Magnetic Resonance Imaging as a Screening Tool for Prostate Cancer

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“The way I see it, if you want the rainbow, you gotta put up with the rain.”

– Dolly Parton

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ABSTRACT

The overall aim of this thesis was to explore the role of Magnetic resonance imaging (MRI) of the prostate as an adjunct to the prostate-specific antigen (PSA)-test in screening for prostate cancer (PCa), focusing on the performance of MRI in detecting clinically significant PCa within the randomised controlled GÖTEBORG Prostate Cancer Screening 2 Trial. By inviting men 50–60 years of age to different screening strategies—PSA cut-off for biopsy 3.0 ng/mL versus 1.8 ng/mL and MRI followed by systematic +/- targeted biopsies—this ongoing trial evaluates whether PSA-testing followed by MRI and targeted biopsies can reduce overdiagnosis, while maintaining the detection of clinically significant PCa, as compared to PSA and systematic biopsy.

Paper I evaluates the performance of prostate MRI outside high-volume centres. A moderate PCa detection rate and large variability between readers were found, underlining the importance of continuing quality assurance initiatives where each local MRI unit records and evaluates its own detection rate, as well as robust training programs for radiologists. **Paper II** describes the study design and assesses the participation rates in the Göteborg-2 trial. Acceptable participation rates were found for PSA, MRI and biopsy. **Paper III** evaluates the value of systematic biopsies in sequential screening for PCa with PSA followed by MRI. With experienced radiologists reporting MRI, omitting systematic biopsies can be feasible in a program with repeat screening and could reduce unnecessary biopsies. **Paper IV** evaluates the role of pre-biopsy prostate MRI in risk stratification for men with newly diagnosed PCa and was found to be of added value. How information from MRI is best utilized in clinical practice remains to be clarified.

In summary, PSA-testing and prostate MRI are cornerstones in screening and early detection of PCa. Further research in the coming years will shed light on how to customize optimal screening strategies.

Keywords: early detection, magnetic resonance imaging, prostate-specific antigen, prostate cancer, screening

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SAMMANFATTNING PÅ SVENSKA

Prostatacancer tar årligen 2 300 svenska mäns liv och är Sveriges vanligaste cancerform. Den metod som under flera decennier har använts som en markör för prostatacancer är ett enkelt blodprov som tas från armvecket för att mäta halten av så kallat PSA i blodet. PSA är en förkortning för prostataspecifikt antigen, ett äggviteämne som bildas i prostatakörteln. Ett högt PSA-värde i blodet kan vara ett tecken på prostatacancer. Vid ett sådant resultat går man vidare med ytterligare undersökningar och provtagningar. Fördelen med PSA-testning är att allvarlig prostatacancer kan upptäckas i ett tidigt skede och därmed öka chansen för att bli botad. Prostatacancern är dock hos många tämligen godartad, och många män lever med prostatacancer utan symptom. En nackdel med PSA-provtagning är alltså att även prostatacancer som aldrig skulle ha utvecklats till en allvarlig sjukdom hittas. I dessa fall kan män komma att bli överbehandlade, det vill säga utredas och behandlas mot prostatacancer i onödan, ofta med biverkningar och försämrad livskvalitet som följd. Dessutom har de flesta män som har ett förhöjt PSA-värde inte prostatacancer, utan oftare till exempel en godartad förstoring av prostata. Ett PSA-prov kan därmed leda till oro i onödan.

Studier har visat att regelbunden provtagning av PSA minskar dödligheten i prostatacancer. Dock anses inte detta överväga nackdelarna och i Sverige har Socialstyrelsen inte funnit skäl nog att rekommendera allmän screening för prostatacancer med PSA-test. Med screening menas att med ett relativt enkelt test i en definierad grupp av befolkningen, t.ex. 50–60-åriga män, upptäcka sjukdom innan den ger symtom och därmed förhindra fortsatt sjukdomsutveckling och död i sjukdomen. För att rekommendera screening för prostatacancer behövs alltså metoder som bättre kan skilja mellan betydelsefull/behandlingskrävande och betydelselös/icke-behandlingskrävande former av prostatacancer. Med en sådan metod skulle balansen mellan nyttan av screening (minskad dödlighet i prostatacancer) och den skada som den kan medföra (överbehandling med biverkningar, oro med mera) kunna förbättras dramatiskt på befolkningsnivå och möjliggöra införandet av allmän screening för prostatacancer. Den skada som menas är obehaget, smärtan och risken för urinvägsinfektion och blodförgiftning vid vävnadsprovtagning med tunna nålar av prostatan, men också risken för impotens och urinläckage som kan uppkomma som komplikationer till behandling av prostatacancer med botande behandling. Metoder som kan minska behovet av vävnadsprovtagning och som bättre kan avgöra vilka individer som verkligen har betydelsefull cancer och därmed nytta av behandling är alltså önskvärda.

Magnetkameraundersökning är en avbildningsteknik som ger detaljrika bilder av prostata. Den kallas ofta magnetröntgen men det är en felaktig och olämplig benämning eftersom undersökningen inte görs med röntgenstrålar utan med hjälp av magnetiska fält. Undersökningen är helt smärtfri och ofarlig. Patienten ligger vid undersökningen på en brits som förs in i en ”tunnel” där utrymmet är relativt trångt vilket kan uppfattas som obehagligt för personer med tendens till klaustrofobi. Under senare år har magnetkameraundersökning av prostata blivit en viktig metod för att undersöka förekomst av cancer i prostatakörteln. Trots snabb teknikutveckling är metodens förmåga att hitta de tumörer som är betydelsefulla och som i framtiden riskerar att utvecklas till aggressiv cancer fortfarande inte helt klarlagd. En stor fördel med magnetkamera-undersökningen är att den möjliggör att vävnadsprov kan tas precis från de områden i prostata där magnetkamerabilderna visat misstänkt cancer. Detta ökar möjligheterna att hitta behandlingskrävande prostatacancer. Rutinen har annars varit att alla män med förhöjda PSA-värden genomgår så kallade systematiska vävnadsprover. Eftersom ett förhöjt PSA-värde inte ger någon vägledning om var en eventuell cancer kan finnas i prostatakörteln, syftar systematisk vävnadsprovtagning till att få god täckning från de delar av prostata där cancer oftast förekommer. Nackdelar med systematisk vävnadsprovtagning är att man dels hittar små oftast ofarliga tumörer (med risk för överbehandling) och dels att man kan missa större potentiellt aggressiva tumörer.

Nyligen genomförda studier har visat att magnetkameraundersökning ger mer tillförlitliga resultat när det gäller att upptäcka betydelsefull prostatacancer än metoden med enbart PSA-prov. Denna slutsats har inneburit ett paradigmskifte där såväl nationella som internationella riktlinjer nu rekommenderar magnetkameraundersökning före vävnadsprovtagning vid misstanke om prostatacancer, som till exempel vid förhöjt PSA-värde. Någon storskalig studie på magnetkameraundersökningens användbarhet vid screening har däremot aldrig genomförts.

Syfte

Syftet med denna avhandling är att undersöka vad magnetkamera-undersökning som metod kan bidra med i screening av prostatacancer, med fokus på dess tillförlitlighet i att finna cancer som är betydelsefull och behöver behandlas.

Metod

Denna avhandling utgörs av fyra olika studier. I den första studien undersöktes magnetkameraundersökningens förmåga att upptäcka prostatacancer. Totalt 97 patienter som genomgått magnetkamera-undersökning av prostata utförda utanför specialiserade enheter, och därefter opererats för prostatacancer, studerades. Efter operation undersöktes hela prostatakörteln med mikroskop. Resultatet från den mikroskopiska analysen har jämförts med vad tre olika röntgenläkare fann när de granskade magnetkamerabilderna som togs innan operationen. På så sätt har magnetkameraundersökningens förmåga att upptäcka den allvarligaste tumören (kallad indextumören, då det kan förekomma flera tumörer i prostata) kunnat skattas.

De tre följande studierna baseras på Göteborg 2-studien som är ett samarbete mellan avdelningarna för urologi och radiologi vid Sahlgrenska akademin, Göteborgs universitet och Sahlgrenska universitetssjukhuset. Göteborg 2-studiens huvudsyfte är att utvärdera om överdiagnostiken kan minskas i screening samtidigt som de betydelsefulla tumörerna upptäcks, genom att kombinera PSA-prov med magnetkameraundersökning för att därefter kunna ta vävnadsprover från tumörmisstänkta områden i prostata. Sedan studien startade år 2015 har man bjudit in över 62 000 män mellan 50–60 år. Dessa män har slumpvis lottats till en kontrollgrupp (23 347 män) och en screeninggrupp (38 770 män). Männen i kontrollgruppen har enbart fått information om studien, samt att de ingår i kontrollgruppen, medan männen som lottats till screeninggruppen har blivit inbjudna till studien och till att lämna PSA-prov. Deltagandet är frivilligt; de män som lämnat PSA-prov har lottats slumpvis till en av tre grupper:

Grupp 1 – alla män med ett PSA-värde på 3 ng/ml eller däröver rekommenderades att genomföra magnetkameraundersökning samt en kompletterande undersökning med systematiska vävnadsprover av prostata. Vid avvikande fynd på magnetkameraundersökningen togs även riktade vävnadsprover från det tumörmisstänkta området i prostata.

Grupp 2 – alla män med ett PSA-värde på 3 ng/ml eller däröver rekommenderades att genomföra magnetkameraundersökning. Enbart vid avvikande fynd på magnetkameraundersökningen togs riktade vävnadsprover från det tumörmisstänkta området i prostata.

Grupp 3 – alla män med ett PSA-värde på 1,8 ng/ml eller däröver rekommenderades att genomföra magnetkameraundersökning. Enbart vid

avvikande fynd på magnetkameraundersökningen togs riktade vävnadsprover från det tumörmisstänkta området i prostata.

Deltagare vars vävnadsprov visat prostatacancer har fått fortsatt vård på Urologkliniken vid Sahlgrenska Universitetssjukhuset. De män i screeninggruppen, där undersökningar inte visat prostatacancer, bjuds in till uppföljande omgångar med PSA-prov och kompletterande undersökningar.

Resultat

I den första studien framkom det att magnetkameraundersökningens förmåga att upptäcka den allvarligaste tumören (indextumören) varierade mellan 67–76 procent, beroende på vilken av röntgenläkarna som granskade bilderna. Dessutom visade det sig att magnetkameraundersökningens förmåga att upptäcka de allra farligaste tumörerna var större än för de mindre allvarliga tumörerna.

Avhandlingens andra studie är delvis ett arbete som ger en detaljerad beskrivning av Göteborg 2-studien, dess olika tillvägagångsätt och frågeställningar som planeras att besvaras, men den undersöker även i hur stor utsträckning de inbjudna männen i screeninggruppen deltar. Det framkom att hälften av de inbjudna männen i screeninggruppen väljer att delta och det har bedömts vara tillräckligt för att på ett tillförlitligt sätt kunna besvara på studiens frågeställningar.

Den tredje studien visade att 66 av 408 (16 procent) av männen i den första gruppen som bjöds in till screening hade behandlingskrävande prostatacancer. Dessa deltagare har genomgått den traditionella undersökningen med systematiska vävnadsprover av prostata, men även vävnadsprover från tumörmisstänkta områden enligt magnetkamera-undersökningen. Bland männen med behandlingskrävande cancer hade tio män (15 procent) prostatacancer som hade missats om man inte genomfört systematiska vävnadsprover. Däremot hade ingen av dessa tio män någon av de allvarligaste formerna av cancer och i hälften av dessa tio fall krävdes inte omedelbar behandling, då de var precis på gränsen för att vara behandlingskrävande.

Från studiestart fram till och med 30 september 2020 diagnosticerades 467 deltagare i Göteborg 2-studiens screeninggrupp med prostatacancer. Underlaget i avhandlingens sista studie utgjordes av den grupp män (183 personer) som senare genomgick operation för prostatacancer. I denna studie undersöktes huruvida magnetkameraundersökning, som ett tillägg till

resultatet från de idag etablerade kliniska metoderna (PSA-prov och information från vävnadsprover), kunde vara värdefullt vid nyupptäckt prostatacancer. Det visade sig att informationen från magnetkamera-undersökningen, som tillägg till de etablerade metoderna, förbättrade möjligheten att avgöra vilka patienter som behöver behandlas direkt och vilka som kan vänta med behandling och istället genomgå fortsatta kontroller innan behandling eventuellt kan komma att behövas i ett senare skede.

Slutsatser

Den övergripande slutsatsen i denna avhandling är att magnetkamera-undersökning, tillsammans med PSA-prov, har en betydelsefull roll i screening för prostatacancer. Fortsatt forskning inom området kommer framöver sannolikt att ytterligare precisera magnetkameraundersökningens roll. En storskalig studie som Göteborg 2-studien kommer på sikt troligen att kunna besvara frågan om fördelarna/nyttan med screening för prostatacancer kan överväga nackdelarna/skadan när kombinationen PSA-prov och magnetkameraundersökning används som metod.

Hur väl magnetkameraundersökning fungerar för att upptäcka behandlingskrävande prostatacancer beror på ett flertal olika faktorer. Bland annat, som denna avhandling har visat, beror det på erfarenheten hos den som granskar bilderna. Röntgenläkare som granskar många bilder vid enheter som gör många magnetkameraundersökningar, såsom i Göteborg 2-studien, har högre träffsäkerhet. Det är därför viktigt att kontinuerligt utvärdera kvaliteten av magnetkameraundersökning som metod (kvalitetssäkring).

Det förefaller vara tryggt att avstå från systematiska vävnadsprov när erfarna röntgenläkare analyserar magnetkameraundersökningens bilder i kombination med ett uppföljande screeningprogram där män återinbjuds till screening. Därmed skulle obehaget och riskerna med vävnadsprovtagningen minska. Konsekvenserna på längre sikt av detta tillvägagångssätt vet vi ännu ingenting om men det kommer att studeras långsiktigt inom ramen för Göteborg 2-studien.

Magnetkameraundersökning kan även vara till hjälp för att besluta om behandling vid nyupptäckt prostatacancer. I kombination med PSA-prov och resultat från vävnadsprovtagning, förbättrar magnetkameraundersökning möjligheten att avgöra vilka män med prostatacancer som behöver behandlas direkt och vilka som kan vänta med behandling.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals (I–IV).

I. **Kohestani K,** Wallström J, Dehlfors N, Sponga OM, Månsson M, Josefsson A, Carlsson S, Hellström M, Hugosson J.

Performance and inter-observer variability of prostate MRI (PI-RADS version 2) outside high-volume centres.

Scand J Urol. 2019; 53(5): 304–311.

II. **Kohestani K,** Månsson M, Arnsrud Godtman R, Stranne J, Wallström J, Carlsson S, Hellström M, Hugosson J.

The GÖTEBORG Prostate Cancer Screening 2 Trial: a prospective, randomised, population-based prostate cancer screening trial with prostate-specific antigen testing followed by magnetic resonance imaging of the prostate.

Scand J Urol. 2021; 22: 1–9.

III. **Kohestani K,** Arnsrud Godtman R, Axcrona U, Egevad L, Hellström M, Khatami A, Pihl CG, Stranne J, Wallström J, Månsson M, Carlsson S, Hugosson J.

The value of systematic biopsies in screening for prostate cancer with PSA followed by MRI – Results from The GÖTEBORG Prostate Cancer Screening 2 Trial *(in manuscript).*

IV. **Kohestani K,** Langkilde F, Carlsson S, Geterud K, Arnsrud Godtman R, Pihl CG, Wallström J, Hellström M, Månsson M, Hugosson J.

Added value of prostate MRI in predicting significant prostate cancer at prostatectomy *(submitted manuscript).*

CONTENT

ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
AS	Active Surveillance
AUA	American Urological Association
AUC	Area Under the receiver operating characteristic Curve
CI	Confidence Interval
CG	Control Group
DCE	Dynamic Contrast Enhanced
DRE	Digital Rectal Examination
DWI	Diffusion Weighted Imaging
EAU	European Association of Urology
ECE	Extracapsular Extension
ERSPC	The European Randomized Study of Screening for Prostate Cancer
ESUR	European Society of Urogenital Radiology
GS	Gleason Score
ISUP	International Society of Urological Pathology
IQR	Interquartile range
MRI	Magnetic Resonance Imaging
NND	Number Needed to Diagnose
PCa	Prostate Cancer
PI-RADS	Prostate Imaging Reporting and Data System

PPV	Positive Predictive Value
PSA	Prostate Specific Antigen
PSAD	Prostate Specific Antigen Density
PZ	Peripheral Zone (of the prostate)
RARP	Robotic-Assisted Radical Prostatectomy
RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristic
RP	Radical Prostatectomy
RRP	Retropubic Radical Prostatectomy
RT	Radiation Therapy
SG	Screening Group
T1WI	T_1-weighted images
T2WI	T_2-weighted imaging
TNM	Tumour-Node-Metastasis
TRUS	Transrectal Ultrasound
TZ	Transition Zone (of the prostate)

1 INTRODUCTION

In recent decades, screening and early diagnosis of prostate cancer (hereafter referred to as PCa) have been enabled by the introduction of the prostate-specific antigen (PSA) and the rapid evolution of diagnostic procedures. Screening for PCa has been a controversial matter ever since the introduction of PSA-testing. The benefits of population-based screening with PSA-testing are generally not considered to outweigh the harms. Nevertheless, extensive PSA-testing has taken place globally. This has led to an increased awareness of the negative impact on those who were subjected to overdiagnosis and overtreatment as a consequence. In order to handle the problem with overdiagnosis, a strategy of active surveillance (AS), postponing treatment and the resulting side-effects until treatment is necessary, has developed. Many have wished for a strategy to detect the disease at a later stage, when it should be treated, instead of early. Different adjuncts to improve the benefit-to-harm-ratio have been proposed, but the answer to the dilemma with PCa screening has yet not been found. In early detection of PCa, none of the several tests proposed as a substitute or as an adjunct to PSA has gained ground as rapidly and substantially as magnetic resonance imaging (hereafter referred to as MRI) of the prostate.

A few years ago, urology guidelines and research articles would include phrases such as ”MRI will hopefully be a useful tool”. Today, in 2021, thanks to massive research over the last couple of years, “hopefully” is disconnected from MRI. Prostate MRI has proven itself a valuable tool in the management of PCa. It is not easy to keep up with the rapid evolvement of the guidelines for detection of PCa. The first indication for MRI in the diagnostic management in Sweden was if a suspicion of PCa still remained after a set of benign biopsies. Since last year, Swedish, European and American guidelines recommend MRI before prostate biopsy. Today, the use of MRI is natural but in hindsight it has not been here that long, and there has truly been a remarkable change in the diagnostic pathway for PCa.

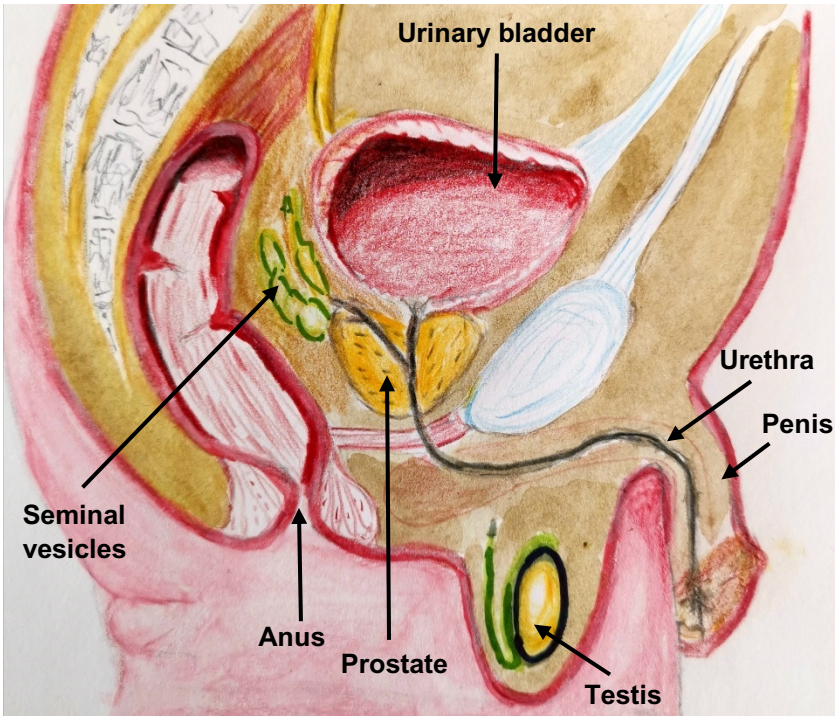
The purpose of this thesis was to explore the role and performance of prostate MRI in screening for PCa and to find out whether incorporation of this imaging modality can contribute to improving the benefit-to-harm-ratio of screening.

1.1 THE PROSTATE

The prostate, a gland situated just beneath the urinary bladder in men, often brings to mind age-related urinary inconveniences. Further associations popping up when mentioning this gland is PCa. Since it is concealed inside the body, not making itself noticed as long as it is healthy, it is quite an anonymous part of the male body. A similar anonymity is seen through history as it was an unnoticed organ for many centuries. It was never described in ancient medical texts nor illustrated in Leonardo da Vinci's anatomical drawings, which otherwise reproduced the seminal ducts and the seminal vesicles accurately[4].

Niccolò Massa, a physician in Venice, first described a gland just under the bladder in 1536. A few years later, this newly discovered gland was drawn for the first time in an anatomy book by Andreas Vesalius, a Flemish anatomist. At this time, it was referred to as "corpus glandulosum", the glandulous body, and there were different theories regarding its function, and it was believed that there were a set of paired organs instead of one single organ with two lobes. In the 1600s, the name "prostatae", derived from a Greek word meaning "standing in front", was being more frequently used. Finally, around 1800, the name was changed to the singular form, "prostata", as it was shown to be a single organ[5,6].

Over time, the anatomy (**Figure 1**) and function of the prostate have been elucidated. Situated under the bladder, encircling the most proximate part of the urethra, size-wise often compared to a chestnut, nutmeg or walnut, approximately 20 cm^3. It has an ellipsoid shape with a broader base towards the neck of the bladder and a narrower apex inferiorly adjacent to the external urethral sphincter. The latter is a voluntary sphincter composed of striated muscles as opposed to the involuntary internal sphincter formed by smooth muscle in the bladder neck. The prostate is enclosed by a capsule with the pubic bone anteriorly and the rectum posteriorly. The vicinity of the prostate and rectum, separated only by the Denonvilliers' fascia, enables transrectal examination of the prostate. The delicate neurovascular bundles, containing the cavernosal nerves responsible for erectile function, are located just lateroposteriorly to the prostate[7]. Damage to these bundles, at radical prostatectomy (RP) or radiation therapy (RT), may cause erectile dysfunction. The seminal vesicles lie posteriorly to the bladder, and the fluid produced in these drains into the prostate and mixes with the prostatic secretion to nurture, protect and facilitate sperm transportation. As such, the prostate plays a pivotal role for reproduction. At ejaculation, the internal sphincter is closed preventing the ejaculate from entering the bladder and



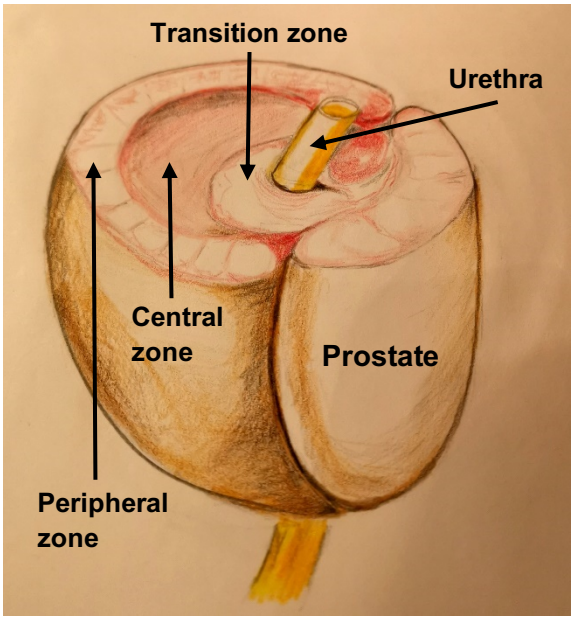


Figure 1 and 2.
Anatomy of the prostate.
Zonal division. Illustrations by Jamshid Kohestani.

preventing urine from mixing with the ejaculate. In the same manner, the ejaculatory ducts are closed during urination. The above-mentioned mechanisms can be ruined by surgical procedures such as transurethral resection of the prostate and RP.

The prostate consists of glandular ducts and fibromuscular stroma, enclosed by a capsule. The generally recognized concept of different zones in the prostate, each with different histologic features, was introduced in the late 1960s and later refined by John McNeal, a clinical pathologist [8-10]. This is illustrated in **Figure 2**. Different diseases arise in different parts of the prostate; cancer most commonly occur in the peripheral zone (PZ) of the prostate whilst benign nodular hyperplasia, that may cause voiding problems, develops in the transition zone (TZ)[11].

1.2 PROSTATE CANCER

Modern paleopathological investigations of a 2 700-year-old skeleton of a 40–50-year-old man have shown convincing signs of metastatic PCa[12]. Moreover, paleopathological studies of skeletal remains from the Roman Empire and Middle Ages have supported the existence of PCa throughout history[13]. Yet, this diagnosis was unknown until the 19th century when an English surgeon and pathologist named George Langstaff, found an ingrowing tumour from the prostate into the bladder upon performing post-mortem examination of a 68-year-old man[14]. Some years later, PCa was histologically described by John Adams, he referred to it as "a very rare disease"[15]. As PCa constitutes a major global health problem today, this may seem a ludicrous statement. On second thought, this is not surprising. The prostate was pretty anonymous until quite recently. Moreover, the average life expectancy for men was not anywhere near what it is nowadays; hence men just did not live long enough to acquire PCa back in those days. A "western lifestyle" has been associated with an increase in PCa incidence, thus changes in environmental factors during the last century may also contribute to PCa in 200 years progressing from a very rare disease to one of the most prevalent cancer forms.

1.2.1 EPIDEMIOLOGY

PCa is a global public health concern with over 1 million estimated new cases diagnosed in 2020 worldwide[16]. After lung cancer, PCa is the most common cancer form among males globally[16]. Sweden is no exception and PCa is the most common cancer form as well as the leading cause of cancer death among Swedish men. Approximately 110,000 men are living with the diagnosis (i.e., the prevalence), 11,000 men are diagnosed with PCa every year (i.e., the incidence) and 2,300 deaths are caused by PCa every year in Sweden, **Figure 3**[2,3].

The PCa incidence has doubled since 1990 and the PCa prevalence in Sweden has actually tripled compared to 20 years ago. This is first and foremost owed to an increased PSA-testing, but also explained by an ageing male population and the introduction of new life-prolonging treatments for metastatic PCa during the last two decades. The widespread use of PSA-testing has lowered the median age at diagnosis from 74 to 69 years, comparing 1995 to 2005[2]. **Figure 4** shows the age-specific incidence, for 1997 to 1999 and 2017 to 2019.

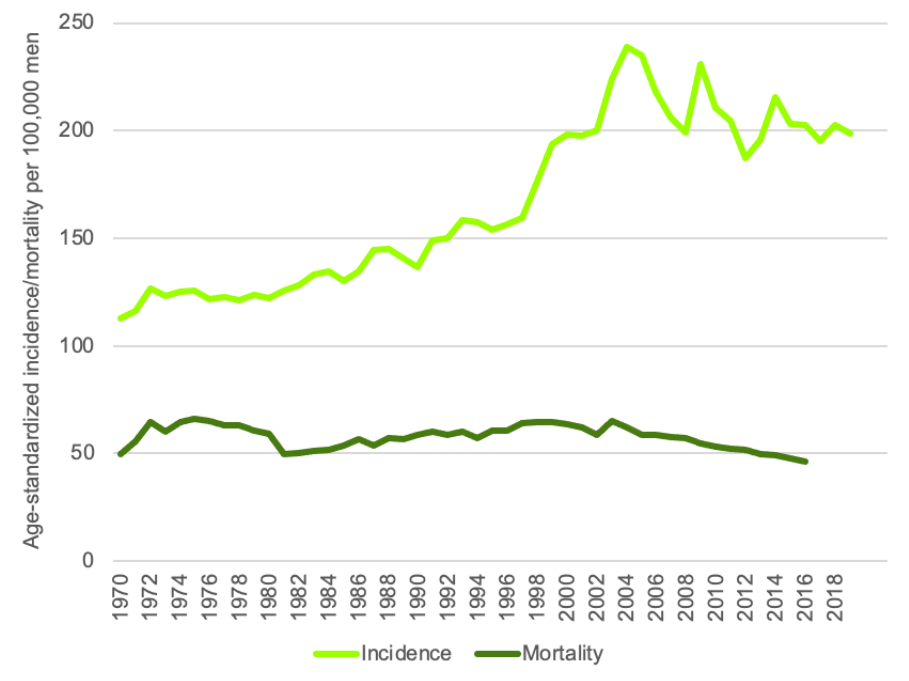


Figure 3. Age-standardized incidence (light green line) and mortality (dark green line) of PCa in Sweden between 1970 and 2019. The numbers represent cases and deaths per 100,000. Sources: the National Board of Health and Welfare Official statistics of Sweden (incidence) and NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 8.2 (mortality)[2,3].

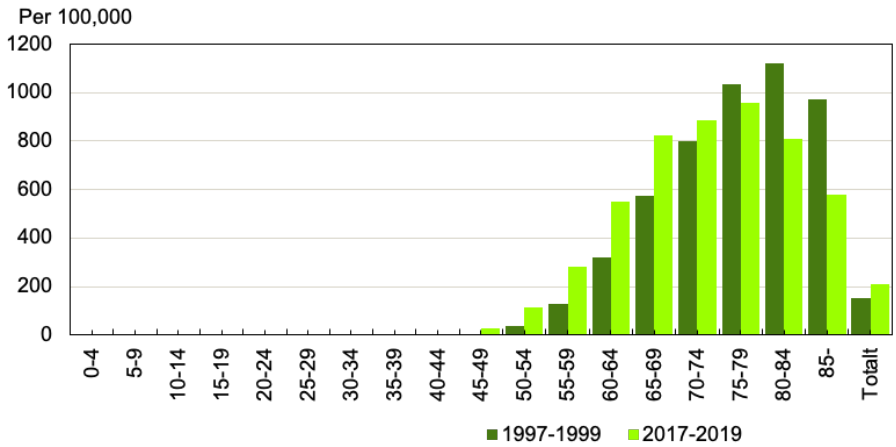


Figure 4. Age-specific incidence of PCa, 1997–1999 and 2017–2019. The numbers represent cases per 100,000 at the 3-year mean value. Source: The National Board of Health and Welfare Official statistics of Sweden[2].

The Covid-19 pandemic has affected health care worldwide including the management of PCa. In a preliminary analysis of the National Prostate Cancer Registry in Sweden, the rate of newly diagnosed PCa dropped 40% during the spring of 2020 compared to the rates of the five previous years[17].

1.3 PROSTATE CANCER DIAGNOSIS

Historically, PCa was found when signs indicating advanced disease, such as pain from bone metastases, urinary obstructive symptoms, renal failure and anaemia, occurred. At this late state, cure is out of reach. PCa is curable when located within the prostate, but in this state, it rarely gives any symptoms. This means that PCa must be looked for to be found in an early, still curable stage. The suspicion of PCa usually arises with abnormal digital rectal exam (DRE) and or elevated PSA. These findings prompt further evaluation with prostate biopsy, and histopathological evaluation is required for the diagnosis. But since DRE and PSA will catch men both with and without PCa in the net for further evaluation, many men are exposed to prostate biopsy unnecessarily. To increase accuracy in diagnosis, to catch fewer men in the net for diagnostic procedures, other tools have been added in the diagnostic pathway. Nevertheless, early diagnosis is crucial for curing PCa.

1.3.1 PROSTATE-SPECIFIC ANTIGEN

Prostate-specific antigen (PSA) is a glycoprotein found almost exclusively in the epithelial cells of the prostate[18,19]. As previously mentioned, the prostatic fluid, including PSA, assists in the reproductive physiology. Thus, PSA is found in much higher concentrations in the ejaculate than in serum. Normal epithelial cells, as well as hyperplastic cells in the prostate, produce more PSA than the PCa cells. It seems that PSA leaks into serum in higher extent from cancer cells due to architectural disturbances, causing elevated PSA[20].

Since the introduction of PSA-testing in 1986 as a potential diagnostic test for PCa, PCa mortality has decreased worldwide. Before the PSA-testing era, PCa was almost always found at advanced, uncurable stages. However, the most common cause of PSA-elevation is prostate enlargement, benign prostatic hyperplasia. Urinary tract infection and acute urine retention are other common causes of PSA-elevation, as are trauma, instrumentation, catheterization and other kinds of manipulation of the lower urinary tract. Nowadays in Sweden, 60% of PCa is detected due to PSA-testing at a health control, i.e. PSA measured without the man having any particular symptoms, compared to 30% 15 years ago[17].

At what level is PSA elevated and should prompt further investigation? As PSA is not cancer-specific and has different diagnostic accuracy depending on the cut-off, this is a delicate question. Lowering the cut-off for further evaluation increases the sensitivity at the cost of decreased specificity. The

Swedish National PCa Guidelines recommend age-dependent values of PSA for further evaluation shown in **Table 1**[21].

Age, years	PSA-cut off for further evaluation, ng/mL
< 70	≥ 3
70–80	≥ 5
80	≥ 7

Table 1. PSA-cut-offs for further evaluation at different ages as recommended by The Swedish National PCa Guidelines[21].

PSA density (PSAD) can be used to help discriminate PSA-elevation due to prostate enlargement. It is calculated as the PSA value (ng/mL) divided by prostate volume (mL). In most literature, until recently, the volume has been measured with transrectal ultrasound, a method known to be user dependent[22]. Further evaluation, with prostate biopsies, can be avoided if PSAD is low. The same reasoning as for cut-off-values for PSA can be applied for cut-offs for PSAD. Hence, it should be regarded as a continuum of risks at different levels. Nevertheless, a cut-off-value is useful in clinical practice. The Swedish National PCa Guidelines supports omission of biopsies at a cut-off of < 0.10 ng/mL/mL in men without other suspicions of PCa. PSAD is also useful in combination with an MRI without tumour suspicion. In such a case, both The Swedish National PCa Guidelines and the European Association of Urology (EAU) 2020 guidelines support a cut-off of < 0.15 ng/mL/mL to avoid unnecessary biopsies[21].

PSA can be a useful prognostic marker. Men with low PSA-values, below 1 ng/mL, have a very low risk of developing metastatic PCa[23]. PSA also plays an essential role in detecting residual or recurring tumour after RP as well as monitoring response after RT[24].

1.3.2 DIGITAL RECTAL EXAMINATION

Digital rectal examination (DRE) of the prostate was for a long time the only way to examine its size, consistency, shape and the presence of palpable tumours. This method is known to be inadequate when it comes to estimation of size[25]. Although inaccurate, it still plays a clear role in the diagnostic procedures and in the risk stratification after diagnosis. It can be performed without any equipment, and abnormalities prompt further evaluation. As the examiner's finger examines the posterior surface of the prostate, ventrally

situated tumours are missed. Neither is early stage PCa easy to detect at DRE. Hence, PCa cannot be ruled out by a normal DRE. On the contrary, a suspicious DRE is, especially in combination with PSA ≥ 3, associated with an increased risk of PCa of a higher grade (a more severe form, this is elaborated in 1.3.6 Grading, staging and risk groups) and prompts further evaluation[26,27].

1.3.3 TRANSRECTAL ULTRASOUND AND BIOPSIES

With the introduction of the transrectal ultrasound (TRUS) in the 1980s, the prostate biopsy procedure was facilitated. The zonal system of the prostate is well illustrated on the greyscale TRUS. TRUS is used for measuring the size of the prostate and noting variations in the normal anatomy, for example the presence of an outgrowing enlarged median lobe, processing into the bladder from the base of the prostate, often causing voiding troubles. Today, TRUS biopsies is the standard method for definitive PCa diagnosis performed under local anaesthesia and mostly a well-tolerated procedure by patients. Only in exceptional cases are biopsies decided against, and diagnosis is made on clinical and laboratorial bases, for example when managing a fragile patient where PSA and DRE strongly and clearly indicates PCa.

Hypoechogenic areas on TRUS raise suspicions of PCa, but have proven to be of little value with a positive predictive value (PPV) of the biopsy of a peripheral hypoechoic lesion at 25%–30%[28]. Targeted biopsies from suspicious DRE, or hypoechogenic lesions on TRUS, was outperformed by the sextant biopsy proposed by Dr. Hodge in 1989. The sextant biopsy, six biopsies taken in a systematic fashion from the apex, middle and base of the prostate, was for many years considered the gold standard[29,30]. Discomfort for the patient was reduced with the peri-prostatic nerve blockade, achieved by administering local anaesthesia at the vascular pedicles on each side of the prostate[31]. Eventually, the 10–12-core biopsy protocol became standard of care as extended number of cores proved to have higher detection rate for PCa[32]. This was until recently the standard technique. But nowadays, MRI is incorporated in the diagnostic pathway for PCa bringing with it the new biopsy procedure of MRI-targeted biopsies.

There are three different methods to take targeted biopsies of suspicious MRI-lesions[33]. In-bore MRI targeted biopsies, taken with MRI-guidance with the patient in the MRI scanner, is a time-consuming procedure requiring general anaesthesia. The other two techniques are guided by ultrasound. Cognitive targeted biopsies, a procedure without any other equipment other

than the traditional ultrasound, are performed after the urologist has viewed the MRI upon which the TRUS-guided biopsy needle is pointed towards the area where the MRI-lesion is located. Fusion-targeted biopsies require software which enables fusion of the MRI-images containing the outlined suspicious lesion with the real time ultrasound image, giving the urologist a marked area to target. Head-to-head comparison showed no superiority for any of the three methods, but all are superior to systematic biopsies[34].

Mild complications such as haematospermia, haematuria, haematochezia and transient lower urinary tract symptoms are common after TRUS biopsies but rarely cause major problems[35]. A serious complication to TRUS biopsies, despite antibiotic prophylaxis, is septicaemia. The incidence of infectious complications requiring hospitalising varies between 0–6.3%[36]. The increasing antimicrobial resistance, especially against fluoroquinolones, the commonly used antibiotic prophylaxis, poses a big challenge. In many countries, the transrectal approach, humorously called transfaecal biopsies, is abandoned in favour of the transperineal approach.

1.3.4 MRI

Within just the last few years, the new kid on the block, MRI, has become a well-established part of the neighbourhood. From being a promising new tool, not present in every urologist's diagnostic arsenal, referral to radiology for prostate MRI is nowadays widely implemented in clinical routine in the diagnostic work-up for PCa.

MRI is short for magnetic resonance imaging, an imaging technique based on nuclear magnetic resonance (NMR). NMR is a physical phenomenon in which atomic nuclei can be flipped/disturbed by electromagnetic waves. The discovery of NMR in solids and water awarded the physicists Edward Purcell and Felix Bloch the Nobel prize in physics in 1952[37-39]. In 2003, the chemist Paul Lauterbur and the physicist Sir Peter Mansfield, shared the Nobel prize in physiology or medicine for their work developing NMR in order to produce images of the body enabling MRI[40-42]. Basically, the patient is inside a magnet that produces a strong magnetic field, which causes the nuclear spins to align. This alignment can be influenced by radiofrequency pulses, and consequently the realignment of nuclear spins in the hydrogen atoms of a patient's tissue, water and fat generates a weak electromagnetic signal. The weak radio-frequency signals emitted from tissues after radio-frequency excitation are detected with receiver coils. To achieve spatial localization of the emitted signals the radiofrequency excitation is repeated numerous times in the presence of varying magnetic

field gradients. Post-processing of the detected signals results in detailed sectional maps of the body with exceptional soft-tissue contrast[43]. Thus, the potentially harmful ionizing radiation used in traditional x-ray and computed tomography (CT) scans is not required for MRI.

In the 1980s, when MRI was first adopted in medical care, it was an exclusive technique only available at a few imaging centres. Nowadays MRI scanners are almost universally available and great advances have been made, both technologically and in terms of protocol development, to obtain images with high lesion conspicuity within a clinically practical scan time. The imaging procedure is usually well-tolerated by the patient, who must remove all metallic and electronic objects such as watches and jewellery before entering the room with the MRI-machine. This machine, or scanner, is a tunnel surrounded by a giant magnet, and the magnetic field gradients make loud noises during the examination. The tunnel is often 1 to 3 meters long with a diameter of 60-70 cm, but there are larger scanners. The preferred field strength of the magnet in prostate MRI is 1.5 or 3.0 Tesla (T). The magnitude of the strength can be illustrated by comparison to the strength of a refrigerator magnet; 10 milliTesla. To avoid blurred images, the patient must remain still during the entire imaging procedure. Depending on the protocol and sequences included, the images of a prostate MRI take approximately 20-40 minutes to acquire. In prostate MRI typically a pelvic phased array coil is used. Better images result with endo-rectal coils. However, because such coils are invasive (the receiver is placed inside a balloon inserted in the rectum) and costly, they are less suited for a screening scenario. In pace with technological advancements, endorectal coils are no longer considered necessary for obtaining high-quality images. Moreover, they are more prone to cause distortion artifacts on diffusion-weighted images.

The extreme or irrational fear of confined places, claustrophobia, can hamper the use of MRI for some persons. Rates of claustrophobia for patients undergoing MRI are between 0.7% and 2% depending on the type of scanner[44], although the rate of claustrophobia among men undergoing prostate MRI might be lower, since it is reported that MRI of the pelvic region is associated with a lower rate of premature termination compared to, for example, MRI of the head[45]. Metallic medical devices and metallic foreign bodies, if not removable and magnetic, are absolute contraindications for MRI[46]. This is due to the fact that the changing magnetic fields can do damage to electronical devices or exert force on magnetic objects, so that they could move or be displaced and cause injury to the surrounding tissue. In addition, metallic objects may lower the image quality by creating artifacts.

In the early 1980s, when the first prostate MRI studies were performed, the examination consisted of gross morphologic assessment, including gland volume estimation and assessment of suspected tumour outside the prostate (staging), but distinction between tumorous and non-tumorous tissue within the prostate was difficult [47-50]. Subsequent development in technology resulted in improved spatial resolution and particularly in reliable and fast acquisition of contrasts, such as T_2-weighted imaging, diffusion-weighted imaging, and Gadolinium contrast-enhanced imaging, which permit superior lesion characterization[48]. *Multiparametric* MRI consists of a protocol combining such sequences.

A standardization of examination protocols and image interpretation was needed to achieve consistency and make evaluation among different MR-units possible, consequently enabling recommendations for clinical care. In 2012, the European Society of Urogenital Radiology (ESUR) published a guideline with recommendations for acquisition, interpretation and reporting of images; Prostate Imaging Reporting and Data System (PI-RADS)[51]. Only three years later, in 2015, due to rapid progress in the field, an updated version, in collaboration with the American College of Radiology and the AdMeTech Foundation, was released; PI-RADSv2[52]. Further refinements and adjustments resulted in PI-RADSv2.1 in 2019[47]. The sequences recommended according to the latest version are: T_2-weighted imaging (T2WI), diffusion-weighted imaging (DWI) and dynamic contrast enhanced imaging (DCE).

The anatomy and the volume of the prostate is assessed on T2WI. In addition to the axial plane, it is recommended to also obtain images either in a sagittal or coronal plane. PCa on T2WI presents as a region with low signal intensity in contrast to the high signal intensity of benign tissue in the PZ. Assessment of TZ can be challenging since benign hyperplastic nodules in the TZ often result in low signal. T2WI is the dominant sequence for determining PI-RADS assessment category of lesions in the TZ. The DWI sequence reflects the random motion of water molecules and is considered a very important sequence in the protocol. The high cell density in clinically significant PCa hinders the diffusion of tissue water and differs from normal glandular prostate tissue where water diffusion is less impeded. Even with the availability of these contrasts it can be difficult to separate tumour lesions from inflammation and benign hyperplasia. Diffusion imaging is the most important sequence for determining PI-RADS lesion score in the PZ. DWI is acquired at different diffusion weighting, also referred to as b values. Multiple b values are used to calculate maps of the apparent diffusion coefficient (ADC), a quantitative estimate of diffusion. An area with low

signal on the ADC map is indicative of PCa. DWI is the sequence most sensitive to artefacts generated by for example orthopaedic hip implants. T_1-weighted images (T1WI) with the administration of intravenous gadolinium-based contrast medium give DCE. The impact of DCE on assessment has diminished with each update of the PI-RADS protocol recommendations. And voices have been raised for the use of so called biparametric MRI, i.e. prostate MRI without contrast medium administration. This would save time for image acquisition, and reporting would be quicker with fewer sequences to scrutinize. In addition, it would be safer with no risk of allergic reactions, and contraindications to gadolinium contrast medium, such as reduced renal function, would be eliminated. Combining the findings in the three multiparametric MRI sequences, any lesion detected is given an overall PI-RADS assessment category score on a 5-point scale, **Table 2**. [47,53,54]

Table 2. PI-RADS™ v2.1 Assessment Categories

Category Score	Likelihood of a clinically significant cancer
PI-RADS 1	Very low (clinically significant cancer is highly unlikely to be present)
PI-RADS 2	Low (clinically significant cancer is unlikely to be present)
PI-RADS 3	Intermediate (the presence of clinically significant cancer is equivocal)
PI-RADS 4	High (clinically significant cancer is likely to be present)
PI-RADS 5	Very high (clinically significant cancer is highly likely to be present)
PI-RADS X	An unsuccessful, non-diagnostic exam.

Table 2. PI-RADS™v2.1 Assessment Categories for each lesion in the prostate. The 5-point scale is based on the likelihood (probability) that the lesions correlate to clinically significant PCa, defined as GS 3+4. Adapted from PI-RADSv2.1[47].

Searching the database PubMed for “prostate” and “MRI” in February 2021 renders over 11,000 articles, half of which were published within the past five years. This illustrates the increasing interest and research efforts in the

field that have resulted in the remarkable, ongoing shift in the diagnostic work-up for PCa. Covering all the clinical situations in which prostate MRI can be used, for example in AS, for planning surgery or radiotherapy, and for assessing suspected PCa recurrence, is beyond the scope of this thesis. Below follows a summary of some landmark studies of the utility of MRI for diagnosing PCa.

In 2017, the PROMIS trial prospectively evaluated 576 biopsy-naïve men, with PSA up to 15 ng/mL, with MRI, TRUS biopsies and template prostate mapping (TPM) biopsies[55]. PCa was found in 408 (71%) men with TPM biopsies. Clinically significant PCa, defined as Gleason score ≥ 4 + 3 = 7 or ≥ 6 mm cancer involvement in any biopsy core, was detected in 230 (40%) of the men. The sensitivity and negative predictive value (NPV) of MRI were 93% (95% confidence interval (CI) 88–96%) and 89% (95% CI 83–94%). However, these figures must be interpreted with a bit of caution; if a man had a suspicious lesion on one side and TPM detected clinically significant PCa on the other side, this was considered as detected by MRI. The sensitivity and NPV of TRUS biopsies were much lower, only 48% (95% CI 42–55%) and 74% (95% CI 69–78%). The sensitivity and NPV of MRI for detecting PCa GS 3+4 were lower, but still higher than for TRUS biopsies.

One year later, the PRECISION trial confirmed the superiority of MRI-based targeted biopsies over systematic biopsies for diagnosing PCa [56]. This multicentre study randomised 500 biopsy-naïve men with clinical suspicion of PCa either to MRI and MRI-targeted biopsies only and no biopsy, if MRI was unsuspicious (252 men), or to standard TRUS-guided systematic biopsies (248 men). In the MRI-targeted biopsy group, Gleason score ≥ 3+4 cancer was found in 38% and in 26% in the systematic biopsy group. There were fewer Gleason score 6 cancers in the MRI-group: 9% versus 22%.

In 2019, two prospective multicentre trials strengthened the evidence that the MRI-based pathway detects more Gleason score ≥ 7 cancers and fewer Gleason score 6 cancers than systematic biopsies. In the 4M trial, all 626 biopsy-naïve men had both systematic and MRI-targeted biopsies[57]. Gleason score ≥ 7 cancers were equally detected in both groups, but fewer Gleason score 6 cancers were detected by the targeted biopsies. The similar comparison was done in the MRI-FIRST trial [58]. In this trial, the detection of Gleason score 6 and Gleason score ≥ 7 cancers was similar for targeted and systematic biopsies. Not surprisingly, the combination of both types of biopsy detected more cancer than either one alone.

A recent systematic review and meta-analysis of 42 studies, with a total of 7,321 included men, showed a substantial variation of the NPV reported from the individual studies. The mean NPV for biopsies targeted to PI-RADS 3–5 lesions to detect Gleason score ≥ 7 cancer in the biopsy-naïve men was 91% (95% CI 88–93%), as compared with biopsy or clinical follow-up [59].

Based on these studies, the evidence is strong that MRI-targeted biopsies outperform systematic biopsies. The European Association of Urology (EAU) 2020 PCa guidelines recommend an MRI before prostate biopsy, both in biopsy-naïve men and men with prior negative biopsy, rating the level of evidence as "1a"[60]. In the biopsy-naïve setting, the guidelines recommend omitting biopsy when the MRI is negative (PI-RADS ≤ 2) and the clinical suspicion is low. In the prior biopsy negative setting, they recommend systematic biopsies when the MRI is negative and the clinical suspicion is high. In all clinical situations, the choice to biopsy or not should be made after shared decision making with the patient. Similar to the EAU guidelines, the American Urological Association recommends an MRI before prostate biopsy in all men who have no previous prostate biopsy[61].

Since March 2020, the Swedish National PCa Guidelines also advocate prebiopsy MRI when investigating men with clinical suspicion of PCa[21], but they state that the evidence is weak for which clinical situations systematic biopsies are indicated in addition to targeted biopsies and for the management of men with no or negative biopsies in an MRI-based diagnostic algorithm.

1.3.5 BIOMARKERS

Several biomarkers are available to guide the decision whether to biopsy or not in case of elevated PSA or positive DRE. Although these tests improve the specificity of PSA for clinically significant PCa and reduce the number of unnecessary biopsies, there is no strong recommendation for their use in the guidelines. This can be explained by the fact that their value in combination with imaging needs further evaluation.

Blood-based biomarker panels including PSA have shown superiority over PSA alone, but none has so far been implemented in any screening protocol. The Prostate Health Index (PHI) test (combining free and total PSA and the [-2]pro-PSA isoform) and the four kallikrein (4K) score test measuring free, intact and total PSA and kallikrein-like peptidase 2 in addition to age, DRE and prior biopsy status perform similarly and reduce biopsies by about 30%, but at the cost of missing 10% high grade cancers[62]. The Stockholm3-test

(a combination of several biomarkers, clinical information and genetic polymorphisms) has a higher predictive accuracy (area under the receiver operating characteristics curve, AUC) for PCa Gleason Score 7 or higher compared to PSA alone and also reduces the number of unnecessary biopsies by about 30%[63].

1.3.6 GRADING, STAGING AND RISK GROUPS

Grading

After tissue sampling of the prostate, the biopsies are sent for histopathological examination. If PCa is found in the biopsies, the report from the pathologist contains the extent of cancer in the cores together with an assessment of the aggressiveness of the cancer. The latter assessment is called grading. The grading system in PCa is named after the American pathologist Donald Gleason[64]. In 1966, he proposed a grading system based on the architectural pattern of the cancer cells, with grades (also referred to as Gleason patterns) ranging from one to five, where grade five was given to the most aggressive and poorly differentiated pattern (**Figure 5**). In the first Gleason grading system, the most common and the second most common grade patterns are combined, which gives a total score from two to ten, with worst prognosis for score ten. This is called the Gleason score (GS).

Since the introduction of the Gleason grading system, it has been validated and undergone further development in step with the changes in diagnostic management of PCa. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of PCa, recommended that the diagnosis of GS 3–4 rarely, if ever, would be made on tissue from biopsy[65]. Although the Gleason grading system ranges from 2 to 10, in practice, PCa is assigned GS 6 to 10. Another change concerned which patterns to add up for the GS, from the sum of the two most dominant patterns to the sum of the most dominant pattern plus the worst (highest) pattern (of what is left when the most dominant pattern has been assessed. A new 5-tier scale was introduced after ISUP's most recent consensus conference in 2014; Grade Groups 1–5[66]. This was an attempt partly to more clearly distinguish GS 3+4 (Grade Group 2) from GS 4+3 (Grade Group 3), as both sum up to GS 7 but with significantly different prognosis, and partly to facilitate the information regarding GS 6 being a low-risk cancer amenable for AS to the patient by renaming it to Grade Group 1. Suggesting "1" will be easier for the patient to accept as a slow-growing tumour than "6". Since the recommendation of reporting both GS and Grade Groups there has been confusion regarding the terminology and its value has been criticized by some[67].

In the pathological report of a prostatectomy specimen, where obviously the entire gland is available for histopathologic examination, the terminology is still GS, and it is still based on the primary and the secondary patterns, with an additional comment if there is a tertiary pattern. Each tumour focus in the specimen is graded separately.

When it comes to grading PCa, there is a well-known and substantial intra- and inter-observer variability among pathologists, even those specialised in uropathology[68-71]. This poses a limitation and makes quality assurance important. Nevertheless, the GS is the strongest predictor of prognosis[72].

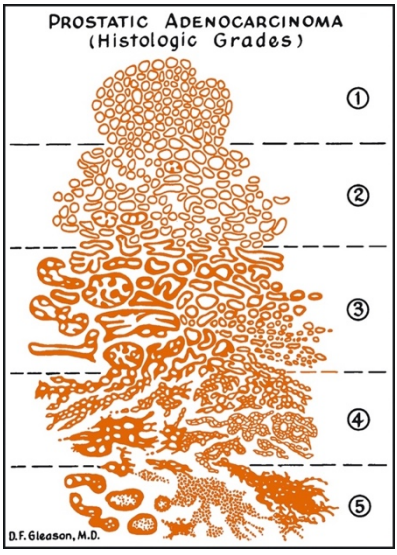


Figure 5. The Gleason schedule presented by Donald F. Gleason in 1966. Adapted from[1]. The numbers represent the five Gleason grades.

Staging

Classification of the disease extent regarding the primary tumour, regional lymph nodes and presence or absence of distant metastases is important for treatment, prognosis and evaluation of research. The Tumour-Node-Metastasis (TNM) is an internationally recognized classification for cancer staging (**Table 3**)[73]. T-stage is determined by clinical examination of the prostate (DRE as described earlier), N-stage and M-stage is determined by computed tomography (CT), MRI or scintigraphy.

T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is not palpable
	T1a Tumour incidental histological finding in 5% or less of tissue resected
	T1b Tumour incidental histological finding in more than 5% of tissue resected
	T1c Tumour identified by needle biopsy (because of PSA elevation)
T2	Tumour that is palpable and confined within the prostate
	T2a Tumour involves one half of one lobe or less
	T2b Tumour involves more than half of one lobe, but not both lobes
	T2c Tumour involves both lobes
T3	Tumour extends through the prostatic capsule
	T3a Extracapsular extension (unilateral or bilateral)
	T3b Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, urinary bladder, rectum, levator muscles, and/or pelvic wall
N – Regional (pelvic) Lymph Nodes	
NX	Regional lymph nodes not assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M – Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
	M1a Non-regional lymph node(s)
	M1b Bone(s)
	M1c Other site(s)

Table 3. Tumour, Node Metastasis (TNM) classification system for prostate cancer (8th edition, 2017). Adapted from[73]). T-stage is based on digital rectal examination only, findings from imaging are not considered.

Risk groups

PCa can present a varying natural course, ranging from slow growing tumours that never cause harm, to potentially life-threatening tumours if left untreated, to uncurable metastatic disease. A disease with this many different expressions, means that accurate risk group classification to discriminate between PCa suitable for deferred versus immediate treatment is important.

In 1998, D'Amico investigated biochemical recurrence after curative treatment for localized PCa and suggested a risk classification system[74]. It is one of the most commonly used systems and is based on PSA level, DRE with clinical T-staging and pathological grading in biopsies with GS. In order to aid treatment/management decisions and predict biochemical recurrence, a modified version of this classification is currently used in Sweden, in which the low risk group is further divided into very low risk and low risk (**Table 4**[21,75].

Table 4. Risk group classification for PCa

	PSA level (ng/mL)	cT-stage	Biopsy GS	Other criteria
Very low risk	< 10	T1c	6	PSAD < 0.15 ng/mL and in total ≤ 8 mm cancer in ≤ 4 cores out of 8–12 systematic biopsy cores
Low risk	< 10	T1–T2a	6	and do not meet criteria for very low risk
Intermediate risk	10–19.9	T2b	7	
High risk	≥ 20 µg/l	T2c–T3	8–10	GS 8-10, or widespread growth of GS 4+3=7 in more than half of the biopsy cores

Table 4. Risk group classification system for localized PCa, adapted from the Swedish National Guidelines for PCa[21].

The Epstein criteria, based on PSA density, DRE and biopsy result, was proposed in 1994 to predict indolent tumours that would never metastasize or cause death[76]. It has been validated several times with decreasing accuracy after the 2005 ISUP Consensus Conference modification of the Gleason grading system, from 73–84% to 39–76% for predicting insignificant PCa[77]. Several other prediction tools have been developed. The Kattan nomogram and the Steyerberg nomogram are two other well-known preoperative prediction models tools for facilitating the treatment decision in newly diagnosed men with PCa showing an AUC for predicting indolent disease in the range of 0.70–0.80[78,79]. Nevertheless, the existing risk group classifications involve the risk of misclassification with upstaging and upgrading as well as downstaging and downgrading after surgery because of biopsy sampling errors and interrater variation in pathological reporting[80-82].

Risk stratification enables reasonably safe AS. AS has become the standard choice of strategy for men with a life expectancy of at least 10 years diagnosed with very low or low risk PCa, considering its natural slow progression [83-86]. Some men with favourable intermediate risk PCa might also be candidates for a period of initial surveillance[87-89]. The strategy of AS diminishes overtreatment by delaying treatment and postponing treatment-related adverse effects while enabling curative treatment if disease progression occurs.

None of the widely accepted risk group classification systems take information from MRI into consideration since they all were developed before the MRI era. The biopsy sampling technique has changed with the introduction of the MRI-targeted biopsies, and today this makes it difficult to know how to assess the pathology result from biopsies. Surely, PCa in 4 cores targeted towards an MRI-lesion are not equal to PCa in 4 cores from systematic biopsies, as the latter provides information that more than one area in the prostate harbours PCa. The new sampling technique also influences the GS. There are only a few studies that have assessed MRI as an aid in treatment decisions in addition to clinical variables or existing risk stratification tools. These studies have unanimously found MRI valuable in discriminating between significant and insignificant PCa, but they lack external validation[90-94]. Thus, the role of MRI in treatment decisions once PCa has been diagnosed remains to be elucidated.

1.4 DEFINING CLINICALLY SIGNIFICANT PROSTATE CANCER

A common initial reaction when men are diagnosed with PCa is wanting to "get rid of" or "cure" the cancer with aggressive therapy, as documented in qualitative interviews with patients[95]. To many men, "cancer is cancer". However, as we know, PCa is a very heterogeneous disease and explaining the difference between a disease that could behave like a slow turtle, a jumping rabbit or a flying bird is a clinical challenge[96]. Autopsy studies of men dying from causes unrelated to PCa document a high underlying prevalence of PCa, so many men diagnosed with PCa die with rather than from the disease[97-99]. Overdiagnosis and overtreatment are significant concerns in early detection of prostate cancer, and AS offers the opportunity to mitigate the side-effects of immediate curative treatment. Therefore, accurate risk stratification and prediction of risk at the time of diagnosis is crucial.

In addition to the PCa aggressiveness, a man's life expectancy and general health also play critical roles in determining treatments. A harmless tumour for a man with 5 years of life expectancy may, however, eventually be fatal for a man with 30 years of life expectancy. Therefore, it is important to assess life expectancy when counselling a man regarding treatment strategies at the time of PCa diagnosis. Several methods for life expectancy estimation have been proposed[100]. An externally validated model, based on patient age, tumour characteristics (stage, grade, PSA) and patient-reported comorbidities, was proposed by Kent and colleagues in 2016[101]. The model predicts 10- and 15-year PCa- and other-cause mortality.

Furthermore, the prevalence of PCa is affected by the diagnostic activity; the more you look, the more you find. To assess the true prevalence, autopsy studies are informative, as they show that many men who die from other causes also have PCa and that although PCa is found in younger men (30–49 years old), it becomes more common with increasing age[97,98,102,103]. Studies also show PCa in men with bladder cancer undergoing cystoprostatectomy[104]. These findings mean that there is a large reservoir of latent PCa, hence there is a "gap" between the incident number of men diagnosed with PCa and the number of men who die from PCa every year, so when we look, i.e., screen, we overdiagnose. Therefore, we need a way of distinguishing the cases of PCa that need management from those that do not (clinically significant versus insignificant PCa) to reduce overtreatment.

In 1993 the American urologist Thomas Stamey compared the prevalence of PCa in cystoprostatectomy specimens with the risk of these men subsequently dying from PCa. Based on his observations, he defined clinically significant PCa as an index tumour with volume > 0.5 mL in RP-specimen[105]. The following year, another American pathologist, Jonathan Epstein, added grade and defined clinically significant PCa as tumour volume of the index tumour > 0.2 ml, GS > 6 or extracapsular extension (ECE) at RP. The previously mentioned Epstein criteria (a definition of clinically insignificant PCa) are derived from this classification system: maximum 2 biopsy cores with cancer, GS 6, maximum 50% cancer core involvement and PSAD < 0.15 ng/ml/ml[76]. Later, another definition was suggested based on a prediction model developed within the Rotterdam section of The European Randomized Study of Screening for Prostate Cancer (ERSPC) (this screening study is further described in chapter 1.6). This definition allows a larger volume of the index tumour on the condition that there is no grade pattern 4 or ECE. This definition, proposed by Tineke Wolters in 2011, outlines clinically significant PCa as: index tumour volume > 1.3 mL and/or non-organ confined disease (> pT2) and/or any Gleason pattern 4 or 5 in RP specimen[106]. However, there is currently no global consensus on the definition of clinically significant PCa amongst urologists and pathologists[107].

1.5 SIDE EFFECTS OF CURATIVE TREATMENT FOR PROSTATE CANCER

The first surgery for PCa, a partial perineal prostatectomy, was performed in 1867 by the German surgeon Theodor Billroth who perhaps is mostly famous for his reconstructive surgeries for gastric ulcer; Billroth I and Billroth II[108]. Dr. Hugh Hampton Young, performed the first RP (radical prostatectomy) in the beginning of the 20th century, also by a perineal approach[109]. It was not until 1947 that the Irish urologist Terence J. Millin removed the prostate retropubically, accessing it behind the pubic bone without entering the intraperitoneal cavity[110]. Five decades later, the laparoscopic prostatectomy was introduced, gaining significant breakthrough first in the 21st century after the addition of the robotic surgical system; da Vinci, to this minimally invasive technique[111]. It is amusing to consider that the tool now used in numerous prostatectomies every year is named after the early scientist who never discovered the existence of the prostate. Similar to surgery for PCa, radiation therapy (RT) has continuously undergone huge improvements since its introduction in the 1960's[112]. Hypofractionated RT has recently become a part of standard practice to maintain oncological outcome with shorter treatment for patients[113].

Neither of these two forms of curative treatment are without side effects; on the contrary, both are associated with high risk of impacting quality of life. The high morbidity and mortality rates seen in the early era of prostatectomies are gone, and perioperative mortality and morbidity in relation to RP are nowadays low[114]. As the external urinary sphincter and the neurovascular bundles necessary for erection might be put under pressure or damaged during prostatectomy due to their vicinity to the prostate, the long-term postoperative side effects include incontinence and erectile dysfunction. The postoperative incontinence rates vary between 4% to 31% at one year in a systematic review[115]. This variation can be partly explained by the different definitions of incontinence in studies. Varying definitions of erectile dysfunction in the literature are also a factor explaining the diverging postoperative rates of erectile dysfunction at one year after surgery; 10% to 46%[116]. Besides different definitions, surgeon-related factors such as previous experience and annual volume as well as patient-related factors such as age, medical comorbidities, preoperative lower urinary tract symptoms, membranous urethral length, body mass index and preoperative erectile dysfunction all affect postoperative outcomes[117-120].

As the radiation techniques have improved, the organs surrounding the prostate (the bladder, the rectum and the urethra) are to a lesser extent

exposed to radiation and, consequently, spared from toxicity. Nevertheless, there are short-term side effects including symptoms from the urinary tract (frequency, urgency, haematuria) and bowel symptoms (rectal bleeding, loose stool, defaecation urgency, faecal leakage)[121]. Usually, these side effects subside within six months, but for some patients they remain longer[122]. Erectile dysfunction is also a side-effect of RT[123].

1.6 SCREENING

The dilemma with PCa screening is the lack of an optimal way to detect aggressive disease early enough for cure, while reducing unnecessary biopsies and overdiagnosis of indolent tumours. There are no longer any controversies regarding the PCa mortality reduction with PSA-screening. As established in The European Randomized Study of Screening for Prostate Cancer (ERSPC), the world's largest randomised controlled trial (RCT) on PSA-screening including 162,388 men between the ages of 55–69 years in 8 European countries, PSA-screening every 2–4 years reduces PCa mortality by 20–22% at 9 to 16 years[124-127]. In one of the participating centres in ERSPC, the Göteborg randomised screening trial, where 20,000 men between the ages of 50-64 years were randomised to biennial PSA-screening or a control group, an even larger reduction in PCa mortality of 35 and 44% was demonstrated at 18 and 14 years of follow-up, respectively. [128,129].

In contrast to these results, the U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) cancer trial including 76,685 men aged 55–74 years showed no difference in PCa mortality between the screening and control arms[130,131]. The PSA-testing in the U.S. during the study period was widespread leading to contamination in PLCO, as the control group had been subjected to almost just as much PSA-testing as the screening group[132,133]. However, reanalysis when the high contamination in the control arm was accounted for, confirmed that screening with PSA reduces PCa mortality[134]. Observational data also support the mortality benefit of PSA-testing. The age-adjusted death rate from PCa was reduced by 35% and 50% in Sweden and the U.S. respectively, compared to the pre-PSA era[3,135].

While often debated, this PCa mortality reduction has generally not been considered to outweigh the harms from screening, and national screening programs for PCa are currently very rare. Given the global burden of PCa as a disease, being the most frequently diagnosed male cancer in Europe and the USA, a screening strategy that maintains the mortality reduction while reducing the harms would benefit a large number of men.

1.6.1 HARMS OF PSA-SCREENING

The blood sampling itself is a well-tolerated procedure not associated with unacceptable harms, only minor discomfort such as bruising, hematoma and dizziness can occur[130]. The biopsy procedure is associated with discomfort, sometimes painful, often limited bleeding as described previously in 1.3.3, and, more severely, infectious complications requiring

hospitalization. The low specificity of PSA causes many men to suffer unnecessary biopsies.

Anxiety is another harm brought on by PSA-testing, caused by concern over whether to take the PSA test, waiting for the result of the test and, if elevated, awaiting result of biopsies, then ultimately worrying about treatment decisions, if cancer is detected[136]. Undoubtedly, having a PSA-test can throw a man and his family into a nerve-racking rollercoaster ride of further testing, discomfortable invasive examinations with risk of complications, overdiagnosis and overtreatment.

To cite Dr. Welch, renowned professor in cancer screening: “Overdiagnosis is the diagnosis of a cancer that would otherwise not go on to cause symptoms or death”[137]. Overdiagnosis is one of the major shortcomings of PCa screening with PSA. The mechanism underlying this is a combination of several factors. Firstly, the prostate often harbours small slow growing tumours never causing symptoms. Secondly, these indolent tumours are detected when the prostate is randomly sampled, which has been the case with the adoption of the standard biopsy protocol. Thirdly, the screening-test, PSA, has low specificity for PCa. The combination of these factors leads to many men subjected to biopsies and consequently overdiagnosis[138,139]. Estimates of overdiagnosis depend on the age of the screened men, the screening interval and the PSA threshold. Regardless of how these variables are arranged, overdiagnosis is substantial in PCa screening with PSA. Estimates of overdiagnosis from 23% to 56% of screen detected cases are reported[140,141]. Another measure indicating overdiagnosis and estimating the benefit-to-harms-ratio, is the number needed to diagnose; NND. This number states the number of men that need to be diagnosed with PCa in order for one man to benefit, meaning avoid PCa death. Longer follow-up shows decreased NND. In ERSPC, NND was 26 at 13 years follow up and reduced to 18 at 16 years[124]. In the Göteborg randomised screening trial NND was 12 at 14 years and 10 at 18 years follow up[128,129].

Overdiagnosis can lead to overtreatment, meaning treating cancer that would never cause any symptoms. Consequently, a person receiving overtreatment can suffer from potential side effects from a never needed treatment. If the risk of side effects was low and the side effects were mild, overtreatment would not be a huge problem. When it comes to PCa, the risk of life changing side effects, as described previously in 1.5, are certainly not negligible. To address this shortcoming, AS emerged in the 2000s. This is a strategy in which patients with low risk PCa are closely monitored, aiming at delaying curative treatment until it is needed or sometimes entirely avoiding

it. In this manner, the side effects of treatment are postponed or avoided[142,143].

1.6.2 THE CURRENT SCREENING SITUATION IN SWEDEN

Reviewing the harms of PSA-testing, one realises why organized population-based screening programmes for PCa with solely PSA are rare. Globally, only two countries in the world, Lithuania and Kazakhstan, have such programmes[144,145]. As much as this controversial issue is debated, generally, in most countries the harms are considered to overshadow the benefits with screening. An optimised screening strategy, where unnecessary biopsies and detection of clinically insignificant tumours are avoided, is desirable. In 2014, the National Board of Health and Welfare in Sweden advised against population based PCa screening with PSA as the favourable effects did not outweigh the negative ones. In the latest assessment in 2018, this position was kept. However, this time, the National Board of Health and Welfare recommended and encouraged evaluation of organised PSA-testing in adjunct with other diagnostic tests for PCa[146]. Partly, the purpose behind this incentive was to improve the scientific basis for making recommendations on screening with PSA in combination with, for instance, imaging. Another reason for this recommendation is the fact that, despite the recommendation against populations-based screening for PCa, PSA-testing among Swedish men already occurs to a large extent[147,148]. This is referred to as “wild” or opportunistic screening.

Programmes for organised PSA-testing have today been launched in several parts of Sweden. After minor delays caused by the Covid-19 pandemic, both the western and southern regions have started such programmes, where men are offered PSA-testing followed by MRI in case of elevated PSA. Several other regions are soon to commence similar programmes. These programmes differ from a national screening programme by offering, not recommending, PSA-testing after providing men with information regarding its pros and cons. Besides forming a basis for future evaluations for scientific progress in the field, these programmes also aim at providing equal opportunities for men to make an informed decision whether or not to undergo testing for PCa. The results from the 18-year follow up of the Göteborg randomised screening trial show that men with lower level of education benefit more by being offered PSA-testing, compared to men with higher level of education[129]. Moreover, regular screening with PSA has a better effect on PCa mortality than opportunistic testing[149]. The programme for organised PSA-testing in the western region has started on a small scale, inviting only 50-year-olds.

When the organization has been fully structured with adjustments overcoming any potential initial hurdles, an expansion is planned to include men in the ages of 50–74 years.

1.6.3 MRI IN SCREENING

Neither the EAU 2020 guidelines nor the American Urological Association (AUA) 2020 position statement on MRI finds sufficient evidence to recommend MRI as an initial screening tool for PCa[60,61]. In a pilot study, evaluating prostate MRI as an initial screening tool in the general population, 50 men were enrolled after a call for volunteers in a newspaper[150]. The conclusion of this study was that MRI alone outperformed PSA alone in predicting PCa. In the last (10^{th}) screening round of the aforementioned Göteborg randomised screening trial, a pilot-study investigating sequential screening with PSA and MRI was embedded[151]. The participating men with elevated PSA underwent MRI and subsequently systematic biopsies. In case of suspicious lesions, MRI-targeted biopsies were added. Each participant was evaluated according to three different screening strategies. The pilot study showed promising results. MRI-targeted biopsies detected almost as many clinically significant PCa as the strategy with systematic biopsies, while diminishing the detection rate of insignificant PCa. Given the previously heavily screened study population with a lower prevalence of PCa, the pilot study was not intended to lead to making strong recommendations regarding screening, but rather to create a base for the GÖTEBORG Prostate Cancer Screening 2 Trial. This large-scale trial was launched in 2015 to explore the role of MRI in PCa screening and will be extensively described in chapter 3, as it forms the basis for **Papers II–IV** in this thesis. Otherwise, there are a couple trials under way investigating screening with PSA and MRI, for example in Germany (PROBASE), Finland (ProScreen), United Kingdom (ReIMAGINE), Canada (MVP) and Sweden (STHLM3MR2).

2 AIM

The overall aim of this thesis was to explore the role of prostate MRI for PCa by expanding the present knowledge of the accuracy and reliability of MRI's performance in detecting clinically significant PCa, with special emphasis on screening.

Objectives of each paper were as follows:

I. To evaluate the performance and variability between readers of prostate MRI outside specialized units with prostatectomy specimen as the reference standard

II. To describe the study design and assess the participation rate of the GÖTEBORG prostate cancer screening 2 trial, a prospective, randomised, population-based trial of PCa screening.

III. To investigate whether it is safe to omit systematic biopsies when combining PSA and prostate MRI in a screening setting.

IV. To evaluate whether clinical variables together with MRI are more accurate in determining clinically significant PCa at whole-mount specimen after RP than clinical variables alone.

3 PATIENTS AND METHODS

Design of The GÖTEBORG Prostate Cancer Screening 2 Trial

The GÖTEBORG Prostate Cancer Screening 2 Trial, also called Göteborg-2 trial, is the base for **Papers II–IV** in this thesis. This study, preceded by the aforementioned Göteborg randomised screening trial, is a prospective, randomised, population-based study of PCa screening with PSA testing followed by prostate MRI with a target accrual of 54,000 men. The primary endpoint of the Göteborg-2 trial is to determine whether changing the screening algorithm for men with PSA ≥ 3 ng/mL from systematic biopsies to pre-biopsy MRI and MRI-targeted biopsies can reduce overdiagnosis.

This ongoing trial is designed as a 2-step, 3-arm randomised screening study. The study layout of the Göteborg-2 trial is shown in **Figure 6**. In the first step, men aged 50–60 years in the city of Gothenburg, Sweden, and six surrounding municipalities were identified from the Total Population Register. Men not meeting the eligibility criteria were excluded from the sample, and the men in the sample were randomised to either the control group (CG) or the screening group (SG). Every three months, the sample was updated from the Total Population Register and the men in the sample were randomised. The initial allocation ratio of 1:1 was altered to 1:2 in order to reach a sufficient sample size in the SG to evaluate the primary objective at four years.

In the second step, men randomised to the CG were not invited and men randomised to the SG were invited for PSA-testing. Men in the SG accepting participation have been further allocated to one of the three screening-arms. Arm allocation, and consequently screening intervention, in participating men in the SG will remain the same in subsequent screening rounds. Screening strategies in the SG:

(1) Arm 1 (reference arm): PSA ≥ 3 ng/mL prompts further evaluation with MRI and systematic biopsies, plus targeted biopsies to suspicious MRI-lesion(s).

(2) Arm 2: PSA ≥ 3 ng/mL prompts further evaluation with MRI and targeted biopsies in case of suspicious MRI-lesion(s).

(3) Arm 3: PSA ≥ 1.8 ng/mL prompts further evaluation identical to the evaluation in Arm 2.

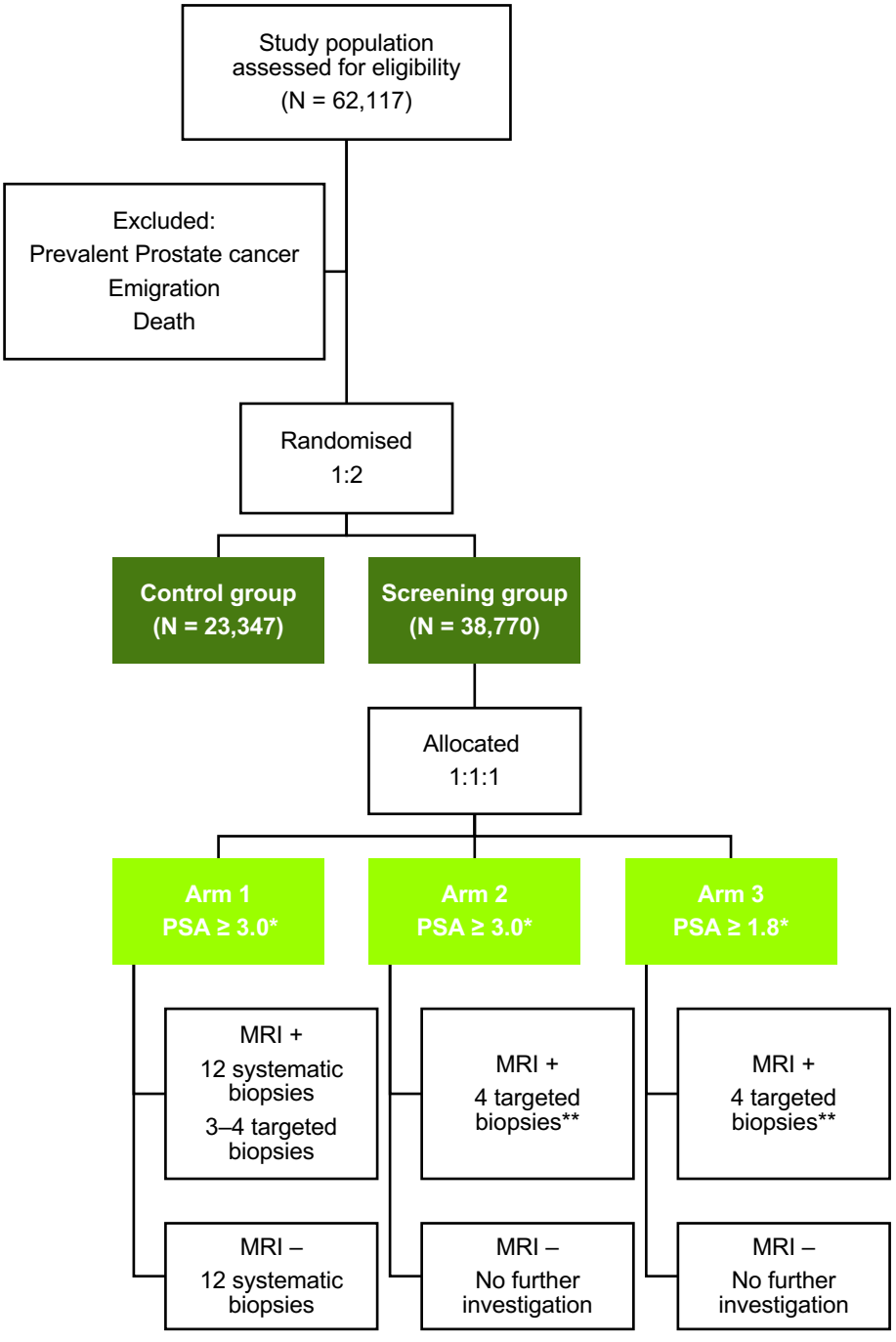
Figure 6. Design of the GÖTEBORG Prostate Cancer Screening 2 Trial.

** Initial allocation ratio was 1:1, From January 2017 it was changed to 1:2.*

*** In order to achieve comparable groups due to the changing allocation ratio half of the men randomised to the CG before January 2017 will be analysed. In total, 23,347 men have been randomised to the CG, of whom 19,385 will be analysed.*

**** 12-core systematic TRUS biopsy was recommended to all men with PSA ≥10.*

***** 12-core systematic TRUS biopsy was recommended to all men with an MRI showing PI-RADS 5*


Study population assessed for eligibility (N = 62,117)
Excluded: Prevalent Prostate cancer Emigration Death
Randomised 1:2
Control group (N = 23,347)
Screening group (N = 38,770)
Allocated 1:1:1
Arm 1 PSA ≥ 3.0*
Arm 2 PSA ≥ 3.0*
Arm 3 PSA ≥ 1.8*
MRI + 12 systematic biopsies 3–4 targeted biopsies
MRI + 4 targeted biopsies**
MRI + 4 targeted biopsies**
MRI – 12 systematic biopsies
MRI – No further investigation
MRI – No further investigation

Suspicious MRI-lesions are defined as PI-RADS 3–5. Participants diagnosed with PCa are transferred to clinical routine care at the Department of Urology, Sahlgrenska University Hospital. Participants in Arms 2 and 3 diagnosed with PCa also undergo systematic biopsies. Participants where interventions did not result in PCa are re-invited to further screening rounds at pre-specified intervals. Consequently, participants with PSA-levels below the cut-offs for further evaluation according to arm allocation, participants where further evaluations resulted in benign biopsies and participants in Arms 2 and 3 without suspicious MRI-lesions were thus re-invited for further screening until termination of screening, which is determined by participant age in combination with the last PSA-value. Men in the SG not participating in the first screening round are continuously invited to PSA-testing in subsequent rounds.

Enrolment in The Göteborg-2 trial started in September 2015, and the participants in the complete cohort were randomised and invited to the first screening round in spring 2020. The analysis of the primary endpoint is planned to be reported in 2021.

Procedures of The GÖTEBORG Prostate Cancer Screening 2 Trial

PSA-testing is offered at 13 health care facilities in the region. MRI is performed at the Department of Radiology, Sahlgrenska University Hospital using a 3-Tesla scanner with a pelvic phased-array coil. Participants are prepared with 4h of fasting and a micro-enema 2h prior to imaging. Acquisition, interpretation and reporting of images is according to PI-RADS (version 2.0. October 1, 2015–May 31, 2019, and version 2.1 since June 1, 2019)[47,52]. The multiparametric protocol includes T2WI and DWI, with b values of 0, 100, 1,000 and 1,500 s/mm2 all but b = 0 used for calculation of the ADC, and DCE T1WI with the administration of gadolinium based contrast medium. From April 2019, the protocol for multiparametric MRI is only used in screening round 1. From this date, for men referred for MRI from screening round 2 and forward, the protocol was adjusted to biparametric MRI, omitting DCE. Images are reported by two out of three radiologists (all with > 5 years of prostate MRI experience) in consensus and blinded to trial arm, PSA-level and clinical data. A negative MRI is defined as PI-RADS scores 1–2 and a positive MRI as PI-RADS scores 3–5. Each lesion is given a localization according to a 24-sector template, based on the Swedish National PCa Guidelines[21].

Further evaluation after MRI; DRE with T-staging, TRUS with estimation of prostate volume and biopsies, is performed by one of six trained urologists at

the Department of Urology, Sahlgrenska University Hospital. Local anaesthesia as well as 750 mg Ciprofloxacin is administered as a single dose before biopsy. Prolonged prophylaxis is given to men with increased risk of infection according to the Swedish National PCa Guidelines[21]. Systematic biopsy with 12 cores is obtained from the peripheral zone of the prostate and their localization described according to the previously mentioned national template. For men with suspicious lesions on MRI (PI-RADS 3–5), cognitive-directed targeted biopsies is obtained with four cores directed towards the sector in which the centre of each MRI lesion is described; if systematic biopsy has already been directed to a sector, only three targeted cores are added. All men in Arms 2 and 3 with PCa detected at targeted biopsy are re-biopsied with systematic biopsies, in order to judge cancer extension in the prostate.

One experienced prostate pathologist (25 years' experience of prostate pathology) reviewed all prostate biopsies. To validate the histopathology diagnoses, currently, all cancers detected during the first screening round are reviewed by two external specialised prostate pathologists. The majority assessment will be applied in case of disagreement in grading. If there is disagreement among all three, the midmost assessment will be considered the final assessment.

Paper	Research questions	Study population	Outcomes	Statistical methods
I.	What is the detection rate of prostate MRI for the index tumour at RP, outside high volume centres? Does the detection rate vary between MRI-readers?	Patients with PCa and preoperative prostate MRI, undergoing RP, at a private hospital in Gothenburg, Sweden January 1, 2012 –December 31, 2014 **(N = 97)**	• Detection rate of index tumour at RP • Inter-reader variability	Overall detection rate, and separate calculation of detection rate of index tumour for each reader. Inter-observer agreement between each pair of readers evaluated using Cohen's κ coefficient, according to Landish and Koch.
II.	To provide a detailed description of the design and procedures of the Göteborg-2 trial. To what extent do men participate in different interventions in PCa-screening?	All men randomised and enrolled in the Göteborg-2 trial, both the CG and the SG October 1, 2015–December 31, 2019 **(N = 62,117)**	• Participation rates in: PSA-testing, prostate MRI and TRUS biopsies • Opt-out rates in CG and SG	Participation rates Opt-out rates
III.	Is it safe to omit systematic biopsy in PCa screening when combining PSA and prostate MRI?	Participants in arm 1 in the SG of the Göteborg-2 trial undergoing their first round of biopsies October 1, 2015–June 30, 2020 **(N = 408)**	• Clinically significant PCa, defined as GS ≥ 3+4=7, at biopsy	Detection rate of clinically significant PCa with a 95% CI
IV.	Is a model with clinical variables together with MRI more accurate in determining clinically significant PCa at RP than clinical variables alone? Can an accurate model for distinguishing significant and insignificant PCa at the time of diagnosis be developed?	Participants in all arms in the SG of the Göteborg-2 trial who were diagnosed with PCa and subsequently treated with RP October 1, 2015–September 30, 2020 **(N = 183)**	• Clinically significant PCa at RP *Definition A:* Index tumour volume > 0.5 mL in RP specimen *Definition B:* Index tumour volume > 1.3 mL and/or non-organ confined disease(>pT2) and/or any Gleason pattern 4 or 5 in RP specimen	Multivariable logistic regression models, comparison of models with likelihood ratio tests. AUC curves with 95% CI. Sensitivity analysis, using multiple imputation for missing cases. The clinical utility of the best model assessed with decision curve analysis as described by Vickers and Elkin.

Table 5. Overview of the papers in this thesis summarizing the research questions and statistical methods. CI = Confidence interval.

3.1 STUDY POPULATION

Paper I

The study participants in **Paper I** constitute a retrospective cohort of men consecutively treated with retropubic radical prostatectomy (RRP) or robotic-assisted radical prostatectomy (RARP) between January 1, 2012 and December 31, 2014, at a private hospital in Gothenburg, Sweden. The patients were both referred from other centres to the private hospital for treatment as well as primarily evaluated there. Before surgery, they all had undergone prostate MRI, mainly after biopsy, as an aid in planning surgery, but in some cases, MRI was performed before biopsy. The flow chart is shown in **Figure 7**.

Paper II

The entire study population of the Göteborg-2 trial, both in the CG and in all the arms in the SG, was current in this paper. Analyses were performed from start of enrolment until 31 December 2019 (except for opt-out rates which were assessed from enrolment until September 2020.

Paper III

Participants in Arm 1 of the Göteborg-2 trial undergoing their first round of biopsies between October 1, 2015, and June 30, 2020, were selected for this paper. The participants all underwent systematic biopsies regardless of MRI results. In case of suspicious MRI-lesions, targeted biopsies were also taken. Participants who did not undergo MRI or biopsies, were excluded. Selection of the final study population of 408 men is shown in **Figure 8**.

Paper IV

As in **Paper I**, the participants in **Paper IV**, have undergone RP. The study population consists of participants in the Göteborg-2 trial diagnosed with PCa and treated with prostatectomy from the start of enrolment in the Göteborg-2 trial, until September 30, 2020. The flow chart in **Figure 9** shows that of the 196 men who underwent RP during that time, 13 were excluded due to lack of MRI, MRI of non- diagnostic quality, lack of tumour volume measurements on prostatectomy specimen and due to more than one year between MRI and RP. This results in a final study population of 183 men.

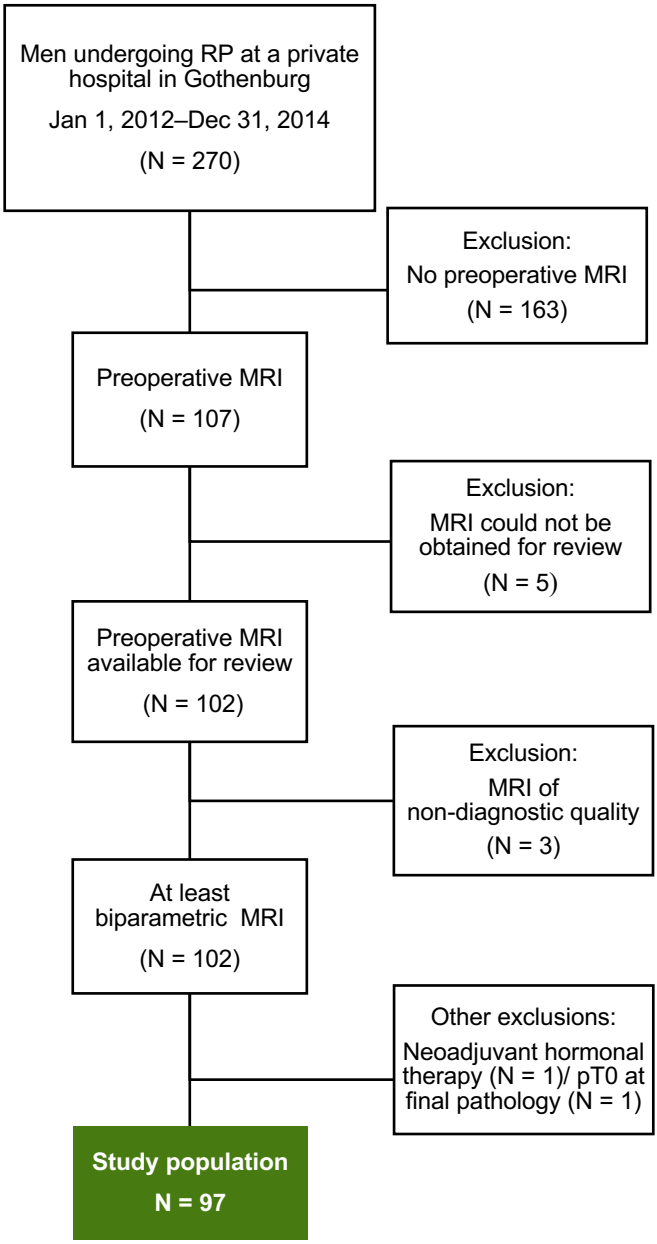


Figure 7. Flow chart of the study population in ***Paper I****.*

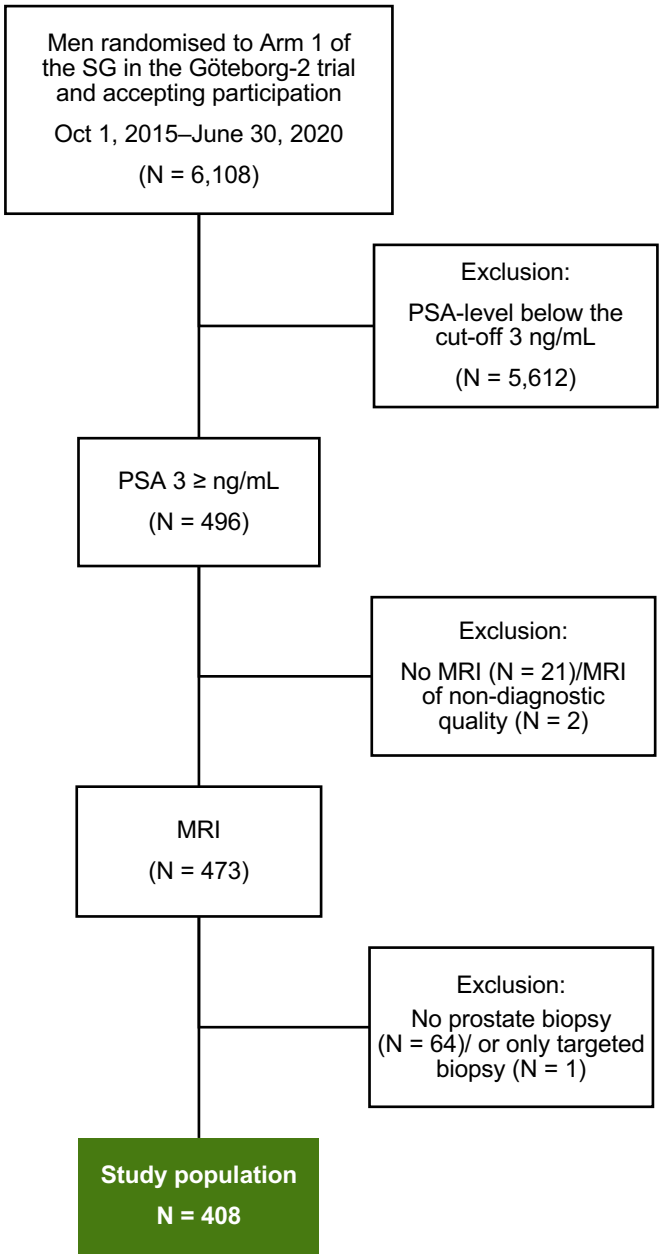


*Figure 8. Flow chart of **Paper III** showing selection of participants undergoing their first round of biopsies.*

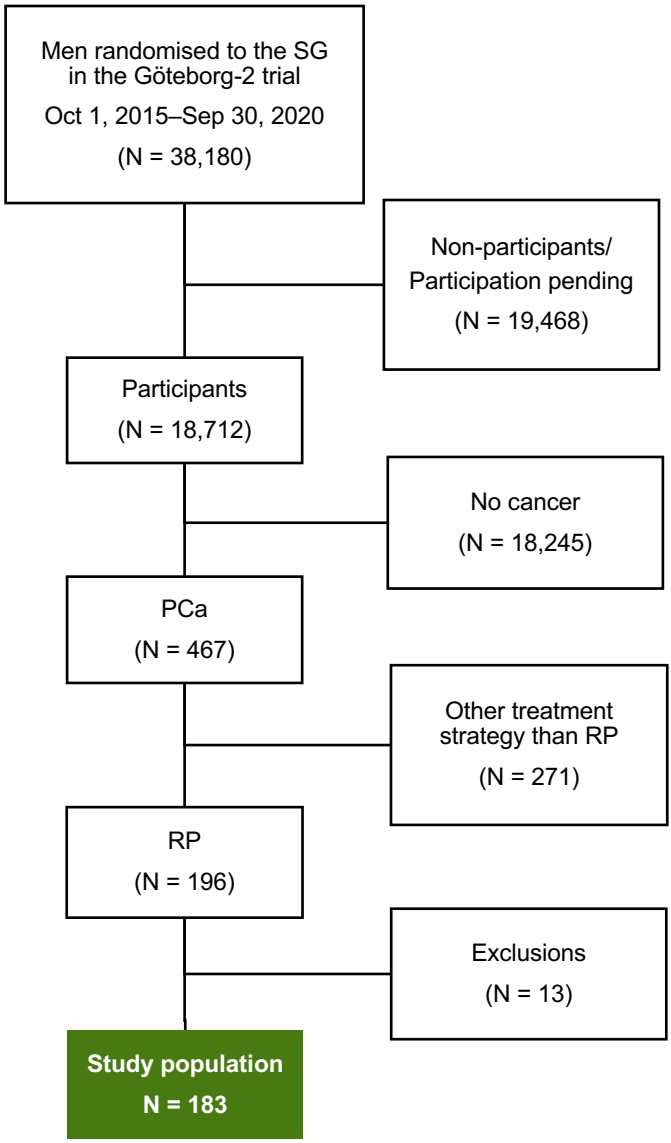


Figure 9. Flow chart showing exclusions and final study population pf ***Paper IV****.*

3.2 METHODOLOGICAL AND STATISTICAL CONSIDERATIONS

The research questions and statistical methods used for the papers in this thesis are summarized in **Table 5**. In this subchapter, the applied methods and statistical analysis are further described and discussed.

3.2.1 DIAGNOSTIC ACCURACY

Diagnostic tests are used to determine if a patient is healthy or has a disease. For PCa, the level of PSA can be measured in blood (serum or plasma). Or, the level of tumour suspicion can be assessed with prostate MRI (PI-RADS). Each test has inherent test properties; there is a balance between false-positive, i.e., healthy individuals falsely diagnosed as having the disease, and false-negative diagnoses, i.e., individuals with the disease who are falsely diagnosed as healthy. A number of different measures can be calculated to assess the accuracy of a diagnostic test: sensitivity, specificity and predictive values are most common. In order to calculate these, one needs the result of the diagnostic test but also the true disease status in the evaluated population. However, as the true status is mostly unavailable the result of the best test is used instead. The 'best' test is referred to as “the gold standard”. The pathological report from biopsies is often used for PCa, but examination of the prostatectomy specimen gives the true status and is often used as the gold standard. Using the biopsies as the gold standard will not always be correct due to sampling bias; not all tumour foci are sampled at prostate biopsy (sampling error).

Sensitivity is the proportion of people with PCa that have a positive test. Specificity is the proportion of people without PCa that have a negative test. These two values are given as percentages and indicate how the test performs on a population level. To reach 100% sensitivity, specificity would be reduced, and vice versa. Changing the threshold level for when a diagnostic test identifies persons with the disease as having the disease, will change the accuracy of the test. For example, in PSA-testing for PCa, the change of the cut-off from 4 ng/mL to 3 ng/mL increased the sensitivity from 21% to 32% at the cost of a drop in specificity from 91% to 85%[152]. This example also illustrates the trade-off between sensitivity and specificity. For many diagnostic tests, including PSA, the distribution of values comes with an overlap, certain intervals contain both those with and without the disease. This can cause misdiagnosis in both directions with false positive and false negative test results.[153,154]

To minimize the misdiagnosis, receiver operating characteristic-analysis was suggested. This method began as the differentiating of signal from noise in radar detection developed during World War II, in the US or Great Britain, depending on who you ask. Receiver operators decided whether the signals on the radar were enemy planes or birds, as these were quite similar on the radar. By calculating and plotting each operator's rates: true positive rate; assessing an enemy plane as an enemy plane, and false positive rate; assessing a bird as an enemy plane, a receiver operating characteristic (ROC)-curve was obtained. Later, this method became commonly used in medicine to make global assessment of the performance of a test, also called diagnostic accuracy. By calculating the sensitivity and specificity at all possible cut-off values and plotting sensitivity against 1-specificity, a ROC-curve is obtained. Ideally, a diagnostic test has a large area under the ROC-curve, abbreviated AUC. AUC ranges from 0.0 to 1.0. A test with AUC 1.0 is perfect, always distinguishing between individuals with and without the disease. The rule of thumb for interpreting the performance of a test is: AUC $\leq$ 0.5 not informative (not better than flipping a coin), AUC $\geq$ 0.7 fair, AUC $\geq$ 0.8 good and AUC $\geq$ 0.9 excellent performance. The value of AUC can be interpreted as the probability that, for each pair of two individuals with and without the disease, the individual with the disease has a higher test value than the person without the disease.[153,155]

To determine the probability that patients with positive test results have the disease, the positive predictive value (PPV) is calculated. The negative predictive value (NPV) addressed the probability of the test having returned a negative result for a healthy individual. These values are affected by the prevalence of the disease in the population. PPV increases with increasing prevalence, and NPV decreases with increasing prevalence.[153,156] This must be considered in this thesis when it comes to the performance of MRI in detecting PCa in different populations. The prevalence of PCa is strongly associated with age, hence age in the study population will affect the predictive values[97,102]. Since a screening population is at lower risk of harbouring PCa, the diagnostic performance of MRI (for example PPV and NPV) as reported in previous studies, when conducted in clinical settings on men with clinical suspicion and indication for biopsy (for example elevated PSA and/or positive DRE), cannot necessarily be transferred to the screening setting but must be studied prospectively in a screening trial. A high NPV, meaning a high probability of not harbouring clinically significant PCa when MRI is negative, must be met in order to safely omit systematic biopsies. Besides disease prevalence, other factors that must be kept in mind are the definition of a positive MRI as well as the definition of clinically significant PCa. These factors affect the performance of MRI, clearly demonstrated in a

systematic review and meta-analysis assessing the NPV of prostate MRI, which also showed that increasing prevalence of PCa resulted in lower NPV[157].

In **Paper I**, the detection of PCa by prostate MRI was assessed by calculating the sensitivity. Sampling bias was avoided by using prostatectomy specimen as true status. As the entire study population in this paper was selected for definite treatment, the prevalence of disease was very high. Therefore, even though important to determine, neither PPV nor NPV were calculated, as it could be misleading if transferred to a population in which not every man has PCa. As none were "healthy" according to the gold standard, meaning the entire study population had PCa, neither was the specificity assessed. The readers reviewing images were aware of the study design in which the complete study population had undergone RP. To reduce the bias arising from this fact (confirmation bias), 11 MRIs originally judged as normal were randomly added to the list for review. The readers were not informed about the number of added MRIs. This, however, cannot be mistaken as mimicking a cohort of men with elevated PSA.

This type of confirmation bias was not an issue in **Paper III** where MRI was interpreted before biopsies. The rate of screened men diagnosed with clinically significant PCa, identified only with systematic biopsy, was calculated with 95% CI. As there were two methods, targeted and systematic biopsies, without final pathology available, assessment of measures of performance was not made. The aim of this study was not to compare the MRI-targeted biopsies and systematic biopsies. This will be assessed by comparing the arms of the Göteborg-2 trial, as the primary endpoint of the trial.

ROC-analysis and AUC are not only used for diagnostic tests of single variables but can also be used to assess the performance of a prediction model as in **Paper IV**. The model is usually a logistical regression model with a binary outcome, diseased or healthy, or as in **Paper IV**, clinically significant PCa or not. This is further described in the section on prediction models, 3.2.3.

3.2.2 AGREEMENT

Agreement between two methods (or persons) depends on how similar they are when measuring the same quantity. Two variables may have strong correlation yet weak agreement. The Bland-Altman plot is preferred to evaluate agreement for continuous variables[153]. This plot shows the pairwise differences between the methods on the y-axis against the mean of

the methods on the x-axis[158]. However, categorical variables must be evaluated differently. Cohen's kappa (κ) is a method used to determine how much more likely the agreement is than pure chance[159]. It is a value between -1 and 1 obtained by comparing the proportion agreement observed with the proportion agreement that can be expected only by chance. By taking the possibility of agreement occurring by chance into consideration the method is more reliable than comparing percent agreement. There are different characterizations of kappa values in the literature. The one suggested by Landis and Koch was used in **Paper I**: $\kappa \leq 0$ considered as no agreement, κ 0.01–0.20 as slight agreement, κ 0.21–0.40 as fair agreement, κ 0.41–0.60 as moderate agreement, κ 0.61–0.80 as substantial agreement and almost perfect agreement when κ 0.81–0.99[160]. Despite these suggestions, interpretation of Cohen's κ is not straightforward since it can be influenced by several factors such as proportion of subjects in each category and the number of categories. Another factor to consider is whether there is a high prevalence of a given observation. This can produce a counter-intuitively low value of Cohen's κ even if the agreement is almost perfect. Nevertheless, Cohen's κ is one of the most used methods to evaluate inter-observer agreement, which was the second research question in **Paper I**.

3.2.3 PREDICTION MODELS

Correlation gives information of whether there is an association between two variables and the strength of it. In addition to this, regression models give the function for this correlation, and to what degree the variables explain the variance of the outcome, also called the goodness of fit. There are several different types of regression models. The most basic and the simplest form of regression model is the simple linear model. But if the outcome variable is not continuous and not normally distributed, this basic form cannot be used. More advanced models, generalised linear models, have been developed mathematically to enable models not fulfilling the two criteria mentioned. There are several models, each appropriate for certain situations given different distributions and outcomes. Logistic regression makes a model that estimates the probability that one of two outcomes, so called binary outcome, occurs. So, the outcome can have two possible values, for instance diseased/not diseased or dead/alive. This type of model can for example be used to estimate the probability that a patient harbours clinically significant PCa or not, and which variables can explain this probability. It is used outside the medical field as well, for instance in economics to predict the likelihood of a homeowner paying their mortgage.

In **Paper IV**, multiple or multivariable logistic regression models were developed for predicting clinically significant PCa at prostatectomy. Given

the binary outcome, the logistic regression model is suitable. Multivariable refers to the use of multiple variables, predictors, in the model. (This should not be confused with multivariate models, which refers to a model with multiple outcomes.) The maximum number of variables that should be used in a prediction model in order to keep the risk of overfitting at a low level, is regulated by the widely used rule of thumb "one in ten rule". According to this rule, the number of events in the less frequent category in the outcome (dependent) variable decides the appropriate number of predictors. There should be 10 events for each additional variable in the model. The study population in **Paper IV** was selected to undergo surgery leading to a low event rate of insignificant PCa.

Evaluating goodness of fit between models in multiple logistic regression models is performed with a likelihood ratio test[161]. Thus, the four models in **Paper IV** are compared with likelihood ratio test. A visual illustration of the tested models' ability to discriminate between significant and insignificant PCa is the use of boxplots showing each model's predictive risk for either outcome. Decision curve analysis was used to assess the clinical utility of the best model across a range of threshold probabilities[162]. The y-axis on the decision curve measures the net benefit, which is calculated by summing the benefits (true positives) minus the harms (false positives); the latter is weighted by a factor relating to the relative harm of doing additional clinical investigations and not performing immediate RP on patients with clinically significant PCa compared to the harm of performing immediate and unnecessary surgery on patients with insignificant cancer.

3.2.4 UNCERTAINTY IN RESULTS

Since evaluation of an entire population is rarely possible, usually a sample is evaluated, ideally drawn as a random sample in order to make inference about the underlying population. This leads to some degree of statistical uncertainty, even if the sample is cautiously chosen in order to be representative of the population. For this reason, point estimates of study results, for example proportions or risks, are generally presented with 95% confidence intervals (CI). The CI is a reflection of the precision of the result or the effect size. If we, based on a sample, calculate a 95% CI for a population mean, the CI, in 95 out of 100 cases, will include the value of the unknown true mean in the underlying population. In other words, the confidence level, commonly 95%, expresses how confident one can be that the result describes the unknown true mean. Repeated samples from the same population would render different CI each time since different individuals, by chance, would be included. Another important aspect is that the CI only

describes the uncertainty rendered by random error, not systematic error or bias, which must be managed by other approaches.[153]

The method for calculating CI depends on the distribution of the data and on the type of point estimate, for example the mean value, odds ratio or prevalence, and can be simple or require advanced statistical understanding. An example where it is easy to calculate a CI is for a proportion in a population, for instance clinically significant PCa, as in **Paper III**. The number of clinically significant PCa follows the so-called binomial distribution. This distribution can, due to the central limit theorem, be approximated by the normal distribution under the condition that sample size is "large enough". (The central limit theorem states that regardless of the distribution of a variable, the mean of a sufficiently large sample will be normally distributed.)[153,163] Sometimes, more advanced methods for calculating CI are needed, for example for studies with small sample sizes or like in **Paper IV**, where CIs for AUC adjusted for overfit were constructed by means of bootstrapping, using 1000 resamples. Bootstrapping is a resampling technique based on the assumption that the empirical distribution of the data at hand approximates the true distribution. Hence, drawing new samples without replacement from the data imitates sampling from the true distribution, and these samples can be used to estimate for instance CI.

3.2.5 POWER AND SAMPLE SIZE

To cover an entire population in a study is, as above stated, hardly ever possible because it is time-consuming as well as expensive. Researchers manage this by making inferences about the studied population based on a representative sample drawn from the target population. Proper sample size is not only necessary in order to answer the research question with appropriate precision but also helps economise resources. The sample size is determined for a specified power and a given significance and effect size, i.e., the quantitative measure of the magnitude of the effect[164]. The statistical power (beta) is the probability of rejecting the null hypothesis when the alternative hypothesis is true. In other words, power is the probability to find an effect of a certain size, if it is really there. Generally, power of 80% is chosen, but might be at a different level depending on the circumstance. With level of power of 80%, in 80 of 100 cases, a real difference between two groups would be detected. But in 20 of 100 cases, the null hypothesis would wrongly be accepted, and an existing/actual difference would not be detected. This is referred to as Type II error. Level of significance (alpha) is the probability of rejecting the null hypothesis when it is true, referred to as Type I error. The most established level for significance is 0.05. Nowadays there

are plenty of software programmes which can be useful for power calculations.

The sample size in the Göteborg-2 trial was calculated for the primary outcome, to detect a 50% reduction in detection of insignificant PCa with the MRI-targeted biopsies strategy as compared to systematic biopsies, with a power of 80% and significance level of 0.05. But the sample size is also large enough to have power to detect a 50% risk reduction in PCa mortality between the CG and SG at 12 years.

Based on previous studies from the Göteborg-1 trial and expert knowledge, the assumption was made that the proportion of men diagnosed with insignificant PC among men with PSA ≥ 3 in Arm 1 (reference arm) would be 9%. This gave a sample size of N=1,164 men with PSA ≥ 3 ng/mL. In the pilot study (embedded within the 10th round of the Göteborg randomised screening trial) that preceded the Göteborg-2 trial, a rate of insignificant cancer of 1.2% was observed in the strategy evaluating men with PSA ≥ 3 ng/mL who underwent systematic biopsy but no MRI, while the corresponding rate was 0.32% in the strategy evaluating men with PSA ≥ 3 ng/mL undergoing MRI and only targeted biopsy in case of suspicious lesions, i.e., a relative difference of 75%, which motivated the hypothesized 50% reduction that forms the basis of the sample size calculation in the Göteborg-2 trial[151]. Furthermore, it was hypothesized that 7% of men attending PSA-screening would have an elevated PSA and that the participation rate would be 50%, which led to the sample size N=33,260 altogether in the three screening arms. Accounting for uncertainty in the hypothesized proportion of insignificant PCs and in the proportion of men with PSA ≥ 3 ng/mL of those screened, led to the final sample size of N=36,000 for the SG. With an allocation rate of 1:2 between the CG and SG, altogether, N=54,000 men needed to be included in the study.

3.2.6 RANDOMISED CONTROLLED TRIAL

Found at the top of the research hierarchy, the randomised controlled trial (RCT) is considered to be the gold standard for the design of experimental research. By randomising participants to different exposures, selection and confounding bias are avoided. RCT has internal validity whereas external validity might be a problem as those who take part in studies tend to be different from those who do not. The only results more robust and valued higher than the result from an RCT are the ones from systematic reviews and metanalysis of RCTs. However, a poorly designed RCT can be full of bias. [165,166]

Proper randomisation and allocation are crucial to avoid selection bias. The randomisation in the Göteborg-2 trial was performed in two steps, as described previously. In the first step, the eligible men were randomised to either the CG or SG. To ensure full allocation concealment, a secure, password-protected computer-based algorithm performed by an external person without the study investigators' involvement was used. The first step of randomisation will make an evaluation possible of the secondary objective concerning PCa mortality reduction between no screening or opportunistic screen and sequential screening with PSA and prostate MRI. Nonetheless, like in the PLCO-trial which suffered from contamination bias, opportunistic PSA-screening in the CG might influence this endpoint[130,131]. An assessment of the proportion of men having a PSA-test during the last 10 years in Gothenburg and the surrounding regions was performed in 2017. The proportion of men having had a PSA-test increased with age: 25% of 50-year-olds, 50% of 60-year-olds and almost 70% of the 70-year-olds had their PSA measured[148]. Regarding PCa mortality reduction, opportunistic PSA-testing is less effective than organised PSA-screening[149]. As PSA-testing occurs in Western society, the aim of the Göteborg-2 trial is to evaluate whether screening with PSA and MRI can reduce PCa mortality compared to no screening or opportunistic screening. Consequently, PSA-contamination in the CG might dilute the difference in PCa mortality between the CG and SG. Dilution bias can lead to Type II error (i.e., concluding there is no difference when there is). To reduce risk of Type II error, contamination must be considered and adjusted for at the time of analysis of this endpoint.

In the second step, the PSA-values of the men deciding to attend were electronically transferred from the blood sampling units to the trial database upon which they were alternatingly allocated into one of the three screening-arms. Preferably, allocation randomisation should be unpredictable and concealed from the people involved in allocating participants, to prevent selection bias. The alternating allocation in the Göteborg-2 trial is predictable yet not impacting the selection to the screening-arms since no person involved in the study can influence the allocation nor the participants.

The statistician Marvin Zelen proposed the randomised consent design in 1979, also known as the prerandomisation design with randomisation preceding informed consent[167,168]. This design is used in the Göteborg-2 trial and allows evaluating the effectiveness of screening. With this approach consent bias, different amount of opting out in the study arms, can yield unreliable results. Hence, the opt-out rates in the CG and the SG must be taken into consideration.

The primary objective of the Göteborg-2 trial is to evaluate whether altering the screening algorithm in men with PSA ≥ 3 ng/mL from systematic biopsies to pre-biopsy MRI and MRI-targeted biopsies can reduce the risk of detecting clinically insignificant PCa. This will be assessed by comparing the proportion of clinically insignificant PCa between the screening-arms. This endpoint could have been assessed simply by the strategy in screening-arm 1. Since participants in this arm undergo both systematic and MRI-targeted biopsies, each man could be his own control. In this view, the strategy with three screening-arms seems excessive. Nonetheless, the chosen design with three screening-arms not only allows evaluation of three different screening strategies including a lower PSA-cut off, but it also allows for the prospective evaluation of the consequence of potentially delayed diagnosis of PCa with a screening strategy without systematic biopsies in subsequent screening rounds after the first round.

Ideally in an RCT, treatment allocation is masked to participants and care providers, often called double blinded. If those assessing the outcome are also blinded, then it is called triple-blinded. Blinding is not always feasible, for example in surgical interventions. In the Göteborg-2 trial participants were not blinded to arm-affiliation nor to the result of PSA, MRI or biopsies. Radiologists were blinded to arm-affiliation and PSA-level. Urologists were blinded to arm-affiliation and to the result of PSA and MRI when assessing findings at DRE and TRUS, but the results were revealed before biopsies were taken.

3.3 ETHICAL CONSIDERATIONS AND SAFETY OF PARTICIPANTS

The Regional Ethics Review Board at Gothenburg University approved the study conducted in **Paper I** in June 2014, registration number 515-14, and the Göteborg-2 trial in January 2015, registration number 890-14, respectively. The latter approval covers **Papers II-IV**.

Paper I was retrospective and since the study participants already had undergone treatment, they were not affected by the MRI-review nor the outcome of the study.

The basis for **Papers II-IV**, the Göteborg-2 trial is a prospective study bringing several ethical considerations. Participation is, naturally, voluntary and can be terminated at any time without having to provide a reason. Men in both the CG and the SG are informed about this and that they by a deliberate action can quit participating in the trial at any time (opt-out procedure). The letters to men enrolled in both groups are shown in **Appendix 1 and 2.** As PSA-testing and further procedures can come with benefits and risks, alongside instructions for how to participate and information about the Göteborg-2 trial, a detailed description of pros and cons, and risk of complications as well as a link to the study website (www.g2screening.se) are enclosed with the letter of invitation to men in the SG.

By having their PSA measured, the men in the SG accept participation. Written informed consent is thus not requested from participants. No active consent is necessary and only men opting out are excluded from the trial and analysis. No need for written informed consent might at first glance be thought as unconventional. But as a detailed description is enclosed with the enrolment letter, and having PSA measured is an active act, the participants are assumed to have taken note of the information provided and made an active, informed and voluntary decision to participate. This assumption was approved by the Ethics Board. Yet assumptions are only assumptions. Hence this subject is planned to be further evaluated regarding the provided information and the decision to participate or not.

Adverse events following the study interventions such as contrast medium allergy requiring medication and infectious complications after biopsies, with or without hospitalization, may occur. Participants are informed about risk of adverse events and can decide to not accept a study intervention. However, declining investigation after being informed about having an elevated PSA that might indicate PCa, is of course not easy for the individual man. Adverse

events should always be monitored and actions taken if necessary. A quality assurance evaluation of the continuous recording of infection after biopsies in the Göteborg 2-trial showed a higher than anticipated number of infections among men undergoing systematic re-biopsies after PCa in targeted biopsies. By delaying the timing of the re-biopsies from approximately three weeks to at least six weeks after the initial biopsy, the rate of infections among these cases dropped. For matters concerning safety issues, an external advisory board with experts in the field is established and consulted. Delaying diagnosis of serious cancer when omitting biopsy in men with a negative MRI (and a PSA < 10 ng/mL) in Arm 2 and 3 is a point of concern with the study protocol. Hence, annual analysis of the incidence of interval cancers in these men is performed as well as studying the incidence of serious cancers detected at follow-up screens in men with elevated PSA and negative MRI in previous screening rounds. The Advisory Board is presented these data for recommendations.

Another risk the participants are subjected to is the risk of overdiagnosis and overtreatment. As previously mentioned, there is already ongoing widespread opportunistic PSA-testing in Sweden. Compared to the opportunistic PSA-testing, the difference for participants in the Göteborg-2 trial is that the PSA-testing will be performed in an organised fashion. The invited men will receive considerably more information to decide whether or not to proceed with a PSA-test than men undergoing PSA-testing in a non-organised way, when oftentimes no information is given at all or measured as part of an annual health check-up without the man's knowledge. The participants are also followed up and re-invited for further screening. Organised PSA-screening is more effective than opportunistic PSA-testing in reducing PCa mortality. However, as in all medical diagnostics and interventions, the benefit of a test or treatment can vary between individuals.

4 RESULTS

The findings of the papers in this thesis and the implications of these findings are summarized in **Table 6**. The detailed results for the studies are provided in the included papers.

Paper	Research questions	Findings	Meaning of the studies
I.	What is the detection rate of prostate MRI for index tumour at RP outside high volume centres? Does detection rate vary between MRI-readers?	Average index tumour detection rate for the readers was 73%. Average detection rate for aggressive tumours (GS≥4+3) was higher; 83%. Inter-observer agreement between pairs of readers were fair to moderate; Cohen's κ coefficient 0.31–0.58. Moderate agreement was seen for PI-RADS 4 and 5-lesions; Cohen's κ coefficient 0.49–0.54.	The moderate detection rate and the variability between readers in this study underscores that the detection rate depends on the MRI-reader. Knowledge about the MRI-units' detection rates is important in the management of patients evaluated with PSA and MRI.
II.	To provide a detailed description of the design and procedures of the Göteborg-2 trial. To what extent do men participate in different interventions in PCa-screening?	The study population was completely randomised in spring 2020. Participation rate in men randomised to the SG was 50%. Of the participating men with PSA elevation, 94% attended further screening intervention with prostate MRI. Attendance for participants who were further invited for screening intervention with TRUS biopsies was 85%. Opt-out rates was 2.2% in the CG and 1.0% in the SG.	The Göteborg-2 trial has progressed well regarding accrual and feasibility, with acceptable participation rates and opt-out rates. The upcoming results of the primary endpoint will provide information whether PSA-testing followed by MRI and targeted biopsy can shift the ratio of benefits-to-harms in PCa screening.
III.	Is it safe to omit systematic biopsy in PCa screening when combining PSA and prostate MRI?	Clinically significant PCa were found in 66/408 men, 16.2%. Of these cases, 15.2%, 10/ 66 men, were only caught by systematic biopsy (8 negative MRI and 2 benign targeted biopsies). Number needed to biopsy to find 1 clinically significant PCa among MR negative men: 31.	With experienced radiologists reading MRI, the vast majority of negative MRIs will result in benign findings on systematic biopsies. In sequential screening with PSA followed by MRI read by experienced radiologists, omitting systematic biopsies, in both negative and positive MRIs will not miss high grade tumours but delay diagnosis in GS 3+4 tumours. The risk of delaying diagnosis of these cancers to the next screening round is probably small hence motivating reducing the number of unnecessary biopsies by omitting systematic biopsies.
IV.	Are clinical variables together with MRI more accurate in determining clinically significant PCa at RP than clinical variables alone? Can an accurate model for distinguishing significant and insignificant PCa at the time of diagnosis be developed?	The AUC of the clinical model was 0.77–0.80. The predictive accuracy of the models with MRI information increased the AUC with approximately 0.03–0.06. The prediction model with clinical variables and PI-RADS from MRI could at an 80% threshold for of clinically significant PCa improve discrimination and be of clinical value. Overtreatment for some men could have been avoided using this model.	The addition of information from prostate MRI to clinical variables improves the prediction of clinically significant PCa. How to incorporate the information from MRI in the risk stratification of patients remains to be elucidated.

Table 6. Overview of the papers in this thesis. The findings of the papers and the implications of these findings are summarized.

5 DISCUSSION

This thesis investigates the role of prostate MRI in screening for PCa. The detection rate of PCa with MRI is a crucial issue when assessing this role. In the beginning of the prostate imaging-era, the studies reporting on MRI emphasized the importance of high-quality MRI-reports read by radiologists who are highly experienced in prostate MRI. The best possible quality is, of course, good to strive for. But, in parallel with technical developments and an increasing number of examinations, it became obvious that MRI could not only be performed and interpreted at a few centres of excellence, but high-quality imaging needed to be implemented in clinical routine and centres all over the world. The performance of MRI in detecting PCa varies substantially. In 2015, a systematic review evaluated the diagnostic accuracy of MRI in detecting clinically significant PCa in 12 studies from 2000 to 2014[169]. The studies showed a wide range in detection rate: 44% to 87%. The range for NPV (negative predictive value) was similarly broad: 63% to 98%. These studies indicate that pre-biopsy MRI improves the detection rate of PCa compared to systematic biopsy without preceding MRI. But the large variability in NPV long prevented a general recommendation on routine use of pre-biopsy MRI in biopsy-naïve patients[170]. It was not until 2019 that the EAU Guidelines recommended performing pre-biopsy MRI in both biopsy-naïve patients and previously biopsied patients with clinical suspicion of PCa[60]. Today, the Swedish National PCa guidelines and the AUA guidelines also endorse pre-biopsy MRI in men with indication for biopsy[21,61]. The reproducibility and consistency of prostate MRI in less experienced settings was, however, unclear.

Therefore, the performance of prostate MRI in routine care, outside high-volume clinics, was sought to be evaluated in **Paper I**. The findings demonstrated a moderate detection rate; 73% which yet was higher for aggressive tumours (GS ≥ 4+3); 83.1%. Moreover, a rather large variability was seen between readers. The MRIs in the study population were performed at 16 different hospitals between 2012 and 2014 with images acquired according to each unit's protocol. The review of images was performed based on the PI-RADSv1, scoring of each pulse sequence individually, and then a conversion was made to PIRADSv2 (after which each lesion was assigned a zone — PZ or TZ —by one of the reviewers). The heterogeneous MRI population and not using PI-RADSv2.1, which is the most updated version currently recommended, form minor limitations regarding generalising the results of **Paper I** into the clinical routine setting of today. The continuous improvements in MRI protocols rendering better image quality might argue

for better performance today, yet it is likely that this issue would not materially have influenced the result. As a matter of fact, the heterogeneous MRI population, in which in one third (31%) lacked DCE, might even be a strength when it comes to generalisability to clinical routine since many units nowadays perform MRI without DCE.

The level of experience of the reviewing radiologists in **Paper I** is comparable to that of many radiologists in everyday setting nowadays. Two of the reviewers were board-certified radiologists with previous experience of approximately 200 and 300 prostate MRI cases, respectively. They had both attended the ESUR (European Society of Urogenital Radiology) prostate MRI workshop prior to the study. The third reviewer, a resident in radiology with previous experience of approximately 50 cases, had a lower detection rate. It is known that expert readers have higher NPV. The literature displays better detection rates with increasing experience. For instance, a second reading, by a subspecialized uroradiologist with more than 1000 cases experience in reading prostate MRI, demonstrated higher NPV for GS $\geq$ 3+4 cancers compared to initial reports from local hospitals, NPV 89 % vs 72%[171]. Another study warranted internal validation of MRI upon finding substantial variation across radiologists with different amounts of experience reporting according to PI-RADS v.2[172]. A third study showed that after a moderate number of MRI cases scrutinized (approximately 40) the PCa detection rate reached a plateau[173].

The previously described landmark studies on diagnostic performance of prostate MRI have all been conducted in specialized centres. Whether their promising detection rates and high NPVs can be generalisable to all settings, and to safely omit biopsy when the MRI is negative, is debateable[59]. The PROMIS trial was conducted at multiple centres but by dedicated uroradiologists with previous experience in reading prostate MRI[55]. In the 4M-trial, images were first analysed by trained radiologists and then reviewed centrally before biopsy by two central radiologists (25 and 5 years of experience with prostate MRI, respectively)[57]. In the MRI-FIRST trial, participants were recruited at multiple centres (16 sites) and MRI was performed and reported at the local site without centralized reading before biopsy, though all radiologists were stated to have experience in prostate MRI (without further definition of experience)[58]. The PRECISION trial was deliberately designed to be generalisable, with multiple centres recruiting participants and MRI read by local radiologists. Indeed, the study population was recruited from 23 sites in 12 countries, which gives the trial geographical width[56]. However, the experience among the MRI-readers in the trial was a median of 5 years and a median 300 prostate MRI readings each year. There

is no universal agreement on what level of experience defines an expert reader, however, the experience of the readers in the PRECISION trial would be considered higher than that of readers in many everyday clinical routine care units.

Comparing **Paper I** with the PROMIS trial regarding the detection rate, shows 73% versus 93%[55]. (The other three landmark studies described above did not assess detection of PCa by MRI against a reference standard but instead compared PCa detected by different management strategies.) Differences in detection rates may also depend on differences between the populations studied, including for example the average age of the study population and prevalence of PCa. Nevertheless, the results from high-volume clinics do not correspond to the performance of prostate MRI in routine care outside these centres, and this limits the generalisability of the results. This does not, however, mean that the implementation of MRI in the diagnostic work-up should be limited to expert centres mainly due to the volume of MRI scans required. Nor does it mean that we should settle for moderate detection rates. It is important to know the detection rates of the reporting MRI units when managing patients evaluated with PSA and MRI, and despite the challenges it is clear that measures must be taken to improve and maintain high quality reports at every unit performing MRI. This can be done by rigorous training programs and continuous re-education of reporting radiologists. The interaction, discussion and continuous meetings between radiologists, urologists and pathologists aid in further improvements as well as in quality assurance. Regular feedback from biopsies and surgery to the reporting radiologist is essential in this regard.

An important issue to consider when comparing detection rates between studies is the definition used, whether it is detection of any PCa or clinically significant PCa (and how this is defined) as well as if the rate is reported per patient or per each tumour focus in the prostate. In **Paper I**, detection rate was calculated for the index tumour at RP specimen. There were 11 men whose index tumours were not identified by any of the readers. Since seven of these men had multifocal disease, and another significant tumour (GS ≥ 3+4) was correctly identified by all readers, one can argue that the per patient detection rate was actually higher than 73%. If the reported lesion had been correctly sampled at biopsy it would have led to the diagnosis of a GS ≥ 3+4 in those patients. Even though the *index tumour* was not described at MRI, those men would have been diagnosed with PCa.

This leads to another important aspect in the detection of PCa in a pathway including MRI: the performance of the urologist obtaining the MRI-targeted

biopsies. Quality assurance is crucial in all the steps of the diagnostic evaluation, not only MRI, but also biopsies and histopathological assessment. In the beginning of the prostate MRI-era a lot of attention was on the performance of the MRI-reader. But now, more and more focus is put on underlining the importance of the entire diagnostic chain, which includes PSA, MRI, TRUS biopsy and histopathology. The idiom "a chain is only as strong as its weakest link" has been used to illustrate this[174]. It becomes irrelevant if the MRI-report is excellent if the biopsies targeted towards suspected lesion are misplaced ("false false negative"). In other words, the biopsy procedure is also operator-dependent, regardless of which of the three methods (in-bore, fusion or cognitive) is used for targeted biopsies. Similarly, as for radiologists, a robust training programme for urologists is necessary. Biopsy sampling error did not constitute a bias in **Paper I**, since the RP specimens were available. As the RP specimen constitutes the "true" status (with a small caveat of a certain degree of inter-reader variability among pathologists), an evaluation of targeted biopsy sampling would have been interesting to assess. However, as the study population was a mix of men with prebiopsy and postbiopsy MRI, i.e., not all men had undergone targeted biopsies, this evaluation was not possible. This was also not possible to determine in **Paper III** since most of the population in this study had not undergone RP and hence lacked a solid reference standard. In **Paper IV** though, based on a study population with prebiopsy MRI, targeted biopsies and RP specimen, the performance of targeted biopsies could theoretically be assessed. This assessment has not been performed as it was not the specific aim of that paper. However, it could be an intriguing issue to explore in the future.

A well-designed RCT is crucial to be able to draw reliable conclusions in order to make recommendations concerning population-based screening. This is an ambitious endeavour that must include a collaborative research team whose members have expertise in their respective areas. Such a study is costly and takes time but is the only study design that can allow for providing level 1 evidence regarding the benefits and harms of a screening programme. The rationale behind **Paper II** was to describe the study design and assess the participation rate of the GÖTEBORG Prostate Cancer Screening 2 Trial (Göteborg-2 trial). The design and procedures of the trial have been extensively covered in Methods, chapter 3. As stated in that section, comparability between the control group and the screening group is important in order to obtain reliable results. The opt-out rates were 2.2% and 1.0% in the control group and the screening group, respectively. Although higher rate in the control group, the difference in opt-out rates is not anticipated to threaten the reliability of the results.

The participation rate at 50% is acceptable but lower than in the Göteborg randomised screening trial, in which 60% of men invited to the first screening round participated, and 76% of the invited men participated at least once during 14 years follow-up[128,175]. At the start of the Göteborg randomised screening trial in 1995, contamination, i.e., opportunistic PSA-testing, was not anywhere near what it is today. Nowadays, it is known that men test for PSA at a significantly higher degree[147]. A lower willingness to participate if a man already has checked his PSA is likely a factor that can explain the different participation rates. In **Paper II**, the participation rate was higher among 60-year-olds compared to 50-year-olds. With time, as the enrolled men are getting older and invited to subsequent screening rounds, the participation rate might increase. However, the lower participation rate of the Göteborg-2 trial as compared to the prior Göteborg randomised screening trial will not be an obstacle in the analysis, since the sample size is calculated at a participation rate of 50%. Of the participating men, the vast majority attended further screening interventions according to their study arm affiliation (MRI 94% and TRUS biopsies 85%). This is comparable to the attendance to TRUS biopsy in the first screening round in the Göteborg randomised screening trial, 93%[175]. Since there is no internationally accepted consensus on the definition of clinically significant PCa, four different definitions will be used in the analysis. In this way, the outcomes can also be assessed across a range of tumour aggressiveness.

The dilemma that makes screening for PCa controversial is how to balance benefits and harms. The risk of missing significant disease must be weighed against the risks of screening-related anxiety, biopsy morbidity, and overdiagnosis. Avoiding unnecessary biopsies has been suggested as a strategy to reduce harms in the diagnostic evaluation of PCa in asymptomatic men. To aid the decision about whether or not to proceed with biopsies in men with elevated PSA, the use of imaging or risk-calculators has been proposed[60]. **Paper III** evaluates whether it is feasible to omit systematic biopsies for men with negative MRI and only perform targeted biopsies for men with positive MRI in a screening programme. Of the screened men in this study, a minor proportion with clinically significant PCa was only detected at systematic biopsy, whereas the majority were detected by targeting the biopsies to MRI-visible suspicious lesions. In other words, few cases with clinically significant PCa would have remained undetected in a screening programme in which only MRI-targeted biopsies were performed. The majority of these cases had a negative MRI (PI-RADS 1-2) but there were also two cases with suspicious lesions described in another part of the prostate than the site of the clinically significant PCa focus. Using systematic biopsy as reference standard, as in this study, poses a limitation due to

sampling error, i.e., cancer missed at biopsy, as opposed to saturation biopsy (sampling the prostate with 20 cores or more), template prostate mapping biopsy (sampling the prostate with a core every 5 or 10mm) or prostatectomy specimens. This risk is, however, believed to be small in the current analysis, because only 2 of 56 targeted biopsies among men with positive MRI and clinically significant cancer were benign. However, as the radiologists in this study were experienced at reading MRIs and used consensus reporting, together with experienced urologists performing targeted biopsy, it is important to acknowledge that the safety of omitting systematic biopsy in case of negative MRIs or only perform MRI-targeted biopsies in positive MRIs, as is the result of **Paper III**, is not necessarily generalisable to all settings.

In comparison, our estimate of the "miss rate" of MRI-targeted biopsies is similar to that of other studies in the literature. A study correlating MRI findings with findings at prostatectomy specimen showed that 16% of clinically important lesions were missed by MRI[176]. Another study using prostatectomy specimen as reference standard, showed that omitting systematic biopsy led to missing 1.9% of GS 3+4=7 cancers and 5.8% of GS 4+3=7 cancers and increased the risk of upgrading after prostatectomy[177]. As described earlier, the pilot study embedded in the last screening round of the Göteborg randomised screening trial investigated sequential screening with PSA and MRI[151]. The diagnostic performance of MRI in terms of NPV and PPV were 84% and 48% respectively. Two recent systematic reviews and meta-analyses have been conducted on the performance of MRI. The first one by Moldovan et al found a large heterogeneity in the diagnostic performance of MRI, with NPV depending on the cancer prevalence and factors such as study design as well as definitions of positive MRI and clinically significant cancer[157]. Moreover, this systematic review found a median overall prevalence of PCa of 51% (IQR, 36–58%), clinically significant cancer of 33% (IQR 28–37%) and a median NPV for clinically significant cancer of 88% (IQR 86–92%) and decreasing NPV with increasing prevalence[157]. Comparing these results to the study population in **Paper III**, we found a lower prevalence of clinically significant PCa of 16% (95% CI 13–20%), which likely reflects the fact that the study population constitutes a screening cohort, and men of relatively younger age (median 59 years) as compared to prior studies of men being evaluated in clinical practice with indications for biopsy (for example elevated PSA, positive DRE or other indications). In the Göteborg-2 trial, the participants reported previous PSA-testing in 45%, but only 9% had undergone previous biopsy. The other systematic review of 42 studies comprising 7,321 men similarly demonstrated substantial heterogeneity in NPV between the

reported studies with a mean NPV among biopsy naïve men of 91% (95% CI 88–93%) with negative MRI defined as PI-RADS < 3 and clinically significant cancer defined as GS ≥7[59]. The importance of knowing one's own institutional performance data of MRI when deciding whether to omit systematic biopsies was emphasized by the authors. In our study, the rate of undetected clinically significant cancer was 3.4% if systematic biopsies were to be omitted in men with negative MRI in that biopsy round.

So, what is the answer to the question of whether or not to perform systematic biopsies in sequential screening with PSA and MRI? Reviewing the characteristics of the "missed" PCa shows that they were all GS 3+4=7 cancers and half of the cases are currently managed with AS. MRI as read by experienced radiologists will not miss high-grade tumours and this supports the omission of systematic biopsies in screening, in order to reduce unnecessary biopsies. To find 1 clinically significant PCa among MRI negative men, 31 men would have needed to undergo systematic biopsies. Avoiding systematic biopsies would have spared many men the anxiety of undergoing evaluation for the suspicion of PCa, the discomfort and risks of bleeding and infectious complications with prostate biopsy, and the risk of being diagnosed with clinically insignificant PCa.

The risk of delaying diagnosis of the undetected GS 3+4 tumours to subsequent screening rounds is probably small. Nonetheless, further prospective research is needed to elucidate the long-term effects of a dynamic screening programme with PSA and MRI followed by systematic +/- targeted biopsy, as the consequence of delaying diagnosis of GS 3+4 tumours to the next screening round has not yet been studied as the study is still ongoing. An analysis of first biopsy results in an ongoing study, as in **Paper III**, does not allow determination of the long-term consequences. Future evaluations of the Göteborg-2 trial will shed light on the role of repeated PSA screening and subsequent re-imaging and re-biopsy strategies among men with persistently elevated PSA and prior targeted biopsy only. Within the next years, the impact of a delayed diagnosis on potential disease progression, prognosis and whether functional outcomes after curative treatment are worse (for instance if it leads to a smaller chance for nerve-sparing surgery), can be explored.

PSAD is an important factor in deciding to proceed or avoid biopsies in diagnostic evaluation of PCa. Evaluating the addition of PSAD to the screening algorithm remains to be studied. A recent review on biopsy-naïve men showed that PSAD can provide further risk stratification when MRI is negative; risks of clinically significant PCa among MRI-negative men with PSAD < 0.10, 0.10–0.15 and 0.15–0.20 ng/mL/mL were 3%, 7% and 8%,

respectively[178]. As the prevalence of clinically significant PCa differs in different populations and this affects the NPV, the value of PSAD must be studied in a screening setting in order to draw conclusions and make recommendations for this setting. Finally, and as previously underscored, quality assurance of the performance variation in all parts of the screening algorithm (Radiology, Urology and Pathology) is essential before considering omission of systematic biopsies.

In the light of the above, it is relevant to reflect on the value of prostate MRI once PCa has been detected in screening. As PCa is a heterogenous disease with a varying natural course, the treatment recommendation is challenging. Customizing an optimal treatment strategy requires methods to accurately pinpoint which form of PCa the patient most likely has. This assessment is usually based on clinical variables; the PSA-level, DRE, TRUS and prostate biopsies. Several risk group classifications have been proposed to help predict prognosis and guide treatment decision[60,74,179,180]. However, there are considerable risks of misclassification[80,181]. Only a few studies have assessed MRI as an aid in treatment decisions in addition to clinical variables or existing risk stratification tools[90-94]. Therefore, the role of MRI in the treatment decision was sought to be investigated in **Paper IV**. The results show that the addition of information from prostate MRI to clinical variables improves the prediction of clinically significant PCa. Using either of the variables from MRI, lesion size or PI-RADS score, added value to the clinical variables. As the prostatectomy specimens were used as reference standard, we were, by design, not able to include and assess men clinically deemed suitable for AS or RT. Our study cohort thus included men with a high prevalence of clinically significant PCa selected for prostatectomy, which is likely to have affected the net benefit. Therefore, before our developed prediction model can be implemented in clinical practice, it needs to be validated in a larger sample of patients treated with RP as well as assessing predicted risk of significant cancer in a large sample of men on AS. Another limitation in **Paper IV** is that neither inter-reader variability in MRI-reports, nor the quality of the targeted biopsies were assessed.

The findings in **Paper IV** corroborate previous findings in the literature. A nomogram combining clinical, biopsy and MRI findings developed in a fairly large cohort of 1837 patients treated with RP, showed that an increased number of patients could have successfully be selected for AS when using the nomogram[90]. Another study developed a prediction model from a group of 614 men and showed improved discrimination for extracapsular extension and seminal vesicle invasion by adding MRI-data to clinical variables[91]. A

third study evaluated the same objective in a subgroup of men with favourable intermediate risk PCa and found that the addition of MRI-data to the model led to a higher net benefit[92]. All three studies lack external validation to date. Another two studies evaluating the benefit of adding MRI to existing stratification tools found better performance when updating the tools with MRI findings[93,94].

To reduce the number of men overtreated and needlessly suffering the consequences of treatment, correct risk classification of PCa is important. **Paper IV** and the above-mentioned studies show that prostate MRI appears beneficial in the initial decision process whether to recommend active treatment or further clinical investigation or AS. Precisely how the information from MRI is best utilized in the selection of patients for definite vis-à-vis deferred treatment or AS, and which MRI parameters to use, remains to be clarified.

6 CONCLUSIONS

The Göteborg-2 trial is a rigorously designed trial, which has the necessary resources and has shown acceptable participation rates. It should, within the next few years, be able to answer pertinent questions regarding the feasibility, harms and benefits of PCa screening, based on PSA and MRI.

In a multicentre setting mirroring clinical routine, MRI shows an acceptable but not perfect detection rate of clinically significant PCa.

In a more optimal setting such as in our randomised Göteborg-2 trial, the sensitivity for MRI in detecting clinically significant PCa is improved reflecting the importance of MRI technology and the MRI-reading.

Omitting systematic biopsies in sequential screening with PSA followed by MRI seems feasible in a setting with high quality-imaging and experienced readers.

Prebiopsy prostate MRI improves the risk stratification for men with PCa diagnosed. Precisely how the information from MRI is best utilized in the selection of patients for definite vis-à-vis deferred treatment remains to be clarified.

Taken together, the overall conclusion of this thesis is that PSA-testing and prostate MRI are the cornerstones in screening and early detection of PCa. Further research should focus on how to optimally select men for screening, how to determine who will need further work-up with MRI and how to appropriately select men for prostate biopsy.

7 FUTURE PERSPECTIVES

If the Göteborg-2 trial finds that sequential screening with PSA and MRI followed by targeted biopsies is superior in terms of the primary outcome, there will be a shift in the balance between harms and benefits in favour for the benefits. This will make it possible to implement a national population-based screening programme for PCa. Setting up such a programme is a complex project with many issues to consider and plan for. Luckily there are other screening programmes, for example for cervical cancer and breast cancer, and also the newly formed local programmes for organised PSA-testing, to learn from.

In a national population-based screening programme there needs to be clear robust recommendations regarding the screening algorithm and interventions. But one size does not fit all – not all men will fit one path in a screening programme. What about claustrophobic men or men with medical contraindications not suitable for MRI? What about men with strong family history of PCa? Is there room for individualized decision making and adjustments of the general path in a potential screening programme for PCa? Can we customize it and in what way? And how do men perceive the provided information regarding pros and cons of PCa screening? Can a screening programme reduce the effects of the present socio-economic disparities, for example that men with high income are less likely to receive a diagnosis of advanced PCa compared to men with lower income in Sweden[182]. These are questions to be assessed in the future.

As previously mentioned, quality assurance is very important in all parts of a potential screening programme. An established forum for exchange and feedback between the radiologist, urologist and pathologist should be present in all centres involved. Recurrent training and education are also a part of this.

Another matter in need of further investigation is the role of biomarkers alongside or in combination with imaging in a screening programme for PCa. A side study within the Göteborg-2 trial, the G2-biomarker study will investigate the diagnostic performance of prostate MRI in combination with 4K score test and the Stockholm3-test. Primarily this study will evaluate whether the specificity can be improved without reducing the sensitivity for PCa GS > 6 by adding these biomarkers before MRI compared to PSA-testing followed by MRI. The number of MRI and biopsies that could have been spared by adding these markers before MRI will also be investigated.

Head-to-head-comparison of these tests in sequence with MRI has not yet been reported and might further optimize screening for PCa. Adding these tests in sequential screening for PCa might not necessarily decrease costs but could aid in decreasing the number of MRI scans and ease the burden on the MRI units, both in obtaining as well as in interpreting the images. Ongoing Artificial Intelligence-projects are also aiming at investigating how to reduce the cost and time involved in scrutinizing the images.

As several germline single nucleotide polymorphisms (SNPs) have been associated with PCa risk, additional tailoring of screening could be achieved with gene profiling[183-185]. The results of the ongoing PROFILE study will hopefully bring clarity to the question whether men with family history of PCa can profit by combining SNP profiling with clinical variables in screening[186].

An issue not discussed in any of the papers in this thesis is the optimal re-screening intervals and the optimal age to start and to stop screening in sequential screening with PSA and MRI. In the coming years, with longer follow-up of the Göteborg-2 trial this matter can hopefully be specified. Hitherto, when it comes to PSA-screening, the age at which screening is terminated has shown to have an impact of being diagnosed with PCa[187]. However, a specific age at which the harms exceed benefits is not established, and flexible individual risk-stratification, based on age and general health, has been proposed to determine the appropriate age to stop[188,189]. Neither is there a strong consensus on the suitable age at which to start PSA screening, but hereditary factors should be considered in further investigation of this[190].

Irrespective of the result in Göteborg-2 trial regarding the balance between harms and benefit in PCa screening, the existing path for early diagnostics in PCa will continue to evolve within the foreseeable future. The MRI-era is still young and the role of MRI as a diagnostic aid in PCa will further be explored in the future. In step with technical advances, improvement in the performance and diagnostic accuracy of MRI is highly probable. Given the previous rapid updates of PI-RADS versions and the large amount of ongoing research on MRI, it seems likely to except a new version in the not-too-distant future. It will be interesting to see whether protocol recommendations regarding the sequences, mainly the value of DCE will change. Perhaps DCE will be excluded and only performed in selected cases? Further, a strategy that can eliminate artefacts rendered from, for instance, hip implants is desirable. Will there be a solution for claustrophobic patients? There have been reports on new scanners associated with less claustrophobic reactions,

and hence a higher degree of patient acceptability, both regarding those which are open and those with short cone shaped bores[44,191].

In 2019, one year before the present recommendation on prebiopsy MRI in Sweden, geographical differences regarding the use of MRI were reported[17]. Of the men diagnosed with PCa in 2019, 25% had had a prostate MRI in their diagnostic pathway. But considerable variation between the different parts of Sweden was seen; from 0% to 57% use of MRI in the detection of PCa. The results for 2020 are not yet available but it is likely that the complete implementation of MRI-based diagnostics in Sweden will take some time. The increased need for prostate MRI and the accelerating number of MRIs performed will also be a matter for future cost and cost-effectiveness-investigations.

The biopsy procedure will also evolve in the coming years. The necessity of the urologist to be familiar with MRI has already become clear. It is important to underline that a deeper understanding and up-to-date knowledge on imaging and targeted biopsies are necessary, regardless of the technique used to obtain targeted biopsies. Areas in need of further clarifications involve assessing the proper number of biopsy cores directed towards suspicious MRI-lesions, further assessments on targeting techniques (in-bore, fusion or cognitive) and approaches (transrectal or transperineal). In contrast to the often-detailed descriptions in the literature of the experience of the reader reporting prostate MRI, the experience of the urologist performing targeted biopsies is often less well described. When it comes to surgery, the variability of the surgeons has been more and more investigated regarding postoperative outcomes. The variability in biopsy results between different urologists taking targeted biopsies remains to be elucidated.

Moreover, besides using MRI as a screening tool or in early diagnostics, MRI have other areas of application in the management of PCa. When it comes to the performance of MRI regarding local tumour staging, i.e. detection of extraprostatic extension and seminal vesicle invasion and lymph node staging, a wide range is reported[192]. Using MRI in staging is currently not recommended in guidelines. An enhancement and less variability in the assessment of tumour extent and lymph node metastasis would aid treatment decision and planning, for example the appropriate degree of nerve-sparing during RP. MRI has opened an opportunity to investigate focal therapy, a treatment where small tumour foci are selectively ablated but the delicate structures around the prostate are spared. In this way, side-effects are proposed to be reduced. Naturally, this sounds desirable, but whether or not it is a safe and viable option when it comes to oncological outcome remains to

be clarified[193,194]. Overdiagnosis can be reduced but will unfortunately never be eradicated. MRI is already incorporated in the management of patients with low risk PCa on AS, but this role will be further studied and elucidated in the future. The result from the Prostate Cancer Active Surveillance Trigger trial/the Scandinavian Prostate Cancer Group-17 trial (PCASTt/SPCG-17-trial) will answer some questions regarding this[195]. This multicentre study started in 2016 and will evaluate the safety of an MRI-based AS protocol, with standardised triggers for repeated biopsies and radical treatment compared to current practice.

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APPENDIX

1) Letter of information to men in the control group.
2) Letter of invitation to men in the screening group.

Datum
20XX-XX-XX

GÖTEBORGS UNIVERSITET

SAHLGRENSKA AKADEMIN

Personnummer	Studienummer	Namn
19 xxxxxx-xxxx	xxxx	Adress
		Postnr Postort

Göteborg 2-studien
Information om studie gällande prostatacancer

Hej!

Vi har startat en stor studie om förekomst av sjukdom i prostatan hos män i åldern 50-60 år. Syftet med studien är att hitta en effektiv metod för tidig diagnostik av prostatacancer. I studien undersöks en slumpmässigt utvald grupp män med en speciell metod. För att utvärdera om metoden är bra och lämplig att införa i en större del av befolkningen, jämförs denna undersökningsgrupp med en annan slumpmässigt utvald grupp män i motsvarande ålder som inte undersöks inom ramen för studien. Du ingår i denna jämförelsegrupp på 20 000 män. Denna grupp ska återspegla hur det ser ut i befolkningen idag bland män i din ålder.

Då du ingår i en jämförelsegrupp, kommer vi inte att bjuda in dig för några kontroller eller undersökningar. Det krävs ingen aktiv åtgärd från dig.

Vad innebär det att vara med i en jämförelsegrupp?

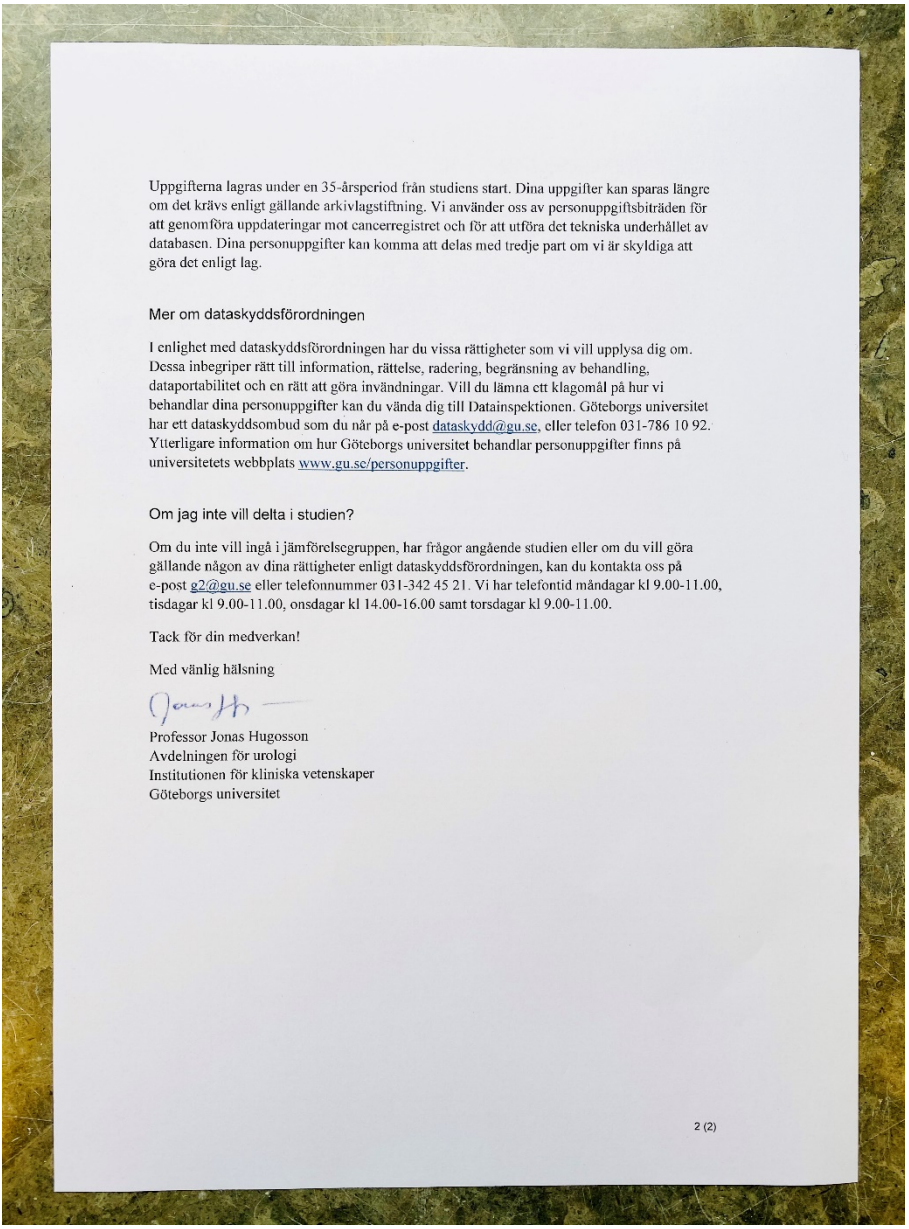
Det innebär att ditt personnummer kommer att användas för att samköra med olika register. Syftet med denna samkörning är att undersöka förekomst av prostatacancer och det generella hälsoläget hos män i din ålder. De register som vi inhämtar uppgifter från är folkbokföringsregistret, cancerregistret, vårdregistret och dödsorsaksregistret. Samkörningarna kommer att genomföras under de kommande 35 åren. Ditt personnummer kommer enbart att användas vid dessa samkörningar. Det krävs inga aktiva åtgärder från dig och vi kommer inte att kontakta dig mer än via detta brev.

Hur behandlas dina personuppgifter?

Det är för att genomföra forskningsstudien och tillhörande sidostudier som vi behöver behandla dina personuppgifter. Vi kan även komma att behandla känsliga personuppgifter om din hälsa. Behandlingen utförs med stöd av den rättsliga grunden allmänt intresse. Forskningsstudien har granskats och godkänts av Etikprövningsnämnden i Göteborg, numera Etikprövningsmyndigheten. Det är Göteborgs universitet som är personuppgiftsansvarig för den behandling av personuppgifter som sker för studiens räkning. Dina personuppgifter behandlas i enlighet med dataskyddsförordningen.

Hur förvaras och delas uppgifterna?

De personuppgifter som vi samlar in lagras och bearbetas i en databas på Göteborgs universitets server. Alla data kommer att kodas och inga personuppgifter kommer att avslöjas.



Uppgifterna lagras under en 35-årsperiod från studiens start. Dina uppgifter kan sparas längre om det krävs enligt gällande arkivlagstiftning. Vi använder oss av personuppgiftsbiträden för att genomföra uppdateringar mot cancerregistret och för att utföra det tekniska underhållet av databasen. Dina personuppgifter kan komma att delas med tredje part om vi är skyldiga att göra det enligt lag.

Mer om dataskyddsförordningen

I enlighet med dataskyddsförordningen har du vissa rättigheter som vi vill upplysa dig om. Dessa inbegriper rätt till information, rättelse, radering, begränsning av behandling, dataportabilitet och en rätt att göra invändningar. Vill du lämna ett klagomål på hur vi behandlar dina personuppgifter kan du vända dig till Datainspektionen. Göteborgs universitet har ett dataskyddsombud som du når på e-post dataskydd@gu.se, eller telefon 031-786 10 92. Ytterligare information om hur Göteborgs universitet behandlar personuppgifter finns på universitetets webbplats www.gu.se/personuppgifter.

Om jag inte vill delta i studien?

Om du inte vill ingå i jämförelsegruppen, har frågor angående studien eller om du vill göra gällande någon av dina rättigheter enligt dataskyddsförordningen, kan du kontakta oss på e-post g2@gu.se eller telefonnummer 031-342 45 21. Vi har telefontid måndagar kl 9.00-11.00, tisdagar kl 9.00-11.00, onsdagar kl 14.00-16.00 samt torsdagar kl 9.00-11.00.

Tack för din medverkan!

Med vänlig hälsning

Professor Jonas Hugosson
Avdelningen för urologi
Institutionen för kliniska vetenskaper
Göteborgs universitet

2 (2)

Datum
20XX-XX-XX

GÖTEBORGS UNIVERSITET

SAHLGRENSKA AKADEMIN

Personnummer
19 xxxxxx-xxxx

Studienummer
xxxx

Namn
Adress
Postnr Postort

Hej!

Du har blivit slumpmässigt utvald att delta i en screeningstudie gällande prostatacancer.

Se bifogad broschyr med information om studien. Om du önskar delta, följ anvisningarna på separat blad. Har du frågor är du välkommen att kontakta oss, se kontaktuppgifter på sista sidan i broschyren.

Vi ser fram emot ditt deltagande!

Bästa hälsningar

Professor Jonas Hugosson

Avdelningen för urologi
Institutionen för kliniska vetenskaper
Göteborgs universitet

DENNA TILLFRÅGAN ÄR GILTIGT TILL OCH MED 20xx-xx-xx

Observera att detta blad, med nedanstående etikett, ska tas med vid provtagning

Användarnamn och lösenord till enkät

Användarnamn:
Lösenord:

Etikett till provtagningsenheten