-based (n = 83) or software-based (n = 206, HI-RVS system; Hitachi, Tokyo, Japan). All prostate biopsies were performed in the axial plane using the end-fire technique by the same operator.

Histopathology and Cancer Significance

For each PCa-positive biopsy core, the location according to the scheme, the biopsy technique, the GS[20] on both patient and lesion levels, and the extent of cancer core involvement (%) were determined by the same genitourinary pathologist. Histopathologic findings were used to define sPCa as (1) any biopsy core with a GS of >6; (2) a maximum cancerous core length of ≥50%; and for $reTRUS_{bx}$ only on a patient level, (3) the presence of ≥3 PCa-positive cores.

Biopsy Comparison

Any sPCa detected by either $reTRUS_{bx}$ or $mpMRI_{bx}$ was considered to be the result of a prior false-negative $TRUS_{bx}$. Biopsy results (pathologically proven cancer location, the GS, and the tumor length) from $reTRUS_{bx}$ and $mpMRI_{bx}$ were compared according to the 18-region prostate scheme. PCa-positive lesions detected solitarily by 1 biopsy technique ($reTRUS_{bx}$ or $mpMRI_{bx}$) were interpreted as missed lesions with the other method. Only PCa-positive $mpMRI_{bx}$ from intermediate- and high-risk lesions (PIRADS score of 3-5) were included in the analysis as a true-positive mpMRI. However, because of the study design, $mpMRI_{bx}$ were also obtained from PIRADS score 2 (low risk) lesions. Thus, any PCa-positive $mpMRI_{bx}$ from these lesions was interpreted as a false-negative mpMRI and an $mpMRI_{bx}$ missed lesion when a recommended biopsy threshold of PIRADS ≥3 was used. As our $TRUS_{bx}$ core length obtained 18-mm tissues samples of the posterior part of the prostate (peripheral zone), the anterior region was defined as a vertical line 18 mm from the prostatic posterior surface independent of prostate size. Consequently, all $reTRUS_{bx}$ PCa-positive lesions were defined as part of the prostate's posterior region according to the scheme.

The diagnostic yields of any PCa and sPCa were compared and stratified by biopsy technique. As the $TRUS_{bx}$ cores were systematically dispersed throughout the prostate targeting 1 core per region, a patient with a GS 6 tumor on $reTRUS_{bx}$ was defined as having sPCa if more than 2 biopsy cores were positive for PCa. However, the number of $mpMRI_{bx}$ positive cores did not influence the definition of sPCa, as more than 1 core often were targeted toward the same prostatic region or lesion.

Suspicious lesions on mpMRI were confirmed to be PCa by positive targeted $mpMRI_{bx}$. Suspicious lesions that involved more than 1 prostatic region and were directly connected on mpMRI were defined as the same lesion and positive if $mpMRI_{bx}$ proved PCa from at least one of the involved regions. Similarly, PCa-positive adjacent regions (medial-lateral and base-mid-apex) on $reTRUS_{bx}$ were defined as the same lesion.

Benign $mpMRI_{bx}$ of a suspicious lesion could be the result of either mpMRI misinterpretation or targeting error because of image-fusion misregistration. A benign $mpMRI_{bx}$ of an mpMRI suspicious lesion that was rectified as a false-negative result by a positive $reTRUS_{bx}$ core from the targeted region was defined as a missed lesion by $mpMRI_{bx}$.

Statistics

Patient characteristics were described by descriptive statistics. Continuous variables (age, PSA, PSA density, prior biopsy sessions, and TRUS volume) were stratified by biopsy outcome and compared using the Mann-Whitney *U* test. The locations of the PCa-positive regions were specified on the 18-region prostate scheme in number and percentage. A McNemar test was used to compare PCa detection rates between $mpMRI_{bx}$ and $TRUS_{bx}$. Cancer significance was compared stratified by biopsy technique ($TRUS_{bx}$ vs $mpMRI_{bx}$ and cognitive-based vs software-based $mpMRI_{bx}$) using chi-squared analyses and the Fisher exact test. A P value of $<.05$ was considered statistically significant. Statistical analyses were

performed using SPSS 22.0 software (IBM Corporation, Armonk, NY).

RESULTS

The characteristics of the 289 included patients are shown in Table 1. Overall, of the 289 patients, PCa was detected in 128 (44%) with 88 (30%) having sPCa. $mpMRI_{bx}$ and $reTRUS_{bx}$ detected any PCa in 96 and 108 patients, among which 81% (78/96) and 55% (59/108) were sPCa (Fig. 1). $mpMRI_{bx}$ detected significantly more men with sPCa ($P = .004$) and significantly less men with insPCa ($P < .001$) compared with $reTRUS_{bx}$, respectively.

Any PCa and sPCa were detected in 165 and 100 separate lesions by either $mpMRI_{bx}$ or $reTRUS_{bx}$. mpMRI identified 435 lesions ranging from low to high suspicion (PIRADS 2-5) and detected PCa in 143 by either a targeted $mpMRI_{bx}$ or a $reTRUS_{bx}$ core from the corresponding suspicious region (Table 2). Of the 143 lesions, 100 were defined as sPCa. No patient without any abnormality on mpMRI (no PIRADS score) had a sPCa detected by $reTRUS_{bx}$. There was an even distribution of lesions between the peripheral and the TZs. Using a biopsy threshold with a PIRADS score of ≥3, mpMRI identified 200 intermediate and high suspicious (PIRADS 3-5) lesions in 155 patients. Of these, any PCa and sPCa were detected in 124 of 200 and in 97 of 200 lesions on either $mpMRI_{bx}$ or $reTRUS_{bx}$. Three PIRADS score 2 lesions harbored sPCa detected by $mpMRI_{bx}$. There was no significant difference in the detection of sPCa comparing $mpMRI_{bx}$ biopsy techniques (cognitive-based vs software-based) on both patient level ($P = .401$, Fig. 1) and lesion level ($P = .992$, Supplementary Table S1). In total, 241 prostatic regions and 124 separate lesions were positive for PCa on $reTRUS_{bx}$ (Supplementary Fig. S1). Of the 124 lesions, 68 were sPCa lesions.

Overall, $reTRUS_{bx}$ and $mpMRI_{bx}$ detected sPCa in 68% (68/100) and 90% (90/100 [3 PIRADS score 2 lesions and 7 PIRADS 3-5 lesions missed by $mpMRI_{bx}$]) of all identified sPCa lesions, respectively. Thus, $reTRUS_{bx}$ and $mpMRI_{bx}$ missed 32 (n = 29, GS >6; n = 3 maximum cancerous core length >50%) and 10 (all GS >6, five using cognitive-based image fusion and five using software-based image fusion) sPCa lesions. The majority of the sPCa lesions (78%) previously missed by the initial $TRUS_{bx}$ and subsequently detected at rebiopsy by either $reTRUS_{bx}$ or $mpMRI_{bx}$ were located anteriorly or in the apical region, especially in the anterior midprostate and apex (52%) (Fig. 2). Missed sPCa lesions at rebiopsy (lesions detected solitarily by 1 biopsy technique) were predominantly located anteriorly (84% [n = 27/32]) for $reTRUS_{bx}$ and posterolateral midprostatic (60% [n = 6/10]) or apically (40% [4/10]) for $mpMRI_{bx}$.

COMMENT

We detected 100 sPCa lesions previously missed by systematic $TRUS_{bx}$ in 88 patients. These lesions were primarily located in the anterior segments (61%) when

Table 1. Patient characteristics

Clinical Characteristics	Total N = 289	PCa Negative n = 161	PCa Positive n = 128	*P* Value
Age (y), median (IQR)	64 (59-67)	62 (57-67)	66 (61-69)	.001
PSA (ng/mL), median (IQR)	12.0 (8.2-19.2)	11.0 (7.9-17.0)	13.4 (9.2-21.0)	.023
PSA density (ng/mL/cc), median (IQR)	0.19 (0.13-0.29)	0.16 (0.12-0.23)	0.25 (0.17-0.42)	.001
Prior biopsy, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	.213
$TRUS_{volume}$, median (IQR)	63 (46-87)	73 (52-93)	52 (39-72)	.001

IQR, interquartile range; PCa, prostate cancer; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

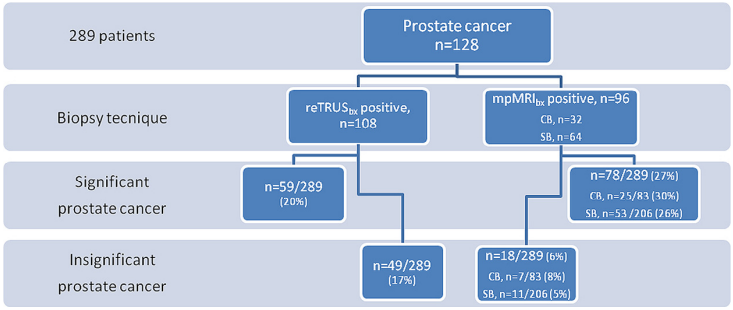

Figure 1. Flowchart of the diagnostic pathway of the 289 included patients. $reTRUS_{bx}$ detected more patients with PCa (37% [108/289] vs 33% [96/289]) compared with $mpMRI_{bx}$, but the difference was not statistically significant ($P = .126$). $mpMRI_{bx}$ was performed using either CB (n = 83 patients) or SB (n = 206 patients) image fusion. CB, cognitive-based; $mpMRI_{bx}$, multiparametric magnetic resonance imaging-guided biopsy; $reTRUS_{bx}$, repeat transrectal ultrasound-guided biopsy; SB, software-based. (Color version available online.)

Table 2. Zonal origin of multiparametric magnetic resonance imaging suspicious lesions in relation to PIRADS score and biopsy results (multiparametric magnetic resonance imaging-guided biopsy and repeat transrectal ultrasound-guided biopsy)

			Biopsy Results			
PIRADS Score (Lesions)			No PCa	InsPCa	sPCa	Total
PIRADS 2	Lesion zone	Peripheral	117	12	2	131
		Transitional	99	4	1	104
	Total		216	16	3	235
PIRADS 3	Lesion zone	Peripheral	8	3	7	18
		Transitional	21	2	2	25
	Total		29	5	9	43
PIRADS 4	Lesion zone	Peripheral	30	8	15	53
		Transitional	14	9	20	43
	Total		44	17	35	96
PIRADS 5	Lesion zone	Peripheral	1	0	19	20
		Transitional	2	5	34	41
	Total		3	5	53	61
Total	Lesion zone	Peripheral	156	23	43	222
		Transitional	136	20	57	213
	Total		292	43	100	435

insPCa, insignificant prostate cancer; PIRADS, Prostate Imaging Reporting and Data System; sPCa, clinically significant prostate cancer. The majority of sPCa lesions were detected in the transitional zone (57% vs 43%), but the difference was not statistically significant ($P = .09$).

considering the prostate as a whole and in the apical region (49%), evaluating only lesions detected in the peripheral zone for better comparison to $TRUS_{bx}$ sampling sites. $TRUS_{bx}$ often miss significant tumors in the anterior part of the prostate because of the systematic sampling errors caused by the limited length and range of the $TRUS_{bx}$ cores. $TRUS_{bx}$ predominantly samples the peripheral zone of the prostate where cancerous lesions may appear as a hypoechoic area with increased Doppler activity compared with the normal peripheral zone. Because TZ cancers cannot be accurately identified and differentiated from benign hyperplastic nodules and primary TZ cancers occur in about only 20% of cases, extended anterior targeted TZ biopsies are not recommended in the initial biopsy setting because of the poor cancer detection yield. Furthermore, the detection rate at the initial biopsy varies significantly with the PCa prevalence in the population studied, the biopsy strategy, and the operator's skills. $TRUS_{bx}$ miss 25%-30% of cancers at first biopsy, and the detection rate at $reTRUS_{bx}$ is 10%-35%,[2,21] with decreasing rates following further repeated procedures. Still, significant cancers are missed because of the poor PCa target identification on TRUS and the untargeted biopsy approach. Therefore, extended biopsy protocols and TZ biopsies may be used in a rebiopsy setting,[2,7] as the sampling locations at rebiopsy ideally should be different from the previous biopsy sites to detect missed tumors. Given the location of missed sPCa lesions in our study by both prior $TRUS_{bx}$ and $reTRUS_{bx}$, the recommendation by Ukimura et al[7] to add anterior samples of the apex, the anterior horn, and the TZ in a rebiopsy setting seems appropriate.

de la Taille et al[22] found that there is an inverse correlation between the prostate volume and the PCa detection yield at biopsy. Thus, some urologists recommend to either increase the overall number of cores,[6,22] adjust the number according to prostate volume,[23] or perform saturation biopsy techniques,[8] especially in a rebiopsy setting. However, even though extending the number of cores and locations may increase the diagnostic yield of sPCa, it may inappropriately increase the detection of insPCa, potentially leading to unnecessary treatments.[7,10] Furthermore, sampling errors may still occur despite the use of extended biopsy protocols, and methods requiring 18 cores or more have significant side effects and do not seem to improve PCa detection rates as reported by Eichler et al.[24] Eichler et al concluded that a 12-core extended biopsy scheme maintains sufficient detection rates with low adverse effects, especially at first biopsy.

The distribution of prostatic segments with missed sPCa lesions at rebiopsy differed depending on the biopsy technique. The sPCa lesions missed by $reTRUS_{bx}$ that were subsequently diagnosed by $mpMRI_{bx}$ were predominantly located anteriorly (84% [n = 27/32]) in accordance with the known undersampling of this region. Missed sPCa lesions by $mpMRI_{bx}$ that were detected by $reTRUS_{bx}$ were predominantly located posterolateral midprostatic (60% [n = 6/10]) or apically (40% [4/10]). Apical lesions can be difficult to detect on mpMRI because of their close location to the prostatic margin and adjacent anatomical structures.[25] Furthermore, smaller subcapsulated or infiltrative tumors are more often missed by mpMRI,[25] which could explain the missed lesions in the posterolateral segment. However, the majority of patients with sPCa missed by $mpMRI_{bx}$ had PIRADS 3-5 lesions indicating mpMRI-TRUS image-fusion sampling errors rather than mpMRI misinterpretation. There is always a risk of misregistration combining 2 image modalities for image fusion. In-bore $mpMRI_{bx}$ may be more accurate because of the per-procedure confirmation of the needle localization. However, in-bore $mpMRI_{bx}$ is time-consuming and occupies

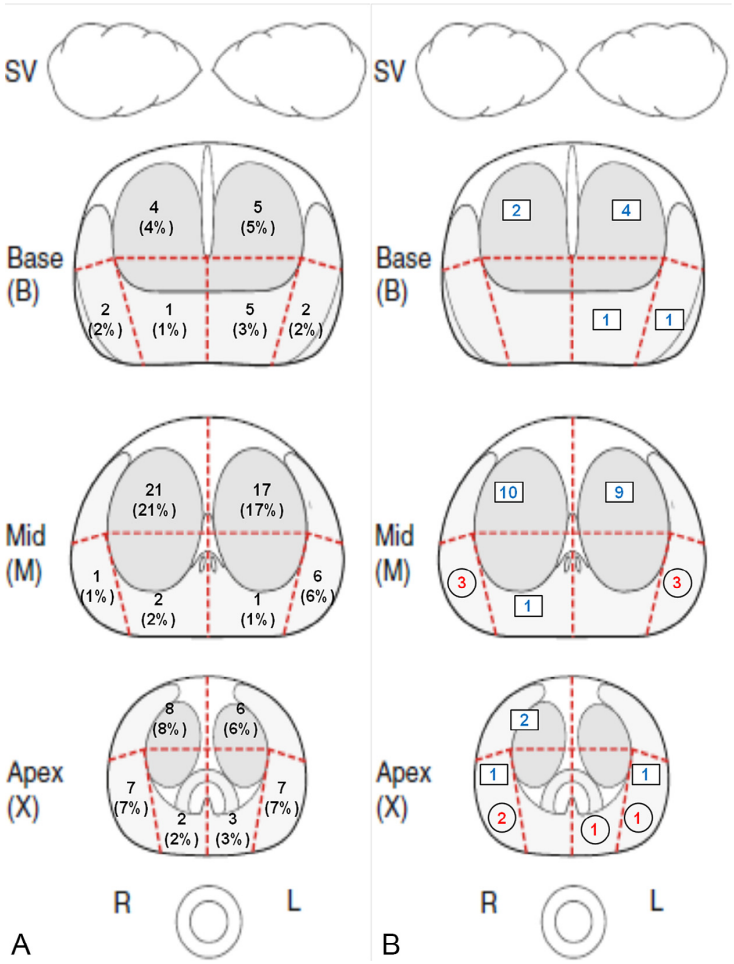

Figure 2. The 18-region modified diagram from the European Consensus Meeting[19] shows **(A)** the location of the 100 missed sPCa lesions previously missed by initial $TRUS_{bx}$ and subsequently detected at rebiopsy by either $reTRUS_{bx}$ or $mpMRI_{bx}$. The majority (61%) of these lesions were located anteriorly. **(B)** The location of missed sPCa lesions at repeat biopsy by either $TRUS_{bx}$ (squared [blue]) or $mpMRI_{bx}$ (circled [red]) that was detected solitarily by the other biopsy technique. The prostate is divided into 12 posterior and 6 anterior regions. Each number represents the number of suspicious lesions primarily located in the region. A lesion could involve more than 1 prostatic region, but only the region containing the bulk of the tumor is marked. L, left; $mpMRI_{bx}$, multiparametric magnetic resonance imaging-guided biopsy; R, right; $reTRUS_{bx}$; repeat transrectal ultrasound-guided biopsy; $TRUS_{bx}$, transrectal ultrasound-guided biopsy; SV, seminal vesicle. (Color version available online.)

the magnetic resonance imaging suite twice. mpMRI-TRUS fusion biopsies can be performed by experienced operators in an outpatient clinic with an acceptable targeting accuracy while saving time and costs. Furthermore, $mpMRI_{bx}$ can be combined with $TRUS_{bx}$, as recommended by both the American Urological Association[26] and the European Association of Urology[3] in a rebiopsy setting. Moreover, $mpMRI_{bx}$ sampling errors may be reduced by obtaining more targeting cores per lesion. We used 1-2 cores per lesion, which may be inadequate, as the majority of studies included in the review by Schoots et al[13] report at least 2 cores per lesion, some even more (4-6).[27] However, even though the recent report from the American Urological Association and the Society of Abdominal Radiology[26] has described that at least 2 cores per lesion should be obtained, there is no established general consensus and recommendations.

Our study describes not only the location of prior missed sPCa lesions by $TRUS_{bx}$ but also the location and the differences of missed sPCa lesions by either $reTRUS_{bx}$ or $mpMRI_{bx}$ in men undergoing rebiopsy. Although patient cohorts are not directly comparable, our results are similar to a recent published study by Schouten et al[28] in biopsy-naive patients where $TRUS_{bx}$ predominantly missed sPCa anteriorly and $mpMRI_{bx}$ in the dorsolateral segment, and both techniques have difficulties in detecting apical lesions.

Our results are clinically important, as there is an ongoing debate on whether or not systematic biopsies should accompany targeted biopsies in a rebiopsy setting.[14,29] At present, guidelines[3,26] recommend combining reTRUS$_{bx}$ with mpMRI$_{bx}$ in a rebiopsy setting. However, in an effort to try to reduce the total number of cores obtained in a combined approach, adding additional systematic cores to mpMRI$_{bx}$ only in the posterolateral midprostatic and apical segments of the prostate may be sufficient to improve the detection of missed sPCa without the need for sampling all prostatic regions using all standard 10-12 reTRUS$_{bx}$ cores. With reference to the recommendation of more targeted cores per mpMRI suspicious lesion,[26,27] this approach might favorably limit the total number of cores used per patient.

LIMITATIONS

Our patient cohort is not homogenous as we included patients with various numbers of prior biopsy sessions (ranging from 1 to 6), and not all had their prior TRUS$_{bx}$ performed at our institution. This finding may have caused a selection bias, as several operators with different experiences may have used different TRUS$_{bx}$ techniques in obtaining the initial biopsies. This may explain the rather high PCa detection rate at reTRUS$_{bx}$, although some PCa foci may also have been missed at reTRUS$_{bx}$, as we used a 10-core biopsy scheme according to the department's standard procedure. Applying other biopsy schemes as reviewed by Presti[5] may have impacted our findings. However, changing biopsy schemes does not change the efficacy of mpMRI and its ability to detect suspicious areas for selective mpMRI$_{bx}$. Furthermore, we used a theoretically defined vertical line 18 mm from the prostatic posterior surface to separate the posterior and anterior segments of the prostate and defined all PCa-positive lesions on reTRUS$_{bx}$ as part of the posterior segments. However, in practice, the reTRUS$_{bx}$ cores (numbers 5 and 10) often sampled the entire height of the prostate in the deeper apex where the peripheral zone often compromises the entire region. This finding may have facilitated a better reTRUS$_{bx}$ sampling of any anteriorly located apical tumor causing false posterior tumor allocation. However, a false posterior tumor allocation will only influence the schematic location of missed tumors and not the efficacy of each biopsy technique.

We used biopsy results as a comparing reference and selected the combined approach as the gold standard to define the presence or the absence of sPCa. PCa lesions may have been missed by both biopsy techniques and the true rate of false-negative readings cannot be assessed. A subanalysis of patients undergoing prostatectomy would provide a better reference standard, although this also is a selected group causing a potential selection bias. However, a recent study shows a good correlation between mpMRI suspicion and sPCa using 5-mm template sampling as a comparing reference.[30] Furthermore, this setup allows the comparison of outcomes between 2 different biopsy techniques in a rebiopsy setting.

CONCLUSION

The majority of sPCa lesions previously missed by TRUS$_{bx}$ were located anteriorly or in the apical region. Both reTRUS$_{bx}$ and mpMRI$_{bx}$ miss sPCa lesions in specific segments of the prostate. Missed sPCa lesions at repeat biopsy were primarily located anteriorly for reTRUS$_{bx}$ and posterolateral midprostatic for mpMRI$_{bx}$. Localization of these segments may improve biopsy techniques in men undergoing repeat biopsies.

References

1. Puppo P. Repeated negative prostate biopsies with persistently elevated or rising PSA: a modern urologic dilemma. *Eur Urol.* 2007;52:639-641. doi:10.1016/j.eururo.2007.04.004.
2. Shariat SF, Roehrborn CG. Using biopsy to detect prostate cancer. *Rev Urol.* 2008;10:262-280.
3. Mottet N, Bellmunt J, Bolla M, et al. EAU–ESTRO–SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol.* 2016;71:618-629. doi:10.1016/j.eururo.2016.08.003.
4. Harvey CJ, Pilcher J, Richenberg J, Patel U, Frauscher F. Applications of transrectal ultrasound in prostate cancer. *Br J Radiol.* 2012;85:S3-S17. doi:10.1259/bjr/56357549. Spec No.
5. Presti JC. Prostate biopsy: current status and limitations. *Rev Urol.* 2007;9:93-98.
6. Ploussard G, Nicolaiew N, Marchand C, et al. Prospective evaluation of an extended 21-core biopsy scheme as initial prostate cancer diagnostic strategy. *Eur Urol.* 2014;65:154-161. doi:10.1016/j.eururo.2012.05.049.
7. Ukimura O, Coleman JA, de la Taille A, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. *Eur Urol.* 2013;63:214-230. doi:10.1016/j.eururo.2012.09.033.
8. Maccagnano C, Gallina A, Roscigno M, et al. Prostate saturation biopsy following a first negative biopsy: state of the art. *Urol Int.* 2012;89:126-135. doi:10.1159/000339521.
9. Ploussard G, Epstein JI, Montironi R, et al. The contemporary concept of significant versus insignificant prostate cancer. *Eur Urol.* 2011;60:291-303. doi:10.1016/j.eururo.2011.05.006.
10. Zaytoun OM, Moussa AS, Gao T, Fareed K, Jones JS. Office based transrectal saturation biopsy improves prostate cancer detection compared to extended biopsy in the repeat biopsy population. *J Urol.* 2011;186:850-854. doi:10.1016/j.juro.2011.04.069.
11. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Diagnostic performance of prostate imaging reporting and data system version 2 for detection of prostate cancer: a systematic review and diagnostic meta-analysis. *Eur Urol.* 2017;72:177-188. doi:10.1016/j.eururo.2017.01.042.
12. Hamoen EHJ, de Rooij M, Witjes JA, Barentsz JO, Rovers MM. Use of the prostate imaging reporting and data system (PI-RADS) for prostate cancer detection with multiparametric magnetic resonance imaging: a diagnostic meta-analysis. *Eur Urol.* 2014;67:1112-1121. doi:10.1016/j.eururo.2014.10.033.
13. Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MGM. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. *Eur Urol.* 2015;68:438-450. doi:10.1016/j.eururo.2014.11.037.
14. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion–guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA.* 2015;313:390-397. doi:10.1001/jama.2014.17942.
15. De Visschere PJL, Naesens L, Libbrecht L, et al. What kind of prostate cancers do we miss on multiparametric magnetic resonance imaging? *Eur Radiol.* 2016;26:1098-1107. doi:10.1007/s00330-015-3894-x.

16. Cash H, Günzel K, Maxeiner A, et al. Prostate cancer detection on transrectal ultrasonography-guided random biopsy despite negative real-time magnetic resonance imaging/ultrasonography fusion-guided targeted biopsy: reasons for targeted biopsy failure. *BJU Int*. 2016;118:35-43. doi:10.1111/bju.13327.
17. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur Radiol*. 2012;22:746-757. doi:10.1007/s00330-011-2377-y.
18. Boesen L, Noergaard N, Chabanova E, et al. Early experience with multiparametric magnetic resonance imaging-targeted biopsies under visual transrectal ultrasound guidance in patients suspicious for prostate cancer undergoing repeated biopsy. *Scand J Urol*. 2015;49:25-34. doi:10.3109/21681805.2014.925497.
19. Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. *Eur Urol*. 2011;59:477-494. doi:10.1016/j.eururo.2010.12.009.
20. Epstein JI, Allsbrook WC, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2005;29:1228-1242.
21. Djavan B, Ravery V, Zlotta A, et al. Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop? *J Urol*. 2001;166:1679-1683.
22. de la Taille A, Antiphon P, Salomon L, et al. Prospective evaluation of a 21-sample needle biopsy procedure designed to improve the prostate cancer detection rate. *Urology*. 2003;61:1181-1186.
23. Ficarra V, Novella G, Novara G, et al. The potential impact of prostate volume in the planning of optimal number of cores in the systematic transperineal prostate biopsy. *Eur Urol*. 2005;48:932-937. doi:10.1016/j.eururo.2005.08.008.
24. Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol*. 2006;175:1605-1612. doi:10.1016/S0022-5347(05)00957-2.
25. Rosenkrantz AB, Verma S, Turkbey B. Prostate cancer: top places where tumors hide on multiparametric MRI. *Am J Roentgenol*. 2015;204:W449-W456. doi:10.2214/AJR.14.13280.
26. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. *J Urol*. 2016;196:1613-1618. doi:10.1016/j.juro.2016.06.079.
27. Meng X, Rosenkrantz AB, Mendhiratta N, et al. Relationship between prebiopsy multiparametric magnetic resonance imaging (MRI), biopsy indication, and MRI-ultrasound fusion-targeted prostate biopsy outcomes. *Eur Urol*. 2016;69:512-517. doi:10.1016/j.eururo.2015.06.005.
28. Schouten MG, van der Leest M, Pokorny M, et al. Why and where do we miss significant prostate cancer with multi-parametric magnetic resonance imaging followed by magnetic resonance-guided and transrectal ultrasound-guided biopsy in biopsy-naïve men? *Eur Urol*. 2017;71:896-903. doi:10.1016/j.eururo.2016.12.006.
29. Schoots IG. Omission of systematic transrectal ultrasound guided biopsy from the MRI targeted approach in men with previous negative prostate biopsy might still be premature. *Ann Transl Med*. 2016;4:205. doi:10.21037/atm.2016.03.53.
30. Ahmed HU, Bosaily AE-S, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet (London, England)*. 2017;389:815-822. doi:10.1016/S0140-6736(16)32401-1.

APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2017.08.028.

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Multiparametric MRI in men with clinical suspicion of prostate cancer undergoing repeat biopsy: a prospective comparison with clinical findings and histopathology

Lars Boesen[1], Nis Nørgaard[1], Vibeke Løgager[2], Ingegerd Balslev[3] and Henrik S Thomsen[2]

Abstract

Background: Multiparametric magnetic resonance imaging (mpMRI) can improve detection of clinically significant prostate cancer (csPCa).

Purpose: To compare mpMRI score subgroups to systematic transrectal ultrasound-guided biopsies ($TRUS_{bx}$) and prostate-specific antigen (PSA)-based findings for detection of csPCa in men undergoing repeat biopsies.

Material and Methods: MpMRI was performed prior to re-biopsy in 289 prospectively enrolled patients. All underwent repeat $TRUS_{bx}$ followed by targeted biopsies (MRI_{TB}) of any mpMRI-identified lesion. MpMRI suspicion grade, PSA level, and density (PSAd) were compared with biopsy results and further matched to the radical prostatectomy (RP) specimen if available.

Results: PCa was detected in 128/289 (44%) patients with median age, PSA, and prior negative $TRUS_{bx}$ of 64 (interquartile range [IQR] = 59–67), 12.0 ng/mL (IQR = 8.3–19.1), and 2 (IQR = 1–3), respectively. $TRUS_{bx}$ detected PCa in 108/289 (37%) patients, of which 49 (45%) had insignificant cancer. MRI_{TB} was performed in 271/289 (94%) patients and detected PCa in 96 (35%) with 78 (81%) having csPCa. MpMRI scores showed a high association between suspicion level and biopsy results on both lesion and patient level ($P < 0.001$). MpMRI was better than PSA and PSAd ($P < 0.001$) to identify patients with missed csPCa. In total, 64/128 (50%) patients underwent RP; 60/64 had csPCa. MpMRI was significantly better in predicting csPCa on RP compared with $TRUS_{bx}$ ($P = 0.019$) as MRI_{TB} and $TRUS_{bx}$ correctly identified 47/60 (78%) and 35/60 (58%) patients, respectively.

Conclusion: MpMRI improves detection of missed csPCa and suspicion scores correlate well with biopsy and RP results on both patient and lesion level.

Keywords
Prostate, primary neoplasm, magnetic resonance imaging, MRI, ultrasound, biopsy

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Introduction

Prostate-specific-antigen (PSA) level and density (PSAd) are traditionally used to distinguish prostatic hypertrophy from PCa and identify men with suspicion of missed clinically significant prostate cancer (csPCa) on systematic transrectal ultrasound-guided biopsies ($TRUS_{bx}$) (1). With the ability to identify high suspicious areas at multiparametric MRI (mpMRI), targeted biopsies (MRI_{TB}) are increasingly replacing $TRUS_{bx}$ in men undergoing repeat biopsies (2,3). Lesions seen

[1]Department of Urology, Herlev Gentofte University Hospital, Herlev, Denmark
[2]Department of Radiology, Herlev Gentofte University Hospital, Herlev, Denmark
[3]Department of Pathology, Herlev Gentofte University Hospital, Herlev, Denmark

Corresponding author:
Lars Boesen, Herlev Gentofte University Hospital, Herlev Ringvej 75, Herlev 2730, Denmark.
Email: lars.boesen@dadlnet.dk

on mpMRI can be stratified according to suspicion, targeted by MRI_{TB}, and improve the detection rate of csPCa. However, due to different study protocols, MRI equipment, expertise, and mpMRI scoring systems, diagnostic accuracy differs among previous published studies (2–5). Previous studies report significant association between Prostate Imaging Reporting and Data System (PIRADS) (6) suspicion scores and detection of PCa using MRI_{TB} (3,7,8). However, as MRI_{TBs} are often limited to target intermediate to high suspicious lesions (4,9), the diagnostic yield of csPCa in relation to each PIRADS score subgroup including low suspicion lesions has not been consistently reported on both patient and lesion levels. Therefore, we prospectively evaluated the diagnostic performance of mpMRI for detection of missed csPCa comparing systematic repeat $TRUS_{bx}$ and MRI_{TB} with clinical findings (PSA and PSAd) and the individual mpMRI scores on both patient and lesion levels.

Material and Methods

Patients

All patients were prospectively enrolled from September 2011 to September 2013 and provided written informed consent, as part of a prospective, single institutional study database approved by the Local Committee for Health Research Ethics (No.H-1-2011-066) and the Danish Data Protection Agency. It was registered at Clinicaltrials.gov (no. NCT01640262). Inclusion criteria required that all had a history of negative $TRUS_{bx}$ findings and a persistent suspicion of PCa based on either PSA level, PSAd, an abnormal digital rectal examination (DRE), or a previous abnormal TRUS-image that warranted a repeat biopsy. The exclusion criteria were patients previously diagnosed with PCa or general contraindications to MRI. All prior $TRUS_{bx}$ sessions included a systematic extended biopsy scheme (10–12 cores) and no patient had previously undergone mpMRI. Parts of the patient data have been included in a previous study (10), but no detailed data on mpMRIs ability to detect missed csPCa with a comparison to RP specimens and clinical findings in this group of patients have been published.

Image analysis

MpMRI (T2-weighted [T2W], diffusion weighed imaging [DWI], and dynamic contrast-enhanced [DCE] imaging) was performed prior to re-biopsy using the same protocol as previously published (10). Imaging parameters appears in Table 1. All mpMRI data underwent blinded evaluation by the same physician who registered and scored all suspicious lesions on an 18-region modified prostate diagram (11) according to the PIRADS v1 classification (summation score; range = 3-15) from ESUR (6). Additionally, each patient was classified on a five-point $PIRADS_{patient}$ score according to the overall probability of having csPCa (1 = very low, 2 = low, 3 = intermediate, 4 = high, and 5 = very high). Patients without any abnormality on mpMRI were classified as very low suspicion mpMRI ($PIRADS_{lesion}$ score 3, $PIRADS_{patient}$ score 1). The modified PIRADS v2 (12) was not available during the timeframe of this study.

Repeat $TRUS_{bx}$ and MRI_{TB}

Ten systematic re-$TRUS_{bx}$ cores (six lateral and four medial from the base, middle, and apex from both the left and right sides) were obtained systematically (blinded to mpMRI findings) from ten prostatic regions and marked separately. The operator then reviewed the mpMRI data on a dedicated workstation in the biopsy room and additional MRI_{TB} (1–2 cores/lesion) were

Table 1. Sequence parameters for 3T multiparametric MRI with PPA coil.

	Pulse sequence	TR (ms)	TE (ms)	FA (°)	FOV (cm)	ACQ matrix	Slices (n)	Slice thickness (mm)
Axial DWI, b = 0, 100, 800, 1400 s/mm^2	SE-EPI	4697	81	90	18 × 18	116 × 118	18	4
Axial T2W	SE-TSE	3129	90	90	16 × 16	248 × 239	20	3
Sagittal T2W	SE-TSE	3083	90	90	16 × 16	248 × 242	20	3
Coronal T2W	SE-TSE	3361	90	90	19 × 19	252 × 249	20	3
Coronal T1W	SE-TSE	675	20	90	40 × 48	540 × 589	36	3.6
Axial 3D DCE	FFE-3d-TFE	5.7	2.8	12	18 × 16	128 × 111	18	4

SE, spin echo; EPI, echo planar imaging; TSE, turbo spin echo; TFE, turbo field echo; FFE, fast field echo; TR, repetition time; TE, echo time; FA, flip angle; ACQ matrix, acquisition matrix.

subsequently targeted towards any identified lesion (range $PIRADS_{lesion} = 4–15$; $PIRADS_{patient} = 2–5$) using mpMRI-TRUS image fusion either cognitive (n = 83) or software-based (n = 206, Hitachi, HI-RVS-system).

Pathological evaluation and clinical significance

For each PCa positive biopsy core, the location, the Gleason score (GS) (13), and the extent of cancer core involvement (%) was determined. Furthermore, all cancerous foci including tumor volume, the overall GS, and the pathological stage (pT; TNM classification (14)) including presence and location of any extra prostatic extension (EPE) were outlined by the pathologist in all patients who subsequently underwent RP.

Histopathological findings were used to define csPCa as: (i) any biopsy core with GS > 6; (ii) maximum cancerous core-length ≥50%; and (iii) for $TRUS_{bx}$ only, presence of ≥3 PCa positive cores. In the RP specimens, csPCa was defined as: (i) GS > 6; (ii) locally advanced disease (≥pT3a); or (iii) tumor volume >0.5 cc.

Statistical analysis

The association of pre-biopsy mpMRI suspicion scores and biopsy results were compared using a Chi-square analysis on both lesion ($PIRADS_{lesion}$) and patient ($PIRADS_{patient}$) levels. Biopsy detection rates on MRI_{TB} and $TRUS_{bx}$ were compared using the McNemar test. Cancer significance was compared in patients stratified by biopsy technique using a Fisher's exact test and a McNemar test in RP patients. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of mpMRI for detection of any PCa and csPCa were calculated according to different mpMRI suspicion score levels and PSAd threshold >0.15 ng/mL/cc. The best PIRADS score cutoff level balancing sensitivity and specificity was calculated using the Youden J statistics (sensitivity + specificity – 1). Receiver operating characteristic (ROC) curves with area under the curves (AUC) calculation were generated to compare the $PIRADS_{patient}$ score with PSA level and PSAd ($PSA/prostate_{volume}$) for discriminating patients with csPCa and no/insPCa. A logistic regression model was used to calculate the predicted probabilities combining the $PIRADS_{patient}$ score with either PSA level or PSAd to assess whether their combination further improved the AUC on ROC curve analysis. DeLong's test was used to test for statically significance between the AUC of two curves. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using software SPSS 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc, version 16.2 (MedCalc Software, Ostend, Belgium).

Table 2. Patient characteristics.

Clinical characteristics		Total (n = 289)
Age (years), median [IQR]		64 [59–67]
PSA (ng/mL), median [IQR]		12.0 [8.3–19]
PSA density (ng/mL/cc), median [IQR]		0.19 [0.13–0.29]
Prior biopsy, median [range]		2 [1–6]
Prostate volume (mL), median [IQR]		63 [46–87]
Time mpMRI ∀ biopsy (d), median [IQR]		6 [1–13]
cT_{DRE} category (n (%))		
Non-palpable foci	cT1	261 (90)
Palpable foci	cT2–T3	28 (10)
MpMRI included foci (n)		449
Foci/patient, mean [range]		1.6 [1–2]
Zone of origin (n (%))		
Peripheral zone		228 (51)
Transitional zone		221 (49)
MpMRI foci with PCa (n)		126
Zone of origin (n (%))		
Peripheral zone		57 (45)
Transitional zone		69 (55)

PSA, prostate specific antigen; DRE, digital rectal examination; mpMRI, multiparametric MRI; PCa, prostate cancer; IQR, interquartile range.

Results

Of the 302 prospectively enrolled patients, 13 were excluded due to technical problems or claustrophobia. The final study population of 289 had a median age and PSA of 64 (IQR = 59–67) and 12.8 ng/mL (IQR = 8.3–19.1), respectively (Table 2). Overall, PCa was detected in 128/289 (44%) patients; 88/289 (30%) had csPCa.

Biopsies: mpMRI identified at least one target lesion ranging from low to high suspicion in 271/289 (94%) men. Of these, MRI_{TB} detected PCa in 96 (35%), of which 18 (19%) and 78 (81%) harbored insPCa and csPCa, respectively. Overall, 449 separate mpMRI lesions ranging from low to high suspicion were identified and targeted by 598 MRI_{TB}. MRI_{TB} was positive for PCa in 28% (126/449) of all targeted lesions. The mpMRI suspicion scores were highly associated with the biopsy results ($P < 0.001$) on both patient and lesion level (Figs. 1 and 2) and the diagnostic yield for detecting csPCa increased with rising PIRADS scores. The sensitivity and specificity for detecting any and csPCa on mpMRI followed by MRI_{TB} altered

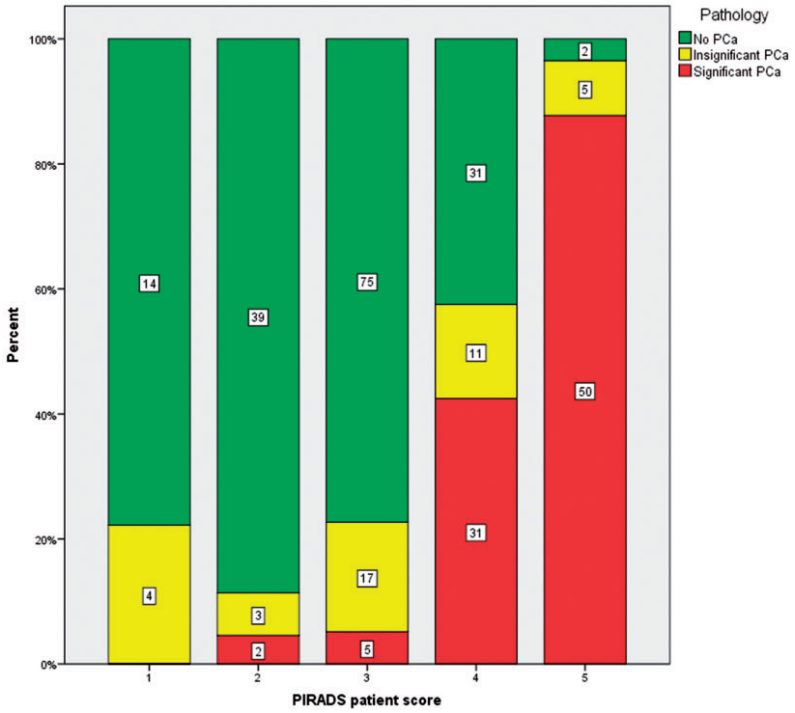

Fig. 1. PCa detection rates for the 289 included patients associated with $PIRADS_{patient}$ scores stratified by cancer significance. The proportion of csPCa in patients with $PIRADS_{patient}$ score of 4–5 was significantly higher ($P < 0.001$) compared with patients with $PIRADS_{patient}$ score of 1–2.

depending on different PIRADS score cutoff levels (Table 3). Using $PIRADS_{lesion}$ score ≥ 11 as best biopsy threshold determined by the Youden index (0.62), the sensitivity/specificity for detecting any PCa and csPCa were 79%/83% and 89%/80% with NPVs of 91% and 97%, respectively. The proportion of lesions with higher malignancy (GS ≥ 7) increased significantly with higher suspicion scores (Fig. 3).

$TRUS_{bx}$ detected PCa in 108/289 (37%) patients, of which 49 (45%) and 59 (55%) harbored insPCa and csPCa, respectively. Overall, $TRUS_{bx}$ detected more patients with PCa compared with MRI_{TB} (37% versus 33%), but the difference did not reach statistical significance (McNemar's test = 2.237, $P = 0.126$). However, the diagnostic yield of csPCa versus insPCa was significantly improved by MRI_{TB} (Table 4). PCa was detected in 76/128 patients on both MRI_{TB} and $TRUS_{bx}$, respectively. An additional 32 patients had PCa detected only by $TRUS_{bx}$, among which 24/32 (75%) harbored insPCa. Conversely, 20 patients had PCa detected only by MRI_{TB} with 16/20 (80%) harboring csPCa (Table 4). Of the 88 patients with csPCa, ten were detected only by $TRUS_{bx}$, 29 only by MRI_{TB}, and 49 by both methods. Only 2/62 patients with low suspicion mpMRI ($PIRADS_{patient} < 3$) had csPCa on confirmatory biopsy. Eighteen patients had no abnormality on mpMRI and were classified as very low suspicion mpMRI. $TRUS_{bx}$ detected insPCa in 4/18 of these patients; none had csPCa. The AUC on ROC curve analysis (Fig. 4) was significantly ($P < 0.001$) higher for the $PIRADS_{patient}$ score (0.90; 95% confidence interval [CI] = 0.86–0.94) compared with PSA level (0.60; 95% CI = 0.52–0.67) and PSAd (0.76; 95% CI = 0.69–0.82) in the ability to differentiate patients with csPCa from patients with no/insPCa. ROC curves for the combined use of the $PIRADS_{patient}$ score with PSA level and density are shown in Fig. 4b.

Radical prostatectomy (RP): in total, 64/128 (50%) PCa patients subsequently underwent RP. Of these, 60 (94%) had csPCa and 33% (21/64) had EPE (Table 5). Rising $PIRADS_{patient}$ scores were associated with more advanced pathological stage and GS at RP. No patient with a score of 1–2 underwent RP. Of the 64 RP treated patients, MRI_{TB} and $TRUS_{bx}$ missed the diagnosis of PCa in ten and nine patients, respectively. Of the ten patients missed on MRI_{TB}, all but one patient had localized disease (pT2) and four had insPCa. All six patients with csPCa had mpMRI intermediate/high suspicious findings ($PIRADS_{lesion} \geq 10$; $PIRADS_{patient} \geq 3$)

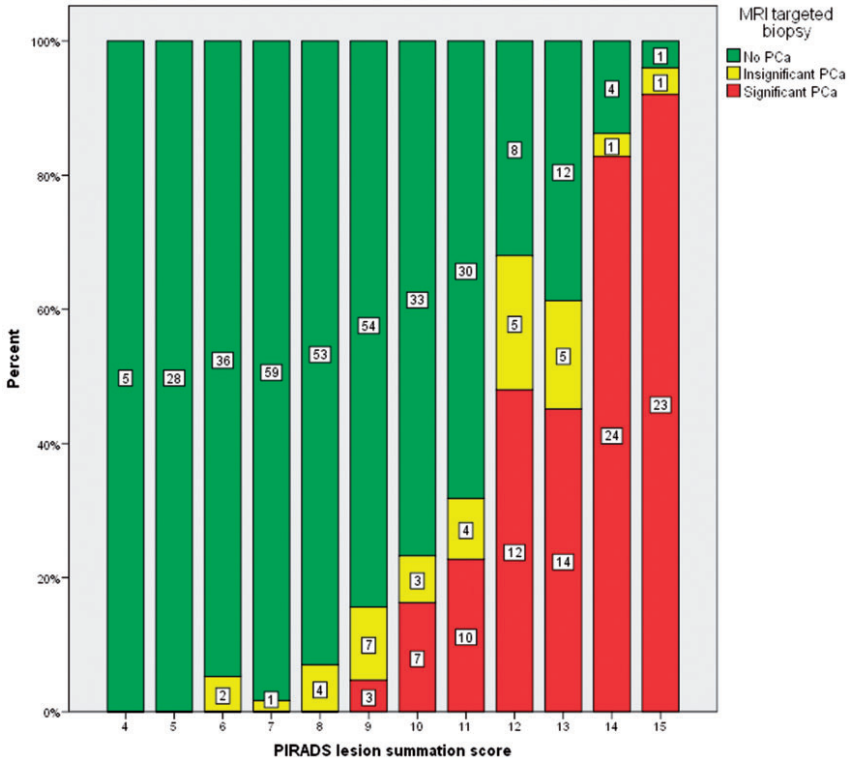

Fig. 2. MRI_{TB} results for each targeted mpMRI suspicious lesion associated with $PIRADS_{lesion}$ scores stratified by cancer significance.

targeted by MRI_{TB} that were benign. Conversely, all nine patients missed on $TRUS_{bx}$ had csPCa and 2/9 had EPE. MpMRI was significantly better to predict postoperative presence of significant cancer (McNemar's test = 5.500, $P = 0.019$), as MRI_{TB} and $TRUS_{bx}$ correctly identified csPCa in the RP specimens in 47/60 (78%) and 35/60 (58%) patients, respectively.

On lesions basis, preoperative MRI_{TB} detected PCa in 74/110 separate mpMRI suspicious lesions. However, the histopathological examination of the RP specimen subsequently revealed PCa in 17/36 of the mpMRI suspicious lesions with benign MRI_{TB}, indicating misregistration and targeting error using fusion biopsies. The RP specimens revealed a csPCa lesion in four patients missed by the mpMRI reader that changed the overall diagnosis in 2/4 patients, as the other lesions were secondary foci to an MRI_{TB} detected index lesion.

Discussion

A significant association between the mpMRI suspicion grade and detection of any PCa and csPCa on both patient and lesion levels ($P < 0.001$) was found. Using PIRADS score derived targets to guide MRI_{TB} improved the detection rate of missed csPCa compared to re-$TRUS_{bx}$ in accordance with previous studies (7,15). It underlines that pre-biopsy mpMRI PIRADS scores are highly predictive of biopsy outcome. Cash et al. (15) evaluated the diagnostic performance of mpMRI for detection of PCa in relation to $PIRADS_{patient}$ score subgroups (score 2–5) and reported a strong correlating between PCa detection rates and rising $PIRADS_{patient}$ scores. Only a small proportion of patients (3/32) with a low suspicion mpMRI (score 2) had csPCa.

We used both scores ($PIRADS_{lesion}$ and $PIRADS_{patient}$ score) to analyze suspicious lesions and patients. The PIRADS v1 classification has previously been prospectively validated in contemporary patient cohorts in relation to repeat prostate biopsies and RP specimens (7,16). However, although the diagnostic yield of csPCa increases with rising mpMRI suspicion scores, there is no consensus regarding the threshold above which a biopsy may be recommended (biopsy threshold), as reported in the meta-analysis by Hamoen et al. (4). In our study, the optimal cutoff levels determined by the Youden index were $PIRADS_{patients}$ score ≥ 4 and $PIRADS_{lesion}$ score ≥ 11. Using this biopsy threshold, the sensitivity and NPV

Table 3. Diagnostic performance of mpMRI scoring and PSAd for detection of any and csPCa on patient ($PIRADS_{patient}$ score) and lesion ($PIRADS_{lesion}$ score) levels depending on cutoff threshold.

		Any PCa/csPCa*			Any PCa / csPCa*				
MpMRI score		+	–	Total	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]	Youden index
$PIRADS_{patient}$ score†									
Score ≥ 5	+	55/50	2/7	57	0.43/0.57	0.99 / 0.97	0.96 / 0.88	0.69 / 0.84	0.42 / 0.54
	–	73/38	159/194	232	[0.34–0.52] / [0.46–0.67]	[0.96–0.99] / [0.93–0.99]	[0.87–0.99] / [0.77–0.94]	[0.65–0.72] / [0.80–0.87]	
	Total	128/88	161/201	289					
Score ≥ 4	+	97/81	33/49	130	0.75/0.92	0.80/0.76	0.75/0.62	0.81/0.96	0.55/0.68
	–	31/7	128/152	159	[0.67–0.83] / [0.84–0.97]	[0.72–0.85] / [0.69–0.81]	[0.68–0.80] / [0.56–0.68]	[0.75–0.85] / [0.91–0.98]	
	Total	128/88	161/201	289					
Score ≥ 3	+	119/86	108/141	227	0.93/0.98	0.33 / 0.30	0.52 / 0.38	0.85 / 0.97	0.26 / 0.28
	–	9/2	53/60	62	[0.87–0.97] / [0.92–0.99]	[0.26–0.41] / [0.24–0.37]	[0.49–0.55] / [0.36–0.40]	[0.75–0.92] / [0.88–0.99]	
	Total	128/88	161/201	289					
$PIRADS_{lesion}$ score†									
PIRADS ≥ 13	+	68/61	18/25	86	0.54/0.66	0.94/0.93	0.79/0.71	0.84/0.91	0.48/0.59
	–	58/32	305/331	363	[0.45–0.63] / [0.55–0.75]	[0.91–0.97] / [0.90–0.95]	[0.70–0.86] / [0.62–0.79]	[0.81–0.86] / [0.89–0.93]	
	Total	126/93	323/356	449					
PIRADS ≥ 12	+	85/73	25/37	110	0.67/0.78	0.92/0.90	0.77/0.66	0.88/0.94	0.59/0.68
	–	41/20	298/319	339	[0.59–0.76] / [0.69–0.76]	[0.89–0.95] / [0.86–0.93]	[0.70–0.83] / [0.59–0.73]	[0.85–0.90] / [0.92–0.96]	
	Total	126/93	323/356	449					
PIRADS ≥ 11	+	99/83	55/71	154	0.79/0.89	0.83/0.80	0.64/0.54	0.91/0.97	0.62/0.69
	–	27/10	268/285	295	[0.70–0.85] / [0.81–0.95]	[0.78–0.87] / [0.76–0.84]	[0.58–0.70] / [0.48–0.59]	[0.88–0.93] / [0.94–0.98]	
	Total	126/93	323/356	449					
PIRADS ≥ 10	+	111/90	88/109	199	0.88/0.96	0.73/0.69	0.56/0.45	0.94/0.98	0.61/0.65
	–	15/3	235/247	250	[0.81–0.93] / [0.91–0.99]	[0.68–0.78] / [0.64–0.74]	[0.51–0.60] / [0.41–0.49]	[0.91–0.96] / [0.96–0.99]	
	Total	126/93	323/356	449					
PIRADS ≥ 9	+	119/93	142/168	261	0.94/1.00	0.56/0.53	0.46/0.36	0.96/1.00	0.50/0.53
	–	7/0	181/188	188	[0.89–0.98] / [0.96–1.00]	[0.50–0.62] / [0.48–0.58]	[0.42–0.49] / [0.33–0.38]	[0.93–0.98] / [1.00]	
	Total	126/93	323/356	449					
PSAd > 0.15 ng/mL/cc	+	98/73	85/110	183	0.77/0.83	0.47/0.45	0.54/0.40	0.72/0.86	0.24/0.28
	–	30/15	76/91	106	[0.68–0.84] / [0.73–0.90]	[0.39–0.55] / [0.38–0.52]	[0.49–0.58] / [0.36–0.44]	[0.64–0.78] / [0.79–0.91]	
	Total	128/88	161/201	289					

*PCa diagnosis is based on MRI_{TB} results for the $PIRADS_{lesion}$ score and combined detection rate (MRI_{TB} and TRUSbx) for the $PIRADS_{patient}$ score.
†Cutoff level for a dichotomized positive MRI.

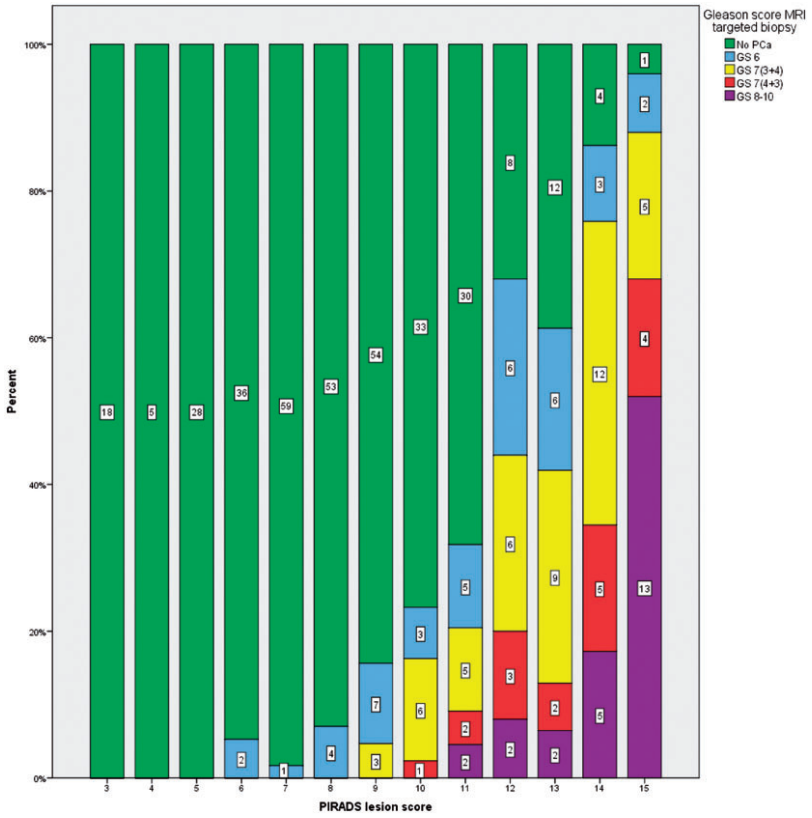

Fig. 3. MRI_{TB} results associated with $PIRADS_{lesion}$ scores stratified by the Gleason score.

Table 4. Cross tabulation of patients with no, clinically insignificant (insPCa), and significant PCa (csPCa) stratified by biopsy technique.

	$TRUS_{bx}$			
	No PCa	InsPCa	CsPCa	Total
MRI_{TB}				
No PCa	161	24	8	193
InsPCa	4	12	2	18
CsPCa	16	13	49	78
Total	181	49	59	289

MRI_{TB} detected significantly more patients with csPCa compared with $TRUS_{bx}$ (McNemar's test csPCa vs. no/insPCa; $P = 0.004$).
PCa, prostate cancer.

were 75%/81% and 81%/96% for detecting and ruling out any PCa and csPCa on the patient level. In a repeat biopsy setting, this high NPV can be used to exclude presence of csPCa and possibly reduce the number of unnecessary re-biopsy sessions. However, although we found similar high sensitivity and NPV on lesion level (Table 3), the specificity was lower. In the PIRADS v1 classification all mpMRI sequence scores (T2W, DWI, and DCE) are weighted equally. However, not all sequences are always equally important when evaluating possible presence of csPCa. DWI has been reported to be the best sequence for lesion detection in the peripheral zone (17) and conversely T2W imaging in the transitional zone (18). Therefore, the PIRADS v2 classification (12) has been developed after the initiation of this study and provides an overall final score in the range of 1–5 driven by the dominant sequence. Although, some preliminary studies show that PIRADS v2 uses a simplified approach that may be less time-consuming and shows similar high diagnostic accuracy and inter-reader agreement compared to PIRADS v1 (19,20), Auer et al. (21) report a lower diagnostic accuracy and Rosenkrantz et al. (22) recommend adjustments to the scoring criteria.

An unexplainable rise in PSA levels or PSAd > 0.15 ng/mL/cc are traditional clinical findings used to select patients for repeat biopsies. However, based upon the AUC on ROC curve analysis,

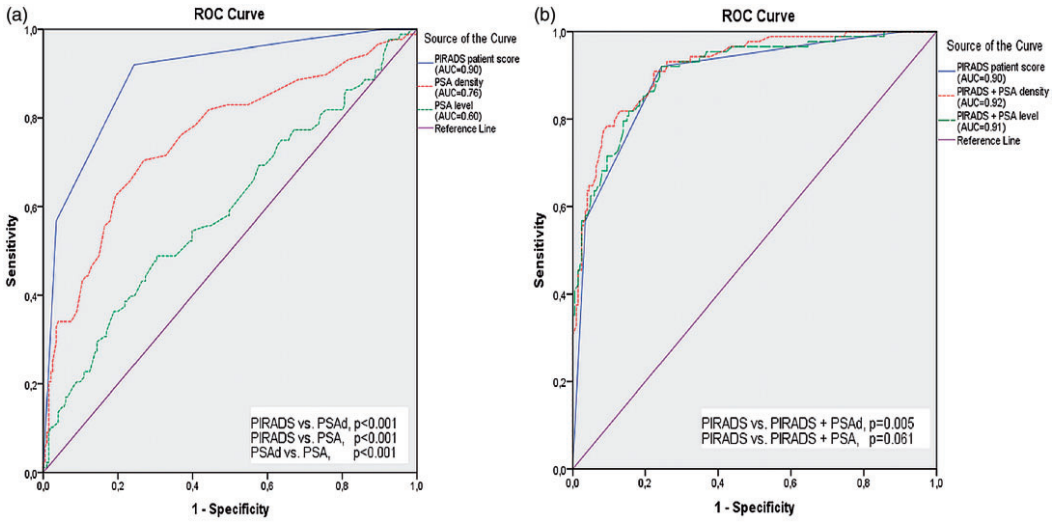

Fig. 4. ROC curve analysis comparing (a) the mpMRI $PIRADS_{patient}$ score with PSA level and PSA density and (b) combined models in discriminating patients with csPCa and no/insPCa. DeLong's test was used to test for statistical significance between the AUC of two curves.

Table 5. Clinical characteristics of patient undergoing RP. (*can be published only online/as supplementary table if necessary*)

Clinical characteristics of RP patients					Total (n = 64)
Age (years), median [IQR]					64 [58–67]
PSA (ng/mL), median [IQR]					13.0 [9.5–20]
PSA density (ng/mL/cc), median [IQR]					0.28 [0.14–0.45]
Prior biopsy, median [range]					2 [1–5]
Prostate volume (mL), median [IQR]					49 [36–69]
PCa significance (RP) (n (%))					
Insignificant cancer					4 (6)
Significant cancer					60 (94)
		$PIRADS_{patient}$ score*			
Gleason score (RP) (n (%))		Score 3	Score 4	Score 5	Total
Gleason score 6		2	6	2	10 (16)
Gleason score 7 (3+4)		2	12	15	19 (45)
Gleason score 7 (4+3)		0	4	13	17 (27)
Gleason score 8–10		0	3	5	8 (13)
Total		4	25	35	64
pT_{RP} category (n (%))					
Localized PCa	pT2a	2	3	1	6 (9)
	pT2b	0	0	1	1 (2)
	pT2c	2	16	18	36 (56)
Locally advanced PCa	pT3a	0	6	12	18 (28)
	pT3b	0	0	3	3 (5)
Total		4	25	35	64

*No patient with $PIRADS_{patient}$ score of 1–2 underwent RP.
PSA, prostate-specific antigen; RP, radical prostatectomy; PCa, prostate cancer; IQR, interquartile range.

mpMRI was the best to identify patients with missed csPCa on subsequent biopsy. Combining the $PIRADS_{patient}$ score with PSAd showed only slight increase in AUC (0.92) compared with the $PIRADS_{patient}$ score alone, although the difference was statistically significant. Rais-Bahrami et al. (23) analyzed the diagnostic PCa detection yield of a bi-parametric MRI compared to PSA-based screening and concluded that MRI criteria outperformed PSA level and density for detection of any PCa.

In total, 64 patients subsequently underwent RP with EPE in 33%. In accordance with biopsy results, rising PIRADS scores were associated with more advanced pathological stage at RP. Even though the RP patient number is limited, MRI_{TB} demonstrated better association with final pathology (RP specimen) in prediction of csPCa compared with $TRUS_{bx}$. A recent meta-analysis by de Rooij et al. (24) correlating mpMRI findings to RP specimens reported mediocre accuracy for mpMRI in local staging and detection of EPE. However, growing evidence indicates that it is not necessary to detect all small multifocal insPCa foci in a given patient, but more importantly to detect the most aggressive lesion—the index lesion—as it is the driver of prognosis and any adverse oncologic outcome (25). Baco et al. (26) showed that MRI_{TB} allowed accurate identification and characterization of the index tumor in 135 RP specimens and Radtke et al. (27) concluded that mpMRI using PIRADS v1 classification identified 92% and 85% of all index and csPCa lesions, while missing 88% of non-significant non-index lesions, respectively.

Incorporating mpMRI findings into everyday clinical decision-making could be the beginning towards the end of blind prostate biopsies (28). However, MRI_{TB} may still miss PCa lesions due to targeting errors caused by misregistration with image-fusion and unnecessary MRI_{TB} may be conducted due to false-positive mpMRI readings, as indicated by lower specificity and PPV in this study. Furthermore, the cost-effectiveness of a diagnostic mp-MRI, the additional use of MRI_{TB}, and the long-term outcome have not been fully explored.

This study has several limitations. Our cohort is not homogeneous as we included patients with a various number of prior biopsy sessions (range = 1–6). Patients were prone to benefit from targeted biopsies, as they usually presented rising PSA levels with prior negative $TRUS_{bx}$. However, the PSA level demonstrated a low AUC (0.60) in predicting presence of csPCa on ROC curve analysis. We used image-fusion (cognitive or software-based) to fuse mpMRI data with real-time TRUS imaging based on anatomical landmarks. However, there is always a risk of misregistration when two image modalities are combined. The fact that 17/36 mpMRI suspicious lesions with benign MRI_{TB} subsequently revealed PCa on the RP specimen confirms targeting error using mpMRI-TRUS image fusion. Several fusion systems have been developed to target mpMRI marked lesions (7,8,29) with potentially increased accuracy. Furthermore, in-bore direct mpMRI guided biopsies within the MRI suite may be more accurate and show good results (30). However, the biopsy procedure is time-consuming and occupies the MRI suite twice.

Because we used biopsy results as the comparing reference, PCa foci may have been missed by mpMRI, MRI_{TB}, and $TRUS_{bx}$ in patients with benign biopsies. Thus, the true rate of false-negative readings cannot be assessed. The sub-analysis of patients who subsequently underwent RP identified some cases and previous studies that adhered to the ESUR guidelines have shown a good correlation between mpMRI findings and the RP specimen (24).

Overall, our findings underline the incremental value of pre-biopsy mpMRI to increase the detection of csPCa previously missed by $TRUS_{bx}$ and to stratify patients and lesions according to suspicion on mpMRI. MRI_{TB} can improve the diagnostic yield csPCa versus insPCa compared with re-$TRUS_{bx}$ and mpMRI is significantly better than PSA level and PSAd to identify patients with prior missed csPCa. Furthermore, our study reports the association between all PIRADS score subgroups on patient and lesion levels, as well as the association to the GS distribution and the pathological stage following RP.

In conclusion, mpMRI suspicion scores correlate well with biopsy and RP results on both patient and lesion level. MpMRI followed by fusion targeted biopsies improves the detection rate of csPCa previously missed by $TRUS_{bx}$.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Vickers AJ, Thompson IM, Klein E, et al. A commentary on PSA velocity and doubling time for clinical decisions in prostate cancer. Urology 2014;83:592–596.
2. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion–guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390–397.
3. Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging–targeted biopsy may enhance the

diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol 2015;68:438–450.
4. Hamoen EHJ, de Rooij M, Witjes JA, et al. Use of the Prostate Imaging Reporting and Data System (PI-RADS) for prostate cancer detection with multiparametric magnetic resonance imaging: a diagnostic meta-analysis. Eur Urol 2015;67:1112–1121.
5. Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol 2013;63:125–140.
6. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. Eur Radiol 2012;22: 746–757.
7. Portalez D, Mozer P, Cornud F, et al. Validation of the European Society of Urogenital Radiology scoring system for prostate cancer diagnosis on multiparametric magnetic resonance imaging in a cohort of repeat biopsy patients. Eur Urol 2012;62:986–996.
8. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol 2013;64: 713–719.
9. Pokorny MR, de Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. Eur Urol 2014;66:22–29.
10. Boesen L, Noergaard N, Chabanova E, et al. Early experience with multiparametric magnetic resonance imaging-targeted biopsies under visual transrectal ultrasound guidance in patients suspicious for prostate cancer undergoing repeated biopsy. Scand J Urol 2015;49:25–34.
11. Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol 2011;59:477–494.
12. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol 2016;69:16–40.
13. Epstein JI, Allsbrook WC, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2005;29:1228–1242.
14. Sobin L, Gospodarowicz M WC. TNM Classification of Malignant Tumours. Urological Tumours. 7th edn. International Union Against Cancer. Hoboken, NJ: Wiley-Blackwell, 2009.
15. Cash H, Maxeiner A, Stephan C, et al. The detection of significant prostate cancer is correlated with the Prostate Imaging Reporting and Data System (PI-RADS) in MRI/transrectal ultrasound fusion biopsy. World J Urol 2016;34:525–532.
16. Delongchamps NB, Lefèvre A, Bouazza N, et al. Detection of significant prostate cancer with magnetic resonance targeted biopsies–should transrectal ultrasound-magnetic resonance imaging fusion guided biopsies alone be a standard of care? J Urol 2015;193: 1198–1204.
17. Langer DL, van der Kwast TH, Evans AJ, et al. Prostate cancer detection with multi-parametric MRI: logistic regression analysis of quantitative T2, diffusion-weighted imaging, and dynamic contrast-enhanced MRI. J Magn Reson Imaging 2009;30:327–334.
18. Hoeks CMA, Hambrock T, Yakar D, et al. Transition zone prostate cancer: detection and localization with 3-T multiparametric MR imaging. Radiology 2013;266: 207–217.
19. Tewes S, Mokov N, Hartung D, et al. Standardized reporting of prostate MRI: comparison of the Prostate Imaging Reporting and Data System (PI-RADS) Version 1 and Version 2. PLoS One 2016;11:e0162879.
20. De Visschere P, Pattyn E, Ost P, et al. Comparison of the Prostate Imaging Reporting and Data System (PI-RADS) Version 1 and 2 in a cohort of 245 patients with histopathological reference and long-term follow-up. J Belgian Soc Radiol 2016;100:108.
21. Auer T, Edlinger M, Bektic J, et al. Performance of PI-RADS version 1 versus version 2 regarding the relation with histopathological results. World J Urol 2017;35: 687–693.
22. Rosenkrantz AB, Babb JS, Taneja SS, et al. Proposed adjustments to PI-RADS version 2 decision rules: Impact on prostate cancer detection. Radiology 2017; 283:119–129.
23. Rais-Bahrami S, Siddiqui MM, Vourganti S, et al. Diagnostic value of biparametric magnetic resonance imaging (MRI) as an adjunct to prostate-specific antigen (PSA)-based detection of prostate cancer in men without prior biopsies. BJU Int 2015;115:381–388.
24. de Rooij M, Hamoen EHJ, Witjes JA, et al. Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. Eur Urol 2016;70: 233–245.
25. Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med 2009;361:1704–1706.
26. Baco E, Ukimura O, Rud E, et al. Magnetic resonance imaging–transectal ultrasound image-fusion biopsies accurately characterize the index tumor: correlation with step-sectioned radical prostatectomy specimens in 135 patients. Eur Urol 2015;67:787–794.
27. Radtke JP, Schwab C, Wolf MB, et al. Multiparametric magnetic resonance imaging (MRI) and MRI-transrectal ultrasound fusion biopsy for index tumor detection: correlation with radical prostatectomy specimen. Eur Urol 2016;70:846–853.
28. Tombal B. Toward the end of blind prostate biopsies? Eur Urol 2012;62:997–998.
29. Sonn GA, Chang E, Natarajan S, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol 2014;65:809–815.
30. Overduin CG, Fütterer JJ, Barentsz JO. MRI-guided biopsy for prostate cancer detection: a systematic review of current clinical results. Curr Urol Rep 2013; 14:209–213.

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Assessment of the Diagnostic Accuracy of Biparametric Magnetic Resonance Imaging for Prostate Cancer in Biopsy-Naive Men

The Biparametric MRI for Detection of Prostate Cancer (BIDOC) Study

Lars Boesen, MD, PhD; Nis Nørgaard, MD; Vibeke Løgager, MD; Ingegerd Balslev, MD; Rasmus Bisbjerg, MD; Karen-Cecilie Thestrup, MD; Mads D. Winther; Henrik Jakobsen, MD; Henrik S. Thomsen, DMC

Abstract

IMPORTANCE Multiparametric magnetic resonance imaging (MRI) enhances detection and risk stratification for significant prostate cancer but is time-consuming (approximately 40 minutes) and expensive. Rapid and simpler (approximately 15-minute) biparametric MRI (bpMRI) using fewer scan sequences could be implemented as a prostate MRI triage test on a larger scale before performing biopsies.

OBJECTIVES To assess the diagnostic accuracy and negative predictive value (NPV) of a novel bpMRI method in biopsy-naive men in detecting and ruling out significant prostate cancer in confirmatory biopsies.

DESIGN, SETTING, AND PARTICIPANTS A single-institutional, paired, prospective cohort study of biopsy-naive men with clinical suspicion of prostate cancer from November 1, 2015, to June 15, 2017.

INTERVENTIONS All patients underwent bpMRI (T2-weighted and diffusion-weighted imaging) followed by standard transrectal ultrasound-guided biopsies (all men) and targeted biopsies of men with suspicious bpMRI findings.

MAIN OUTCOMES AND MEASURES Suspicion grades of bpMRI, biopsy results, and NPV of bpMRI were evaluated for detection of or ruling out significant prostate cancer (Gleason score ≥4 + 3 or maximum cancerous core length >50% for Gleason score 3 + 4). We compared the diagnostic performance of standard biopsies in all men vs standard plus targeted (combined) biopsies restricted to men with suspicious bpMRI findings. The reference standard was combined biopsy results from all men.

RESULTS A total of 1020 men were enrolled, with a median age of 67 years (interquartile range, 61-71 years) and a median prostate-specific antigen level of 8.0 ng/mL (interquartile range, 5.7-13.0 ng/mL). Combined biopsies detected any and significant prostate cancer in 655 of 1020 men (64%) and 404 of 1020 men (40%), respectively. Restricting combined biopsies to men with suspicious bpMRI findings meant 305 of 1020 men (30%) with low-suspicious bpMRIs could avoid prostate biopsies (biopsy in 715 men with suspicious bpMRIs vs all 1020 men who required standard biopsies [70%]; $P < .001$). Significant prostate cancer diagnoses were improved by 11% (396 vs 351 men; $P < .001$), and insignificant prostate cancer diagnoses were reduced by 40% (173 vs 288 men; $P < .001$) compared with our current diagnostic standard, standard biopsies alone in all men. The NPV of bpMRI findings in ruling out significant prostate cancer was 97% (95% CI, 95%-99%).

(continued)

Key Points

Question What are the diagnostic accuracy and negative predictive value of novel biparametric magnetic resonance imaging (MRI) in biopsy-naive men in detecting and ruling out significant prostate cancer?

Findings In this cohort study of 1020 men who underwent both biparametric targeted and standard transrectal ultrasound-guided biopsies, low-suspicion biparametric MRI had a high negative predictive value (97%) in ruling out significant prostate cancer on confirmatory biopsies.

Meaning The biparametric MRI used as a triage test in this study was associated with improved prostate cancer risk stratification and may be used to exclude aggressive disease and avoid unnecessary biopsies in 30% of men with clinical suspicion of prostate cancer, although further studies are needed to fully explore this new diagnostic approach.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE Low-suspicion bpMRI has a high NPV in ruling out significant prostate cancer in biopsy-naive men. Using a simple and rapid bpMRI method as a triage test seems to improve risk stratification and may be used to exclude aggressive disease and avoid unnecessary biopsies with its inherent risks. Future studies are needed to fully explore its role in clinical prostate cancer management.

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Introduction

Standard diagnostic transrectal ultrasonography (TRUS)–guided biopsies are offered to men with clinical suspicion of prostate cancer due to elevated prostate-specific antigen (PSA) levels and/or abnormal digital rectal examination results. However, men without prostate cancer undergo unnecessary biopsies because elevated PSA is not cancer specific. Given the high false-positive rate of PSA, its use for screening purposes is controversial and an area of continuous debate within the medical and urological communities.[1] As standard biopsies are prone to sampling errors because of difficulties in prostate cancer target identification on TRUS, clinically significant prostate cancer may be missed and insignificant prostate cancer detected by the random untargeted sampling, potentially leading to overdetection and overtreatment.[2] In addition, biopsies are invasive and may lead to patient anxiety and morbidity.[3] These limitations have highlighted the need for better diagnostic tools, such as risk calculators, biomarkers, or imaging techniques,[4] to improve selection of men with increased risk of significant prostate cancer who require diagnostic biopsies and subsequent treatment from the proportion of men with either a benign condition or an insignificant prostate cancer that can be managed with expectancy. However, risk calculators are highly influenced by the population studied and newer biomarkers can be costly, may be limited by availability, and have not yet been proven to have the desired level of accuracy in biopsy-naive men with prostate cancer.[5,6] Accurate methods that improve detection of significant prostate cancer while minimizing overdetection and unnecessary biopsies by reducing the number of false-positive results are highly warranted. Growing evidence supports the use of multiparametric magnetic resonance imaging (mpMRI) to solve this problem.[7,8] Magnetic resonance imaging–guided biopsies (targeted biopsies) can be targeted toward the most aggressive part of suspicious lesions detected by mpMRI, improving the detection of significant prostate cancer compared with standard biopsies alone.[9-12] Conversely, low-suspicion mpMRI may noninvasively exclude the presence of aggressive disease.[13] Accordingly, mpMRI could potentially be used as a triage test to identify biopsy-naive men with clinical suspicion of prostate cancer who might safely avoid unnecessary biopsies.

However, guidelines on prostate MRI[14-16] recommend a full mpMRI prostate examination that includes several anatomical and functional scan sequences as well as intravenous contrast media. This is time-consuming (approximately 40 minutes), expensive, and might be difficult to implement on a large scale. Over time it has become evident that contrast-enhanced imaging and multiple imaging planes often do little to improve the overall clinical picture, especially in the detection and localization of significant prostate cancer. In contrast, a rapid and simple biparametric MRI (bpMRI) method that uses fewer scan sequences and no intravenous contrast media might decrease image acquisition time (approximately 15 minutes) and costs, while retaining sufficient diagnostic accuracy to detect and rule out significant prostate cancer in biopsy-naive men. Such a bpMRI protocol could provide a basis for a prostate MRI triage test prior to biopsy. Consequently, this prospective study assesses the diagnostic accuracy of bpMRI in detecting and ruling out significant prostate cancer in biopsy-naive men with clinical suspicion of prostate cancer. We evaluated the clinical significance of detected cancers and assessed whether bpMRI could be used as a triage test to improve the diagnosis of significant prostate cancer and identify patients who could safely avoid unnecessary biopsies.

Methods

This Biparametric MRI for Detection of Prostate Cancer (BIDOC) study is a prospective, single-institution, paired-cohort study. It was approved by the Local Committee for Health Research Ethics and the Danish Data Protection Agency. Participants provided written informed consent and were enrolled from November 1, 2015, to June 15, 2017. This study conformed to the Standards of Reporting for MRI-Targeted Biopsy Studies consortium criteria for MRI biopsy studies[17] and adhered to the Standards for Reporting of Diagnostic Accuracy (STARD) reporting guideline criteria.[18] The study inclusion criteria required all men to have clinical suspicion of prostate cancer (PSA ≥4 ng/mL [to convert to micrograms per liter, multiply by 1.0] and/or abnormal digital rectal examination results) that warranted a diagnostic prostate biopsy. The exclusion criteria were prior prostate biopsies, evidence of acute urinary tract infections, acute prostatitis, general contraindications for MRI (eg, claustrophobia, a pacemaker, metal implants), and prior hip replacement surgery or other metallic implants in the pelvic area.

Outcome Measures

The primary end points were the diagnostic accuracy and negative predictive value (NPV) of low-suspicion bpMRI findings in ruling out significant prostate cancer in confirmatory biopsies from biopsy-naive men. Secondary end points included the overall prostate cancer detection rate and detection rates of significant prostate cancer and insignificant prostate cancer stratified by biopsy technique. We also evaluated the clinical value of using bpMRI as a triage test prior to biopsies and estimated the proportion of men who could safely avoid unnecessary biopsies based on low-suspicion bpMRI findings.

bpMRI (Index Test) and Image Analysis

Prior to biopsies, bpMRI was performed using a 3-T MRI magnet (Philips Healthcare) with a pelvic-phased-array coil (Philips Healthcare) positioned over the pelvis. The bpMRI protocol included axial T2-weighted and diffusion-weighted images (*b* values: 0, 100, 800, and 2000) with reconstructions of the corresponding apparent diffusion coefficient map, because these 2 parameters are the dominant sequences for prostate cancer lesion detection on mpMRI.[15] A sagittal T2-weighted luxury scout image supported the axial sequences for MRI/TRUS image fusion. The overall bpMRI image acquisition time was approximately 15 minutes. Imaging parameters are listed in eTable 1 in the Supplement.

All bpMRI images were reviewed by the same prostate MRI physician (>5 years of experience) blinded to clinical findings. Suspicious lesions were scored on a 5-point scale according the Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) criteria.[15] However, as the bpMRI protocol does not include dynamic contrast-enhanced imaging, scoring of lesions in the peripheral zone relied solely on diffusion-weighted image findings (dominant sequence), and an equivocal score of 3 was not potentially upgraded to a score of 4 due to lack of positive dynamic contrast-enhanced findings. All patients were graded overall using this modified PI-RADS score according to their likelihood of having significant prostate cancer (1, highly unlikely; 2, unlikely; 3, equivocal; 4, likely; and 5, highly likely). A modified PI-RADS suspicion score of 2 or lower was perceived as a low-suspicion or negative bpMRI scan result. Patients with no suspicious lesions were assigned an overall modified PI-RADS score of 1.

Standard and Targeted Biopsies

Initially, all patients underwent systematic standard biopsies (10-core extended sextant biopsy scheme) according to guidelines.[19] Any suspicious lesion detected by TRUS was sampled as part of the standard biopsy scheme. Standard biopsies were immediately followed by additional targeted biopsies of any bpMRI suspicious lesions (modified PI-RADS ≥3; 1-2 cores/lesion) using 1 of 2 rigid MRI/TRUS image-fusion systems: HI-RVS system (Hitachi; n = 877) and Uro-Nav system (Invivo;

n = 143) for men biopsied. All prostate biopsies were potted separately and obtained using an end-fire biopsy technique by 1 of 2 operators with extensive experience in performing standard biopsies and reasonable experience in software-based image fusion for targeted biopsies (4 years and 1 year). Performance and analysis of standard biopsies and bpMRI were blinded with respect to each other.

Histopathological Evaluation and Cancer Significance

All biopsy samples were reviewed by the same genitourinary pathologist (>15 years of experience). For each prostate cancer-positive biopsy core, the location, Gleason score (GS) based on the International Society of Urological Pathology 2005 consensus,[20] and percentage of cancerous tissue per core were determined. In addition, patients were allocated using the International Society of Urological Pathology 2014 consensus Gleason-grade groups[21] based on the GS scoring criteria.[20] The primary definition of significant prostate cancer included both cancer GS grade and volume, and significant prostate cancer was defined as any core with high-grade prostate cancer (GS ≥7 [4 + 3]) or maximum cancerous core length greater than 50% of GS 7 (3 + 4) prostate cancer. Other definitions of significant prostate cancer were additionally assessed.

Statistical Analysis

Patient characteristics were stratified by biopsy results and reported using descriptive statistics. Continuous variables (eg, age, PSA level, PSA density, and prostate volume) were compared using the Wilcoxon rank sum test. Fisher exact test was used to compare the clinical tumor stage determined by digital rectal examination pooled in nonpalpable and palpable tumor groups. Prebiopsy bpMRI suspicion (modified PI-RADS) scores were compared with biopsy results using a χ^2 analysis to determine the association between bpMRI suspicion and positive biopsy findings. We compared the diagnostic performances of the following clinical strategies: (1) standard biopsies in all men, (2) standard plus targeted (combined) biopsies restricted to men with suspicious bpMRIs, and (3) combined biopsies in all men, which served as reference standard. Any patient with significant prostate cancer in either standard or targeted biopsies was classified as having significant prostate cancer on combined biopsies. A McNemar test was used to compare prostate cancer detection rates between biopsy strategies in 2 × 2 contingency tables. The sensitivity and NPV for detecting and ruling out any prostate cancer and significant prostate cancer comparing standard biopsies in all men vs combined biopsies restricted to men with suspicious bpMRIs were calculated to assess our primary outcome measures. Furthermore, the clinical value of the biopsy strategies comparing benefits (significant prostate cancer detection) and harms (unnecessary biopsies) were evaluated using net benefit and decision curve analyses. All anayses were 2-tailed and a *P* value of less than .05 was considered significant. Statistical analyses were performed using SPSS statistical software version 22.0 (SPSS Inc).

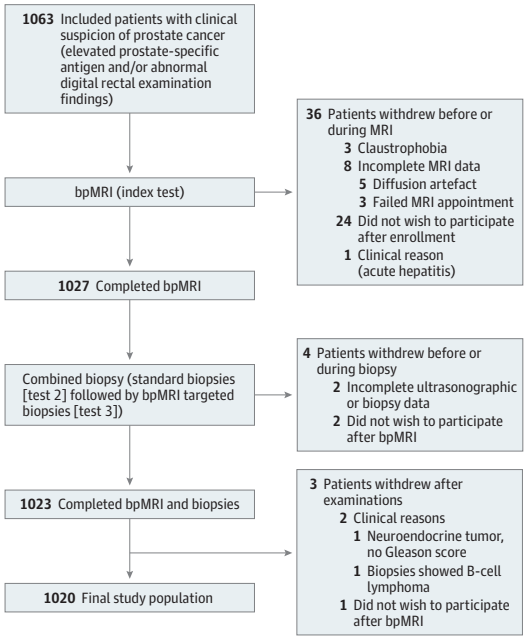
Results

A total of 1063 men were prospectively enrolled and 43 were excluded for various reasons (**Figure 1**). The final study population consisted of 1020 men with a median age of 67 years (interquartile range, 61-71 years) and a median PSA level of 8.0 ng/mL (interquartile range, 5.7-13.0 ng/mL). The patients' demographic data and baseline characteristics are listed in **Table 1**. Overall, prostate cancer was detected in 655 of 1020 men (64%), and 404 of 1020 men (40%) had significant prostate cancer according to the primary definition. Standard biopsies detected prostate cancer and significant prostate cancer in 639 of 1020 men (63%) and 351 of 1020 men (34%), respectively, with 402 of 639 men (63%) having lower-grade prostate cancer (Gleason-grade group 1 or 2). We found a lower NPV for any prostate cancer (72%) for a modified PI-RADS score of 3 or higher, but a higher NPV for significant prostate cancer (97%). Targeted biopsies were performed for 715 of 1020 men (70%) with suspicious bpMRIs (modified PI-RADS ≥3) and detected prostate cancer and significant

prostate cancer in 478 of 715 men (67%) and 338 of 715 men (47%), respectively. Patients with low-suspicion bpMRIs (305 men [30%]) did not have targeted biopsies. Of these, standard biopsies detected prostate cancer in 86 of 305 men (28% [8% of the entire cohort]) stratified into 78 of 305 men (26% [8% of the entire cohort]) with insignificant prostate cancer and 8 of 305 men (3% [0.8% of the entire cohort]) with significant prostate cancer (**Table 2**).

The bpMRI modified PI-RADS suspicion scores were associated with the biopsy results ($P < .001$) (eFigure 1 in the Supplement). The diagnostic yield of significant prostate cancer increased at higher modified PI-RADS scores, and there was a significantly lower significant prostate cancer detection rate in men with low-suspicion bpMRI findings compared with men who had highly

Figure 1. Flowchart of the Study Population



A total of 1063 men were included. However, 43 were excluded for various reasons. The final study population consisted of 1020 men who completed all examinations. MRI indicates magnetic resonance imaging; bpMRI, biparametric MRI.

Table 1. Patient Characteristics

Clinical Characteristic	Prostate Cancer Negative (n = 365)	Prostate Cancer Positive (n = 655)[a]	*P* Value	Total (N = 1020)
Age, median (IQR), y	64 (59-69)	68 (62-72)	<.001	67 (61-71)
PSA, median (IQR), ng/mL	6.4 (5.2-8.9)	9.2 (6.1-19.9)	.03	8.0 (5.7-13.0)
Prostate volume, median (IQR), cm^3	65 (49-88)	47 (36-61)	<.001	53 (40-72)
PSA density, median (IQR), $ng/mL/cm^3$	0.10 (0.07-0.14)	0.20 (0.12-0.43)	<.001	0.15 (0.10-0.27)
Time from bpMRI to biopsy, median (IQR), d	7 (4-11)	7 (5-9)	.44	7 (7-9)
cT_{DRE} stage, No. (%)				
Nonpalpable tumor				
Tx	106 (29)	69 (11)		175 (17)
T1c	208 (57)	260 (40)		468 (46)
Palpable tumor			<.001[b]	
T2	46 (13)	199 (30)		245 (24)
T3	5 (1)	120 (18)		125 (12)
T4	0	7 (1)		7 (1)

Abbreviations: bpMRI, biparametric magnetic resonance imaging; cT_{DRE}, tumor stage determined by digital rectal examination; IQR, interquartile range; PSA, prostate-specific antigen.

SI conversion factor: To convert PSA to micrograms per liter, multiply by 1.0.

[a] Based on biopsy results of combined biopsies in all men.

[b] A Fisher exact test was used to compare the cT_{DRE} stage pooled in nonpalpable and palpable tumor groups.

suspicious (modified PI-RADS 4-5) bpMRI findings (8 of 305 [3%, or 0.8% of the entire cohort] vs 379 of 585 [65%, or 57% of the entire cohort]; $P < .001$). The diagnostic performances of standard and combined biopsies are shown in **Figure 2**. The value of using bpMRI as a diagnostic triage test to identify men most suitable for prostate biopsies—to identify significant prostate cancers and avoid unnecessary biopsies—was assessed by comparing standard biopsies in all men vs combined biopsies restricted to men with suspicious bpMRIs (**Table 3**). Restricting combined biopsies to men with suspicious bpMRI findings meant 305 of 1020 men (30%) with low-suspicious bpMRIs could avoid primary prostate biopsies (biopsy 715 men with suspicious bpMRIs vs all 1020 men who required standard biopsies [70%]; $P < .001$). Significant prostate cancer diagnoses were improved by 11% (4% absolute improvement; 396 vs 351 men; $P < .001$), and insignificant prostate cancer diagnoses were reduced by 40% (11% absolute reduction; 173 vs 288 men; $P < .001$) using fewer biopsy cores compared with standard biopsies alone. The NPV of bpMRI findings in ruling out significant cancer was 97% (95% CI, 95%-99%). Standard biopsies detected significant prostate cancer in 8 men with modified PI-RADS scores of 2 or lower (eTable 2 in the Supplement). Other definitions of significant prostate cancer were also used to evaluate the 2 biopsy strategies (Table 3). Although the prevalence of significant prostate cancers changed when other definitions were used, the reduction in diagnoses

Table 2. Comparison of bpMRI Suspicion Scores With Biopsy Gleason Scores and Grade Groups[a]

	Combined Biopsies, No.[c]							
		Insignificant Prostate Cancer		Significant Prostate Cancer				
bpMRI Modified PI-RADS[b]	No Prostate Cancer	GS 6, GGG 1	GS 3 + 4, GGG 2, MCCL ≤50%	GS 3 + 4, GGG 2, MCCL >50%	GS 4 + 3, GGG 3	GS 8, GGG 4	GS 9 to 10, GGG 5	Total
1	123	44	8	1	2	2	1	181
2	97	20	5	0	2	0	0	124
3	64	38	11	7	6	2	2	130
4	47	38	29	29	22	15	7	187
5	35	39	18	74	76	64	92	398
Total	366	179	71	111	108	83	102	1020

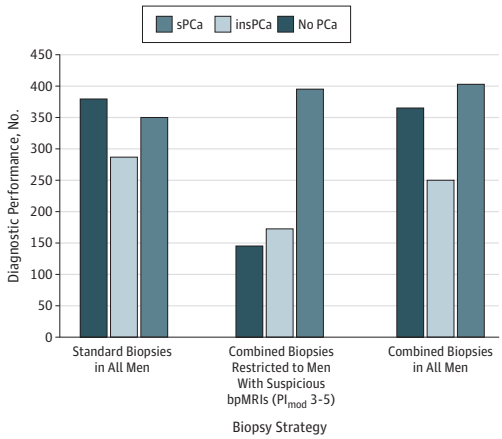
Abbreviations: bpMRI, biparametric magnetic resonance imaging; GGG, Gleason-grade group; GS, Gleason score; MCCL, maximum cancer-core length; PI-RADS, Prostate Imaging Reporting and Data System.

[a] Biopsy results of all patients were stratified by GS/GGG and bpMRI modified PI-RADS. Gleason-grade group 2 (GS 3 + 4) was subdivided into 2 groups (MCCL ≤50% and MCCL >50%).

[b] A bpMRI modified PI-RADS score of 1 or 2 indicates low-suspicion or negative bpMRI findings; a bpMRI modified PI-RADS score of 3 or 5 indicates suspicious bpMRI findings.

[c] Patients with a modified PI-RADS score of 1 or 2 only underwent standard transrectal ultrasound-guided biopsies. Combined biopsies are standard plus targeted.

Figure 2. Comparison of the Diagnostic Performances of Biopsy Strategies



The diagnostic performance consisted of standard biopsies in all men (N = 1020), combined (standard plus targeted) biopsies restricted to men with suspicious biparametric magnetic resonance imaging (bpMRI) findings (n = 715), and combined biopsies in all men (reference standard) (N = 1020). Biopsy results were stratified by cancer significance (primary definition). insPCa indicates insignificant prostate cancer; PCa, prostate cancer; PI_{mod}, modified Prostate Imaging Reporting and Data System score; and sPCa, significant PCa.

in men with insignificant prostate cancer when bpMRI was used as a triage test did not change markedly. However, for the tertiary definition of significant prostate cancer (GS ≥3 + 4), the detection rate for the comparison between standard and combined biopsies did not reach the level of statistical significance (McNemar test, *P* = .11). Sensitivities, NPVs, and net benefit with decision curve analyses are compared in **Table 4** and eFigure 2 in the Supplement. Furthermore, restricting combined biopsies to men with suspicious bpMRIs compared with performing combined biopsies in all men reduced overdiagnosis of insignificant prostate cancer by 31% (n = 77; 173 vs 250 men).

Discussion

This study showed that a low-suspicion bpMRI had a high NPV in ruling out significant prostate cancer in confirmatory biopsies. The results suggest that bpMRI may be used as a triage test to exclude the presence of aggressive disease and avoid unnecessary biopsies with its inherent complications (severe infection, rectal bleeding, etc).[3,22] Biparametric MRI suspicion scores were associated with prostate cancer detection rates, and performing combined biopsies (standard and targeted) in all men significantly enhanced the detection of significant prostate cancer compared with standard biopsies alone, which is the recommended diagnostic standard approach in biopsy-naive men. If combined biopsies were restricted solely to patients with suspicious bpMRIs, only 8 men with significant prostate cancer would have been missed and significantly fewer men (n = 77) with insignificant prostate cancer would have been diagnosed. Therefore, 305 of 1020 men (30%) could have safely avoided biopsies because most of these men had low-risk disease qualifying for surveillance. Reducing overdiagnoses of insignificant prostate cancer compared with standard biopsies (−40%) or combined biopsies in all men (−31%) might also reduce overtreatment.[2]

Our findings are consistent with those of the PROMIS study by Ahmed et al[7] that provided level 1b evidence for the diagnostic accuracy of MRI in detecting prostate cancer. Those findings suggested that if mpMRI were used as a triage test, 1 in 4 men might safely avoid prostate biopsies and the diagnostic ratio of significant prostate cancer vs insignificant prostate cancer would be improved. In

Table 3. Comparison of Biopsy Strategy[a]

Significant Prostate Cancer Definition	Biopsies, No. (% [95% CI])[b]		Difference, % (95% CI)		*P* Value, McNemar Test
	Standard (All Men)	Combined (modified PI-RADS 3-5)	Absolute	Relative	
Men with biopsy performed	1020 (100 [99 to 100])	715 (70 [67 to 73])	-30 (-33 to -27)	-30 (-33 to -27)	<.001
Biopsy cores, No.	9268	7339[c]	-21 (-22 to -20)	-21 (-22 to -20)	<.001
No prostate cancer on biopsy	381 (37 [34 to 40])	146 (14 [12 to 17])	-23 (-27 to -19)	-62 (-68 to -55)	<.001
Primary definition of significant prostate cancer[d]					
Insignificant prostate cancer	288 (28 [26 to 31])	173 (17 [15 to 19])	-11 (-15 to -8)	-40 (-49 to -29)	<.001
Significant prostate cancer	351 (34 [32 to 37])	396 (39 [36 to 42])	4 (0.2 to 9)	11 (0.6 to 21)	<.001
Secondary definition of significant prostate cancer[e]					
Insignificant prostate cancer	262 (25 [23 to 29])	145 (14 [12 to 17])	-11 (-15 to -8)	-45 (-54 to -34)	<.001
Significant prostate cancer	377 (37 [34 to 40])	424 (42 [39 to 45])	5 (0.4 to 9)	11 (0.9 to 21)	<.001
Tertiary definition of significant prostate cancer[f]					
Insignificant prostate cancer	198 (19 [17 to 22])	115 (11 [9 to 13])	-8 (-11 to -5)	-42 (-53 to -28)	<.001
Significant prostate cancer	441 (43 [40 to 46])	454 (45 [41 to 48])	1 (to 3 to 6)	3 (−7 to 12)	.11

Abbreviation: PI-RADS, Prostate Imaging Reporting and Data System.

[a] Comparison of the diagnostic strategies of standard biopsies in all men vs combined (standard plus targeted) biopsies restricted to men with suspicious biparametric magnetic resonance imaging findings (modified PI-RADS score 3-5) using different definitions of significant prostate cancer.

[b] The total number of patients (N = 1020) was used as the denominator for calculating all percentages.

[c] Includes 6231 standard biopsies and 1108 targeted biopsies.

[d] Gleason score of 4 + 3 or greater or maximum cancer-core length greater than 50% with a Gleason score of 3 + 4. The prevalence was 404 men (40% [95% CI, 37%-43%]).

[e] Gleason score of 4 + 3 or greater or maximum cancer-core length greater than 50% with any PCa. The prevalence was 436 men (43% [95% CI, 40%-46%]).

[f] Gleason score of 3 + 4 or greater. The prevalence was 475 men (47% [95% CI, 44%-50%]).

addition, the results from the PROTECT study by Hamdy et al[23] were a critical landmark in showing that overdiagnosis and overtreatment of low-risk disease, resulting from the standard biopsy approach, showed minimal patient survival benefits, although it did decrease metastasis rates. The fact that more than three-fourths of the included patients had low-risk disease (the rest mostly intermediate risk) emphasizes the need to avoid biopsies and overtreatment of men.

Prior studies evaluated the diagnostic accuracy of bpMRI alone,[24] combined with PSA levels,[25] or compared with mpMRI.[26] In a recent study of 161 biopsy-naive men who underwent bpMRI followed by targeted and standard biopsies, Jambor et al[24] found that restricting biopsies to men with equivocal to highly suspicious bpMRI findings reduced the number of men undergoing biopsies by 24%, while failing to detect only 2% with significant prostate cancer. Although their results are similar to ours, Jambor and colleagues used a different bpMRI scoring system, they relied on cognitive targeted biopsies, and their biopsy operator was not blinded to the bpMRI findings before performing standard biopsies.

At present, the US Preventive Services Task Force recommends that PSA screening should be based on shared decision making and patient preferences for men aged 55 to 69 years. However, opponents of screening argue that the test has no net benefit and the harms (eg, high false-positive rate, overdetection of insignificant prostate cancer, and biopsy complications) outweigh the benefits demonstrated in randomized clinical trials.[27-29] However, using MRI as a secondary triage test in men with elevated PSA levels could potentially minimize uncertainties and improve the balance between benefits and harms by reducing the number of false-positive PSA results that would otherwise lead

Table 4. Comparison of Sensitivities and NPVs

Prostate Cancer Definition[a]	% (95% CI)		
	bpMRI Modified PI-RADS 3-5 (n = 715)[b]	Standard Biopsies, All Men (N = 1020)	Combined Biopsies, Modified PI-RADS 3-5 (n = 715)
Any prostate cancer[c]			
Sensitivity	86 (84-89)	98 (96-99)	86 (84-89)
NPV	72 (67-76)	96 (93-97)	81 (78-84)
Significant prostate cancer, primary definition[d]			
Sensitivity	98 (96-99)	87 (83-90)	98 (96-99)
NPV	97 (95-99)	92 (90-94)	99 (97-99)
Significant prostate cancer, secondary definition[e]			
Sensitivity	97 (95-99)	86 (83-90)	97 (95-99)
NPV	96 (93-98)	91 (89-93)	98 (97-99)
Significant prostate cancer, tertiary definition[f]			
Sensitivity	96 (93-97)	93 (90-95)	96 (93-97)
NPV	93 (90-95)	94 (92-96)	96 (94-98)

Abbreviations: bpMRI, biparametric magnetic resonance imaging; NPV, negative predictive value; PI-RADS, Prostate Imaging Reporting and Data System.

[a] The sensitivities and NPVs for detecting and ruling out any PCa and sPCa are shown for bpMRI alone and for the 2 diagnostic strategies (1) standard biopsies in all men and (2) combined biopsies (standard plus targeted) restricted to men with suspicious bpMRIs (modified PI-RADS 3-5) using various definitions of significant PCa. Overall detection rates of PCa and sPCa in combined standard transrectal ultrasonography-guided biopsies and bpMRI targeted biopsies of all patients was used as the reference standard.

[b] The bpMRI score was dichotomized by low-suspicion or negative bpMRI findings (modified PI-RADS 1-2) and suspicious bpMRI findings (modified PI-RADS 3-5).

[c] Prevalence was 655 men (64% [95% CI, 61%-67%]).

[d] Gleason score of 4 + 3 or greater or maximum cancer-core length greater than 50% with a Gleason score of 3 + 4. The prevalence was 404 men (40% [95% CI, 37%-43%]).

[e] Gleason score of 4 + 3 or greater or maximum cancer-core length greater than 50% with any PCa. The prevalence was 436 men (43% [95% CI, 40%-46%]).

[f] Gleason score of 3 + 4 or greater. The prevalence was 475 men (47% [95% CI, 44%-50%]).

to unnecessary invasive biopsies. The net benefit and decision curve analyses in our study showed that restricting biopsies to men with suspicious (modified PI-RADS 3-5) bpMRI lesions achieved the highest clinical value for all threshold probabilities compared with our current practice—standard biopsies in all men. However, at very low biopsy threshold probabilities, the preferable approach is to perform combined biopsies in all men. Assuming that no urologist would routinely carry out a biopsy in a man with less than a 5% risk of significant prostate cancer (equivalent to performing biopsies in 20 men to find 1 additional significant prostate cancer), using bpMRI to determine whether to perform a biopsy achieved the best clinical outcome balancing benefits and harms.

In general, we should cautiously consider using bpMRI or mpMRI as a triage test to identify individuals who can avoid prostate biopsies. Numerous factors, including image quality, interpretation, and definition of significant prostate cancer including disease prevalence, can affect the performance of targeted biopsies and the NPV of an MRI. A recent meta-analysis found that the median mpMRI NPVs (suspicion score ≥3) for ruling out any prostate cancer and significant prostate cancer were 82% and 88%, respectively. However, these values were strongly influenced by disease prevalence in the populations studied.[13] We found a lower NPV for any prostate cancer (72%) for a modified PI-RADS score of 3 or higher, but a higher NPV for significant prostate cancer (97%), although the definitions of significant prostate cancer differed. Performing MRI can be expensive and time-consuming, and it would be a major challenge for any health care system to systematically use mpMRIs to diagnose prostate cancer before all biopsies. However, our results confirm that a more rapid and simple bpMRI approach is feasible, is sufficient for MRI/TRUS image fusion, and provides an accurate sector map of the prostate for targeted biopsies. It improves prostate cancer detection and risk stratification in biopsy-naive men and maintains the high diagnostic accuracy of mpMRI.[30,31] Kuhl et al[26] found no significant differences in the diagnostic accuracy of bpMRI and mpMRI in 542 men with elevated PSA who underwent repeated biopsies. However, it is important to note that a low-suspicion bpMRI did not unequivocally rule out any prostate cancer. Nevertheless, the key concern in clinical practice is to detect and rule out significant disease while avoiding unnecessary biopsies.

Limitations

Our study had limitations. It was performed at a single center with 1 dedicated MRI physician reading the bpMRIs and 2 highly experienced TRUS operators performing biopsies. As a result, no interreader variability analyses were done. Less experienced readers and operators might not achieve the same diagnostic yield. Further work would be necessary to evaluate variability between experts and nonexperts. Second, all the patients in our study were from a non-PSA-screened population in whom benign reasons for elevated PSA levels (eg, urinary retention, urinary tract infections) had been ruled out before inclusion. This might explain both the rather high prostate cancer detection rate using standard biopsies and the higher median PSA level (8.0 ng/mL) compared with other studies.[7,11,12,24] The diagnostic accuracy and NPVs of bpMRIs might be different in other patient populations. Third, we used biopsy results comparatively in this study, and the combined biopsy results from all patients were used as the reference standard. There may have been undetected prostate cancer lesions in both standard and targeted biopsy procedures, and the true rate of false-negative readings cannot be assessed. Nevertheless, we performed standard biopsies on all study participants, including those with low-suspicion bpMRI findings. This enabled us to compare outcomes among the different biopsy techniques and make comparisons that reflect clinical practice. Finally, the criteria for significant prostate cancer diagnoses depended on the histopathological assessment of biopsies. Although our definition is similar to that used in the PROMIS study by Ahmed et al,[7] other investigators have used and suggested different definitions that might change the overall diagnostic accuracy of bpMRIs. A clear consensus for defining significant prostate cancer in MRI biopsy studies will be required to allow interstudy comparisons and to develop redefined risk calculators that include biopsy results from additional MRI targeted biopsies, as most of the currently available

predictive nomograms and risk calculators are based on standard biopsy results with the inherent limitations of standard biopsy.

Despite these limitations, our data provide evidence for the reliability of using low-suspicion bpMRI findings as a noninvasive diagnostic tool to rule out more aggressive prostate cancer and avoid unnecessary biopsies. Although the use of prebiopsy bpMRI and targeted biopsies significantly improve risk stratification and could benefit clinical practice, the cost-effectiveness and long-term health outcomes using MRI have not been fully explored. Follow-up data and the long-term outcomes of these study patients will be assessed in the future. Furthermore, because bpMRI is a new diagnostic imaging approach, further studies are needed to validate our findings and fully explore the role of bpMRI in prostate cancer management before more widespread implementation into clinical practice.

Conclusions

Low-suspicion bpMRI has a high NPV in ruling out significant disease in biopsy-naive men with clinical suspicion of prostate cancer. Furthermore, bpMRI suspicion scores are strongly associated with prostate cancer detection rates and performing biopsies (standard plus targeted) only in men with suspicious bpMRI findings is the preferred approach for improving the diagnostic ratio of significant prostate cancer to insignificant prostate cancer compared with our current diagnostic standard—standard biopsies in all men. Therefore, bpMRI used as a triage test improves risk stratification and allows for 30% of men with clinical suspicion of prostate cancer to safely avoid unnecessary prostate biopsies with their inherent risks. Further studies are needed to fully explore its future role in clinical prostate cancer management.

ARTICLE INFORMATION

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Corresponding Author: Lars Boesen, MD, PhD, Department of Urology, Herlev Gentofte University Hospital, Herlev Ringvej 75, Herlev, Denmark 2730 (lars.boesen@dadlnet.dk).

Author Affiliations: Department of Urology, Herlev Gentofte University Hospital, Herlev, Denmark (Boesen, Nørgaard, Bisbjerg, Jakobsen); Department of Radiology, Herlev Gentofte University Hospital, Herlev, Denmark (Løgager, Thestrup, Winther, Thomsen); Department of Pathology, Herlev Gentofte University Hospital, Herlev, Denmark (Balslev).

Author Contributions: Dr Boesen had full access to all the data in the study and takes responsibility for the integrity and the accuracy of the data analysis.

Concept and design: Boesen, Nørgaard, Løgager, Winther, Jakobsen, Thomsen.

Acquisition, analysis, or interpretation of data: Boesen, Nørgaard, Løgager, Balslev, Bisbjerg, Thestrup, Winther, Jakobsen.

Drafting of the manuscript: Boesen, Nørgaard, Thomsen.

Critical revision of the manuscript for important intellectual content: Boesen, Nørgaard, Løgager, Balslev, Bisbjerg, Thestrup, Winther, Jakobsen.

Statistical analysis: Boesen.

Obtained funding: Boesen.

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REFERENCES

1. Eggener SE, Cifu AS, Nabhan C. Prostate cancer screening. *JAMA*. 2015;314(8):825-826.

2. Gandaglia G, Briganti A, Fossati N, et al. The problem is not what to do with indolent and harmless prostate cancer—the problem is how to avoid finding these cancers. *Eur Urol*. 2016;70(4):547-548.

3. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. *Eur Urol*. 2013;64(6):876-892.

4. Litwin MS, Tan H-J. The diagnosis and treatment of prostate cancer: a review. *JAMA*. 2017;317(24):2532-2542.

5. Loeb S, Dani H. Whom to biopsy: prediagnostic risk stratification with biomarkers, nomograms, and risk calculators. *Urol Clin North Am*. 2017;44(4):517-524.

6. Cucchiara V, Cooperberg MR, Dall'Era M, et al. Genomic markers in prostate cancer decision making. *Eur Urol*. 2017;(73):572-582.

7. Ahmed HU, El-Shater Bosaily A, Brown LC, et al; PROMIS Study Group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet*. 2017;389(10071):815-822.

8. Hamoen EHJ, de Rooij M, Witjes JA, Barentsz JO, Rovers MM. Use of the Prostate Imaging Reporting and Data System (PI-RADS) for prostate cancer detection with multiparametric magnetic resonance imaging: a diagnostic meta-analysis. *Eur Urol*. 2015;67(6):1112-1121.

9. Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MGM. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. *Eur Urol*. 2015;68(3):438-450.

10. Fütterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? a systematic review of the literature. *Eur Urol*. 2015;68(6):1045-1053.

11. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA*. 2015;313(4):390-397.

12. Filson CP, Natarajan S, Margolis DJA, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. *Cancer*. 2016;122(6):884-892.

13. Moldovan PC, Van den Broeck T, Sylvester R, et al. What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? a systematic review and meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. *Eur Urol*. 2017;72(2):250-266.

14. Barentsz JO, Richenberg J, Clements R, et al; European Society of Urogenital Radiology. ESUR prostate MR guidelines 2012. *Eur Radiol*. 2012;22(4):746-757.

15. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging—reporting and data system: 2015, version 2. *Eur Urol*. 2016;69(1):16-40.

16. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. *J Urol*. 2016;196(6):1613-1618.

17. Moore CM, Kasivisvanathan V, Eggener S, et al; START Consortium. Standards of Reporting for MRI-Targeted Biopsy Studies (START) of the prostate: recommendations from an international working group. *Eur Urol*. 2013;64(4):544-552.

18. Bossuyt PM, Reitsma JB, Bruns DE, et al; STARD Group. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *Clin Chem*. 2015;61(12):1446-1452.

19. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer, part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2017;71(4):618-629.

20. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL; ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol*. 2005;29(9):1228-1242.

21. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. *Am J Surg Pathol*. 2016;40(2):244-252.

22. Liss MA, Ehdaie B, Loeb S, et al. An update of the American Urological Association white paper on the prevention and treatment of the more common complications related to prostate biopsy. *J Urol*. 2017;198(2):329-334.

23. Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):1415-1424.

24. Jambor I, Boström PJ, Taimen P, et al. Novel biparametric MRI and targeted biopsy improves risk stratification in men with a clinical suspicion of prostate cancer (IMPROD Trial). *J Magn Reson Imaging*. 2017;46(4):1089-1095.

25. Rais-Bahrami S, Siddiqui MM, Vourganti S, et al. Diagnostic value of biparametric magnetic resonance imaging (MRI) as an adjunct to prostate-specific antigen (PSA)-based detection of prostate cancer in men without prior biopsies. *BJU Int*. 2015;115(3):381-388.

26. Kuhl CK, Bruhn R, Krämer N, Nebelung S, Heidenreich A, Schrading S. Abbreviated biparametric prostate MR imaging in men with elevated prostate-specific antigen. *Radiology*. 2017;285(2):493-505.

27. Schröder FH, Hugosson J, Roobol MJ, et al; ERSPC Investigators. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. 2014;384(9959):2027-2035.

28. Andriole GL, Crawford ED, Grubb RL III, et al; PLCO Project Team. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst*. 2012;104(2):125-132.

29. Tsodikov A, Gulati R, Heijnsdijk EAM, et al. Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO Trials. *Ann Intern Med*. 2017;167(7):449-455.

30. Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: a systematic review. *Eur Urol*. 2015;68(1):8-19.

31. Gayet M, van der Aa A, Beerlage HP, Schrier BP, Mulders PFA, Wijkstra H. The value of magnetic resonance imaging and ultrasonography (MRI/US)-fusion biopsy platforms in prostate cancer detection: a systematic review. *BJU Int*. 2016;117(3):392-400.

SUPPLEMENT.

eTable 1. Biparametric MRI Sequence Parameters
eTable 2. Patient Characteristics of Men (n = 8) With Low-Suspicion bpMRIs (PI_{mod} 1-2)
eFigure 1. Comparison of bpMRI Suspicion Scores to Cancer Significance
eFigure 2. Decision Curve Analysis

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Prebiopsy Biparametric Magnetic Resonance Imaging Combined with Prostate-specific Antigen Density in Detecting and Ruling out Gleason 7–10 Prostate Cancer in Biopsy-naïve Men

Lars Boesen [a,*], *Nis Nørgaard* [a], *Vibeke Løgager* [b], *Ingegerd Balslev* [c], *Rasmus Bisbjerg* [a], *Karen-Cecilie Thestrup* [b], *Henrik Jakobsen* [a], *Henrik S. Thomsen* [b]

[a] *Department of Urology, Herlev Gentofte University Hospital, Herlev, Denmark;* [b] *Department of Radiology, Herlev Gentofte University Hospital, Herlev, Denmark;* [c] *Department of Pathology, Herlev Gentofte University Hospital, Herlev, Denmark*

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Abstract

Background: Multiparametric magnetic resonance imaging (MRI) combined with prostate-specific-antigen density (PSAd) enhances the detection of significant prostate cancer (sPCa). However, it is unclear whether simple biparametric (bp) MRI, which reduces scan sequences, time, and cost, may be an equally effective noninvasive tool for detecting and ruling out sPCa and avoiding biopsies in biopsy-naïve men.

Objective: To assess the diagnostic accuracy, predictive values, and best biopsy strategy combining bpMRI and PSAd in detecting and ruling out sPCa (Gleason score $\geq$7).

Design, setting, and participants: Assessment of 808 biopsy-naïve men with clinical suspicion of localised PCa (prostate-specific antigen $<$20 ng/ml, rectal examination $<$cT3), prospectively enrolled between November 2015 and June 2017.

Intervention: All men underwent upfront bpMRI (T2- and diffusion-weighted imaging) followed by standard and targeted biopsies of any suspicious bpMRI findings.

Outcome measurements and statistical analysis: Various bpMRI scores and PSAd thresholds were assessed using sPCa detection rates, predictive values, and proportion of biopsies avoided. Net benefits and decision curve analyses were compared. Combined biopsies from all men were used for reference.

Results and limitations: Significant prostate cancers were detected in 283/808 (35%) men with median age and PSA (interquartile range) of 65 yr (60–70) and 6.9 ng/ml (5.4–9.5), respectively. PSAd significantly influenced the predictive values of bpMRI in detecting and ruling out sPCa. The best strategy was restricting biopsies to men with highly suspicious bpMRI findings (score $\geq$4) or PSAd $\geq$0.15 ng/ml/cc. This reduced the number of men requiring biopsies by 41% (329/808) and overdiagnosis of insignificant cancers by 45% (79/177), while missing only 5% (17/329) of men with sPCa. Study limitations included single-centre analysis and combined biopsies as the reference standard.

Conclusions: Combination of bpMRI with PSAd improves diagnostic accuracy and predictive values for sPCa detection in biopsy-naïve men. Restricting biopsies to men with highly suspicious bpMRI findings (score $\geq$4) or PSAd $\geq$0.15 ng/ml/cc was the best biopsy strategy in our patient cohort, effectively balancing risks and benefits. Studies are needed to validate our findings in other patient populations.

Patient summary: This report shows that biopsy-naïve men with clinical suspicion of prostate cancer who have low- or equivocal-suspicion biparametric magnetic resonance imaging results and a low prostate-specific antigen density may not require immediate prostate biopsies.

* Corresponding author. Department of Urology and Urological Research, Herlev Gentofte University Hospital, Herlev Ringvej 75, Herlev 2730, Denmark. Tel.: +45 38681041; Fax: +45 38684657.
E-mail address: lars.boesen@dadlnet.dk (L. Boesen).

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1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) followed by MRI targeted biopsies (TBx) has rapidly emerged as an alternative diagnostic tool for improved detection of significant prostate cancer (sPCa) compared with transrectal ultrasound-guided biopsies ($TRUS_{bx}$) alone [1–3]. Conversely, studies have tried to validate low-suspicion mpMRI results that can noninvasively rule out sPCa, avoiding the need for biopsies [2,4]. However, sPCa can be missed by MRI and TBx [5], and the negative predictive value (NPV) for exclusion of PCa reportedly ranges from 63% to 98% [6]. Furthermore, radical prostatectomy specimens suggest that tumour foci with Gleason scores (GS) of $\geq$7 may be missed by mpMRI in up to 28% of cases [7,8]. Therefore, additional predictors are needed to supplement MRI and separate men who require diagnostic biopsies from those who might safely avoid them. Measuring the prostate-specific antigen (PSA) density (PSAd [PSA/$prostate_{volume}$]) may provide such a predictor [9,10]. PSAd alone has limited usefulness for making biopsy decisions [9,11], but when combined with mpMRI results, the NPV for ruling out sPCa appears to improve significantly [12–14]. In addition, prediction models using mpMRI data and clinical parameters have recently been developed to further refine prebiopsy individualised risk assessment [15]. As mpMRI is time consuming and costly, efforts have been made to try to reduce scan time and costs by introducing a simpler, more rapid biparametric MRI (bpMRI) method that uses fewer scan sequences and no intravenous contrast media [16]. However, although bpMRI apparently maintains the high diagnostic accuracy of mpMRI in biopsy-naive men [17,18], not all cancers are visible by MRI and lesions may be misinterpreted [19,20]. Therefore, the objective of this study was to assess whether combining a novel bpMRI method with PSAd could improve diagnostic accuracy and predictive values in detecting and ruling out sPCa (GS $\geq$7) in biopsy-naive men with clinical suspicion of localised PCa. In addition, we determined the best biopsy strategy and the proportion of men who could safely avoid prostate biopsies based on bpMRI scores and PSAd thresholds.

2. Patients and methods

2.1. Patient selection

Biopsy-naive men with clinical suspicion of localised PCa (PSA <20 ng/ml and digital rectal examination [DRE] <cT3) were selected from our prospective single institutional database (BIDOC database, www.clinicaltrials.gov; NCT02584179), which was approved by the institutional review board and designed to assess the diagnostic accuracy of bpMRI in biopsy-naive men [21]. A total of 808 patients met the inclusion criteria. The study conformed to the START consortium criteria for MRI biopsy studies [22], and patients were enrolled between November 2015 and June 2017, providing written informed consent. The exclusion criteria were as follows: prior prostate biopsies, prior prostate MRI, PSA $\geq$20 ng/ml, DRE with suspicion of locally advanced PCa ($\geq$cT3), evidence of acute urinary tract infections, acute prostatitis, general contraindications for MRI (eg, claustrophobia, a pacemaker, metal implants, etc.), and prior hip replacement surgery or other metallic implants in the pelvic area.

2.2. Biparametric MRI and prostate biopsies

Prior to biopsies, bpMRI was performed using a 3.0 T magnet (Philips Healthcare, Best, The Netherlands) with a pelvic-phased-array coil positioned over the pelvis, as previously reported [21]. The overall bpMRI image acquisition time was approximately 15 min. Imaging parameters are listed in Supplementary Table 1.

All bpMRI results were evaluated and scored on a five-point scale blinded to clinical findings by the same prostate MRI expert according to the Prostate Imaging Reporting and Data System (PI-RADS) version 2 criteria [23]. However, peripheral zone lesions were scored solely by diffusion-weighted imaging, as contrast-enhanced imaging was not used. The bpMRI scores were separated into three suspicion groups: low (score = 1–2), equivocal (score = 3), and high (score = 4–5).

All patients underwent a systematic 10-core $TRUS_{bx}$ procedure (extended sextant biopsy scheme) according to international guidelines [24], which was performed by one of two operators who were blind to the bpMRI results. $TRUS_{bx}$ was immediately followed by additional TBx (one to two cores per lesion) of any suspicious lesions (bpMRI score $\geq$3) using one of two rigid MRI/TRUS image-fusion systems, as previously reported [21]. Patients with low-suspicion bpMRI scores (1–2) underwent $TRUS_{bx}$ only. Biopsy samples were marked and potted separately.

2.3. Histopathological evaluation and significant cancer assessment

All biopsy samples were reviewed by the same experienced genitourinary pathologist. For each PCa-positive biopsy core, the location, GS [25], Gleason grade group (GGG) [26], and percentage of cancerous tissue were determined. The histopathological assessment of the biopsies was used to define three grade groups based on cancer aggressiveness: low grade (GS $\leq$6/GGG 1), intermediate grade (GS 3 + 4/GGG 2), and high grade (GS $\geq$4 + 3/GGG $\geq$3). Insignificant PCa (insPCa) and sPCa were defined as low- and intermediate/high-grade PCa (GS 7–10), respectively.

2.4. Statistical analysis

Patient characteristics were stratified by biopsy results and assessed using descriptive statistics. Continuous variables were compared using the Wilcoxon rank-sum test, and a chi-square analysis was used to compare the clinical T stage (cT_{DRE}) and the bpMRI suspicion scores with the biopsy results. Prostate volume was measured using the ellipsoid formula (width $\times$ height $\times$ length $\times$ π/6), and four PSAd groups were defined: PSAd <0.10, 0.10–0.14, 0.15–0.19, and $\geq$0.20 ng/ml/cc. The sensitivity, specificity, positive predictive value (PPV), and NPV of bpMRI results and PSAd (separately and combined) in detecting and ruling out sPCa were calculated according to variable thresholds above which biopsies would be recommended (biopsy thresholds). The effect of PSAd on predictive values for each bpMRI suspicion group was evaluated. A chi-square test was used to compare proportions. The best cut-off point for a biopsy threshold that balanced sensitivity and specificity was calculated using Youden's J index (sensitivity + specificity–1). The clinical value of different biopsy strategies that combined bpMRI results and PSAd was further assessed using a net benefit analysis that compared benefits (sPCa detection) and risks (performing unnecessary biopsies). A decision curve analysis was performed for the six best biopsy strategies with the highest net benefit using threshold probabilities ranging from 5% to 20%. We used the results from combined biopsies (CBx [$TRUS_{bx}$ + TBx]) as the reference standard to assess outcomes. Any patient with sPCa on either $TRUS_{bx}$ or TBx was classified as having sPCa on CBx. A two-sided p value of <0.05 was considered statistically significant. The analyses were performed using SPSS software (ver. 22.0; SPSS, Inc., Chicago, IL, USA).

Table 1 – Patient characteristics

Clinical characteristics		No PCa (n = 348)	Insignificant PCa (n = 177)	sPCa (n = 283)	p value[a]	Total (n = 808)
Age (yr), median (IQR)		64 (59–69)	64 (59–69)	68 (62–71)	<0.001	65 (60–70)
PSA (ng/ml), median (IQR)		6.3 (5.1–8.7)	6.3 (5.3–8.8)	8.4 (6.0–11.2)	<0.001	6.9 (5.4–9.5)
Prostate volume (cc), median (IQR)		67 (50–88)	53 (41–66)	43 (33–59)	<0.001	54 (40–75)
PSA density (ng/ml/cc), median (IQR)		0.10 (0.07–0.13)	0.12 (0.09–0.16)	0.18 (0.13–0.27)	<0.001	0.12 (0.09–0.18)
cT_{DRE} category, n (%)						
cTx		103 (30)	33 (19)	27 (10)	<0.001	163 (20)
cT1c		201 (58)	121 (68)	127 (45)		449 (56)
cT2a		25 (7)	16 (9)	68 (24)		109 (14)
cT2b		10 (3)	6 (3)	41 (15)		57 (7)
cT2c		9 (3)	1 (1)	20 (7)		30 (4)
PSAd group, n (%)						
1	<0.10	168 (48)	46 (26)	25 (9)	<0.001	239 (30)
2	0.10–0.14	113 (33)	74 (42)	70 (25)		257 (32)
3	0.15–0.19	45 (13)	25 (14)	65 (23)		135 (17)
4	≥0.20	22 (6)	32 (18)	123 (44)		177 (22)

cT_{DRE} = tumour stage by digital rectal examination; IQR = interquartile range; PCa = prostate cancer; PSA = prostate-specific-antigen; PSAd = PSA density; sPCa = significant PCa.
[a] Patients with sPCa are compared with patients in the no/insignificant PCa categories.

3. Results

Clinical characteristics of the 808 patients included in the study are listed in Table 1. Any PCa and sPCa was detected in 57% (460/808) and 35% (283/808) of patients, respectively. Rising bpMRI suspicion scores and increasing PSAd within each bpMRI suspicion score group were associated with increased detection of sPCa and high-grade PCa (Fig. 1). The sensitivity, specificity, and predictive values for detecting and ruling out sPCa depended on bpMRI scores and PSAd biopsy thresholds (Table 2).

3.1. *Influence of PSAd on NPV and PPV of bpMRI*

The NPV of low- or equivocal-suspicion bpMRI results in ruling out sPCa was significantly influenced by PSAd values (Table 3). The NPV increased from 83% to 95% (p = 0.002) for bpMRI scores of 1–2 and from 53% to 93% ($p < 0.001$) for a bpMRI score of 3 when PSAd was <0.15 ng/ml/cc. Likewise, the PPV increased from 7% to 47% (p = 0.002) for a bpMRI score of 3 and from 47% to 74% ($p < 0.001$) for bpMRI scores of 4–5 when PSAd was ≥0.15 ng/ml/cc.

3.2. *Recommended biopsy strategy*

Youden's J index determined that a bpMRI score of ≥4 and a PSAd value of ≥0.15 ng/ml/cc as single parameters were optimal thresholds for recommending a biopsy (Table 2). However, 16% (44/283) and 34% (95/283) of all significant prostate cancers were missed using these bpMRI and PSAd thresholds, respectively. However, if the thresholds were combined and biopsies were restricted to men with either a bpMRI score of ≥4 or a PSAd value of ≥0.15 ng/ml/cc, the sensitivity and NPV increased to 94% and 95% for detecting and ruling out sPCa, respectively. The proportion of missed sPCa dropped to 6% (17/283), 41% (329/808) of patients avoided a prostate biopsy, and 45% (79/177) avoided a diagnosis of insPCa. The majority (65% [11/17]) of the missed significant prostate cancers were GS 3 + 4/GGG 2 cancers. The decision curve analysis showed that at biopsy thresholds ranging from 7.5% to 15%, restricting biopsies to men with a bpMRI score of ≥4 or a PSAd value of ≥0.15 ng/ml/cc produced the highest net benefit (Fig. 2 and Supplementary Table 2). Table 4 presents the diagnostic results of combining bpMRI scores and PSAd to evaluate various biopsy strategies and thresholds. For each biopsy strategy, the number of biopsies and insPCa diagnoses that were avoided and the number of significant prostate cancers that were missed are reported, together with analyses of the diagnostic and predictive values for detecting and ruling out sPCa.

4. Discussion

Overall, our study shows that biopsy-naive men with clinical suspicion of localised PCa who have low- or equivocal-suspicion bpMRI and a PSAd value of <0.15 ng/ml/cc might be spared immediate prostate biopsies. We found that PSAd significantly influences PPVs and NPVs derived from bpMRI results in detecting and ruling out sPCa. Restricting biopsies to men with highly suspicious bpMRI scores (≥4) or a PSAd value of ≥0.15 ng/ml/cc meant that 41% (329/808) could avoid a prostate biopsy and only 5% (17/329) with sPCa were missed, with the majority of these having GS 3 + 4/GGG 2 cancers. In addition, diagnosis of insPCa, which can often be managed expectantly, decreased by 45% (79/177), reducing the number of men needing extensive surveillance programmes. This biopsy strategy also proved best for sPCa detection, effectively balancing benefits and risks on a decision curve analysis at biopsy thresholds ranging from 7.5% to 15%. This is equivalent to

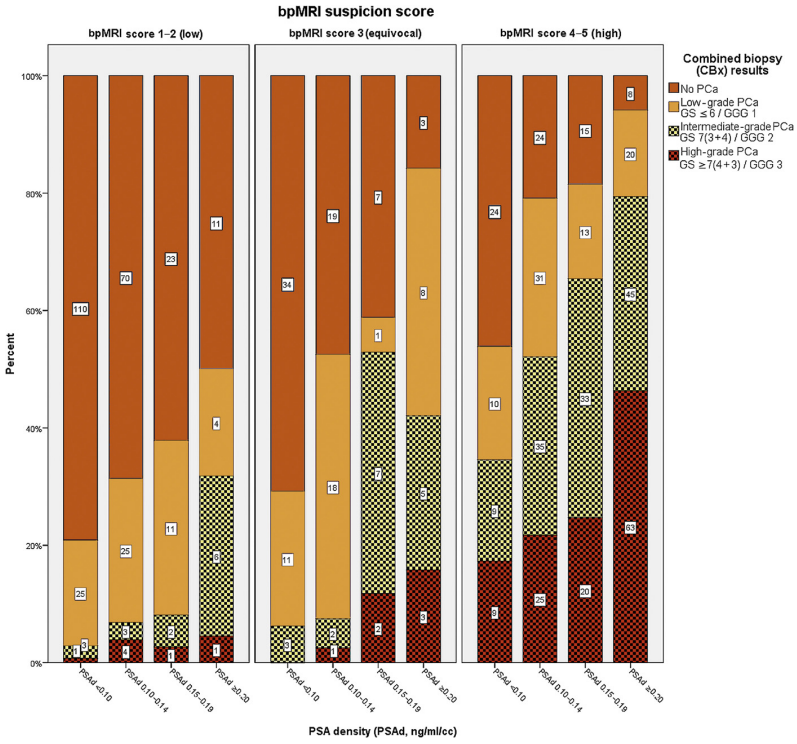

Fig. 1 – Prostate cancer (PCa) detection rates for all patients (*N* = 808) based on combined biopsy results stratified by bpMRI suspicion scores, PSA density, and PCa grade groups. Confirmatory biopsies showed that 7% (21/300) of patients with low-suspicion, 19% (23/124) with equivocal-suspicion, and 62% (239/384) of patients with high-suspicion bpMRI results had significant PCa (sPCa). Of the 283 patients with sPCa, 9% (25/283) had PSAd <0.10, 25% (70/283) had PSAd of 0.10–0.14, 23% (65/283) had PSAd of 0.15–0.19, and 44% (123/283) had PSAd ≥0.20. bpMRI = biparametric magnetic resonance imaging; CBx = combined biopsies [TRUSbx + TBx]; GGG = Gleason grade group; GS = Gleason score; PCa = prostate cancer; PSA = prostate-specific-antigen; PSAd = PSA density (ng/ml/cc); TBx = bpMRI targeted biopsies; $TRUS_{bx}$ = standard transrectal ultrasound-guided biopsies.

Table 2 – Sensitivity, specificity, and predictive values for significant prostate cancer detection at various thresholds of bpMRI score and PSA density

Restrict biopsies to	Avoided biopsies, *n* (%)[a]	Missed sPCa, *n* (%)[b]	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)	Youden's J index
bpMRI score, n (%)							
bpMRI score ≥5, *n* = 207 (26%)	601 (74)	140 (49)	0.51 (0.45–0.57)	0.88 (0.85–0.90)	0.69 (0.63–0.74)	0.78 (0.74–0.79)	0.39
bpMRI score ≥4, *n* = 384 (48%)	424 (52)	44 (16)	0.84 (0.80–0.88)	0.72 (0.68–0.76)	0.62 (0.59–0.66)	0.90 (0.87–0.92)	0.56
bpMRI score ≥3, *n* = 508 (63%)	300 (37)	21 (7)	0.93 (0.89–0.95)	0.53 (0.49–0.57)	0.52 (0.49–0.54)	0.93 (0.90–0.95)	0.46
PSA density, n (%)[a]							
PSAd ≥0.20, *n* = 177 (12%)	631 (78)	160 (57)	0.43 (0.38–0.49)	0.90 (0.87–0.92)	0.69 (0.63–0.75)	0.75 (0.73–0.77)	0.33
PSAd ≥0.15, *n* = 312 (39%)	496 (61)	95 (34)	0.66 (0.61–0.72)	0.76 (0.73–0.80)	0.60 (0.56–0.64)	0.81 (0.78–0.83)	0.42
PSAd ≥0.10, *n* = 569 (70%)	239 (30)	25 (9)	0.91 (0.87–0.94)	0.41 (0.37–0.45)	0.45 (0.43–0.47)	0.90 (0.85–0.93)	0.32

bpMRI = biparametric magnetic resonance imaging; CBx = combined biopsies ($TRUS_{bx}$ + TBx); CI 95% = 95% confidence interval; NPV = negative predictive value; PCa = prostate cancer; PPV = positive predictive value; PSA = prostate-specific-antigen; PSAd = PSA density (ng/ml/cc); sPCa = significant PCa; TBx = bpMRI targeted biopsies; $TRUS_{bx}$ = standard transrectal ultrasound-guided biopsies.

[a] Number of patients below the biopsy threshold (% of total number *n* = 808).

[b] Missed sPCa if biopsies were not performed in men below the biopsy threshold (% of total number *n* = 283). Detection of sPCa was based on CBx results.

performing biopsies on seven (15% threshold) to 13 (7.5% threshold) men to find one additional sPCa. Whether clinicians and patients find this threshold range acceptable is a matter of preference and individual risk assessment. However, missing 5% of sPCa compares favourably with the prevalence (9%) of undiagnosed GS ≥7 PCa found in autopsies of unscreened Caucasian men [27] in a population comparable with our study cohort, and corresponds to the prevalence (also 5%) of PCa with a GS of ≥7 among men with a benign DRE and a PSA level of 2.1–4.0 ng/ml in a placebo-arm subanalysis from the Prostate Cancer Prevention Trial (PCPT) [28]. As the diagnosis of sPCa used in the PCPT was

Table 3 – Effect of PSA density on predictive values for detecting and ruling out significant prostate cancer in each bpMRI suspicion group

bpMRI score	Total		Diagnostic evaluation			
	Total *n* (%)	sPCa *n* (%)	PPV (CI 95%)	*p* value (PPV)	NPV (CI 95%)	*p* value (NPV)
bpMRI score 4–5	384 (48)	239 (84)				
And						
PSAd ≥0.20	136 (35)	108 (45)	0.79 (0.73–0.85)	<0.001	0.21 (0.15–0.27)	<0.001
PSAd <0.20	248 (65)	131 (55)	0.53 (0.49–0.56)		0.47 (0.44–0.51)	
PSAd ≥0.15	217 (57)	161 (67)	0.74 (0.70–0.78)	<0.001	0.26 (0.22–0.30)	<0.001
PSAd <0.15	167 (43)	78 (33)	0.47 (0.41–0.52)		0.53 (0.48–0.59)	
PSAd ≥0.10	332 (86)	221 (92)	0.66 (0.64–0.69)	<0.001	0.34 (0.31–0.36)	<0.001
PSAd <0.10	52 (14)	18 (8)	0.35 (0.24–0.47)		0.65 (0.53–0.76)	
bpMRI score 3	124 (15)	23 (8)				
And						
PSAd ≥0.20	19 (15)	8 (35)	0.42 (0.25–0.62)	0.004	0.58 (0.38–0.75)	0.004
PSAd <0.20	105 (85)	15 (65)	0.14 (0.11–0.18)		0.86 (0.82–0.89)	
PSAd ≥0.15	36 (29)	17 (74)	0.47 (0.36–0.59)	0.002	0.53 (0.41–0.64)	<0.001
PSAd <0.15	88 (71)	6 (26)	0.07 (0.04–0.13)		0.93 (0.87–0.96)	
PSAd ≥0.10	76 (61)	20 (87)	0.26 (0.22–0.31)	0.005	0.74 (0.69–0.78)	0.005
PSAd <0.10	48 (39)	3 (13)	0.06 (0.02–0.16)		0.94 (0.84–0.98)	
bpMRI score 1–2	300 (37)	21 (7)				
And						
PSAd ≥0.20	22 (7)	7 (33)	0.32 (0.18–0.50)	<0.001	0.68 (0.50–0.82)	<0.001
PSAd <0.20	278 (93)	14 (67)	0.05 (0.04–0.07)		0.95 (0.93–0.96)	
PSAd ≥0.15	59 (20)	10 (48)	0.17 (0.11–0.26)	0.002	0.83 (0.75–0.89)	0.002
PSAd <0.15	241 (80)	11 (52)	0.05 (0.03–0.07)		0.95 (0.93–0.97)	
PSAd ≥0.10	161 (54)	17 (81)	0.11 (0.09–0.13)	0.008	0.89 (0.87–0.91)	0.008
PSAd <0.10	139 (46)	4 (19)	0.03 (0.01–0.07)		0.97 (0.93–0.99)	

bpMRI = biparametric magnetic resonance imaging; CI 95% = 95% confidence interval; NPV = negative predictive value; PCa = prostate cancer; PPV = positive predictive value; PSA = prostate-specific-antigen; PSAd = PSA density (ng/ml/cc); sPCa = significant prostate cancer.

based on nontargeted sextant sampling and Gleason scoring before revision in 2005 [25], the prevalence of GS ≥7 PCa was probably underestimated. Additionally, most urological guidelines do not recommend biopsies in men with PSA <4.0 ng/ml; therefore, missing 5% of GS ≥7 PCa on immediate prostate biopsies seems acceptable.

The use of MRI in PCa diagnosis has been studied extensively, and results from two large level 1 evidence trials have recently been published. Both the PRECISION [3] and the PROMIS [2] trial found that mpMRI used as a triage test saved one in four men from prostate biopsies and improved the diagnostic ratio of sPCa versus insPCa compared with our current standard approach—$TRUS_{bx}$ for all men. However, both studies used lengthy mpMRI protocols (approximately 40 min scan times) that required intravenous contrast media and suggested that all mpMRI equivocal findings (score 3) should be biopsied. Our study used a simple and rapid (approximately 15 min) bpMRI protocol with fewer scan sequences and no contrast media, and recommends restricting biopsies to men with suspicious bpMRI findings or PSAd ≥0.15 ng/ml/cc.

Few retrospective studies have been published on the diagnostic accuracy of combining bpMRI and PSAd [16,29]. In a study of 143 biopsy-naïve men who underwent mpMRI, Rais-Bahrami et al. [16] found that combination of bpMRI and PSA or PSAd data improved the diagnostic accuracy of detecting PCa compared with using either parameter alone. These findings were validated by the same study group, emphasising that they also applied to GS ≥7 PCa [29]. However, both these studies used retrospectively culled data where patients with normal or very-high risk MRI findings were excluded. In contrast, our bpMRI data were prospectively obtained and all men underwent biopsies, including those with low-suspicion bpMRI findings. This enabled us to analyse and compare outcomes that reflect current clinical practice ($TRUS_{bx}$ for all men). Although limited bpMRI study data are available, recent studies showed that PSAd significantly influences the predictive values of mpMRI suspicion scores for detecting and ruling out GS ≥7 PCa [12–14]. In a study comparable with ours, Washino et al. [14] included 288 biopsy-naïve men and found no GS ≥7 PCa in men with low- or equivocal-suspicion mpMRI findings (PI-RADSv2 score ≤3) and a PSAd value of <0.15 ng/ml/cc, when using standard biopsies plus TBx as a reference standard.

Overall, our study not only reinforces these previous studies and confirms that MRI combined with PSAd improves the diagnostic accuracy and predictive values for sPCa (GS ≥7) detection, but it also validates the efficacy of a simpler rapid bpMRI protocol and defines an optimal biopsy threshold. This less expensive bpMRI approach may facilitate more widespread clinical implementation of prostate MRI prior to biopsies, especially in the larger patient populations found in the western world where PCa prevalence is high. Although bpMRI and PSAd could be used as risk assessment tools to avoid unnecessary biopsies, they do not rule out any PCa. Nevertheless, because the vast majority of GS ≤6 prostate cancers, irrespective of volume, are considered indolent with negligible metastatic potential

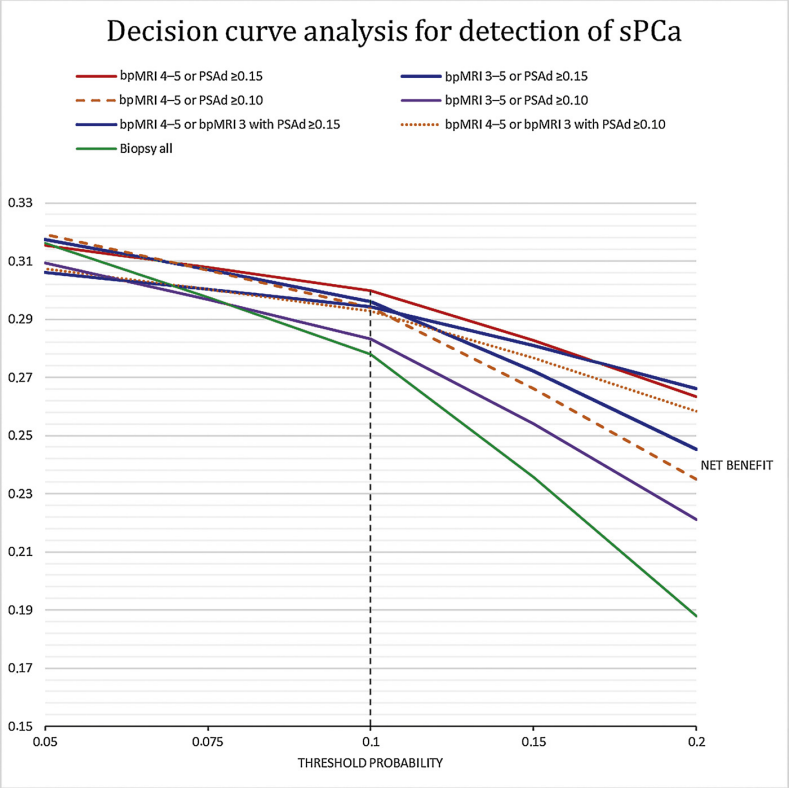

Fig. 2 – Decision curve analysis for the six best biopsy strategies with the highest net benefit using threshold probabilities ranging from 5% to 20%, which is equivalent to performing biopsies in 20 men for the 5% threshold and in five men for the 20% threshold to find one man with significant prostate cancer (sPCa). The reference strategy was to biopsy all men. The biopsy strategy with the highest net benefit in detecting sPCa at a specific threshold probability had the greatest clinical value. The dotted vertical line indicates a biopsy threshold of 10%, equivalent to performing biopsies in 10 men to find one additional sPCa. bpMRI = biparametric magnetic resonance imaging; PCa = prostate cancer; PSA = prostate-specific-antigen; PSAd = PSA density (ng/ml/cc).

[30], the primary objective of clinical practice is to detect and rule out significant disease.

4.1. Limitations

Our study has limitations. First, all our patients were from a non–PSA-screened population, and benign reasons for elevated PSA (eg, urinary infections and residual urine) had been ruled out prior to inclusion. The diagnostic performance of bpMRI and PSAd might differ in other populations (eg, a screened population with lower median PSA levels) that are less enhanced for pretest PCa suspicion. Second, our reference test was limited to the combined results of $TRUS_{bx}$ and TBx, which is not a perfect gold standard. Significant lesions may have been missed by bpMRI or CBx, despite using software-based fusion registration. However, this approach facilitated comparisons with the outcomes of current clinical practice, and the results suggest that cancers that are not detected by bpMRI or PSAd are unlikely to be sPCa subsequently detected by standard $TRUS_{bx}$. Third, the lack of contrast-enhanced imaging might have influenced a small percentage of the detection rates stratified by PI-RADS bpMRI scores, as an equivocal bpMRI score 3 lesion in the peripheral zone was not upgraded to a score of 4 due to a lack of positive contrast enhancement.

Finally, all bpMRI readings were reported by a single experienced uroradiologist, and no inter-reader assessments were performed. The performance of less experienced readers might vary. However, this approach reflects our everyday clinical practice, and the results may generally be relevant. Nevertheless, clinicians must be cautious when MRI results suggest that prostate biopsies are unnecessary. Several factors, including image quality, disease prevalence, and experience of the reporting radiologist may affect the PPVs and NPVs from MRI, and every institution should know their own test performance statistics when making clinical decisions based on MRI findings.

Despite these limitations, our results suggest that immediate $TRUS_{bx}$ is of limited clinical value for sPCa detection in biopsy-naïve men with low- or equivocal-suspicion bpMRI results and a PSAd value of <0.15 ng/ml/cc. However, bpMRI is a novel approach, and its cost effectiveness and long-term outcomes have not been explored fully;

Table 4 – Results of different biopsy strategies and the sensitivities, specificities, and predictive values for detecting and ruling out significant prostate cancer when bpMRI scores are combined with various PSA density thresholds

Biopsy strategy Restrict biopsies to	Biopsies		InsPCa		sPCa		Diagnostic evaluation (sPCa)			
	Performed *n* (%)[a]	Avoided *n* (%)[a]	Detected *n* (%)[b]	Avoided *n* (%)[b]	Detected *n* (%)[b]	Missed *n* (%)[b]	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
All men	808	0	177	0	283	0	Ref	Ref	Ref	Ref
bpMRI score 3–5	508 (63)	300 (37)	112 (63)	65 (37)	262 (93)	21 (7)	0.93 (0.89–0.95)	0.53 (0.49–0.57)	0.52 (0.49–0.54)	0.93 (0.90–0.95)
Or										
PSAd ≥0.20	530 (66)	278 (34)	116 (66)	61 (34)	269 (95)	14 (5)	0.95 (0.92–0.97)	0.50 (0.46–0.55)	0.51 (0.49–0.53)	0.95 (0.92–0.97)
PSAd ≥0.15	567 (70)	241 (30)	127 (72)	50 (28)	272 (96)	11 (4)	0.96 (0.93–0.98)	0.44 (0.40–0.48)	0.48 (0.46–0.50)	0.95 (0.92–0.97)
PSAd ≥0.10	669 (83)	139 (17)	152 (86)	25 (14)	279 (99)	4 (1)	0.99 (0.96–1.00)	0.26 (0.22–0.30)	0.42 (0.40–0.43)	0.97 (0.93–0.99)
bpMRI score 4–5	384 (48)	424 (52)	74 (42)	103 (58)	239 (84)	44 (16)	0.84 (0.80–0.88)	0.72 (0.68–0.76)	0.62 (0.59–0.66)	0.90 (0.87–0.92)
Or										
PSAd ≥0.20	425 (53)	383 (47)	86 (48)	91 (52)	254 (90)	29 (10)	0.90 (0.86–0.93)	0.67 (0.63–0.71)	0.60 (0.57–0.63)	0.92 (0.90–0.95)
PSAd ≥0.15	479 (59)	329 (41)	98 (55)	79 (45)	266 (94)	17 (6)	0.94 (0.91–0.96)	0.59 (0.55–0.64)	0.56 (0.53–0.58)	0.95 (0.92–0.97)
PSAd ≥0.10	621 (77)	187 (23)	141 (80)	36 (20)	276 (98)	7 (2)	0.98 (0.95–0.99)	0.34 (0.30–0.39)	0.44 (0.43–0.46)	0.96 (0.92–0.98)
bpMRI score 4–5 or bpMRI score 3										
With										
PSAd ≥0.20	403 (50)	405 (50)	82 (46)	95 (54)	247 (87)	36 (13)	0.87 (0.83–0.91)	0.70 (0.66–0.74)	0.61 (0.58–0.65)	0.91 (0.88–0.93)
PSAd ≥0.15	420 (52)	388 (48)	83 (47)	94 (53)	256 (90)	27 (10)	0.90 (0.86–0.94)	0.69 (0.65–0.73)	0.61 (0.58–0.64)	0.93 (0.90–0.95)
PSAd ≥0.10	460 (57)	348 (43)	101 (57)	76 (43)	259 (92)	24 (8)	0.92 (0.88–0.94)	0.62 (0.57–0.66)	0.56 (0.53–0.59)	0.93 (0.90–0.95)

bpMRI = biparametric magnetic resonance imaging; CI 95% = 95% confidence interval; InsPCa = insignificant prostate cancer; NPV = negative predictive value; PCa = prostate cancer; PPV = positive predictive value; PSA = prostate-specific-antigen; PSAd = PSA density (ng/ml/cc); sPCa = significant prostate cancer.

[a] The total number of patients (*N* = 808) was used as the denominator for calculating percentages.

[b] The total number of PCa detected (InsPCa/sPCa) was used as the denominator for calculating percentages.

further studies are needed to validate its future role in PCa management.

5. Conclusions

Biparametric MRI combined with PSAd improves the diagnostic accuracy and predictive values for sPCa detection in biopsy-naïve men with clinical suspicion of localised PCa. Restricting biopsies to men with highly suspicious bpMRI scores ($\geq$4) or PSAd $\geq$0.15 ng/ml/cc proved to be the best biopsy strategy in our patient cohort, effectively balancing benefits and risks. Studies are needed to validate our findings in other patient populations.

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

Study concept and design: Boesen, Nørgaard, Jakobsen, Thomsen.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2018.09.001.

References

[1] Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. Eur Urol 2015;67:627–36.
[2] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.
[3] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767–77.
[4] Thompson JE, van Leeuwen PJ, Moses D, et al. The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol 2016;195:1428–35.
[5] Moldovan PC, Van den Broeck T, Sylvester R, et al. What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. Eur Urol 2017;72:250–66.
[6] Fütterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol 2015;68:1045–53.
[7] Borofsky S, George AK, Gaur S, et al. What are we missing? False-negative cancers at multiparametric MR imaging of the prostate. Radiology 2018;286:186–95.
[8] Le JD, Tan N, Shkolyar E, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol 2015;67:569–76.
[9] Nordström T, Akre O, Aly M, Grönberg H, Eklund M. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. Prostate Cancer Prostatic Dis 2018;21:57–63.
[10] Magheli A, Hinz S, Hege C, et al. Prostate specific antigen density to predict prostate cancer upgrading in a contemporary radical prostatectomy series: a single center experience. J Urol 2010;183:126–32.
[11] Jue JS, Barboza MP, Prakash NS, et al. Re-examining prostate-specific antigen (PSA) density: defining the optimal PSA range and patients for using PSA density to predict prostate cancer using extended template biopsy. Urology 2017;105:123–8.
[12] Distler FA, Radtke JP, Bonekamp D, et al. The value of PSA density in combination with PI-RADS™ for the accuracy of prostate cancer prediction. J Urol 2017;198:575–82.
[13] Hansen NL, Barrett T, Koo B, et al. The influence of prostate-specific antigen density on positive and negative predictive values of multiparametric magnetic resonance imaging to detect Gleason score 7–10 prostate cancer in a repeat biopsy setting. BJU Int 2017;119:724–30.
[14] Washino S, Okochi T, Saito K, et al. Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy naïve patients. BJU Int 2017;119:225–33.
[15] Mehralivand S, Shih JH, Rais-Bahrami S, et al. A magnetic resonance imaging-based prediction model for prostate biopsy risk stratification. JAMA Oncol 2018;4:678.
[16] Rais-Bahrami S, Siddiqui MM, Vourganti S, et al. Diagnostic value of biparametric magnetic resonance imaging (MRI) as an adjunct to prostate-specific antigen (PSA)-based detection of prostate cancer in men without prior biopsies. BJU Int 2015;115:381–8.
[17] Kuhl CK, Bruhn R, Krämer N, Nebelung S, Heidenreich A, Schrading S. Abbreviated biparametric prostate MR imaging in men with elevated prostate-specific antigen. Radiology 2017;285:493–505.
[18] Jambor I, Boström PJ, Taimen P, et al. Novel biparametric MRI and targeted biopsy improves risk stratification in men with a clinical suspicion of prostate cancer (IMPROD Trial). J Magn Reson Imaging 2017;46:1089–95.
[19] De Visschere PJL, Naesens L, Libbrecht L, et al. What kind of prostate cancers do we miss on multiparametric magnetic resonance imaging? Eur Radiol 2016;26:1098–107.
[20] Filson CP, Natarajan S, Margolis DJA, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. Cancer 2016;122:884–92.
[21] Boesen L, Nørgaard N, Løgager V, et al. Assessment of the diagnostic accuracy of biparametric magnetic resonance imaging for prostate cancer in biopsy-naive men. JAMA Netw Open 2018;1:e180219. http://dx.doi.org/10.1001/jamanetworkopen.2018.0219.

[22] Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: recommendations from an international working group. Eur Urol 2013;64:544–52.
[23] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2. Eur Urol 2016;69:16–40.
[24] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618–29.
[25] Epstein JI, Allsbrook WC, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005;29:1228–42.
[26] Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244–52.
[27] Zlotta AR, Egawa S, Pushkar D, et al. Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. J Natl Cancer Inst 2013;105:1050–8.
[28] Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤4.0 ng per milliliter. N Engl J Med 2004;350:2239–46.
[29] Fascelli M, Rais-Bahrami S, Sankineni S, et al. Combined biparametric prostate magnetic resonance imaging and prostate-specific antigen in the detection of prostate cancer: a validation study in a biopsy-naive patient population. Urology 2016;88:125–34.
[30] Van Der Kwast TH, Roobol MJ. Defining the threshold for significant versus insignificant prostate cancer. Nat Rev Urol 2013;10:473–82.

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ARTICLE

Clinical Research

A predictive model based on biparametric magnetic resonance imaging and clinical parameters for improved risk assessment and selection of biopsy-naïve men for prostate biopsies

Lars Boesen[1] · Frederik B. Thomsen[1] · Nis Nørgaard[1] · Vibeke Løgager[2] · Ingegerd Balslev[3] · Rasmus Bisbjerg[1] · Henrik S. Thomsen[2] · Henrik Jakobsen[1]

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Abstract

Background Prostate cancer risk prediction models and multiparametric magnetic resonance imaging (mpMRI) are used for individualised pre-biopsy risk assessment. However, biparametric MRI (bpMRI) has emerged as a simpler, more rapid MRI approach (fewer scan sequences, no intravenous contrast-media) to reduce costs and facilitate a more widespread clinical implementation. It is unknown how bpMRI and risk models perform conjointly. Therefore, the objective was to develop a predictive model for significant prostate cancer (sPCa) in biopsy-naive men based on bpMRI findings and clinical parameters.

Methods Eight hundred and seventy-six biopsy-naive men with clinical suspicion of prostate cancer (prostate-specific antigen, <50 ng/mL; tumour stage, <T3) underwent pre-biopsy prostate bpMRI (T2-weighted and diffusion-weighted) followed by 10-core standard biopsies (all men) and MRI-transrectal ultrasound fusion targeted biopsies of bpMRI-suspicious lesions (suspicion score, ≥3). Prediction models based on bpMRI scores and clinical parameters (age, tumour stage, prostate-specific-antigen [PSA] level, $prostate_{volume}$, and $PSA_{density}$) were created to detect sPCa (any biopsy-core with Gleason grade-group, ≥2) and compared by analysing the areas under the curves and decision curves.

Results Overall, sPCa was detected in 350/876 men (40%) with median (inter-quartile range) age and PSA level of 65 years (60–70) and 7.3 ng/mL (5.5–10.6), respectively. The model defined by bpMRI scores, age, tumour stage, and $PSA_{density}$ had the highest discriminatory power (area under the curve, 0.89), showed good calibration on internal bootstrap validation, and resulted in the greatest net benefit on decision curve analysis. Applying a biopsy risk threshold of 20% meant that 42% of men could avoid a biopsy, 50% fewer insignificant cancers were diagnosed, and only 7% of significant cancers (grade-group, ≥2) were missed.

Conclusions A predictive model based on bpMRI scores and clinical parameters significantly improved risk stratification for sPCa in biopsy-naïve men and could be used for clinical decision-making and counselling men prior to prostate biopsies.

Introduction

Prostate cancer (PCa) risk prediction models that combine clinical parameters (e.g., age, prostate-specific-antigen [PSA] level, digital rectal examination [DRE], and trans-rectal ultrasound [TRUS] findings) have traditionally been used in pre-biopsy risk assessments to differentiate between men with an increased risk of PCa who require invasive diagnostic biopsies and men who are likely to have benign conditions or insignificant PCa (insPCa) and can safely avoid biopsies [1, 2]. However, although such pre-biopsy risk calculators are superior to the use of PSA levels alone, the models show limited discriminatory power in detecting and ruling out sPCa (area under the curve [AUC],

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✉ Lars Boesen
lars.boesen@dadlnet.dk

[1] Department of Urology and Urological Research, Herlev Gentofte University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark

[2] Department of Radiology, Herlev Gentofte University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark

[3] Department of Pathology, Herlev Gentofte University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark

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0.69–0.74) [3]. Novel risk tools based on clinical variables and extended blood and/or urine tests with genetic and protein biomarkers, such as the Four-Kallikrein panel (4Kscore) [4], the STHLM3 test [5], the Prostate Health Index (PHI) [6], or the Prostate Cancer Antigen 3 gene scores (PCA3) [7], have been developed to predict the presence of sPCas. While, the 4Kscore and the STHLM3 test include clinical variables in the inherent diagnostic test results, PHI and PCA3 scores can be combined with clinical parameters in nomograms for improved diagnostic accuracy [7, 8]. However, these risk models predict the likelihood of having sPCa but do not identify intra-prostatic tumour location or size, and they are often based solely on results from TRUS-guided biopsies ($TRUS_{bx}$), which can be affected by sampling errors [9–11].

Multiparametric magnetic resonance imaging (mpMRI) can also enhance sPCa detection and risk assessment when combined with clinical parameters [12, 13] and can improve the accuracy of risk calculators that are currently available (AUC, 0.83–0.84) [14, 15]. MpMRI not only estimates the risk of sPCa but can also provide information on cancer location and volume for targeted biopsies. However, Gleason grade group (GG) ≥2 tumours are missed by mpMRI in up to 24–28% of cases [16, 17], using 5-mm template mapping biopsies or radical prostatectomy as standard reference. Therefore, additional clinical predictors are needed to supplement MRI as a triage test to rule out sPCas and spare many men from unnecessary invasive prostate biopsies [16, 18, 19]. Furthermore, state-of-the-art mpMRI is time-consuming (~40 min) and expensive. A simpler, more rapid biparametric MRI (bpMRI) method (~15 min) that uses fewer scan sequences, no intravenous contrast media and maintains high diagnostic accuracy [20] would decrease costs and could facilitate a more widespread clinical implementation of pre-biopsy prostate MRI [20–22]. Therefore, the objective of this study was to develop a novel predictive model based on bpMRI findings and clinical parameters to detect and rule out sPCa in biopsy-naïve men, using results from advanced biopsy techniques ($TRUS_{bx}$ plus MRI-targeted biopsies) as standard reference.

Materials and methods

Patient selection

We used prospective data from a single institutional database (BIDOC database, www.clinicaltrials.gov, NCT02584179). Data collection was approved by the institutional review board and designed to assess the diagnostic accuracy of bpMRI for PCa in biopsy-naive men. Inclusion criteria required all men to have clinical suspicion of PCa (PSA >4 ng/mL and/or suspicious DRE results) warranting diagnostic prostate biopsies. Exclusion criteria were prior prostate biopsies, prior prostate MRI, evidence of acute urinary tract infection, prostatitis, general contraindications for MRI (e.g., claustrophobia, pacemaker, metal implants), and prior hip replacement surgery or other metallic implants in the pelvic area. All men were enroled between November 2015 and June 2017 and provided written informed consent. Patients aged under 75 years with PSA levels of <50 ng/mL were selectively chosen from our database for this study. Baseline characteristics were recorded for the final study cohort of 876 patients including age, PSA levels, DRE results, $prostate_{volume}$, $PSA_{density}$ (PSAd; PSA level/$prostate_{volume}$), bpMRI findings and biopsy results from $TRUS_{bx}$ and bpMRI-targeted biopsies. All patients underwent bpMRI and no patient refused biopsies following a bpMRI negative result. A detailed description of the initial study design and population with primary inclusion and exclusion criteria were previously reported [22].

Imaging and prostate biopsies

All patients underwent bpMRI prior to biopsies using a 3.0T magnet (Philips Healthcare, Best, the Netherlands), including axial T2-weighted and diffusion-weighted imaging and reconstructions of the corresponding apparent diffusion coefficient map. Overall bpMRI image acquisition time was approximately 15 min. Imaging parameters are listed in supplementary information (SI) Table 1.

The bpMRI scans were scored by the same dedicated uroradiologist on a five-point scale according to their likelihood of indicating sPCa (1-highly unlikely, 2-unlikely, 3-equivocal, 4-likely and 5-highly likely) using modified (no contrast-enhanced imaging) Prostate Imaging Reporting and Data System (PI-RADS) version 2 criteria [23]. The bpMRI results were stratified as negative (score 1–2), equivocal (score 3), and positive (score 4–5) findings. A detailed description of bpMRI acquisition and reporting was previously published [22].

All patients underwent standard 10-core $TRUS_{bx}$ plus additional targeted biopsies (1–2 cores/lesion) of any bpMRI suspicious lesion (score 3–5) by one of two operators using MRI/TRUS image-fusion. The definition of sPCa was any core with GG ≥2 (Gleason score ≥3 + 4) based on the International Society of Urological Pathology 2014 GG consensus [24].

Statistical analysis

Baseline patient characteristics were assessed using descriptive statistics and compared using a Wilcoxon rank-sum test (continuous variables) and chi-squared analysis (categorical variables). All potential predictors of sPCa

(age, PSA, $cT_{DRE\ [normal/abnormal]}$, $prostate_{volume}$, PSAd, and bpMRI scores) were assessed for all patients. For a simple clinical approach, the two continuous variables $prostate_{volume}$ (measured on TRUS and bpMRI using the ellipsoid formula [width × height × length × π/6]) and PSAd were divided into groups as follows: $prostate_{volume}$ (G_{PV}) of <30, 30–39, 40–49, 50–69, 70–89 and ≥90 mL; PSAd (G_{PSAd}) of <0.07, 0.07–0.09, 0.10–0.14, 0.15–0.19, 0.20–0.24 and ≥0.25 ng/mL/cc. These reflect previously used PSAd cut-offs [25] and $prostate_{volume}$ distribution percentiles. Multicollinearity was assessed for the continuous variables age, PSA, $prostate_{volume}$ and PSAd using Pearson's correlation matrix. An association between variables was present at a correlation coefficient ≥0.30.

Univariate and multivariate logistic regression models were used to analyse the significance of all included variables (single and multiple explanatory factors) as predictors of sPCa and calculate probabilities when bpMRI scores and clinical parameters were combined. In cases of multicollinearity, multivariate logistic regression analysis with backward selection (p-value cut-off, 0.2) was used to determine which variables generated the best model. For clinical use, we compared four multivariable models that estimated the probability of sPCa at biopsy; a baseline model including PSA and cT_{DRE}; an imaging model based solely on bpMRI scores; an advanced model that included all significant independent clinical variables in a multivariate analysis; and an advanced imaging model that included the advanced model's clinical variables and bpMRI scores. Receiver operating characteristic (ROC) curves and AUCs were used to compare clinical variables and bpMRI scores and quantify the discriminatory accuracy of each multivariable model in identifying men with and without sPCa. The best model, defined as that with the greatest AUC on ROC-curve analysis, was presented as a nomogram for clinical application. DeLong's test was used to identify statistically significant differences between the AUCs. A calibration plot was used to explore the performance of the prediction model and compare predictions with outcomes. Internal validation was performed using bootstrap resampling, as recommended by Steyerberg et al. [26] and a Hosmer–Lemeshow test was used to assess the goodness-of-fit of the predictive models.

In addition, net benefit analyses based on the presence of sPCa at biopsy were used to assess the clinical value of the four predictive models by comparing benefits (sPCa detection) and harms (performing unnecessary biopsies). A decision curve analysis was performed and the biopsy strategy with the greatest net benefit at a specific threshold probability identified as that with the greatest clinical value. Subgroup analyses of men with non-palpable tumour (cTx–T1c) and PSA <20 ng/mL were performed.

Biopsy results from combined biopsies ($TRUS_{bx}$ plus bpMRI-targeted biopsies) were used as histological reference standards. Any patient with sPCa on either $TRUS_{bx}$ or a targeted biopsy was classified as having sPCa on combined biopsies. A two-sided p-value of <0.05 was considered statistically significant. The data were analysed using SPSS (ver. 22.0; SPSS, Inc., Chicago, IL, USA), MedCalc (ver. 16.2; MedCalc, Ostend, Belgium), and R software (ver. 3.5.1; R Development Core Team, 2018).

Results

Study population

Patient characteristics are listed in Table 1. Median age, PSA level, and PSAd (with inter-quartile ranges) were 65 years (60–70), 7.3 ng/mL (5.5–10.6), and 0.13 ng/mL/cc (0.09–0.21), respectively. Men with sPCas were slightly older, had higher PSA levels and PSAds, and higher rates of suspicious bpMRI findings ($p < 0.001$). Overall, PCa was detected in 60% (523/876) of patients, stratified by insPCa in 20% (173/876) and sPCa in 40% (350/876). Combined biopsies detected sPCa in 7% (21/296) of patients with negative, 21% (27/129) with equivocal and 67% (302/451) with positive bpMRI results.

Development of the predictive model and internal validation of the nomogram for predicting sPCa

All included clinical parameters (age, PSA level, $prostate_{volume}$, cT_{DRE}, PSAd and bpMRI score) were significant ($p < 0.001$) as single explanatory predictors of sPCa on logistic regression analysis (SI Table 2). However, Pearson's correlation matrix showed that PSAd was strongly associated with PSA levels ($\rho = 0.62$) and $prostate_{volume}$ ($\rho = -0.54$). Because PSAd had the greatest AUC on ROC-curve analysis (0.79) and PSA level was discarded as non-significant ($p = 0.236$) on multivariate analysis using backward selection, only PSAd was included in addition to age, cT_{DRE}, and bpMRI score in the advanced multivariable models to avoid multicollinearity.

ROC analysis showed that the AUC for bpMRI (0.83) was significantly greater ($p < 0.001$) than for PSAd (0.79), cT_{DRE} (0.71) or age (0.63) in distinguishing patients with and without sPCas (SI Fig. 1). ROC-curve analysis of the multivariable models showed that the advanced imaging model had the greatest AUC (0.89). This was significantly greater ($p < 0.001$) than the baseline (0.78), imaging (0.84) and advanced (0.85) models AUCs (Table 2). Logistic regression coefficients of the multiple explanatory variables age, cT_{DRE}, PSAd and bpMRI score were used to develop a nomogram for the advanced imaging model (Fig. 1). The

Table 1 Patient characteristics

Clinical characteristics		Total $n = 876$	No PCa $n = 353$	Insignificant PCa $n = 173$	Significant PCa $n = 350$	p-value[a]
Age (years), median [IQR]		65 [60–70]	64 [59–68]	64 [59–68]	67 [62–71]	<0.001
PSA (ng/mL), median [IQR]		7.3 [5.5–10.6]	6.4 [5.1–8.9]	6.3 [5.3–8.8]	9.1 [6.4–16.0]	<0.001
Prostate volume (cc), median [IQR]		53 [39–73]	66 [49–88]	52 [41–65]	43 [34–58]	<0.001
PSA density (ng/mL/cc), median [IQR]		0.13 [0.09–0.21]	0.10 [0.08–0.14]	0.12 [0.09–0.17]	0.20 [0.14–0.36]	<0.001
cT_{DRE}, n (%)						
Non-palpable tumour	cTx–cT1c	615 (70%)	306 (87%)	152 (88%)	157 (45%)	<0.001
Palpable tumour	cT2–cT3	261 (30%)	47 (13%)	21 (12%)	193 (55%)	
BpMRI score, n (%)						
Negative	1	177 (20%)	119 (34%)	44 (26%)	14 (3%)	<0.001[b]
	2	119 (14%)	91 (26%)	21 (12%)	7 (2%)	
Equivocal	3	129 (15%)	64 (18%)	38 (22%)	27 (8%)	
Positive	4	173 (20%)	47 (13%)	34 (20%)	92 (26%)	
	5	278 (32%)	32 (9%)	36 (21%)	210 (60%)	

[a]Patients with sPCa are compared with patients in the no/insignificant PCa categories

[b]Fisher's exact test was used to compare the bpMRI score pooled in negative vs. equivocal/positive findings

PCa prostate cancer, *PSA* prostate-specific-antigen, *PSAd* PSA density, G_{PSAd} PSA density group, cT_{DRE} tumour stage by digital rectal examination, *bpMRI* biparametric magnetic resonance imaging, *IQR* interquartile range

Table 2 Logistic regression analysis of the multivariable models that estimate the probability of significant prostate cancer at biopsy

	Baseline model (PSA, cT_{DRE})	Imaging model (bpMRI)	Advanced model (age, PSAd, cT_{DRE})	Advanced imaging model (age, PSAd, cT_{DRE}, bpMRI)
Multiple variable analysis	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Age			1.08 (1.05–1.11)	1.06 (1.03–1.09)
PSA	1.12 (1.08–1.15)			
PSAd group (G_{PSAd})[a]			2.07 (1.83–2.33)	1.72 (1.51–1.96)
cT_{DRE} category[a]	6.75 (4.78–9.55)		5.11 (3.49–8.46)	3.31 (2.19–5.01)
BpMRI score[a]		2.90 (2.51–3.35)		2.01 (1.74–2.35)
	AUC (95% CI)	AUC (95% CI)	AUC (95% CI)	AUC (95% CI)
	0.78 (0.75–0.82)	0.84 (0.81–0.86)	0.85 (0.83–0.88)	0.89 (0.87–0.92)

[a]Assessed as continuous variables

PSA prostate-specific-antigen, *PSAd* PSA density, G_{PSAd} PSA density group, cT_{DRE} tumour stage by digital rectal examination, *bpMRI* biparametric magnetic resonance imaging, *CI* confidence interval, *AUC* area under the curve

model showed good calibration with a slight underestimation of predicted probabilities compared to actual outcomes for clinically relevant thresholds (SI Fig. 2). The Hosmer–Lemeshow test produced a nonsignificant result ($p = 0.143$), which supports the goodness-of-fit of the model. The decision curve analysis showed that the clinical performance of the advanced imaging model was superior (highest net benefit) to the other models (Fig. 2) for clinically relevant thresholds >5% (SI Table 3).

Table 3 shows the various biopsy risk-threshold probabilities for the multivariable models and their sensitivities, specificities, and predictive values for detecting/ruling out sPCa. The advanced imaging model can identify men with sPCas and avoid unnecessary biopsies. For example, applying a biopsy risk threshold of 20% meant that 42% of all men could avoid a biopsy, insPCa diagnoses were reduced by 50%, and only 7% of sPCas were missed. At this risk threshold, the advanced imaging model had greater positive and negative predictive values (65 and 94%, respectively) than the baseline (46 and 82%) and advanced (57 and 89%) models. We found very similar results (superiority of the advanced imaging model) in the subgroup analyses of $n = 592$ men with normal DREs (cTx–T1c) and PSA<20 ng/mL. The AUC for predicting sPCa for the advanced imaging model decreased from 0.89 to 0.85, still with a very high NPV of 94%, but a lower PPV of 51% for a biopsy risk threshold of ≥0.20 (SI Table 4 and SI Fig. 3).

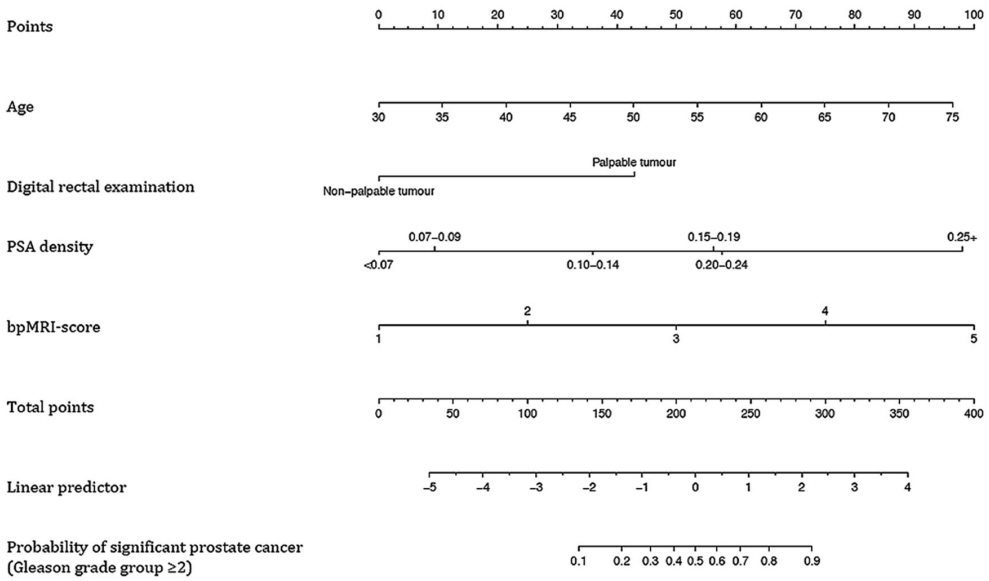

Fig. 1 Nomogram of the advanced imaging model (age, cT_{DRE}, PSAd and bpMRI score) that predicts the probability of significant prostate cancer (Gleason grade group ≥2) in biopsy-naïve men. Points from each individual predictive variable are totalled and a straight line from the total point score gives the probability of harbouring significant prostate cancer

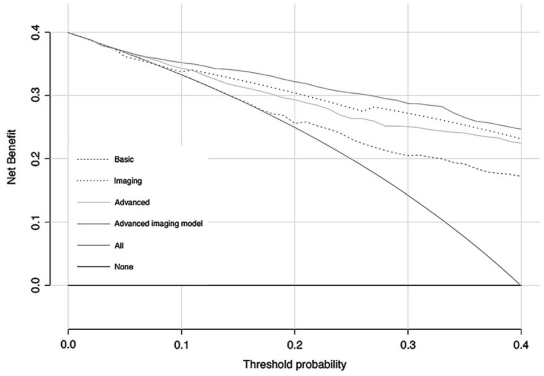

Fig. 2 Net benefit decision curve analysis of the four prediction models for detection of significant prostate cancer. For example, for clinically relevant threshold probabilities ranging from 5 to 20% is equivalent to performing biopsies in 20 men for the 5% threshold and in five men for the 20% threshold to find one man with significant prostate cancer. The reference strategies were to biopsy all men or none. The model with the greatest net benefit at a given risk threshold had the greatest clinical value

Discussion

In this study, we present a predictive model for sPCa detection that combines clinical variables and imaging results from a simple rapid bpMRI method. Our study shows that the MRI-derived score was the strongest single explanatory predictor of sPCa and the AUC was significantly enhanced when MRI scores were combined with age, cT_{DRE}, and PSAd. Decision curve analysis showed that this model had the greatest value for clinically relevant thresholds >5% (equivalent to perform biopsies in 20 men to find one sPCa) in balancing detection of sPCa (benefits) against the risk of undergoing unnecessary biopsies (harms). This model provides an individualised actual probability of having GG ≥2 PCa on prostate biopsy and can be used to counsel men considering the option of avoiding invasive biopsies. Whether a patient finds a certain probability threshold acceptable is a matter of preference and individualised risk assessment. For instance, an older man with comorbidities may value a higher risk of missing or delaying diagnosis of sPCa (e.g., 15–20%) compared to a younger, healthier man (e.g., 5–10%). Clinical tools that can inform patients on a personal level are needed in this era of clinical shared decision-making.

We chose to include only PSAd in the advanced models to avoid multicollinearity because this was a stronger predictor than PSA level and $prostate_{volume}$. However, although determining PSAd requires an accurate assessment of $prostate_{volume}$ using imaging, the indication for biopsy is often set by the urologist based on PSA level and DRE results (our baseline model) before TRUS is performed. Therefore, the decision to make a secondary risk-assessment using TRUS or MRI has already been made and these

Table 3 The results of different biopsy strategies and their sensitivities, specificities, and predictive values in detecting/ruling out significant prostate cancer using multivariable models

Biopsy approach	Biopsies		Insignificant PCa		Significant PCa		Diagnostic evaluation				
	Performed *n* (%)	Avoided *n* (%)	Detected *n* (%)	Avoided *n* (%)	Detected *n* (%)	Missed *n* (%)	Sensitivity [95% CI]	*Ref*	Specificity [95% CI]	*Ref*	NPV [95% CI]
All men	876	0	173	0	350	0	*Ref*		*Ref*		*Ref*
Risk baseline model											
≥0.10	876 (100%)	0 (0%)	173 (100%)	0 (0%)	350 (100%)	0 (0%)	1.00 [0.99–1.00]		0.00 [0.00–0.01]	0.40 [0.40–0.40]	N/A
≥0.15	872 (99%)	4 (1%)	173 (100%)	0 (0%)	350 (100%)	0 (0%)	1.00 [0.99–1.00]		0.01 [0.00–0.02]	0.40 [0.40–0.40]	1.00 [1.00–1.00]
≥0.20	678 (77%)	198 (23%)	122 (71%)	51 (29%)	315 (90%)	35 (10%)	0.90 [0.86–0.93]		0.31 [0.27–0.35]	0.46 [0.45–0.48]	0.82 [0.77–0.87]
Risk advanced model											
≥0.10	719 (82%)	157 (18%)	137 (79%)	36 (21%)	342 (98%)	8 (2%)	0.98 [0.96–0.99]		0.29 [0.25–0.32]	0.48 [0.46–0.49]	0.95 [0.90–0.97]
≥0.15	625 (71%)	251 (29%)	108 (62%)	65 (38%)	330 (94%)	20 (6%)	0.94 [0.91–0.96]		0.44 [0.40–0.48]	0.53 [0.51–0.55]	0.92 [0.88–0.95]
≥0.20	548 (63%)	328 (37%)	89 (51%)	84 (49%)	315 (90%)	35 (10%)	0.90 [0.86–0.93]		0.56 [0.51–0.60]	0.57 [0.55–0.60]	0.89 [0.86–0.92]
Risk advanced imaging model											
≥0.10	622 (71%)	254 (29%)	113 (65%)	60 (35%)	341 (97%)	9 (3%)	0.97 [0.95–0.99]		0.47 [0.42–0.51]	0.55 [0.53–0.57]	0.96 [0.93–0.98]
≥0.15	546 (62%)	330 (38%)	95 (55%)	78 (45%)	335 (96%)	15 (4%)	0.96 [0.93–0.98]		0.60 [0.56–0.64]	0.61 [0.58–0.64]	0.95 [0.93–0.97]
≥0.20	505 (58%)	371 (42%)	86 (50%)	87 (50%)	327 (93%)	23 (7%)	0.93 [0.90–0.96]		0.66 [0.62–0.70]	0.65 [0.62–0.68]	0.94 [0.91–0.96]

PCa prostate cancer, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value, *N/A* not applicable

imaging results can be used to accurately measure the $prostate_{volume}$. In contrast to TRUS, MRI results provide additional information (e.g., bpMRI scores) that can be used to make a better assessment of the overall risk of sPCa. Furthermore, using additional genetic- and/or protein-based biomarkers (e.g., kallikrein-related peptidases) is laboratory-dependent and expensive, whereas easily obtainable PSAd measurements are more suitable for routine use in clinical practice.

To the best of our knowledge, this is the first nomogram that combines a prospectively derived bpMRI score with easily obtainable clinical parameters and uses results from advanced biopsy techniques ($TRUS_{bx}$ plus MRI targeted biopsy) as standard reference. A retrospective study of 59 biopsy-naïve patients by Fascelli et al. [27] found that combining bpMRI with PSA level or PSAd improved the detection of sPCa compared with either PSA level or PSAd alone. However, in contrast to our study, Fascelli et al. culled bpMRI sequences from mpMRI data, did not include age or cT_{DRE} data, and only included patients with suspicious MRI results. While only limited bpMRI-derived suspicion score data are available, the results of recent mpMRI studies are consistent with our findings [12–14] and show improved diagnostic accuracies of 3–20% for multivariable imaging models that combine mpMRI results with baseline clinical parameters. In a study comparable to ours, Mehralivand et al. [13] showed that when mpMRI PI-RADS scores were combined with age, PSA, cT_{DRE}, prior biopsy, and ethnicity data to detect GG ≥2 PCas, the AUC increased from 0.64 to 0.84. Similarly, van Leeuwen et al. [12] showed that a risk prediction model could be used to reduce unnecessary biopsies.

Overall, our study not only validates the results of previous studies, but also demonstrates that similar diagnostic accuracies are attainable using MRI findings from a simpler faster bpMRI approach. MRI is increasingly used for prostate cancer diagnoses. At present, guidelines recommend mpMRI before repeat biopsies and for men enroled in active surveillance [28, 29]. However, several evidence level 1 studies of MRI in biopsy-naïve men have recently been published [30–32]. They all favour an MRI-influenced diagnostic pathway to selectively triage men for prostate biopsies. Implementing pre-biopsy mpMRI for all biopsy-naïve men constitutes a fundamental paradigm shift in the diagnosis of PCa and could place a significant financial and resource burden on the healthcare system [33]. The use of a simple, rapid and less expensive bpMRI method appears to maintain the high diagnostic accuracy of mpMRI [20, 21] and could facilitate a more widespread implementation of MRI as a secondary triage test in clinical practice. Using MRI to triage men for biopsies is also likely to be cost-effective because it will reduce unnecessary biopsies, associated infection rates, patient distress, and insPCa

diagnoses [34]. Overall, by combining clinical and imaging information our model improved shared decision-making regarding prostate biopsy.

The main limitation of our study was the use of biopsy results as a reference standard. Significant lesions could have been missed and the true rate of false-negatives cannot be assessed because final pathology is unknown. In addition, the baseline and advanced models' reference test included targeted biopsies from MRI results that indicated the presence of suspicious lesions. This may have overestimated the diagnostic performance of these models given MRI data were not available. This risk model was developed for sPCa diagnosis and cannot be used to rule out all PCas; however, in clinical practice, the primary objective is to detect and rule out significant disease. Moreover, our risk models were developed using data from a Scandinavian population, where systematic PSA screening is not performed. This might explain the rather high proportion of men (30%) with abnormal pre-biopsy DRE findings. The models might perform differently in a PSA-screened or more ethnically heterogeneous cohort. However, the advanced imaging model still produced the highest net benefit on decision curve analysis and proved best for sPCa detection at clinically relevant biopsy thresholds (>5%) when men with abnormal DREs and high PSA (≥20 ng/mL) were excluded in the subgroup analysis.

Despite these limitations, our study provides an individualised clinical tool based on easily obtainable clinical variables and a novel abbreviated bpMRI approach for improved risk assessment and selection of biopsy-naïve men for prostate biopsies. Still, although we found good discrimination and calibration for the advanced imaging risk model using bootstrap internal validation, future external validation in other cohorts will be needed as more bpMRI data become increasingly available. As a result, further studies are needed to fully explore and establish bpMRIs future role in PCa management.

Conclusions

A predictive multivariable model based on bpMRI imaging and clinical parameters significantly improves risk stratification for sPCa in biopsy-naïve men and could be used to inform clinical decision-making and to counsel men considering the option of an invasive prostate biopsy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Roobol MJ, Van Vugt HA, Loeb S, Zhu X, Bul M, Bangma CH, et al. Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators. Eur Urol. 2012;61:577–83.
2. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst. 2006;98:529–34.
3. Foley RW, Maweni RM, Gorman L, Murphy K, Lundon DJ, Durkan G, et al. European randomised study of screening for prostate cancer (ERSPC) risk calculators significantly outperform the Prostate Cancer Prevention Trial (PCPT) 2.0 in the prediction of prostate cancer: a multi-institutional study. BJU Int. 2016;118:706–13.
4. Parekh DJ, Punnen S, Sjoberg DD, Asroff SW, Bailen JL, Cochran JS, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. Eur Urol. 2015;68:464–70.
5. Grönberg H, Adolfsson J, Aly M, Nordström T, Wiklund P, Brandberg Y, et al. Prostate cancer screening in men aged 50–69 years (STHLM3): a prospective population-based diagnostic study. Lancet Oncol. 2015;16:1667–76.
6. Loeb S, Sanda MG, Broyles DL, Shin SS, Bangma CH, Wei JT, et al. The prostate health index selectively identifies clinically significant prostate cancer. J Urol. 2015;193:1163–9.
7. Wei JT, Feng Z, Partin AW, Brown E, Thompson I, Sokoll L, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer? J Clin Oncol. 2014;32:4066–72.
8. Loeb S, Shin SS, Broyles DL, Wei JT, Sanda M, Klee G, et al. Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer. BJU Int. 2017;120:61–68.
9. Shariat SF, Roehrborn CG. Using biopsy to detect prostate cancer. Rev Urol. 2008;10:262–80.
10. Ukimura O, Coleman JA, de la Taille A, Emberton M, Epstein JI, Freedland SJ, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol. 2013;63:214–30.
11. Van Der Kwast TH, Roobol MJ. Defining the threshold for significant versus insignificant prostate cancer. Nat Rev Urol. 2013;10:473–82.
12. van Leeuwen PJ, Hayen A, Thompson JE, Moses D, Shnier R, Böhm M, et al. A multiparametric magnetic resonance imaging-based risk model to determine the risk of significant prostate cancer prior to biopsy. BJU Int. 2017;120:774–81.
13. Mehralivand S, Shih JH, Rais-Bahrami S, Oto A, Bednarova S, Nix JW, et al. A magnetic resonance imaging–based prediction model for prostate biopsy risk stratification. JAMA Oncol. 2018;4:678–85.
14. Radtke JP, Wiesenfarth M, Kesch C, Freitag MT, Alt CD, Celik K, et al. Combined clinical parameters and multiparametric magnetic resonance imaging for advanced risk modeling of prostate cancer—patient-tailored risk stratification can reduce unnecessary biopsies. Eur Urol. 2017;72:888–96.
15. Alberts AR, Roobol MJ, Verbeek JFM, Schoots IG, Chiu PK, Osses DF, et al. Prediction of high-grade prostate cancer following multiparametric magnetic resonance imaging: improving the Rotterdam European Randomized Study of screening for prostate cancer risk calculators. Eur Urol. 2018;75:310–8. https://doi.org/10.1016/j.eururo.2018.07.031.

16. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389:815–22.
17. Le JD, Tan N, Shkolyar E, Lu DY, Kwan L, Marks LS, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol. 2015;67:569–76.
18. Schoots IG, Petrides N, Giganti F, Bokhorst LP, Rannikko A, Klotz L, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. Eur Urol. 2015;67:627–36.
19. Thompson JE, van Leeuwen PJ, Moses D, Shnier R, Brenner P, Delprado W, et al. The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol. 2016;195:1428–35.
20. Sherrer RL, Glaser ZA, Gordetsky JB, Nix JW, Porter KK, Rais-Bahrami S. Comparison of biparametric MRI to full multiparametric MRI for detection of clinically significant prostate cancer. Prostate Cancer Prostatic Dis. 2018. https://doi.org/10.1038/s41391-018-0107-0.
21. Kuhl CK, Bruhn R, Krämer N, Nebelung S, Heidenreich A, Schrading S. Abbreviated biparametric prostate MR imaging in men with elevated prostate-specific antigen. Radiology. 2017;285:493–505.
22. Boesen L, Nørgaard N, Løgager V, Balslev I, Bisbjerg R, Thestrup K-C, et al. Assessment of the diagnostic accuracy of biparametric magnetic resonance imaging for prostate cancer in biopsy-naive men. JAMA Netw Open. 2018;1:e180219.
23. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS prostate imaging—reporting and data system: 2015, Version 2. Eur Urol. 2016;69:16–40.
24. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016;40:244–52.
25. Nordström T, Akre O, Aly M, Grönberg H, Eklund M. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. Prostate Cancer Prostatic Dis. 2018;21:57–63.
26. Steyerberg EW, Harrell FE, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54:774–81.
27. Fascelli M, Rais-Bahrami S, Sankineni S, Brown AM, George AK, Ho R, et al. Combined biparametric prostate magnetic resonance imaging and prostate-specific antigen in the detection of prostate cancer: a validation study in a biopsy-naive patient population. Urology. 2016;88:125–34.
28. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2017;71:618–29.
29. Rosenkrantz AB, Verma S, Choyke P, Eberhardt SC, Eggener SE, Gaitonde K, et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. J Urol. 2016;196:1613–8.
30. El-Shater Bosaily A, Parker C, Brown LC, Gabe R, Hindley RG, Kaplan R, et al. PROMIS—Prostate MR imaging study: a paired validating cohort study evaluating the role of multi-parametric MRI in men with clinical suspicion of prostate cancer. Conte Clin Trials. 2015;42:26–40.
31. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378:1767–77.
32. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: A Large Prospective Multicenter Clinical Study. Eur Urol. 2018;75:570–8. https://doi.org/10.1016/j.eururo.2018.11.023.
33. Kim SJ, Vickers AJ, Hu JC. Challenges in adopting level 1 evidence for multiparametric magnetic resonance imaging as a biomarker for prostate cancer screening. JAMA Oncol. 2018;4:1663–4. https://doi.org/10.1001/jamaoncol.2018.4160.
34. Barnett CL, Davenport MS, Montgomery JS, Wei JT, Montie JE, Denton BT. Cost-effectiveness of magnetic resonance imaging and targeted fusion biopsy for early detection of prostate cancer. BJU Int. 2018;122:50–58.

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Lars Boesen

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REVIEW ARTICLE

Magnetic resonance imaging—transrectal ultrasound image fusion guidance of prostate biopsies: current status, challenges and future perspectives

Lars Boesen

Department of Urology and Urological Research, Herlev Gentofte University Hospital, Herlev, Denmark

ABSTRACT

The use of multiparametric magnetic resonance imaging (mpMRI) in prostate cancer (PCa) diagnosis is rapidly evolving to try to overcome the limitations of the current diagnostic pathway using systematic transrectal ultrasound-guided biopsies ($TRUS_{bx}$) for all men with clinical suspicion of PCa. Prostate mpMRI allows for high quality lesion detection and characterization and has been shown to improve detection of significant PCa with a more accurate Gleason score grading. Suspicious lesions can be stratified by suspicion and sampled by selective MRI-guided targeted biopsies (TBx) for improved diagnostic accuracy. Several TBx methods have been established and include MRI/TRUS image fusion biopsies (cognitive or software-assisted) and in-bore biopsies, but none have yet proven superior in clinical practice. However, while MRI in-bore biopsy is not routinely used due to its costs and limited availability, MRI/TRUS image fusion is rapidly embraced as it allows skilled urologists to perform TBx in an outpatient clinic. Furthermore, it gives the operator the advantage of adding TBx to the systematic standard biopsy scheme, which is the currently recommended approach. With the anticipated increased future use of prebiopsy mpMRI, a more widespread implementation of MRI/TRUS image fusion platforms is concurrently expected in clinical practice. Therefore, the objective of this review is to assess the current status, challenges and future perspectives of prostate MRI/TRUS image fusion biopsies.

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Diagnostic imaging; image-guided biopsy; magnetic resonance imaging; prostate biopsy; prostate cancer; ultrasound imaging

Introduction

Each year more than 50,000 men under suspicion of prostate cancer (PCa) in the Nordic countries undergo invasive prostate biopsies. Since the transrectal ultrasound-guided biopsy technique ($TRUS_{bx}$) was introduced nearly 30 years ago, it has been the standard-of-care to either confirm the diagnosis or exclude the presence of disease [1]. During the $TRUS_{bx}$ procedure, 10–12 needle-cores are obtained systematically from pre-defined anatomical regions of the prostate. However, the poor PCa target identification of $TRUS_{bx}$ often leads to missed significant cancers (sPCa) [2] and risk of possible Gleason score (GS) under-grading [3,4]. Furthermore, men without PCa undergo unnecessary biopsies, because elevated serum prostate-specific-antigen is not cancer-specific. Thus, men at risk regularly undergo multiple biopsy sessions that may cause severe infections, bleeding, and anxiety combined with an increased risk of detecting insignificant low grade disease leading to possible over-treatment [5–7]. Because $TRUS_{bx}$ systematically, but untargeted primarily samples the peripheral zone of the prostate, it may miss significant cancers in the anterior part (systematic sampling errors) caused by the limited length and range of the $TRUS_{bx}$ needle cores. These limitations have highlighted the need for better methods to improve the diagnostic information gained by the invasive prostate biopsies and maximize detection of sPCa while minimizing over-detection of insignificant disease and unnecessary biopsies. Growing evidence supports the use of multiparametric MRI (mpMRI) and targeted biopsies (TBx) to aid this problem [8]. In general, MRI-guided TBx is a biopsy technique where mpMRI images are used to identify suspicious lesions and guide prostate biopsy sampling sites. Several TBx methods have been established, but none have yet proven superior in clinical practice. The objective of this review is to assess the current status, challenges and future perspectives of prostate MRI/TRUS image fusion biopsies.

Multiparametric MRI

The use of mpMRI of the prostate allows for high quality lesion detection and characterization of the entire prostate gland. It has been shown to improve sensitivity and detection of sPCa [9–11] with a more accurate GS grading [12–14]. Suspicious lesions identified on mpMRI can be stratified by suspicion and sampled by selective MRI-guided TBx for improved diagnostic accuracy [15]. With this ability to identify highly suspicious areas at mpMRI, TBxs are increasingly accompanying or replacing multiple systematic $TRUS_{bx}$ cores (Figure 1).

However, due to different study protocols, MRI equipment, expertise and mpMRI scoring systems, the diagnostic accuracy differs among previous published studies [15–17]. As a result, clinical guidelines by the European Society of

CONTACT Lars Boesen lars.boesen@dadlnet.dk Urology and Urological Research, Herlev Hospital, Herlev Ringvej 75, Herlev, 2730 Denmark

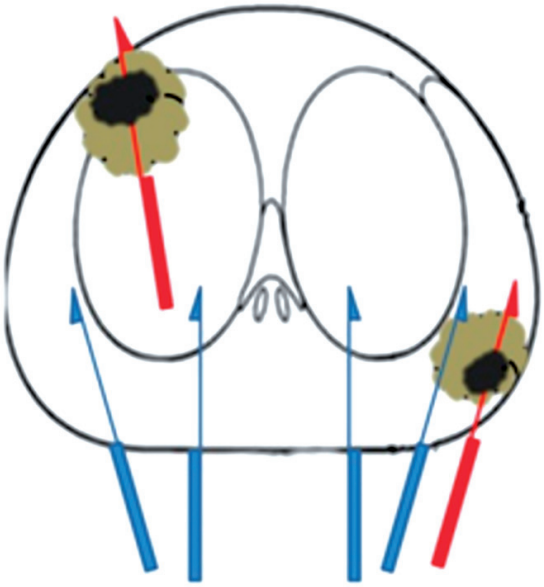

Figure 1. The poor prostate cancer target identification of transrectal ultrasound-guided biopsy ($TRUS_{bx}$) cores (blue cores) often leads to missed significant cancers and/or risk of missing the most aggressive part (dark area), leading to possible Gleason score under-grading. In addition, the limited length of the $TRUS_{bx}$ cores leads to inadequate sampling of the anterior part. Targeted biopsies (red cores) can be guided by multiparametric MRI for improved diagnostic accuracy.

Urogenital Radiology (ESUR) and the American College of Radiologists (ACR) have been published [10,18]. These include a structured uniform Prostate Imaging Reporting and Data System (PI-RADS) to standardize and promulgate uniform high-quality mpMRI acquisition, interpretation and reporting with accurate communication between all involved physicians. Although the mpMRI protocol may be optimized for different clinical scenarios, the guidelines overall recommend the use of T2-weighted imaging (T2W), diffusion-weighed imaging (DWI) with its corresponding ADC (apparent diffusion coefficient) map, and dynamic contrast enhanced (DCE) imaging for optimal PCa lesion detection and characterization. In practice, all suspicious lesions are registered on a regional prostate diagram and scored from 1–5 using the currently applicable PI-RADS v2 classification [18] according to their probability of being sPCa (1 = very low, 2 = low, 3 = intermediate, 4 = high and 5 = very high). PI-RADS v2 suspicion scores are highly associated with biopsy results and increased diagnostic yield of sPCa at higher assessment categories [15,19]. Although several prostate mpMRI scoring systems exist, PI-RADS v2 is endorsed by the ESUR and the ACR to be globally adopted. However, it is important to remember that PI-RADS v2 scoring cannot be used to detect/rule out any PCa. It is a lesion-based scoring system that uses assessment categories to predict the likelihood of sPCa defined as Gleason score $\geq$7 and/or volume $\geq$0.5 cc and/or extra prostatic extension. PI-RADS v2 is an 'evolving guideline' that can be adjusted [20] as data and experience matures. For example, a status update that summarizes the current accuracy, strengths and weaknesses, as well as discusses pathway implications and outlines opportunities for future improvements of PI-RADS v2 was recently published by the PI-RADS steering committee [21] and an updated PI-RADS v2.1 version is expected to be published anytime soon.

Fusion targeted biopsy methods

Multiple approaches exist for TBx of mpMRI suspicious lesions [22]. Direct in-bore TBx in the MRI suite can accurately sample lesions of interest with direct image confirmation of needle deployment within the target. It is, therefore, considered to be the gold standard of MRI-guided TBx, but is associated with considerable costs, limited availability and does not allow for concurrent systematic sampling. However, fusing mpMRI data with TRUS (MRI/TRUS fusion) combines the superior imaging of mpMRI coupled with the easier-to-use ultrasound guidance, which allows skilled operators to perform TBx in real-time in an outpatient clinic, saving time and costs, while preserving adequate targeting accuracy [23–25]. Furthermore, TBx can be combined with systematic biopsies, as recommended in the European Association of Urology (EAU) guidelines [3].

Fusion TBx can be done either 'cognitively' (use your brain) or assisted by software that has been developed to increase targeting accuracy. There are now several commercial software platforms available (Table 1) that differ in both technology (image acquisition and tracking mechanism) and biopsy route (transrectal—sidefire/endfire or transperineal). An MRI T2W sequence is most often used for prostate/target contouring during MRI/TRUS image fusion, due to its high anatomical resolution and lower risk of artefacts. However, other mpMRI sequences can be used depending on preferences and fusion-software.

Cognitive targeted biopsies

Cognitive 'fusion' is the simplest, cheapest and first technique by which MRI/TRUS fusion TBx was done. A pre-biopsy mpMRI is used to localize the target and the TRUS-operator uses this knowledge to aim the biopsy needle at this prostatic anatomical area/zone. The main advantage is that cognitive TBxs are performed without any additional hardware or software. However, it requires high experience and training as the operator must visually match suspicious lesions on the mpMRI to the corresponding real-time 2D TRUS image and translate it all into a 3D representation of the prostate based on zonal anatomy and tissue landmarks (visual registration). Overall, cognitive TBx seems to be superior to standard $TRUS_{bx}$ in the review by Moore et al. [11]. In a study of 555 biopsy-naïve men with clinical suspicion of PCa, Haffner et al. [26] compared $TRUS_{bx}$ in all men with cognitive TBx restricted to men with suspicious mpMRIs and found the latter approach detected more high-grade cancer using fewer biopsy cores in fewer men. However, cognitive TBx constitutes a potential of human error in the extrapolation of targets from mpMRI to TRUS without an image-overlay. Consequently, prior study results have been inconsistent [11]

Table 1. Overview of assorted commercially available MRI/TRUS fusion platforms (with reservations to non-complete descriptions and present platform assortment).

Trade name	TRUS image	Tracking	biopsy route	Comments
MIM-Symphony / bkFusion	Semi-automatic contouring	Electromagnetic tracking with external generator	Transrectal / transperineal	Predictive fusion, free hand transrectal manipulation
Biojet	Manual sweep with fixed probe	Mechanical arm with encoders; fixed probe stepper	Transrectal / transperineal	Rigid registration, manual contouring
Ascendus / HI-RVS	Real-time manual TRUS, no sweep/prostate contouring	Electromagnetic tracking with external generator	Transrectal / transperineal	Rigid registration, alignment using anatomical landmarks
BioBot	Automatic sweep	Robotic mechanical arm, organ-based 3D fusion biopsy planning	Transperineal	Elastic registration, manual contouring, Automatic needle positioning
Urostation	3D automatic sweep	Organ-based real time fusion, 3D navigation	Transrectal / transperineal	Elastic registration, virtual targeting
Artemis	Manual sweep with fixed axis	Mechanical arm with probe and encoders, 3D navigation	Transrectal / transperineal	Stabilized probe
UroNav	Manual freehand sweep	Electromagnetic tracking with external generator, 3D navigation	Transrectal / transperineal	Free hand transrectal manipulation

and cognitive TBxs may be more likely to fail when targeting smaller lesions in larger prostates, especially if located in the transitional zone. Furthermore, cognitive TBx does not enable allocation of biopsies for re-evaluation (e.g. before repeat biopsies or during active surveillance).

Software-assisted targeted biopsies

MRI/TRUS image-fusion software platforms have been developed to increase targeting accuracy and several features are common to all. First, pre-biopsy mpMRI data is obtained, the prostate is segmented, and the lesions are identified by the radiologist. At this stage, it is important to recognize how the segmentation of the targets will be used by the operator performing the biopsies. Some systems and operators prefer to minimize the ROI (region-of-interest) to the centre or the most suspicious part of the lesion to maximize detection of possible high-grade cancer on TBx. Others prefer to outline and sample the whole lesion to incorporate volume into the overall risk assessment and to minimize sampling errors. Second, the relevant mpMRI data (often limited to T2W- and/or ADC images) is imported into the TRUS fusion platform before the biopsy session. During the biopsy session, real-time TRUS images are obtained by sweeping or acquiring different scan planes of the prostate to which the segmented MRI data is electronically fused for biopsy guidance. During this step TRUS and MRI images are aligned based on morphology, anatomical landmarks and/or contouring of the prostate, while adjusting for patient movement and TRUS probe deformation. Once the images are aligned, the MRI data is translated into 'live'-images that move correspondingly in the same way the TRUS probe/image moves, while accounting for real-time changes/deformation of the prostate during the procedure (not all platforms). This allows the operator to use mpMRI data obtained previously for biopsy guidance during the dynamic TRUS session. Several platforms can track and record biopsy sites during the procedure. This enables the operator to return to prior biopsy sites for either re-sampling in men under active surveillance or identify and re-evaluate previously sampled areas in men with prior negative biopsies and persistent suspicion of PCa undergoing re-biopsy.

However, it is important to recognize that all image-fusion platforms encompass some degree of mis-registration and there will be a margin of error despite careful efforts to align the MRI and TRUS images. The different methods of fusing images affect the accuracy of TBx. A main difference is the way MRI and TRUS images are fused—either 'rigidly' or 'non-rigidly/elastic'. In *rigid fusion*, the MRI and TRUS images are overlaid without real-time adjustment for patient movement or prostate deformation during the biopsy procedure. A *non-rigid fusion* system tries to compensate for this by fusing organ volumes and using 3D contouring with elastic deformation algorithms. However, although limited by large heterogeneity of included studies, the recent meta-analysis by Venderink et al. [27] did not identify any difference in PCa detection rates between rigid and non-rigid fusion methods.

Another difference between MRI/TRUS fusion platforms is the way the images are tracked. *Electromagnetic tracking* is a popular method that has been validated by several institutions [28,29]. It uses a small electromagnetic emitter and a receiver that tracks the spatial location of the TRUS probe. This technique is rather fast and allows for great freedom of motion, but may suffer from electromagnetic interference and only tracks the TRUS probe and not the prostate itself. Thus, mis-registration between the prostate contour and internal landmarks/targets may occur. To improve the registration and rigid overlay, some platforms have incorporated software sensors into either a *robotic arm* (e.g. Artemis) [30] or *the needle guide* (e.g. UroNav) [31] and included a 3D reference volume for segmentation and contouring. Still, real-time adjustment for patient movement or prostate deformation during the biopsy procedure is a challenge.

Organ-based image registration is a non-rigid platform that tracks the organ (prostate) itself [32]. It requires a specialized 3D TRUS probe that the operator uses repeatedly and at any time during the procedure to create a 3D-scan of the prostate that is automatically registered and fused with the segmented MRI data to create a final overlay of matching TRUS and MRI volumes. MRI targets are then overlaid on TRUS for TBx. This method is developed to try to account for patient movement and deformation during the procedure. However, once the probe is moved, the target is lost.

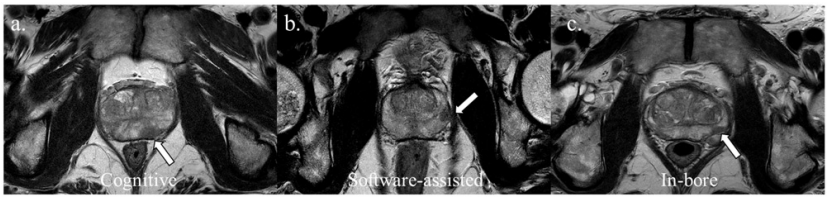

Figure 2. The preferred biopsy technique for multiparametric MRI positive lesions (white arrows) may depend on lesions size and location. A large lesion located in the posterior peripheral zone (a) can often be identified, targeted and sampled sufficiently by cognitive biopsies. However, if the lesion is smaller and/or located laterally or anteriorly (b), then a software-assisted biopsy platform may preferably support the operator for improved targeting accuracy. For small lesions (c), regardless of location, the in-bore biopsy technique within the MRI suite may be superior, because a confirmatory MRI can verify direct needle position and sampling site during the procedure.

Overall, software-assisted MRI/TRUS fusion TBx has been shown to be superior to standard $TRUS_{bx}$ and demonstrated higher detection rates of sPCa [25]. However, there is no clear advantage of one MRI/TRUS fusion platform compared to others [33] and there seems to be no difference in registration errors between rigid and elastic registration [27,34]. Operator experience and cognitive adjustments based on zonal anatomy and tissue landmarks are still essential during the software-assisted procedure to reduce registration errors, regardless of the method being used. This was recently emphasized in a prospective, randomized study by Hamid et al. [35], who compared visual registration (cognitive) targeting with software-assisted image fusion. In this study of 129 men, Hamid et al. [35] concluded both TBx techniques should be combined to detect the highest rate of sPCa. Nevertheless, there is currently no consensus on which TBx method (cognitive vs software-assisted vs in-bore vs combined approach) performs best in a given situation. Whereas the meta-analysis by Wegelin et al. [22] showed superiority of software-assisted and in-bore biopsies compared with cognitive biopsies, the recent multi-centre, randomized FUTURE trial [36] did not find any significant differences in the detection rates of PCa among the three MRI-based TBx techniques. However, this study was limited by sample size, as only 234/655 men had suspicious findings warranting TBx, which yielded ~78 men in each biopsy arm to assess primary outcome (underpowering). Thus, because there is no consensus on which biopsy technique should be preferred, the key challenge is to ensure appropriate expertise and training rather than focusing on an optimal technology or platform. Furthermore, the volume and location of the tumour might guide the preferred strategy for individualized biopsy-planning (Figure 2). In addition, limited data suggest that a transperineal MRI-guided biopsy route may be preferred for detecting anteriorly located cancers [37]. All three MRI-guided TBx approaches (in-bore, cognitive and software-assisted) can be performed via either the transrectal or transperineal route and most of the commercially available platforms (software-assisted fusion) allow for both biopsy routes. There is no major difference in the matching and registration of TRUS and MRI images between the transrectal and transperineal approach, as most fusion platforms use a rectal TRUS probe insertion for both approaches. It is the biopsy routes that differ. Because of the anatomical location of the prostate and the feasibility of the procedure, the transrectal approach has been the standard and most commonly used biopsy route for decades. However, transrectal biopsies require prophylactic antibiotics, as each biopsy-needle must pass through the rectal wall with risk of inoculating the prostate with rectal bacteria. Therefore, the increasing worldwide prevalence of antibiotic-resistant bacteria of the rectal flora have led to a wider acceptance and use of transperineal biopsies, due to its lower risk of septic complications [37]. In transperineal biopsies, all cores are obtained by puncturing the disinfected perineal skin guided by either a brachy-grid, using robotic guidance or by free-hand. As neither the rectal-wall nor the urinary tract is penetrated, it is considered to be an aseptic procedure with only limited use of antibiotics. However, although sepsis rates are low/negligible following transperineal biopsies, there is an increased risk of urinary retention and most procedures are performed under general anaesthesia (although with possibilities for use under local anaesthesia), which makes it less suitable for routine clinical practice.

Limitations, caveats and future perspectives

It is important to recognize that not all cancers are visible on mpMRI [38] and lesions may be misinterpreted. Prior studies have shown a fairly consistent rate of sPCas that are detected by standard $TRUS_{bx}$ and missed by TBx [15,39]. Each step of the process from mpMRI acquisition, interpretation and reporting to segmentation, image-fusion method and the biopsy approach itself encloses its own risks of error. MpMRIs may be misinterpreted, TBx may miss PCa lesions due to targeting errors and unnecessary TBx may be conducted due to false-positive mpMRI readings. Furthermore, because of possible prostate deformation and movement during the MRI/TRUS biopsy session, it is difficult to confirm real-time accurate biopsy-deployment within the target. Sampling errors may be reduced by spacing biopsies and obtaining more targeted cores per lesion (focal lesion saturation). However, even though the report from the American Urological Association (AUA) and Society of Abdominal Radiology [40] recommends that at least two cores/lesion should be obtained, there is no established general consensus yet. Another option (if possible) is to switch to MRI in-bore re-biopsies, which offers direct image confirmation of needle deployment within the target, if MRI/TRUS biopsy targeting errors are suspected. Thus, if an unexpected biopsy result occurs, it is important to re-evaluate each step of the process from quality control of mpMRI acquisition,

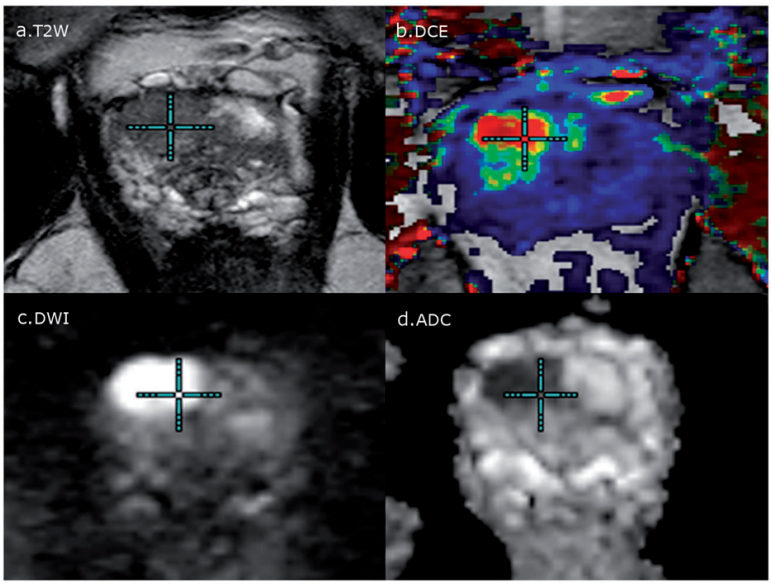

Figure 3. Multiparametric MRI (T2-weighted, diffusion-weighted with corresponding apparent diffusion coefficient map and dynamic contrast-enhanced imaging) shows a 21 mm tumour suspicious PI-RADS 5 lesion (cross marker) in the anterior part of the prostate previously missed by systematic $TRUS_{bx}$. Software-based MRI/TRUS fusion TBx of the lesion revealed a Gleason score 7 (4 + 3) prostate cancer.

interpretation and reporting to the actual fusion- and biopsy procedure to identify any potential risks of error.

Although the use of mpMRI and TBx for PCa detection have shown significant advantages over $TRUS_{bx}$, a head-to-head comparison between published studies is difficult because of substantial heterogeneity in both study designs and reporting. Various institutions use different fusion platforms, diverse selection criteria, biopsy route and number of TBx cores as well as different mpMRI scoring systems and definitions of sPCa. Furthermore, the prevalence of the disease and the gold standard reference test used to confirm the diagnosis (e.g. $TRUS_{bx}$/TBx/combined biopsies, template mapping biopsies or radical prostatectomy specimens) are other confounding factors that alter the diagnostic accuracy of a given test. For example, the negative predictive value (NPV) of an mpMRI is strongly influenced by disease prevalence in the population studied [39]. Thus, when the diagnostic accuracy of an mpMRI is assessed, it is important to recognize if the test is applied to a PSA-screened population with lower disease prevalence compared with an unscreened population and whether the studied cohort includes either biopsy-naïve men, men with prior negative or positive biopsies (repeat biopsy/active surveillance) or a mixture of all. In addition, mpMRIs that do not adhere to the minimum standards as recommended by the ESUR [10] may result in lower diagnostic yields. This might partly explain the variation in NPVs of mpMRI in previous studies [39]. However, even though the guidelines [10,18] are followed, interpretation is still subjective and highly depended on operator experience, as illustrated by Hansen et al. [41]. They compared initial prostate mpMRI reads with tertiary centre second opinions and concluded that the NPV and positive predictive value were significantly improved by specialist readings and education, training and experience reduced false positive interpretations.

Another major challenge is that the definition of sPCa traditionally is based on $TRUS_{bx}$ findings and clinical parameters. However, with the introduction of mpMRI, the biopsies are now aimed and targeted directly at highly suspicious lesions. Consequently, TBx frequently demonstrate longer cancer-core length, higher ratio of positive vs negative cores and higher GS compared with $TRUS_{bx}$ cores. Therefore, we cannot directly apply TBx results into currently available predictive nomograms and risk calculators which are based solely on $TRUS_{bx}$ findings with its inherent limitations. A clear consensus for defining sPCa in mpMRI-biopsy studies is urgently needed to allow interstudy comparisons and develop redefined risk calculators that include results from additional TBx and mpMRI findings.

Overall, the substantial differences in methodology and reporting of mpMRI and TBx affect the overall outcome and make it difficult to reliably compare results between institutions. Thus, every institution should know their own test performance statistics when making clinical decisions based on mpMRI and TBx findings.

Future perspectives

There is no doubt that the use of mpMRI and TBx has the potential to alter the diagnostic pathway of PCa. Until recently the EAU and the AUA guidelines [3,40] recommended that mpMRI primarily should be used before repeat biopsy when clinical suspicion of missed sPCa persists despite prior negative biopsies (Figure 3).

However, several high-quality evidence level 1 studies of mpMRI in biopsy-naïve men have recently been published

[9,19,42,43]. They all support an MRI-influenced diagnostic pathway and conclude that prebiopsy mpMRI used as a triage test improves risk stratification and the diagnostic ratio of significant vs insignificant cancer, while avoiding unnecessary biopsies. These convincing results all favour the use of prebiopsy mpMRI as a triage test for all biopsy-naïve men under suspicion of PCa. As a results, the EAU guideline just changed its recommendation to recommend mpMRI before prostate biopsy for all men (biopsy-naïve and men with prior negative biopsies. Such a strategy constitutes a fundamental paradigm shift in PCa diagnostics and incorporating mpMRI findings and TBx into everyday clinical decision-making could be the beginning towards the end of blind prostate biopsies [44]. In addition, MRI/TRUS fusion platforms will continue to evolve. Future developments include automatic segmentation and deformable co-registration with real-time motion correction combined with improvements in the biopsy procedure (e.g. improved US resolution and biopsy allocation) to further improve targeting accuracy. However, while the adoption of fusion-biopsy platforms rapidly expands, appropriate utilization and the best biopsy strategy for various individual patient populations that will benefit the most have yet to be defined. Further advancement may also include the use of additional US techniques beyond grey-scale (e.g. use of contrast, elastography or micro-ultrasound) for refined MRI/TRUS image-fusion. Moreover, an area that goes beyond the biopsy procedure itself is the likely future possibility of replacing the biopsy-needle with a catheter for focal treatment. Thus, as MRI/TRUS image-fusion platforms improve, they may allow for focal treatments under local anaesthetics outside the MRI/operating suite in the future.

Hopefully, as the technologies evolve, market forces may reduce the cost of fusion equipment and combined with improved risk tools for the selection of men needing biopsies, the number of patients requiring this technology may also be reduced. Furthermore, there is an ongoing debate whether or not systematic biopsies should accompany TBx, especially in the repeat biopsy setting [45,46]. However, due to the abovementioned limitations, both the quality and the interpretation of the pre-biopsy mpMRI are uncertain but essential factors which, combined with the risk of TBx sampling errors, could lead to significant cancers and may remain undetected in a 'targeted-only' approach. Therefore, the present guidelines [3,40] recommend combining $TRUS_{bx}$ with TBx in a combined approach for MRI-positive patients. However, in an effort to try to reduce the total number of cores obtained, adding additional systematic cores to TBx only in specific segments of the prostate where TBxs are prone to miss targets [47,48] may be sufficient to improve detection of sPCa without the need for sampling all prostatic regions using all 10–12 $TRUS_{bx}$ cores. Similarly, focal saturation of an mpMRI-positive lesion, as suggested by the PI-RADS steering committee [21], may also prove sufficient for accurate diagnosis and risk assessment, while avoiding systematic cores.

Although the use of mpMRI as a triage test before TBx seems to improve risk stratification and could benefit clinical practice, the cost-effectiveness of a diagnostic mpMRI scan, the additional use of TBx including purchase of expensive MRI/TRUS image-fusion platforms and the long-term outcomes have not been fully explored. However, despite the abovementioned limitations, an image-based mpMRI-strategy seems to improve patient quality-of-life by reducing overdiagnosis and overtreatment at comparable costs to the currents standard $TRUS_{bx}$ approach [49].

Conclusion

Multiparametric MRI is increasingly used in clinical practice to guide TBx toward suspicious lesions and improve detection of sPCa. MRI/TRUS fusion allows skilled urologists to perform targeted biopsies in an outpatient clinic and gives the operator the advantage of adding TBx to the systematic standard biopsy scheme, which is still the recommended standard approach. There is no clear advantage of one MRI/TRUS fusion platform compared to others. Costs, local preferences and usability should be guiding the choice of which fusion platform to use.

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References

[1] Hodge KK, McNeal JE, Terris MK, et al. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol. 1989;142:71–74.
[2] Shariat SF, Roehrborn CG. Using biopsy to detect prostate cancer. Rev Urol. 2008;10:262–280.
[3] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2017;71:618–629.
[4] Harvey CJ, Pilcher J, Richenberg J, et al. Applications of transrectal ultrasound in prostate cancer. BJR. 2012;85:S3–S17.
[5] Ukimura O, Coleman JA, de la Taille A, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol. 2013;63:214–230.
[6] Zaytoun OM, Moussa AS, Gao T, et al. Office based transrectal saturation biopsy improves prostate cancer detection compared to extended biopsy in the repeat biopsy population. J Urol. 2011;186:850–854.
[7] Boccon-Gibod LM, Dumonceau O, Toublanc M, et al. Micro-focal prostate cancer: a comparison of biopsy and radical prostatectomy specimen features. Eur Urol. 2005;48:895–899.
[8] Padhani AR, Petralia G, Sanguedolce F. Magnetic resonance imaging before prostate biopsy: time to talk. Eur Urol. 2016;69:1–3.
[9] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389:815–822.
[10] Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. Eur Radiol. 2012;22:746–757.
[11] Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol. 2013;63:125–140.

[12] Hambrock T, Hoeks C, Hulsbergen-van de Kaa C, et al. Prospective assessment of prostate cancer aggressiveness using 3-T diffusion-weighted magnetic resonance imaging-guided biopsies versus a systematic 10-core transrectal ultrasound prostate biopsy cohort. Eur Urol. 2012;61:177–184.
[13] Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol. 2013;64:713–719.
[14] Boesen L, Noergaard N, Chabanova E, et al. Early experience with multiparametric magnetic resonance imaging-targeted biopsies under visual transrectal ultrasound guidance in patients suspicious for prostate cancer undergoing repeated biopsy. Scand J Urol. 2015;49:25–34.
[15] Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging–targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol. 2015;68:438–450.
[16] Hamoen EHJ, de Rooij M, Witjes JA, et al. Use of the prostate imaging reporting and data system (PI-RADS) for prostate cancer detection with multiparametric magnetic resonance imaging: a diagnostic meta-analysis. Eur Urol. 2015;67:1112–1121.
[17] de Rooij M, Hamoen EHJ, Fütterer JJ, et al. Accuracy of Multiparametric MRI for prostate cancer detection: a meta-analysis. AJR Am J Roentgenol. 2014;202:343–351.
[18] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging – Reporting and Data System: 2015, Version 2. Eur Urol. 2016; 69:16–40.
[19] van der Leest M, Cornel E, Israël B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: a large prospective Multicenter Clinical Study. Eur Urol. 2019;75;570–578.
[20] Rosenkrantz AB, Babb JS, Taneja SS, et al. Proposed adjustments to PI-RADS version 2 decision rules: impact on prostate cancer detection. Radiology. 2017;283:119–129.
[21] Padhani AR, Weinreb J, Rosenkrantsz AB, et al. Prostate imaging-reporting and data system steering committee: PI-RADS v2 status update and future directions. Eur Urol. 2019;75(3):385–396.
[22] Wegelin O, van Melick HH, Hooft L, et al. Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: a systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. Is there a preferred technique? Eur Urol. 2017;71:517–531.
[23] Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/Ultrasound fusion–guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA. 2015;313: 390–397.
[24] Sonn GA, Natarajan S, Margolis DJA, et al. Targeted biopsy in the detection of prostate cancer using an office based magnetic resonance ultrasound fusion device. J Urol. 2013;189:86–92.
[25] Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging–ultrasound fusion targeted biopsy: a systematic review. Eur Urol. 2015;68:8–19.
[26] Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU Int. 2011;108:E171–E178.
[27] Venderink W, de Rooij M, Sedelaar JP, et al. Elastic versus rigid image registration in magnetic resonance imaging–transrectal ultrasound fusion prostate biopsy: a systematic review and meta-analysis. Eur Urol Focus. 2018;4:219–227.
[28] Rastinehad AR, Turkbey B, Salami SS, et al. Improving detection of clinically significant prostate cancer: magnetic resonance imaging/transrectal ultrasound fusion guided prostate biopsy. J Urol. 2014;191:1749–1754.
[29] Pinto PA, Chung PH, Rastinehad AR, et al. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. J Urol. 2011;186:1281–1285.
[30] Bax J, Cool D, Gardi L, et al. Mechanically assisted 3D ultrasound guided prostate biopsy system. Med Phys. 2008;35:5397–5410.
[31] Singh AK, Kruecker J, Xu S, et al. Initial clinical experience with real-time transrectal ultrasonography-magnetic resonance imaging fusion-guided prostate biopsy. BJU Int. 2008;101: 841–845.
[32] Mozer P, Baumann M, Chevreau G, et al. Mapping of transrectal ultrasonographic prostate biopsies: quality control and learning curve assessment by image processing. Ultrasound. 2009;28: 455–460.
[33] Gayet M, Van Der Aa A, Beerlage HP, et al. The value of magnetic resonance imaging and ultrasonography (MRI/US)-fusion biopsy platforms in prostate cancer detection: a systematic review. BJU Int. 2016;117:392–400.
[34] Hale GR, Czarniecki M, Cheng A, et al. Comparison of elastic and rigid registration during magnetic resonance imaging/ultrasound fusion-guided prostate biopsy: a multi-operator phantom study. J Urol. 2018;200:1114–1121.
[35] Hamid S, Donaldson IA, Hu Y, et al. The smarttarget biopsy trial: a prospective, within-person randomised, blinded trial comparing the accuracy of visual-registration and magnetic resonance imaging/ultrasound image-fusion targeted biopsies for prostate cancer risk stratification. Eur Urol. 2018. Epub ahead of print. doi: 10.1016/j.eururo.2018.08.007.
[36] Wegelin O, Exterkate L, van der Leest M, et al. The FUTURE Trial: a multicenter randomised controlled trial on target biopsy techniques based on magnetic resonance imaging in the diagnosis of prostate cancer in patients with prior negative biopsies. Eur Urol. 2019;75:582–590.
[37] Grummet J, Pepdjonovic L, Huang S, et al. Transperineal vs. transrectal biopsy in MRI targeting. Transl Androl Urol. 2017;6: 368–375.
[38] Tan N, Margolis DJ, Lu DY, et al. Characteristics of detected and missed prostate cancer foci on 3-T multiparametric MRI using an endorectal coil correlated with whole-mount thin-section histopathology. Am J Roentgenol. 2015;205:W87–W92.
[39] Moldovan PC, Van den Broeck T, Sylvester R, et al. What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? a systematic review and meta-analysis from the european association of urology prostate cancer guidelines panel. Eur Urol. 2017;72: 250–266.
[40] Rosenkrantz AB, Verma S, Choyke P, et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. J Urol. 2016;196:1613–1618.
[41] Hansen NL, Koo BC, Gallagher FA, et al. Comparison of initial and tertiary centre second opinion reads of multiparametric magnetic resonance imaging of the prostate prior to repeat biopsy. Eur Radiol. 2017;27:2259–2266.
[42] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378:1767–1777.
[43] Rouvière O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol. 2019;20:100–109.
[44] Tombal B. Toward the end of blind prostate biopsies? Eur Urol. 2012;62:997–998.
[45] Salami SS, Ben-Levi E, Yaskiv O, et al. In patients with a previous negative prostate biopsy and a suspicious lesion on magnetic resonance imaging, is a 12-core biopsy still necessary in addition to a targeted biopsy? BJU Int. 2015;115:562–570.
[46] Schoots IG. Omission of systematic transrectal ultrasound guided biopsy from the MRI targeted approach in men with previous

negative prostate biopsy might still be premature. Ann Transl Med. 2016;4:205–205.

[47] Schouten MG, van der Leest M, Pokorny M, et al. Why and where do we miss significant prostate cancer with multi-parametric magnetic resonance imaging followed by magnetic resonance-guided and transrectal ultrasound-guided biopsy in biopsy-naïve men? Eur Urol. 2017;71:896–903.

[48] Boesen L, Nørgaard N, Løgager V, et al. Where Do Transrectal Ultrasound- and magnetic resonance imaging-guided biopsies miss significant prostate cancer? Urology. 2017;110:154–160.

[49] de Rooij M, Crienen S, Witjes JA, et al. Cost-effectiveness of Magnetic Resonance (MR) imaging and mr-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective. Eur Urol. 2014;66:430–436.