Prostate Biopsy

Cancer detection and risk of complications

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ABSTRACT

The overall aim of this thesis was to investigate if a sampling protocol with anterior biopsies of prostate increase cancer detection at first repeat biopsy, to evaluate if a clinical routine with urine culture prior to transrectal prostate biopsy influences risk for post-biopsy infection and to identify risk factors for infection after transrectal prostate biopsy.

A prostate biopsy is a common invasive procedure in urology. Every prostate biopsy, no matter the route, carries a risk for complication and is an uncomfortable procedure for the patient. It is therefore important that every procedure has a high precision for detecting significant prostate cancer and is carried out with knowledge of how to minimize procedural morbidity.

Paper I reports a randomised trial for sampling of the anterior prostate with end-fire technique at first repeat transrectal prostate biopsy to increase detection rate of prostate cancer. It included 344 men from 2010 to 2018 in Region Kronoberg. The sampling with anterior biopsies using end-fire technique did not significantly increase cancer detection at first repeat biopsy. In 2014, as part of an antimicrobial stewardship program, our region initiated a routine with a urine culture prior to prostate biopsy. **Paper II** reports a register-based evaluation of this clinical routine with a historical control group. We concluded that the routine with urine culture prior to prostate biopsy did not reduce the rate of post-biopsy infection. In **Paper III**, a regional register study was designed to identify risk factors for infection after transrectal prostate biopsy. Diabetes and a previous urinary tract infection were confirmed as risk factors, but also potentially new risk factors such as a previous treatment with non-UTI antibiotics and symptoms from lower urinary tract. Risk factors associated with infection in **Paper III** were then used in **Paper IV**. A nationwide register study to investigate the cumulative effect of risk factors for infection after transrectal prostate biopsy also including immunosuppressive treatment, systemic corticosteroids and treatment for overactive bladder as factors.

The cumulative risk for infection after transrectal prostate biopsy increased from 4 % if none to 12 % if three risk factors were present.

Keywords: prostate biopsy, infection, transrectal, risk factor, prostate cancer, cumulative risk

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SAMMANFATTNING PÅ SVENSKA

Prostatacancer är den vanligaste cancerformen i Sverige och leder till döden hos 1 av 20 svenska män. Med införandet av PSA-prov och mer effektiva behandlingar har dödligheten i prostatacancer minskat betydligt. Sjukdomen var tidigare diagnostiserad sent i förloppet och då utom bot.

Diagnostiken idag syftar till att hitta rätt cancer, hos rätt man, alltså en behandlingskrävande cancer som leder till lidande och död hos en man som kan botas för sjukdomen. Överdiagnostik och överbehandling drabbar många män även idag och de utreds i onödan med oro och lidande som följd. Att utreda prostatacancer med biopsi (vävnadsprovtagning från prostatakörteln) har i många år varit en vanlig invasiv åtgärd inom urologi och alla invasiva åtgärder har risker. Därför behöver varje biopsi vara motiverad, ha goda förutsättningar att hitta en cancer som kan ha betydelse och vara minimalt riskabel för varje patient som utreds.

Denna avhandling handlar om den tidiga utredningen av prostatacancer. Det första delarbetet planerades under en tid då systematiska biopsier utfördes på grund av klinisk misstanke om prostatacancer, antingen med ett avvikande fynd när man känner på prostatakörteln eller ett stegrat PSA-värde. Om misstanke fanns utfördes vävnadsprover (biopsi) ultraljudslett via ändtarmen med 10-12 systematiska biopsier. Om misstanke om prostatacancer kvarstod efter en omgång utfördes ytterligare biopsier (re-biopsi), då utan möjlighet till föregående bilddiagnostik som idag är standard. Side-fire teknik var den mer utbredda i klinisk vardag och kanalen för biopsinålen utgår från ultraljudsstaven i vinkel (bild senare i arbetet) medan biopsierna med end-fire teknik går från toppen av staven, vilket möjliggör att lättare nå de främre delarna av prostatakörteln. Efter att en observationsstudie visat att biopsier med end-fire teknik kan öka detektionen av cancer designade och planerade vi första arbetet. **Studie I** designades 2010 som en randomiserad studie där vi jämförde två olika sätt att ta biopsier från prostatakörteln hos män som tidigare hade genomgått en omgång biopsier utan fynd av prostatacancer: standardmetoden med 12 vävnadsprov från bakre delarna och en experimentell metod med 6 vävnadsprov från de bakre delarna plus 6 från den främre delen av körteln. Studien hade som mål att inkludera 360 patienter men stängde efter inkluderade 344 på grund av införande av magnetkameraundersökning i det

nationella vårdprogrammet för prostatacancer. Vi fann inget stöd för att tillägg med end-fire biopsi vid första re-biopsi ökar cancerdetektion men det verkar öka risken för komplikation efter biopsi något.

I Region Kronoberg infördes under 2014 en rutin med urinodling inför transrektal prostatabiopsi. Syftet med rutinen var dels att minska användning av bredspektrumantibiotika som förebyggande behandling vid biopsi, dels en möjlig minskning av risk för infektion efter biopsi om vi identifierade män med icke symptomgivande bakterier i urinen. I **studie II** utvärderades rutinen med urinodling inför transrektal prostatabiopsi. Studien utformades som en observationsstudie med nästan 6000 biopsitillfällen hos över 4000 män under åren 2010-2019. Under perioden med urinodling som rutin identifierades 2971 biopsitillfällen, som jämfördes med 2818 biopsitillfällen i samma region under 2010-2014 då urinodling inte utfördes rutinmässigt inför biopsi. En infektion efter biopsi definierades som en förskrivning av antibiotika mot urinvägsinfektion i öppenvård eller slutenvård 1-10 dagar efter biopsi eller att ha vårdats på sjukhus för urinvägsinfektion 0-10 dagar efter biopsi. Under perioden med urinodling registrerades 5,0% infektion inom 10 dagar efter biopsi och under perioden utan odling 4,3%. Resultatet talar för att en rutin med urinodling inför transrektal prostatabiopsi inte minskar risken för infektionskomplikation.

Att drabbas av en infektion efter prostatabiopsi är den vanligaste svåra komplikationen. Identifiering av riskfaktorer för infektion kan leda till att biopsier kan utföras med mindre risker för patienten. I Region Kronoberg har vi ett sammanhållet datajournalsystem med möjlighet att samla utdata och med tillgång till en mikrobiologisk databas med mycket hög täckningsgrad i regionen. Vi designade en studie för att analysera riskfaktorer för infektion efter transrektal prostatabiopsi. I **studie III** användes samma biopsitillfällen som i **studie II** från Region Kronoberg men uppföljningstiden utökades till 30 dagar efter biopsitillfälle. Resultatet visade att diabetes mellitus och att ha haft en tidigare urinvägsinfektion nästan dubblerar risken för att drabbas av infektion som komplikation och de var också starkast associerade med ökad risk för inneliggande vård för infektion efter biopsi. Att ha fått någon förskrivning av antibiotika eller symtom av godartad prostataförstoring ökade också risken för infektion.

PCBaSe Sverige är en databas för prostatacancerforskning, inkluderande data från nationella prostatacancerregistret och flera andra nationella register. I PCBaSe finns för varje man med prostatacancer data från fem män som inte har prostatacancer från samma region och i samma ålder som en jämförande population. I **studie IV** användes PCBaSe 5.0 med insamlade data fram till 2020 för att analysera de identifierade riskfaktorerna i **studie III** samt tillägg av immunosupprimerande behandling, kortison, prostatastorlek, och behandling för överaktiv blåsa för att undersöka hur den sammanvägda effekten av flera riskfaktorer påverkar risken for infektionskomplikation efter transrektal prostatabiopsi.

Resultatet visar att risken ökar gradvis från 4%, utan någon riskfaktor, till 6% med en, 8% med två, till 12% om tre riskfaktorer finns samtidigt. I **studie IV** verifierades diabetes, tidigare urinvägsinfektion och identifierade immunosupprimerande behandling samt symtom från nedre urinvägar som riskfaktorer. Resultatet från **studie IV** talar för att symtom från nedre urinvägar är associerat med infektion efter biopsi och inte själva läkemedelsbehandlingen eller en förstorad prostatakörtel i sig.

LIST OF PAPERS

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

I. **Örtegren J**, Holmberg JT, Lekås E, Mana S, Mårtensson S, Richthoff J, Sundqvist P, Kjölhede H, Bratt O & Liedberg F.

A randomised trial comparing two protocols for transrectal prostate repeat biopsy: 6 lateral posterior plus 6 anterior cores versus standard posterior 12-core biopsy.

Scand J of Urol 2019; 53(4): 217-221.

II. **Örtegren J,** Wimmerstedt A, Åberg D, Janson H, Kjölhede H, Kahlmeter G & Bratt O.

The clinical value of a routine urine culture prior to transrectal prostate biopsy.

Euro Urol Open Sci; 2023 (48): 54-59.

III. **Örtegren J,** Elvstam O, Kohestani K, Åberg D, Janson H Kjölhede H, Kahlmeter G & Bratt O.

Risk factors for post-biopsy infection after transrectal prostate biopsy - a population-based register study.

Euro Urol Open Sci; 2024 (67): 1-6.

IV. **Örtegren J,** Elvstam O, Kohestani K, Styrke J, Stattin P, Kjölhede H & Bratt O.

The cumulative effect of risk factors for infection after transrectal prostate biopsy - a nationwide population-based study.

Manuscript.

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CONTENT

ABBREVIATIONS

AS	Active Surveillance
ATC	Anatomical Therapeutical Classification System
AUA	American Urological Association
BPE	Benign Prostatic Enlargement
CCI	Charlson Comorbidity Index
CI	Confidence Interval
DRE	Digital Rectal Exam
EAU	European Association of Urology
EMR	Electronic Medical Records
FQ	Fluoroquinolones
IQR	Interquartile Range
ISUP	International Society of Urological Pathology
LUTS	Lower Urinary Tract Symptoms
MRI	Magnetic Resonance Imaging
NPCR	National Prostate Cancer Register of Sweden
OAB	Overactive Bladder
PIRADS	Prostate Imaging Reporting and Data System
PSA	Prostate-specific Antigen
PSAD	Prostate-specific Antigen Density

RCT	Randomised Controlled Trial
STROBE	Strengthening the Reporting in Observational Studies in Epidemiology
TNM	Tumour Node Metastasis
TRUS	Transrectal Ultrasound
UTI	Urinary Tract Infection

DEFINITIONS IN SHORT

Charlson Comorbity Index	A prediction tool for mortality based on the concomitant diseases of a patient.
EMR	Electronic medical record. The digital version of the medical record for patients.
Epidemiology	The knowledge and study about what cause, and reasons are for health and disease in a defined population. Developing knowledge of how to prevent and control disease or disorder in a population.
INCA	A platform for information networks on cancer care in Sweden (Informationsnätverk för Cancervården)
Observational study	Study design where participants are observed, or outcomes measured without intervention from study design.
PCBaSe Sweden	A database for clinical epidemiological prostate cancer research that includes data from the National Prostate Cancer Register of Sweden and other nationwide registers.
Randomised controlled trial	A study design where participants are randomly assigned to a specified intervention without the possibility to choose or affect to assignment.
Radical prostatectomy	Surgical removal of prostate gland and seminal vesicles.

STROBE	Strengthening the Reporting in Observational Studies in Epidemiology is an international collaborative association aiming at clarifying the conduct of and dissemination of observational studies

1 INTRODUCTION

One reason for the interest and motivation for carrying out scientific studies is that the scientific field of investigating prostate cancer is dynamic and rapidly moving. Prostate cancer is a common malignant disease, and the investigation of prostate cancer is a common procedure affecting many individuals. This thesis moves from the primary investigation with transrectal prostate biopsies in the era before magnetic resonance imaging (MRI) to focus on post-biopsy infections and risk factors affecting patients.

The purpose of this thesis was to investigate i) if adding end-fire biopsies at first repeat biopsy increases rate of cancer detection, ii) if a pre-biopsy urine culture reduces the risk for post-biopsy infection and iii) risk factors for infection after transrectal prostate biopsy.

1.1 THE PROSTATE

The prostate is a gland found in most male mammals. To understand where the prostate is situated and its purpose, explains how investigating and treating prostate cancer affect men.

The word originates from Greek “prostates” which literally means one who stands before, or protector, guardian. An explanation likely related to its position below the bladder.

Since when first mentioned in literature to today, the interest in the gland for medical, practical and for emotional purposes. The prostate gland is about the size of a walnut or a ping-pong ball in its normal state (Figure 1). How can a small gland below the urinary bladder, around the urethra cause so much bother?

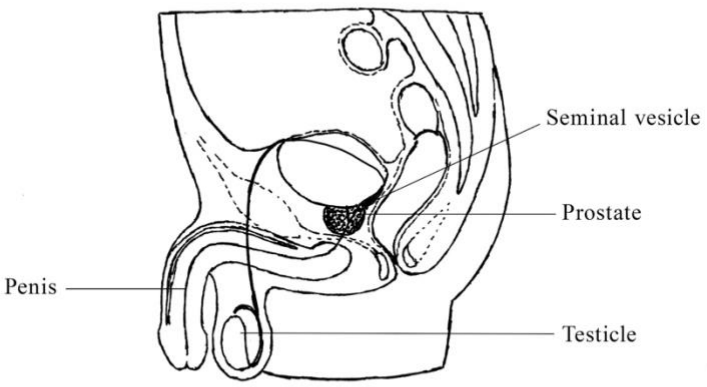

Figure 1. Sagittal view of lower abdomen and male pelvis with anatomical markings.

The prostate is made of glandular and fibromuscular tissue, surrounded by a thin connective tissue. The prostate is divided into different zones (Figure 2), each zone with slightly different histological features, as shown in the late 1960´s by McNeal (1). The primary function of the prostate is in reproduction to produce prostatic fluid containing prostate specific antigen (PSA), which contributes to semen and helps transport and protect sperm. During ejaculation, the prostate squeezes this fluid into the urethra where it combines with sperm cells from testicles to form semen. PSA regulates the seminal viscosity and decreases it to facilitate the migration of semen to the cervix and promoting fertility (2).

The two most frequently occurring diseases in the prostate often arise in different zones (Figure 2): prostate cancer in the peripheral zone and benign prostatic enlargement in the transition zone (3). In a normal sized prostate the peripheral zone is three times larger than transition zone, but cancer originates seven times more often in the peripheral zone (4). Besides originating from the same gland and both histological and hormonal similarities there is no clear connection between prostate cancer and benign prostatic enlargement (BPE) even if they both arise in the same organ and become more common with age (5).

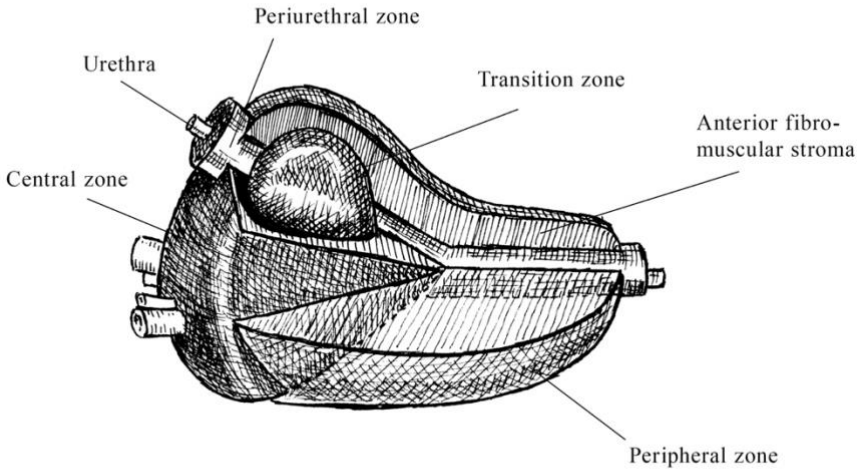

Figure 2. Prostate gland with zonal division and anatomical markings.

1.2 PROSTATE CANCER

The word “cancer” is often associated with negative and worrying feelings. Cancer arises in our own cells because of damage to the genetic material. The origin of the word cancer can be traced back to Hippocrates description of

tissue looking like “carcinos” the Greek word for crab. A tumour as the crab’s body with growths spreading like its legs.

In the middle of the 19th century, one of the first to describe prostate cancer was John Adams (6) and it was then described as a rare disease and detected in a late stage. The main reasons for the increase in incidence of prostate cancer cases worldwide is the increase in life span but also increased diagnostic activity, particularly testing for serum prostate specific antigen (PSA) with subsequent systematic prostate biopsy since the early 1990s.

The first suspicion of prostate cancer today is usually an elevated PSA-level or a suspected finding at digital rectal exam.

1.2.1 EPIDEMIOLOGY

Prostate cancer is a global health concern with over 1.4 million new cases diagnosed worldwide, the fourth most common cancer and almost 400,000 deaths in 2022 (7). In Sweden more than 12,000 new cases was diagnosed in 2022 (8) and 1 out of 20 Swedish men die from prostate cancer every year. This is a disease that affect many men, and diagnostics should be carried out with vigilance to minimize morbidity to many men (9).

Between 1995 and 2022 the incidence of discovered prostate cancer in Sweden more than tripled (10). In Figure 3, the age-standardized incidence and mortality of prostate cancer in Sweden is visualised. The increase in incidence at the turn of the century was mainly because of increased PSA-testing and systematic biopsies. The age-standardised mortality from prostate cancer has decreased since the beginning of the 21st century, but the number of men dying of prostate cancer is stable around 2,400 men every year due to an aging population.

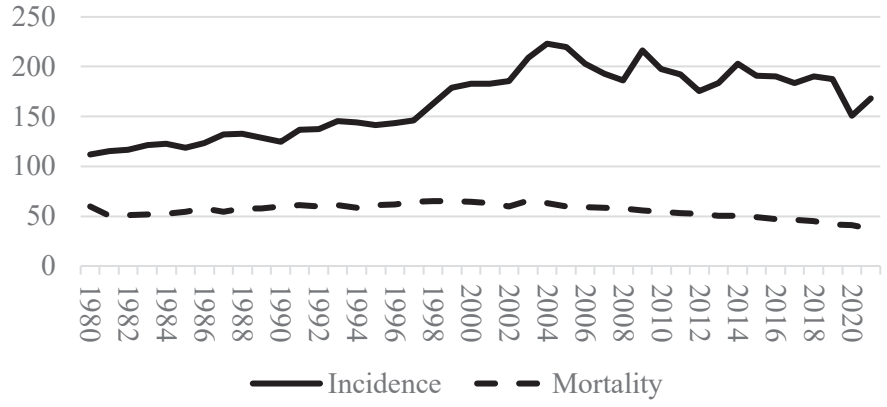

Figure 3. Age-standardized incidence (black line) and mortality (dashed line) of prostate cancer per 100 000 men in Sweden 1980-2022 (10).

1.2.2 CLASSIFICATION OF PROSTATE CANCER

Classification of the extent of prostate cancer at diagnosis and during treatment is used for guiding patients and clinicians to treatment options, prognosis and equalising care to similar clinical outcome. A prognostic measurement provides information about the likely course of a disease, such as recurrence or progression, regardless of the treatment received. It is an indicator of the natural history of the patient's condition and helps to estimate the patient's overall prognosis.

On the other hand, a predictive measurement is specifically related to the effect of a particular therapeutic intervention. It indicates whether a patient is likely to benefit from a specific treatment, thus guiding therapeutic decisions.

1.2.2.1 STAGE

The Union for International Cancer Control (UICC) 8th Edition: the Tumour-Node-Metastasis (TNM) classification is international standard and shares structure with all cancers but adapts to specific cancers (11). T-stage is based on clinical examination of the prostate, N-stage and M-stage are based on radiological examinations (Table 1). It is still notable in the progressive field of imaging, that clinical staging is mainly through DRE of the prostate, and

extra-prostatic extension on MRI may still be categorized as cT1 and added information from MRI is reported separately.

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 defined 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 Tumour Extracapsular extension (unilateral or bilateral)
	T3b Tumour invades seminal vesicles
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: externa 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 nodes metastasis

M	Distant metastasis
M0	No distant metastasis
M1	Distant metastasis
	M1a None-regional lymph node(s)
	M1b Bone(s)
	M1c Other site(s)

Table 1 Tumour Node Metastasis (TNM) classification system for Prostate Cancer (8th edition, 2017).

1.2.2.2 GRADE

The appearance of prostate cancer under the microscope is graded in a system named after the American pathologist Donald Gleason, who originally described it in 1966 (12). The grading then ranged from one to five depending on the cancer cells' growth pattern. Prostate cancer is in many cases heterogenous and the score is a strong predictor for long-time prognosis (13). In the early grading system, the most common and second most common patterns were combined on a total score from two to ten, named the Gleason score (Figure 4). Pattern five has the most aggressive and poorly differentiated pattern, and a great proportion of Gleason pattern five in needle biopsies is associated with poor prognosis (14). In 2005 the International Society of Urological Pathology (ISUP) Consensus Conference a modified Gleason score with a recommendation that Gleason grade 1 and 2 were limited to rarely, if ever, be diagnosed at biopsy (15).

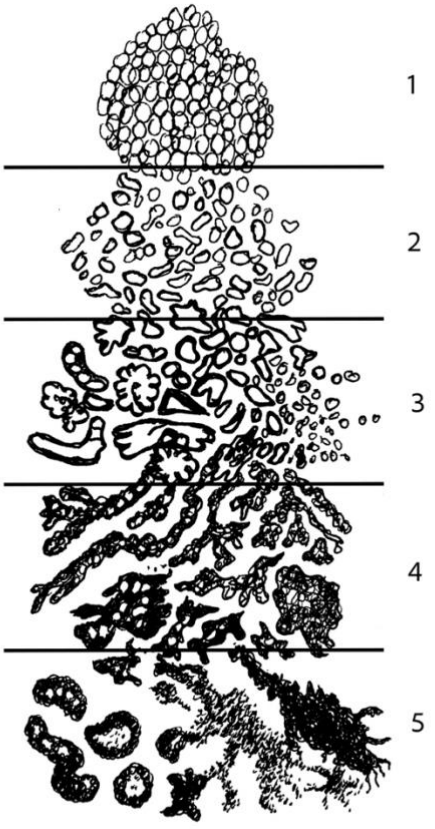

Figure 4 Gleason grading after original description by Donald Gleason. Grading 1-5 with worsening prognosis with increasing number (13).

The Gleason grading system has since been validated and revised in the most recent ISUP consensus conferences and since 2014 a 5 graded scale was introduced: Gleason Grade Groups (ISUP) 1-5 to distinguish Gleason score 3+3 (low risk prostate cancer) to ISUP 1 and the difficult group Gleason score 7 (Gleason score 3+4 = ISUP 2 and Gleason score 4+3 = ISUP 3) where prognosis differ (16, 17) see Table 2.

Table 2 ISUP grade compared to Gleason score for prostate cancer.

ISUP grade	Gleason score
1	3+3
2	3+4
3	4+3
4	8
5	9-10

1.2.2.3 RISK GROUPS

Since the natural course of prostate cancer ranges from slow growing tumours to aggressive life-threatening tumours, and primary metastatic diseases, the discrimination between risk groups for treatment decisions is important. In 1998 D'Amico et al. classified risk for biochemical recurrence in non-metastatic prostate cancer as low, medium or high based on Gleason score, T-stage and PSA-level prior to treatment (18) and it is still widely used.

In Swedish national guidelines the division into risk groups is based on D'Amico classification, Cambridge Prognostic Groups (19), American Urological Association and American Society of Radiation Oncology (AUA/ASTRO) (20) and modified based on data for Swedish men with prostate cancer in National Prostate Cancer Register (NPCR) (21).

Risk group evaluations are the foundation for decision making if further investigation is indicated and treatment discussion.

1.2.3 TREATMENT OF PROSTATE CANCER

Many men diagnosed with prostate cancer will never have severe symptoms or shortened life expectancy related to the diagnosis. The first important decision is often whether to treat or to merely follow the disease with the option of deferred treatment, either with the intention to cure (active surveillance) or with hormonal treatment without any curative intention (watchful waiting).

1.2.3.1 LOCALISED DISEASE

Watchful waiting is recommended for older men with a life expectancy of less than 10-15 years and low to intermediate risk prostate cancer. All curative treatment options have potential side-effects (22, 23) and men with low risk of

progression or death, benefit from conservative management. Long term follow-up of patients starting with watchful waiting have shown up to 80-95% cancer specific survival at ten years (24) and cancer specific survival at 15 years of 80% and at 20 years of 57% (25).

Active surveillance is the primary option for men diagnosed with a low risk prostate cancer who have a long life expectancy (26). During active surveillance follow-up with PSA, MRI and clinical examinations is keystone and curative treatment if the cancer progresses to significant disease. In the ProtecT-study, active surveillance without repeat biopsies or imaging was as effective as active treatment with either radical prostatectomy or radiotherapy at 15 years. Incidence of local progression, metastasis and long-term androgen deprivation therapy were all reduced by radical treatments, but there was no difference in mortality at 15 years (27). A long-term follow up of an active surveillance protocol showed over 99% cancer specific survival and less than 2% had metastatic disease (28). Active surveillance of men with low-risk and intermediate prostate cancer is currently studied in a randomised trial in Scandinavia (29).

The first radical prostatectomy was performed 1867 through a perineal incision by surgeon Theodor Billroth (30). In Sweden, 3,348 radical prostatectomies was performed in 2023 (21), of which 99% were robotically assisted. A radical prostatectomy removes the entire prostate gland and the seminal vesicles recreating continuity of the bladder outlet with a vesico-urethral anastomosis. The major side effects after surgery include urinary incontinence and erectile dysfunction.

Radiotherapy has been a treatment for prostate cancer in Sweden since the 1960's. Nowadays around 50% of men undergoing curative treatment receive radiotherapy. Side effects after radiotherapy include bowel and bladder toxicities (31) and a small increase in secondary malignancies in adjacent organs (32). For locally advanced disease a current prospective evaluation comparing surgery to radiotherapy with hormonal treatment is ongoing in SPCG-15 (33).

An alternative to treating the whole gland is to use focal therapy, i.e., treating only the part of the prostate where the cancer is situated. This treatment option gives fewer side-effects on surrounding organs: urinary bladder, intestines and nerves. Focal therapy causes anatomically limited cell death, and there are several techniques available to achieve this. In Sweden a randomised trial

comparing irreversible electroporation (IRE) to robot-assisted radical prostatectomy and external radiotherapy is ongoing (34). Focal therapy is promising for the future treatment of prostate cancer but to date, limited to recommendations in study protocols.

During treatment discussion with patients, cancer characteristics, symptoms related to the pelvic organs, potential side-effects, expectations from patient and life expectancy are all weighed up to individualise treatment. Using a clinical tool for prognostication and for treatment decision may facilitate the discussion and decision both for patient and clinicians (35, 36).

1.2.3.2 METASTATIC DISEASE

If prostate cancer has spread to other parts of the body, curative treatment is no longer possible. Metastatic disease may cause the first symptoms of prostate cancer but may also develop after failed treatment with curative intent. In this stage of the disease, the corner stone treatment aims to reduce the testosterone available to cancer cells, and in 2015 the addition of cytostatic regimen was shown to prolong survival of men with primary metastatic hormonal sensitive prostate cancer (37).

The hormonal treatment of prostate cancer was described by Charles B. Huggins in 1941 (38). He received the Nobel Prize in Medicine in 1966 for the discovery that removal of testosterone through castration counteracts disease progression (39). Castration may be achieved surgically by bilateral orchidectomy or pharmacologically by female sex hormone estrogen. In 1984 Herbst et. al showed that GnRH-analogues had equal effect on cancer treatment but with fewer side-effects than estrogen treatment (40). In the past 15 years there has been a dramatic progress in treatment options in metastatic prostate cancer, both in primary assessment and in late disease, which has led to median survival going from 2-3 years to 4-6 years for metastatic prostate cancer (41).

1.3 DIAGNOSING PROSTATE CANCER

Historically, prostate cancer was found due to symptoms from locally advanced or metastatic disease: urinary symptoms, pain from the pelvic floor or from bone metastasis, anaemia or renal failure, and cure was out of reach.

Today, prostate cancer has good prognosis in the majority of cases and multiple treatment options even in late stages of disease.

At the early stage it can be difficult to discriminate between a malignant disease and a benign reason for an elevated PSA. The diagnostic pathway is initiated due to an elevated PSA-level or abnormal digital rectal examination, but today imaging technique MRI plays an important role as do biomarkers in focusing on methods to decrease the over-diagnosing of prostate cancer.

Not all prostate cancer needs to be found, and it may be difficult to define what a significant cancer is.

Clinicians and patients together need to consider the patient's individual gain of investigating a suspected prostate cancer, where co-morbidities, age, therapeutic consequences and life-expectancy also should be considered.

1.3.1 DIGITAL RECTAL EXAMINATION

A digital rectal examination (DRE) still has a role in diagnosing prostate cancer and other abnormalities. At the exam, consistency, shape, size, and palpable abnormalities are examined. A DRE is usually performed prior to ultrasound to rule out obstruction in the anal canal or rectum and to add information in the primary investigation (42). The examination can only evaluate the posterior part of the prostate, but abnormalities together with a raised PSA-level may indicate an increased risk for prostate cancer and should be further investigated (43). In a screening population of young men (45 years old at invite) DRE had a low positive predictive value as a screening tool for detecting prostate cancer (44).

1.3.2 BIOMARKERS

A biomarker may be considered predictive if it can identify patients who will respond favourably to a certain treatment.

To accurately determine whether a biomarker or clinical factor is predictive, it is essential to have a control group. This allows for the evaluation of the interaction between the treatment benefit and the biomarker or clinical factor. Without a control group, it is not possible to discern whether the observed effect is due to the treatment or other variables.

There are several biomarkers available in the early decision making and investigation of prostate cancer.

Prostate-specific antigen (PSA)

Epithelial cells of the prostate produce prostate-specific antigen (PSA), a glycoprotein and a tissue kallikrein (45) almost exclusively found in the prostate and seminal fluid. Only small amounts of the protein leak into blood where it is detected as a factor for diseases in the prostate gland. PSA was first described in literature in 1979 by Wang et. al (46). It was introduced as a potential marker for prostate cancer (47) and since the 1987 landmark article by Stamey et. al. where they showed that serum levels of PSA correlate with cancer progression when used as a diagnostic test for prostate cancer (48). The PSA concentration in the blood can be elevated in the presence of prostate cancer, although other conditions can also raise PSA level. The use of PSA-density (PSAD), PSA-value divided with prostate volume, may guide whether to do a biopsy or not. A PSAD above 0.1-0.15 is predictive of prostate cancer (49) and a low PSAD may indicate a low risk for prostate cancer and avoid unnecessary biopsies (50).

Table 3 PSA-cut off at different ages for investigation with diagnostic steps according to Swedish National Guidelines.

Age, years	PSA-level (ng/ml)
<70	≥ 3
70-80	≥ 5
>80	≥ 7

A PSA-test has a high specificity for abnormality in the prostate gland, but it cannot identify what kind of problem reside in the prostate. Different causes may produce an elevated PSA-level: urinary tract infection, benign prostatic enlargement, prostate cancer, acute urinary retention, and trauma

(catheterisation, instrumentation). Table 3 shows age dependent cut-off levels of PSA for further investigation for a suspicious prostate cancer according to National Swedish Guidelines (51).

Other blood-based biomarkers have shown higher specificity than PSA alone for clinically significant prostate cancer and reduce the number of unnecessary biopsies, but there is still no clear recommendation in the Swedish guidelines on their use.

Stockholm3

Stockholm3 is a biomarker developed in Stockholm, Sweden. It constitutes a combination of clinical information about the patient, protein-analyses including PSA and a genetic score (52). Stockholm3 has been studied in combination with MRI and leads to similar detection of significant prostate cancer with fewer MRI exams and biopsy procedures (53).

4K Score

The 4K Score includes free PSA, intact PSA, total PSA and human kallikrein 2 (hK2), together with information about age, DRE and prior biopsy. It reduces biopsies by 30 % but risks missing around 10% of high risk cancers (54).

Prostate Health Index

Prostate Health Index (PHI) is a model including total PSA, fPSA (free PSA) and isoforms of fPSA (55) and has, like other biomarkers, shown the potential to reduce unnecessary biopsies in men with moderately raised PSA-levels (56). There is no direct comparison between Stockholm3 and PHI, but it may have potential to also reduce the number of MRI exams and biopsies and improve detection of significant prostate cancer (57).

1.3.3 ULTRASOUND

Visualisation of the prostate gland is usually done via rectum but is possible via perineum in men without rectum, and transabdominal, for measuring prostate volume, but the transabdominal route has been shown to misjudge prostate size by around 10 ml (58). Medical ultrasound as a diagnostic tool was partly developed in Sweden by Edler and Hertz (59) in cardiology and

gynaecology neurology and then spread to other medical fields. Being able to evaluate ultrasound live images has aided everyday work in urology, even though guiding biopsies against hypoechoic lesions on ultrasound have limited value (60). Even though the transrectal ultrasound (TRUS) has low sensitivity and specificity for detecting prostate cancer (61), it is important for capturing images of the prostate and its zonal distribution, measuring prostate size, and guiding needle biopsies when sampling prostate tissue. TRUS guided biopsies under local anaesthesia is the standard method for diagnosing prostate cancer. A novel high-frequency micro-ultrasound (MicroUS) with comparable cancer detection rate to MRI is currently evaluated in an RCT, either as alone modality or in combination with MRI (62, 63), and is maybe a new way to make ultrasound once more the finger extension of the urologist.

1.3.4 MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) has since its introduction in late 1980s proved useful in diagnostic medicine. The discovery of the physical phenomenon that atomic nuclei can be affected by electromagnetic waves was first described by Edward Purcell (64) and Felix Bloch (65) in 1946 and earned the Nobel Prize in Physics in 1952. The discoveries and development of magnetic resonance imaging for producing images was rewarded the 2003 Nobel Prize in Physiology or Medicine to Paul C. Lauterbur and Sir Peter Mansfield (66-68). The prostate MRI is assessed by a radiologist and reported on according to the Prostate Imaging-Reporting and Data System (PIRADS v 2.1) (69).

In 2017 the PROMIS trial showed that using MRI can reduce diagnosis of clinically insignificant cancer and increase detection of significant cancer in men with PSA up to 15 ng/ml (70). The PRECISION trial confirmed that MRI with target biopsies was superior to systematic biopsies for diagnosing prostate cancer (71). The use of MRI in investigation of prostate cancer has led to fewer men with raised PSA going through a biopsy and being diagnosed with clinically insignificant prostate cancer (53).

2 PROSTATE BIOPSY

Today, a prostate biopsy is recommended if a suspicious lesion at MRI, a raised PSA or DRE, suggest the possibility of prostate cancer. The early pioneers on biopsies from the prostate with the technique described by Martin and Ellis (72) and perineal approach were Barringer and Ferguson in 1930 where they retrieved histological confirmation of prostate cancer in 17.5% (73, 74). The first to describe a transrectal prostate biopsy was Astraldi in a published paper from 1937 (75) .

In 1989, the transrectal ultrasound-guided sextant biopsy regimen proved superior to targeted biopsies from suspicious findings at DRE or hypoechoic lesions at TRUS and was therefore for many years recommended (76). A protocol with 10-12 cores (77) outperformed the old sextant and was until recently standard. Prior to the paradigm shift with MRI, biopsy protocols were performed in a non-targeting mode, aiming at covering the prostate with each biopsy procedure and not to miss any prostate cancer (78, 79). This made transrectal prostate biopsy a very common procedure. In 2009, a retrospective study from Cleveland indicated an increased detection rate of prostate cancer when using end-fire biopsy technique compared to standard side-fire (80). This result inspired to study probe configuration for increasing cancer detection.

The transrectal route has been standard of care for a long time (81). In European Guidelines from 2021 transperineal was deemed equal to transrectal regarding both cancer detection and complications (82), but from 2022 European Guidelines recommend transperineal as first choice for prostate biopsy (83). The AUA Guidelines deem the two routes “of choice” for the urologist (84). The two guidelines resulted in different recommendations based on the same evidence, and the switch or exit from transrectal to transperineal was preceded by an emotionally charged academic debate (85), where TREXIT, a paraphrase for Brexit, Great Britain’s exiting the European Union, was in the centre (86).

Prior to any prostate biopsy a ultrasound guided peri-prostatic anaesthesia is recommended using 10 ml of local anaesthetic (87) in transrectal route and up to 30 ml if using periprostatic bloc in transperineal route.

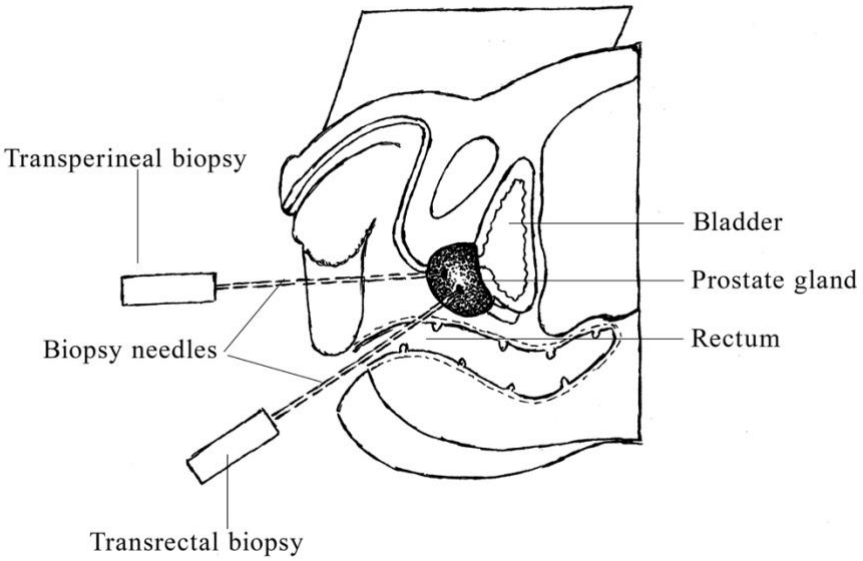

Figure 5. Description of biopsy routes: transrectal and transperineal with needle markings and topographic anatomy.

The tissue samples collected during the biopsy are sent to a laboratory, where a pathologist examines them under a microscope to determine if cancer cells are present and, if so, assess how aggressive the cancer is. The classification according to Gleason score is crucial for determining the appropriate recommendation for treatment discussion. No matter what the route (Figure 5), the biopsy procedure implies complications, often self-limiting, such as bleeding and pain, but also serious complications requiring admittance to secondary care (9, 88). Although serious complications are rare, since a biopsy procedure is a common procedure they cause significant morbidity to patients and cost for health care (89).

In the past years a dramatic shift towards transperineal route for prostate biopsy has taken place, due to the lesser risk for post biopsy infection, but it is also an academic trend (86). The first well designed randomised trials comparing transrectal and transperineal showed similar rates of post-biopsy infections

after transrectal with antibiotic prophylaxis and transperineal without antibiotic prophylaxis (88, 90). In the study by Hu et. al a secondary outcome was similar cancer detection in the two groups. In a systematic review of transperineal biopsy under local anesthesia it was judged comparable to a transrectal biopsy with similar cancer detection but lower risk for infectious complications, even though the study designs limit the conclusions (91). The transperineal route is a bit more technically challenging than the transrectal approach, more time consuming and demands financial investments (92).

2.1 TRANSRECTAL PROSTATE BIOPSY - COMPLICATIONS AND RISKS

A complication may affect the outcome or development of a new disease related to intervention or treatment. All medical investigations with invasive methods have the same basic risk for unfavourable result: pain, infection and bleeding as the most commonly described complications. In surgical procedures the Clavien-Dindo classification of surgical complications is recommended in European Guidelines for urologic interventions (83) for the standardized and reproducible outcome assessment (93).When investigating prostate cancer, clinicians and patients should be well informed of the risk for complication (9, 94) after procedure. This is related to both the risk for overdiagnosis or unnecessary findings, and to the risk of procedural complications. In the context of prostate cancer management, risk stratification tools are employed to predict outcomes and tailor individual care. These tools function as mathematical equations that incorporate multiple patient-specific factors to estimate the likelihood of future clinical events within a defined timeframe.

2.1.1.1 BLEEDING

Bleeding is the most common complication after prostate biopsy and the number of biopsies affect this risk (95, 96). Bleeding after prostate biopsy is reported from urine (haematuria), from rectum (haematochezia) and in sperm (haematospermia). Haematuria after transrectal prostate biopsy ranges from 10 - 80% (97, 98). Haematospermia and rectal bleeding is reported in the same range, around 5-78% (99). Bleeding is in most cases self-limiting but can last for 2-4 weeks and in some cases need intervention.

2.1.1.2 PAIN

To go through a 10-12 core transrectal prostate biopsy is reported to be associated with procedural pain in 47 % of patients (99). Anorectal compliance, prostate volume, number of cores taken and younger age are predictors for pain at transrectal prostate biopsy (9). Local anaesthetics is recommended prior to transrectal prostate biopsy.

2.1.1.3 INFECTION

During the beginning of 21st century concerns regarding microbiological resistance (100) and increasing rate of post-biopsy infection (101) led to greater awareness of the risk of infection after transrectal prostate biopsy. The rate of post-biopsy infection varies in studies and is hard to compare due to study design and regional differences but is reported to be around 3-10% (102-104). The infection ranges from mild forms with urinary tract infection to severe infections and in rare cases death (105). In 2013 Loeb et. al estimated that more than 1 million prostate biopsies are done yearly respectively in USA and Europe (9), stressing that post-biopsy infections is a major concern in health care and for the affected men. When describing the cost of infectious complications, an estimated cost of €8031 per hospitalization due to post-biopsy infection was reported from a Swedish study (106) and approximately €11500 in a study in a US setting (107).

2.1.1.4 PROPHYLACTIC MEASURES TO REDUCE INFECTION

There are prophylactic measures to decrease risk for post-biopsy infection after transrectal prostate biopsy. The EAU Urological Infections Guidelines Panel published two papers on evidence for antibiotic (108) and non-antibiotic measures for prevention of post-biopsy infections (109) and Pilatz et. al published practical recommendations based on this evidence in 2021 (110). Areas to focus on, in decreasing infectious complications after transrectal prostate biopsy, is to do the biopsy on the right patient, avoiding unnecessary biopsies, consider optimal route, use prophylactic antibiotics according to regional guidelines, povidone-iodine cleansing prior to biopsy and identifying risk individuals for infectious complication. The recommended routine with peri-prostatic nerve block does not increase risk for post-biopsy infection (109).

Unspecific antibiotic prophylaxis

Prophylactic antibiotics are usually given at the time of the biopsy to minimize the risk of infection. There are randomised trials showing superiority of prophylactic antibiotics to minimise infections after biopsy (111-113), and a Cochrane review showed that antibiotic prophylaxis reduces the rate of hospitalisation as well as post-biopsy infections (114). Even though the prophylactic antibiotic use is reducing infection rate, the prescription affects microbial resistance, and the adherence to guidelines is a significant part in antimicrobial stewardship programmes (115). Antimicrobial stewardship aims at optimising clinical outcomes and ensure cost-effective therapy whilst minimising unintended consequences of antimicrobial use such as healthcare associated infections. During the period patients were included in the studies in this thesis, a single oral dose of 750 mg ciprofloxacin was broadly used (116) and was in 2022 still recommended in national guidelines (117).

Targeted antibiotic prophylaxis

A meta-analysis by Roberts et. al from 2015 supported the use of targeted prophylaxis instead of fluoroquinolone monotherapy (118), but a more recent systematic review failed to support a recommendation for targeted antibiotic prophylaxis (119). To target antibiotic prophylaxis on fecal culture or a rectal swab may be a viable option. One prospective study reported a significantly lower risk for post-biopsy infection with targeted prophylaxis when compared to a single dose ciprofloxacin 500 mg (120) but the microbial resistance in that population was 56%. The use of a rectal swab with subsequent bacterial culture for prebiopsy screening may, in areas with high prevalence of microbial resistance, still be useful but need further prospective studies.

Povidone-Iodine cleansing

A meta-analysis of 34 RCTs showed that rectal cleansing with povidone-iodine significantly lowered infections after biopsy after transrectal prostate biopsy (121). A subsequent prospective investigation of routine with povidone rectal cleansing showed decreased rate of infection after transrectal prostate biopsy (122).

The European guidelines recommend the following prophylactic actions on prostate biopsies: transperineal approach, surgical disinfection of perineal skin when performing transperineal biopsy, and rectal cleansing with povidone-iodine prior to transrectal prostate biopsy. are all strong recommendations. The use of either target prophylaxis on rectal swab or augmented prophylaxis with two or more different antibiotic classes are graded as a weak recommendation (83). The use of fluoroquinolone as prophylaxis is since 2019 suspended after a regulation by European Commission (123).

2.1.2 RISK FACTORS FOR POST-BIOPSY INFECTION

A risk factor is an environmental exposure or an individual characteristic that is associated with the subsequent occurrence of a health-related condition. A risk factor may be unknown at the time of event. Risk factors for the two most common biopsy routes differ in some but are alike in others. To initiate preventive measures, risk factors need to be known and accurately identified.

Neither the definition of a post-biopsy infection, nor how long after the biopsy it may occur, is well defined, making comparisons a bit difficult. Factors that have been associated with post-biopsy infection but not related to the actual procedure include:

Positive urine culture

All patients with a urinary catheter, nephrostomy or other foreign material are at risk of infection and should be evaluated for prophylactic measures prior to biopsy. In recommendations for urological procedures and primary health care, a routine with screening with urine culture in asymptomatic men is recommended if risk of damage to barriers in order to minimise the risk for post-procedural infection (124). In a retrospective study a positive urine culture was not associated with infection (125). All pathogenic bacteria have virulence factors enabling invasion of a host, cause a disease and affect host defense against infection. To acquire virulence factors in bacteria, Mobile Genetic Elements is one described mechanism. Why some men have asymptomatic bacteriuria and others develop urinary tract infection is not completely known but virulence factors are often needed for symptoms to develop. Mobile Genetic Elements were investigated in a study to clarify the relationship

between asymptomatic and symptomatic disease for *E.coli* in the urinary tract, and to understand the development of virulence, but Mobile Genetic Elements can only partly explain virulence (126). In areas with high microbial resistance, a urine culture may still play a role in guiding targeted antibiotic prophylaxis prior to prostate biopsy.

Urinary Tract Infection

A urinary tract infection (UTI) may lead to persistent bacteria in both the urine and the prostate and is consistently associated with post-biopsy infection. In a systematic review UTI was judged a risk factor for infection (127), and in an observational study, a previous UTI increased risk for post-biopsy infection (128).

Microbial resistance

In Sweden, an increase in fluoroquinolone resistance was identified and described as early as in 1991 (129). The large intestine is the natural habitat for *E. coli* and bacteria do not cause disease under normal circumstances. A prostate biopsy perforates the natural boundary between the rectum and the urinary tract and exposes the immune system to bacteria from the rectum. *E.coli* is the main agent in the majority of infections both in the urinary tract and after prostate biopsy (130). In material from Australia, ST131 was the most common subtype in severe infections after prostate biopsy (131) and related to resistance (132). One of the main vectors for maintaining resistance and how resistance is transferred is by plasmids on *E.coli (133).* A plasmid is a small extrachromosomal DNA-molecule that may replicate by itself and may carry resistance (134).

Antibiotic prophylaxis reduces the risk for infection, but antibiotic treatment prior to biopsy is associated with subsequent post-biopsy infection (135, 136). A major causal relation for developing resistance to fluoroquinolones is previous treatment (137) and travels to areas with high microbial resistance, in a retrospective study from Sweden with a low prevalence in population of fluoroquinolone resistance in rectal samples of 6%, treatment with ciprofloxacin within 6 months prior to biopsy did not increase resistance in fecal flora or increase risk for post-biopsy infection, but travel outside of Europe the last 12 months (138) was an associated risk factor for carrying

microbial resistance for fluoroquinolone. Long-time treatment with fluoroquinolone increases the risk of developing resistance and risk for complications (139), but a short antibiotic treatment may also lead to antibiotic resistance. Carriers of fluoroquinolone resistant *E.coli* in rectum have an increased risk for both infection and sepsis after transrectal prostate biopsy (135, 140). Over time, both resistance to fluoroquinolones and infectious complications have increased (141, 142).

Immunosuppression

Immunosuppressive treatments are commonly used for inhibiting or preventing activity in the immune system. Immunosuppressive treatments are generally non-selective, affecting the immunologic response by reducing the activation of immune cells and lowering the inflammatory response required to eliminate pathogens and therefore causes an increased risk for infections (143). Glucocorticoids are thought to increase susceptibility to infections due to genomic regulation, affecting immune cell survival and inflammatory cytokines (144). There is probably a dependency of risk related to dose, treatment duration, other simultaneous immunosuppressive therapies, and host specific factors affect the risk. The authors of a recent review article recommend preventive measures for glucocorticoid treated patients (143). Immunosuppressive treatment was in a previous Swedish study not associated with either antibiotic prescription or admission to hospital after transrectal prostate biopsy (104).

Diabetes

The pathophysiological mechanisms behind the increased risk of infections for people with diabetes are not entirely understood (145). It could be related to the metabolic disturbances, co-morbidities with diabetes or the altered immune response seen in diabetics. If compared to a age-matched control, diabetics have significantly higher rates of infection, especially bacterial infections such as cystitis or pyelonephritis (146). Diabetes mellitus is well known to increase risk for urinary tract infection, mainly from older studies where patients likely had, compared to today, less medically managed blood sugar-control. In relation to prostate biopsy, diabetes has consistently been associated with increased risk for post-biopsy infection (127).

Benign prostatic enlargement

Benign prostatic enlargement (BPE) is the term for the benign growth of the prostate gland and benign prostatic hyperplasia (BPH) is the term for the histologic pattern of prostate growth, and both definitions are used in included studies. A benign prostatic enlargement of more than 40 cm^3 was found in a screening setting associated with post-biopsy infection, on both univariate and multivariate analysis (147). In a multicentre clinical setting, as part of the Global Prevalence Study of Infections in Urology, no association between prostate size and risk for infection was found (103).

Previous antibiotic treatment

Antibiotic treatment is a heterogenous risk factor, and how different antibiotic exposures affect risk is not well studied. An earlier antibiotic exposure has previously been associated with a post-biopsy infection (148) and also previous exposure to fluoroquinolone, both increasing risk of post-biopsy infection (137) as development of microbial resistance. A clear division between antibiotic exposures may be important for discriminating different exposures as potential risks. In one study, only 27% of the men with fluoroquinolone resistant *E.coli* and subsequent post-biopsy infection had previous treatment with fluoroquinolones, (149), and in a study from Denmark, a narrow spectrum antibiotic treatment increased risk for infection after biopsy (135) indicating that other antibiotic exposures may also be of importance.

Previous prostate biopsy

Men under active surveillance for prostate cancer may go through several biopsies. In a study in an active surveillance setting, repeated biopsies increased the risk for post-biopsy infection (OR 1.33; 95% CI 1.01-1.74) (150) but in a retrospective study without active surveillance protocol, repeat prostate biopsy was not associated with infection (135).

Comorbidities

Having multiple diseases is previously described as a risk factor (104). Impaired renal function, cardiopulmonary dysfunction, valvular heart disease, and overweight are systemic diseases and should be identified by the treating urologist prior to a biopsy decision. Another model for describing

comorbidities is the Charlson Comorbidity Index (CCI), in which concurrent conditions sums up to a total score predicting mortality (151). Comorbidity measured in CCI has previously been described as a risk factor in a Swedish register study (104). In CCI, diabetes is one of the included diseases, and in relation to post-biopsy infection the association may also relate to diabetes mellitus as the CCI for the association with infection. Also chronic obstructive pulmonary disease has previously been described as risk factor for infection after biopsy (127) and this is also included in CCI and related immunological exposures that may affect and partly explain the association to post-biopsy infection (152).

2.1.3 COMPLICATIONS OF TRANSPERINEAL PROSTATE BIOPSY

Until some years ago, a transperineal prostate biopsy usually involved multiple skin perforations under general anaesthesia using transrectal probe. In recent years, transperineal prostate biopsy under local anaesthesia is in widespread clinical use in some countries, including Sweden.

In a systematic review from 2016, Bennet and co-authors state that given the practical advantages of transrectal route, the transperineal route should be reserved for those with increased risk of sepsis or pre-dominantly anterior tumours (153). A more recent systematic review came to the conclusion that transperineal prostate biopsy decreases the risk for fever and rectal bleeding, but increase risk for procedural pain significantly (154). A comprehensive analysis of complications within 30 days in a multicentre study from Germany showed 3.6% post-biopsy infections, 1.5% any bleeding complication, 2.0 % acute urinary retention, but surprisingly 14.4% patients reported erectile dysfunction after biopsy (155). No prophylactic antibiotic was used.

In a randomised, open-label non-inferiority study on the role of procedural antibiotics when performing transperineal prostate biopsy, the results concluded that risk for serious infection is low with the transperineal biopsy route, and there was no statistically significant difference of post-biopsy infection with antibiotic prior to prostate biopsy and without (156), and this was also supported in a systematic review of transperineal prostate biopsy with and without antibiotic prophylaxis (157). There is limited knowledge of risk factors for infectious complications after transperineal prostate biopsy.

2.2 WHAT DID WE START WITH

Diagnosing prostate cancer is a highly dynamic field from both the scientific and a practical point of view. The wide-spread increase in PSA-testing and increase of active surveillance follow-up in managing prostate cancer led to an increase in prostate biopsies until the introduction of MRI.

Paper I was planned and designed in the pre-MRI era, when transrectal prostate biopsy with side-fire technique was the primary investigation, often with the ambition to detect all cancer, and repeat biopsies were common. At the time, the number of biopsy cores and the optimal way to cover the entire prostate, including its anterior parts, were challenging parts of everyday urology. A retrospective study on detection rates comparing side-fire and end-fire set the scene for a prospective trial.

Paper II and III were planned as regional studies and focused on the potential benefit of a routine with urine culture prior to prostate biopsy and based on current variables to collect data on risk factors for infection after transrectal prostate biopsy. Individualized medical judgements should play a role in contemporary clinical practice, and a well-planned intervention carried out by a well-prepared clinician ensures a safe procedure and hopefully include a well-informed patient. Some of the risk factors when investigating prostate cancer are well described and established, whereas others are less well-defined resulting in contradictory findings, some of which these studies aim to investigate in these papers.

In **Paper IV,** previous described risk factors are investigated in a large national population-based study making it possible to further clarify relevant risk factors and calculating the cumulative effect of multiple risk factors for a post-biopsy infection.

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3 AIMS

This doctoral thesis consists of 4 papers with the following main aims:

I: To test the hypothesis that a combination of 6 posterior and 6 anterior cores increase cancer detection compared to 12 posterior cores at a transrectal prostate biopsy in men who have had one previous benign systematic biopsy.

II: To investigate if a clinical routine with urine culture prior to transrectal prostate biopsy led to fewer post-biopsy infections.

III: To identify risk factors for a post-biopsy infection after transrectal prostate biopsy.

IV: To investigate the cumulative effect of several risk factors for the risk of an infection after transrectal prostate biopsy and explore previously suggested risk factors.

4 PATIENTS AND METHODS

Paper I-III were based on men in urological care in Region Kronoberg, a region with two urological units at the hospitals in Växjö and Ljungby, and one primary care centre (Gränsbygdskliniken) that offers urological consultation. **Paper IV** used PCBaSe, a database for epidemiological research, with data from the NPCR and linkage to other nationwide registers.

4.1 STUDY POPULATIONS

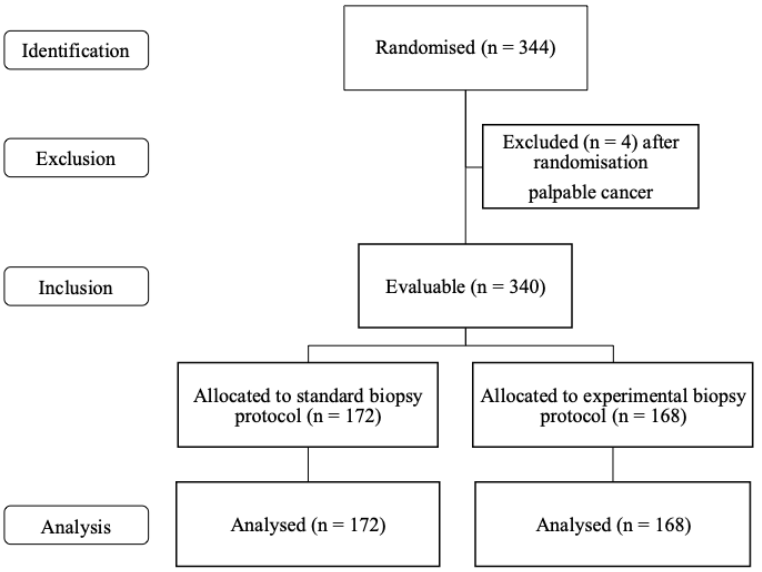
Paper I

The study participants in **Paper I** were included from December 2010 to study close in February 2018. The study included men scheduled for a repeat prostate biopsy at any of the two urology outpatient departments in Region Kronoberg. The inclusion criteria were one previous set of benign transrectal biopsies with a side-fire probe, a clinical indication for a repeat biopsy.

The exclusion criteria were a palpable tumour with clinical stage ≥ T2b, previously diagnosed prostate cancer, and more than one previous set of prostate biopsies. An informed consent was signed by all participants (*See Appendix*). Consort flow chart for **Paper I** in Figure 6.

In a study by Andriole et. al a cancer detection rate of around 15% at first repeat biopsy was found (158) and a clinically relevant increase was decided at 27% for adding anterior biopsies with the end-fire technique. To detect this specified difference between groups with a power of 80% and two-sided alfa of 0.05, we needed 180 participants in each group, and we planned for inclusion of 360 men.

Figure 6. Consolidating Standards of Reporting Trials (CONSORT) flow chart for study population in paper I.



Paper II and Paper III

All outpatient transrectal prostate biopsy procedures with procedure code TKE00 or KEB00 in Region Kronoberg from 1 January 2010 to 31 December 2019 were included in study II and III, flow chart in Figure 7 for **Paper II** and figure 8 for **Paper III**.

As part of a regional work with antibiotic prophylaxis, a routine urine culture was collected prior to transrectal prostate biopsy from January 2015. The study reported in **Paper II** investigated rate of infection after biopsy, in the observational, population-based study design we used a previous period in the same region as historical control. The study period for biopsy procedures was 1January 2015 and 31 December 2019. The control period was 1 January 2010 and 31 December 2014, when a urine culture was obtained only on a clinical suspicion of infection or bacteriuria.

Paper III was designed as a register study of risk factors for infection after transrectal prostate biopsy. Potential risk factors for a post-biopsy infection were investigated in 5,788 biopsy procedures done 2010-2019. The years 2010 to 2014 (n=2,817) with no routine urine culture prior to biopsy were used for a sensitivity analysis for emulating health care where a urine culture is not routine.

Exclusion criteria in both **Paper II and Paper III** were biopsy procedure during inpatient care, and urine culture from catheter, nephropyelostomy, or urostomy, as patients with any of these factors are at high risk of having antibiotic resistant bacteria and typically receive preventive measures also in the absence of a positive urine culture. In **Paper III** one more biopsy procedure was excluded due to biopsy during inpatient care identified at journal control of a post-biopsy infection missing antibiotic prescription.

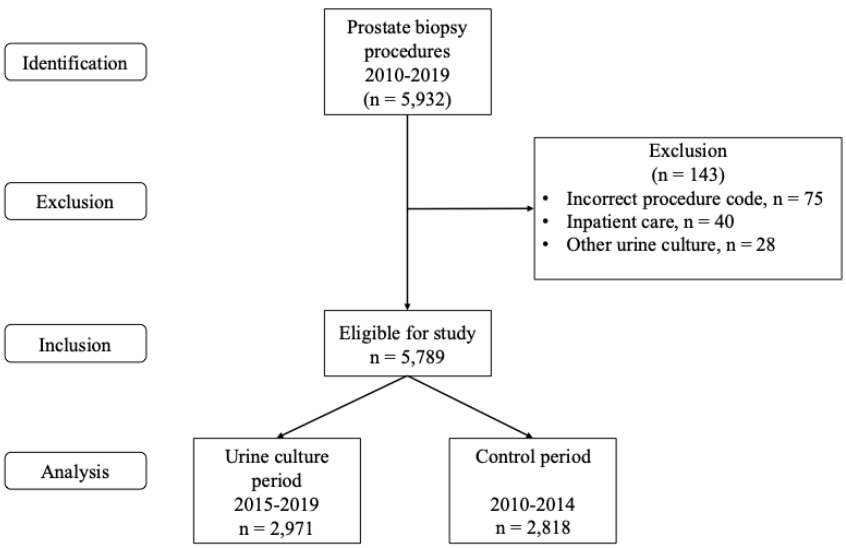


Figure 7 STROBE flow chart on included biopsy procedures in Paper II.

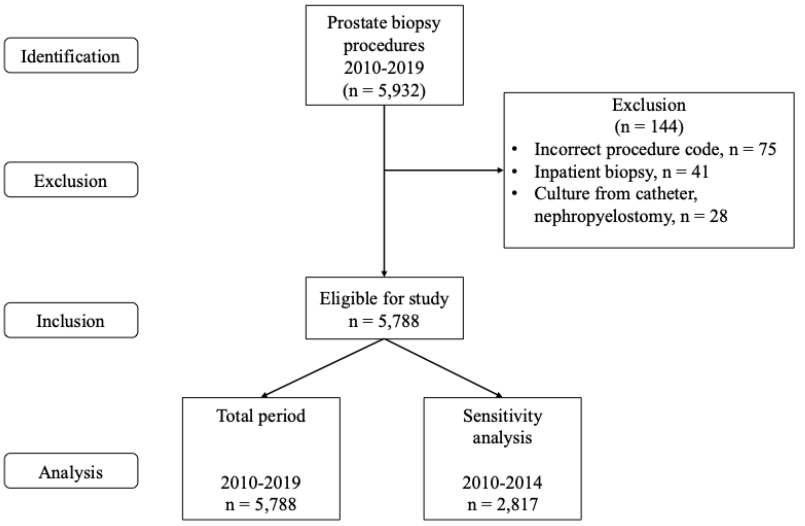


Figure 8. STROBE Flow chart of included procedures in Paper III.

In **Paper II, III and IV** we used the same definition for assessing a post-biopsy infection: either a prescription of UTI antibiotics or an inpatient diagnosis code matching a post-biopsy infection. In **Paper II** a 10-day follow-up was used but in **Paper III and IV** a 30-day follow-up was used. To validate the accuracy of the outcome assessment in **Paper II and III,** a random selection of patients with registered post-biopsy infection according to our definition was reviewed in the EMR; in all these a correct registration of post-biopsy infection was confirmed.

Paper IV

In this nationwide study, we used PCBaSe Sweden a clinical epidemiological prostate cancer database including data from NPCR and other nationwide registers: we used version 5 with data to 2020 (159). PCBaSe has data on patients in NPCR and for every registered case in NPCR there are five individuals matched on year and region. Diagnosis and procedural codes in the National Patient Register and prescriptions in the Swedish Prescribed Drug Register were used. Prostate biopsy procedures in 2006-2020 that lead to a prostate cancer diagnosis (n=64,217) and biopsy procedures in the matched

population that did not lead to a prostate cancer diagnosis (n=74,839) were included in the study (Figure 9).

Biopsy procedures in the matched population that was later diagnosed with prostate cancer were excluded to avoid double registration. In the matched population, we defined biopsy procedures from 2006 to 2019 as TKE00 (a prostate needle biopsy), and from 2020 divisive codes for transrectal and transperineal biopsy was introduced (160). In the matched population from 2020, procedural code TKE10 was included in the study. Prior to 2020, transperineal prostate biopsy was rarely done in Sweden and all procedures prior to 2020 were therefore considered transrectal.

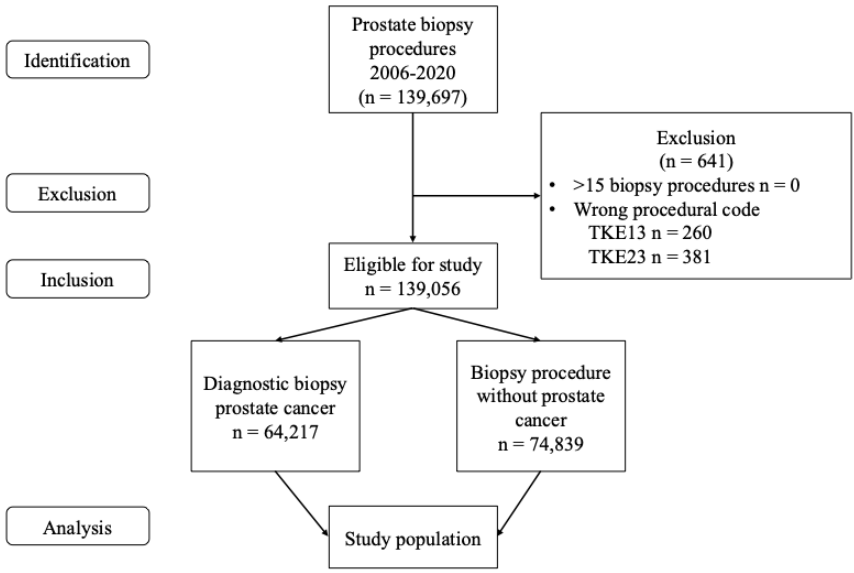


Figure 9 STROBE flow chart of study population from PCBaSe version 5.0 used in ***Paper IV****.*

4.2 DATA SOURCES

Since 1985, the Department of Clinical Microbiology receives all clinical samples from Region Kronoberg, and from 2012 also from Region Blekinge, related to diagnostic request in bacteriology, virology, tropical medicine and antimicrobial susceptibility testing. Information on relevant dates, sample type, bacterial findings and their antimicrobial susceptibility pattern are stored in the laboratory database (Adbakt) and can be retrieved when appropriate scripts are used. Since 2002, when international guidelines became available, all analyses are performed according to guidelines of European Committee of Antibiotic Susceptibility Testing (EUCast) (161).The Department of Clinical Microbiology and the database are since 2017 the national reference center for antibiotic resistance in Sweden (162) and a WHO Collaborating Centre.

All microbiological data in **Paper II and III** is aggregated from the AdBakt database and evaluated in close collaboration with the Department of Clinical Microbiology.

The National Prostate Cancer Register of Sweden (NPCR) is a national register covering information regarding diagnostics and primary treatment of prostate cancer in Sweden (163). The register was started to enable systematic monitoring of the prostate cancer related health care to all men with prostate cancer and as a potential basis for scientific research. Reports from NPCR enable caregivers, health care organizations and patients to assess available care. NPCR covers around 98% of prostate cancer cases diagnosed since 1998 in Sweden (164). All data collection is reported by forms available at INCA-platform from over 100 treatment centers around Sweden (165). To enable evaluation of symptoms after treatment and as tool for discussion with the patient, NPCR is working with patient reported outcome measures (PROM) and Individual Patient Overview (IPÖ) as extension of the primary reported register.

Paper IV: PCBaSe, a national population-based research database that includes data from NPCR, covers 95% of men diagnosed with prostate cancer in Sweden since 1998 (163) and data from several other nationwide registers. NPCR is connected to health registers and databases for demographics. PCBaSe includes data for all men registered in NPCR and for five matched men without prostate cancer, randomly selected from men of the same age in the general population of the same region as their respective prostate cancer

case at the time the case's prostate cancer diagnosis (166). With this connection it has been possible to study compliance to guidelines, co-morbidity and long-term outcomes after treatment (159, 167, 168). Combined data from health care systems and data from the national quality register enables important opportunities of clinical prostate cancer research.

4.3 METHODS

Paper I

Randomisation was a 1:1 model between study groups. Biopsy procedures were carried out by experienced urologists using Profocus 2202 Ultrasound system with probe 8808 or a BK3000 ultrasound system with triplane probe E14C4t (both BK Medical, Herlev, Denmark). Figure 10 shows the latter with side-fire canal blue line and end-fire canal red line. The side-fire mode has a biplanar projection with the transverse (horizontal plane) and the longitudinal (sagittal plane). In the end-fire mode, a single sagittal plane allows a more versatile biopsy projection to reach the anterior parts of prostate.

The experimental biopsy procedure consisted of 6 biopsy cores from the lateral peripheral zone with side-fire mode and 6 cores from the anterior parts using the end-fire mode. The standard procedure consisted of 12 cores from the lateral peripheral zone through the side-fire mode. All biopsy cores were acquired with a 18G single-use coaxial core biopsy needle. All procedures were performed with local anaesthesia using Lidocaine 10 mg/ml, and prophylactic antibiotics. Standard prophylactic regimen was a single oral dose of ciprofloxacin 750 mg prior to biopsy and individualised antibiotic treatment to patients with increased risk of infection.

Primary endpoint was rate of prostate cancer detection and secondary endpoint were rate of Gleason score ≥ 7, total biopsy cancer length and complication that lead to intervention.

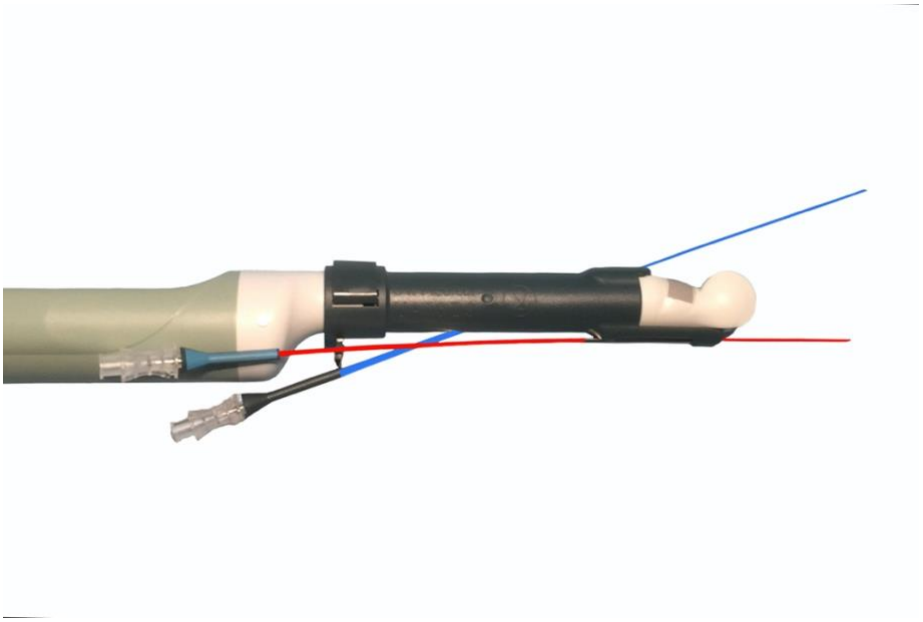


Figure 10. Transrectal Ultrasound probe BK Medical Triplane E14C4t with biopsy channel for side-fire biopsy (blue line) and end-fire (red line).

The histopathological assessment was done according to standard routines at the Department of Pathology, Växjö County Hospital. The randomisation status was known to the pathologist at the time of evaluation.

Paper II and III

In Region Kronoberg the Electronic Medical Record (EMR) include all healthcare services in the region. P**aper II and III** included all outpatient procedures coded TKE00 (prostate needle biopsy) and KEB00 (prostate biopsy). In **Paper II** a post-biopsy infection was defined as antibiotic prescription 1-10 days after biopsy or admittance to hospital 0-10 days for a post-biopsy infection. In **Paper II, III and IV** a prescription the same day was considered as prophylaxis and not as treatment of a post-biopsy infection.

In **Paper II** antibiotic prescription that may be used for a UTI was defined by prescription with ATC as J01CA penicillin with extended spectrum, J01DD third generation cephalosporins, J01DB first-generation cephalosporins, J01EE combinations of sulphonamides J01EA trimethoprim and derivates, and trimethoprim, J01MA fluoroquinolones, J01RA combination of antibacterials

and J01XE nitrofuran derivates. To define an in-patient care episode related to biopsy following diagnoses were registered: N39 UTI, N30 cystitis, T81 complications after surgical intervention and A41 sepsis.

Primary endpoint in **Paper II** was proportion of biopsy procedures followed by post-biopsy infection in 10 days and secondary endpoint were the number of urine cultures with fluoroquinolone-resistant bacteria and changed prophylaxis.

For included biopsy procedures in **Paper II-III** the standard antibiotic prophylaxis was one oral dose of 750 mg ciprofloxacin. For patients with fluoroquinolone allergy a single dose of oral sulfamethoxazole/trimethoprim 800/160 mg was used. During the study period all positive urine cultures were evaluated by the treating physician and antibiotic treatment guided by microbial resistance pattern. Prior to prostate biopsy a new urine culture was obtained, which was supposed to be negative prior to biopsy.

After the completement of **Paper II**, we reconsidered the time for post-biopsy complication based on the more established 30-day follow-up after surgical procedures.

When planning for a risk factor study, careful description of factors is crucial for evaluating the causal relationships between a factor and outcome. In both **Paper III and IV** we used some factors that are well defined and known (as age, diabetes, antibiotic treatments), and some factors that we defined by variables closely related to the actual factor (LUTS and urinary tract infection). In the planning phase of study III, previous variables to define factors for different antibiotic exposure, history of urinary culture and defined drug treatments directed the study design. In both previous studies, clinical suspicion of association to post biopsy infection led us to factors of age, diabetes mellitus (E10/E11), prostate cancer (C61), previous prostate biopsy, more than two biopsies in 24 months, previous positive urine culture, more than two negative urine cultures and four antibiotic exposures (UTI-antibiotic within 6 weeks prior to biopsy, non-fluoroquinolone UTI-antibiotic, fluoroquinolone antibiotic and non-UTI antibiotic all three 1 year to 6 weeks prior to biopsy).

In **Paper III** any post biopsy infection within 30 days after biopsy was defined as a dispensed prescription of antibiotics for UTI 1-30 days after date of biopsy or inpatient care for specified diagnoses 0-30 days after date of biopsy.

Primary endpoint was any post-biopsy infection and secondary endpoint was inpatient care with specified diagnoses compatible with post-biopsy infection.

Paper IV

Factors analysed for association with post-biopsy infection was age, diabetes mellitus, previous UTI, previous dispensed prescription of fluoroquinolones or non-UTI antibiotics, immunosuppressive treatment, systemic corticosteroid treatment, prostate enlargement and urinary tract symptoms. To define factors we used following definitions: Diabetes was defined with diagnose code E10 or E11 but also dispensed prescription of ATC code A10, a previous UTI as dispensed prescription of fluoroquinolone with ATC code J01MA or non-fluoroquinolone UTI antibiotics with ATC code J01CA penicillin with extended spectrum, J01DD third generation cephalosporins, J01DB first-generation cephalosporins, J01EE combinations of sulphonamides J01EA trimethoprim and derivates, and trimethoprim, J01RA combination of antibacterials and J01XE nitrofuran derivate. To capture non-UTI antibiotics ATC code J01 excluding antibiotics non-fluoroquinolone UTI and fluoroquinolone, and all antibiotic exposures were defined with dispensed prescription 4 weeks to 1 year prior to biopsy. The four-week limit was to not capture high risk procedures for infection identified for prophylactic actions. Systemic corticosteroid treatment was defined with ATC H02a more than two prescriptions within 7 months and immunosuppressive treatment ATC L04 dispensed prescription within 4 months before biopsy. LUTS was divided between LUTS/OAB ATC G04BD and LUTS/BPH ATC G04C with dispensed prescription any time before or within 6 months after biopsy. To receive a prescription for LUTS is likely related to symptoms and since the symptoms may be the reason for a PSA-test, a prescription after a biopsy may reflect the desired factor.

Primary outcome was any infection (either a dispensed prescription or inpatient care); secondary outcome was inpatient care. After the result in univariable regression analyses, we merged related variables for a multivariable regression analysis to assess their association to a post-biopsy

infection. For calculating the cumulative risk of infection, we used the same merged variables as in the multivariable analysis.

During inclusion period for **Paper IV** a single oral dose of ciprofloxacin 750 mg was prophylaxis in majority of procedures (116) and still is in national guidelines (169).

4.4 STATISTICAL METHODS

Paper I

For testing association between categorical variables Fisher's exact test was used. Sample size for cancer detection was n = 76 in total and choosing an exact test is recommended for small sample sizes, even if the sample size in this study would suffice for a Chi2-test. For biopsy core length t-test was used for evaluating difference in means and Mann-Whitney U-test for cancer length was assumed a skewed distribution, a small sample size and test for median it is more appropriate with a non-parametric test as Mann-Whitney.

The randomisation design should evenly spread possible confounders between the two groups. The randomisation was known to both patient and physician at time for biopsy, but that should not affect the outcome of the different biopsy.

The trial became underpowered due to a premature closure caused by a change in national guidelines for prostate cancer. Interpretation of results are difficult in underpowered studies since the study did not reach the planned inclusion, it may increase risk for selection bias and for type 2 error. To prospectively plan a study size and estimate a relevant or clinical important difference is difficult. In our study it was not discussed to meet inclusion criteria due to both that the study was close to finished, and patient safety due to the clinical benefit of imaging with MRI prior to biopsy filtering the men that do not need a biopsy.

Paper II

For comparing proportions between the two study populations Fisher's exact test was used, and we chose to use one test on all analytic statistics, but another statistical test for categorical data could have been used. Some variables were

in small sample sizes and for these Fisher's exact test was better suited than the Chi-2 test.

The control period for comparing (2010-2014) was not different in any other clinical routine than the urine culture period (2015-2019).

Paper III

The defined potential risk factors were analysed by univariable logistic regression. Odds ratio for outcome with 95% confidence intervals was analysed for the association with post-biopsy infection within 30 days after biopsy procedure. The potential risk factors were analysed as dichotomous variables except for age, which was analysed as a continuous variable. Age was not associated with post-biopsy infection, but some of the other variables may have a covariation with age and were therefore adjusted for age in the model. The incidence of complications to test for was low (n = 450 out of 5788 biopsies), despite a rather small sample size per variable, the confidence intervals is narrow and the risk of bias due to small sample size should be less important. A separate sensitivity analysis of the period 2010-2014 was done as pre-biopsy urine cultures were then not routinely obtained (as in clinical practice).

Paper IV

After considering the results in **Paper III** and additional variables were selected for the fourth study a Directed Acyclical Graph (DAG; Figure 11) was constructed to describe the causal relations between the independent variables, unknown exposures and the outcome. As in previous paper the defined potential risk factors were analysed by univariable logistic regression with odds ratio for outcome with 95% confidence intervals for the association with post-biopsy infection within 30 days after biopsy procedure. In agreement to Paper III, age in Paper IV was analysed as a continuous variable. Prostate volume was categorised as below 40 cm^3, between 40 to 79 cm^3 and above 80 cm^3 . If a prostate enlargement was a risk factor for post-biopsy infection, the risk should increase with larger volume.

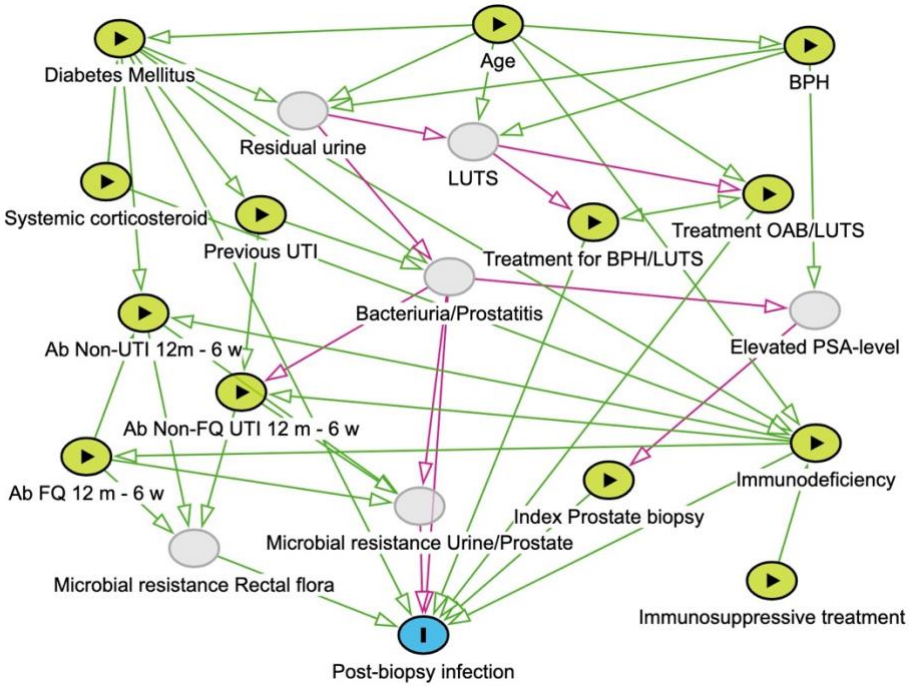


Figure 11. Directed Acyclical Graph describing variables associated with the outcome post-biopsy infection (blue) and their mutual relationship. The known exposures are green and the unknown grey.

For the multivariable regression model, closely related factors were grouped together. Adjustment was made for calendar year so that a change in post-biopsy infection over the study period would not affect the interpretation of the results.

In **Paper IV** we analysed factors for the outcome after the event in a theoretical model to be able to evaluate if treatment as such or the actual symptoms were the risk factor for post-biopsy infection.

4.5 ETHICAL CONSIDERATIONS

Paper I was approved by the Regional Ethical Review Board in Linköping with reference number 2010/358-31. The study was prospectively registered at ClinicalTrials.gov number: NCT02761135 and all study participants signed informed consent to be randomised in the trial (Patient information in Appendix). Written information was handed to all participants with a guide to medical care if signs of complication appeared. The study had a superiority design regarding cancer detection, and prior to study start we had no evidence of increased risk of complication for study participants in relation to the use of the end-fire technique. The end-fire technique had been in clinical use in our and other clinics without alarming events when compared to side-fire and was therefore judged safe in everyday care.

Paper II and III had ethical approval from the Swedish Ethical Review Authority (reference number 2020-02066), for data collection without informed consent from included men. The study data was kept pseudonymised in a local database only accessible by the statistician and the local principal investigator.

Paper IV used data from PCBaSe version 5.0 (166, 170), a database for epidemiological prostate cancer research. PCBase comprises data from several national registers in Sweden. The most recent version (5.0) has ethical approval from the Swedish Ethical Review Authority (2020 – 0437). The study reported in Paper IV was specifically approved as an amendment to the previous approval (2023 - 06181 – 02).

The extending data analysis in study III from 10 days to 30 days after biopsy were not part of the study protocol submitted for ethical approval and was discussed with the regional entity responsible for research and considered not harmful for the individuals providing data to the studies.

5 RESULTS

The main findings are described in this section, and more detailed results are found in the included papers.

Paper I

Owing to updated national guidelines recommending MRI and target biopsies (51), the study prematurely closed in end of February 2018, before including the planned 360 patients. The study included 344 patients, but four men were excluded due to ≥T2b palpable cancer, leaving 340 patients for analysis: the standard biopsy group n = 172 and the experimental group n = 168 (*Figure 6)*.

The baseline characteristics of the patients for both groups were comparable, apart from hypoechoic lesions that were detected more often in the experimental group (15% versus 6% in the standard biopsy group). Prostate cancer was detected in 21% of patients in the standard biopsy group and 25% in the experimental group (p = 0.44). Gleason Grade Group (ISUP) ≥ 2 cancer was detected in 7% of the standard biopsy group and 12% of the experimental group (p = 0.14).

A biopsy-related complication that led to medical intervention occurred in three men in the standard biopsy group and ten in the experimental group. Three patients in the experimental biopsy group had haematuria that required intervention, one of which had a clot evacuation under general anaesthesia, a Clavien-Dindo grade 3a complication .

A pre-biopsy MRI was not regularly performed even at first repeat biopsy until the change of guidelines in 2017. In 2017 around 250 MRI prostate were done in Region Kronoberg compared to around 800 MRI in 2023. The majority of MRI in 2017 was part of dose planning prior to external radiation therapy.

Paper II

From 1 January 2010 to 31 December 2019, 5,932 prostate biopsy procedures were identified. After excluding 143 procedures for wrong procedural code, biopsy during inpatient care and wrong urine culture a total of 5,789 biopsy procedures in 4,041 patients remained for analysis. The study was divided into

two periods: the urine culture period (2015-2019) with 2,971 biopsies with 90% of biopsies preceded by a urine culture, and the control period (2010-2014) with 2,818 biopsies, of which 4.8% had a preceding urine culture.

Infections following prostate biopsy were a little more common during the urine culture period compared to the control period (5.0 vs 4.3%, p = 0.17), with inpatient care for infections also being more common in the former (3.5% vs. 2.2%, p = 0.002). Positive blood cultures were recorded in 0.9% of the biopsied men during the urine culture period and in 0.5% during the control period. No patient met sepsis criteria or required treatment at an intensive care unit.

During the urine culture period, 5.4% of pre-PB urine cultures were positive, leading to antibiotic prescriptions in nearly all cases. Infectious complications followed 6.3% of PBs with positive pre-PB urine cultures. In the control period, 0.9% of PBs (n = 25) had positive pre-PB urine cultures, with one leading to an infectious complication.

The study identified that 8.8% of pre-biopsy cultures during the urine culture period contained fluoroquinolone-resistant bacteria, compared to 8.0% in the control period, with no infectious complications in these patients.

After extending the time to the 30-day follow up in study III, the outcome from **Paper II** was re-analysed with 30-day follow-up for adapting to more commonly used follow-up and standardising the included studies.

The extended 30-day follow-up increased the rate of infection from 5.0% to 7.0 % for any post-biopsy infection and 3.5% to 3.6% for inpatient care during urine culture period, and 4.3% to 7.0 % any post-biopsy infection, and 2.2% to 2.3% for inpatient care during control period. Proportion of infections over time with 30-day follow up is presented in Figure 12.

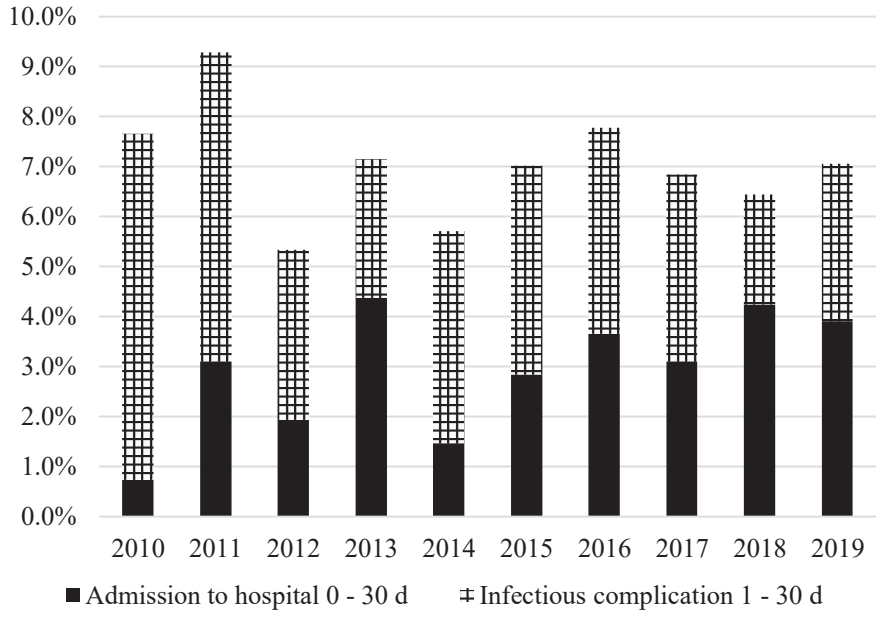


Figure 12. Proportion of infectious complications within 30 days after prostate biopsy (Admission to hospital 0-30 d after procedure (filled part of the bars) and Any infectious complication 1-30 days after procedure in checked bar).

Paper III

Between 2010 and 2019, a total of 5,788 prostate biopsy procedures were performed in 4,040 patients.

Out of these procedures, 405 (7.0%) resulted in a post-biopsy infection within 30 days, with 170 (2.9%) leading to hospital admission. A thorough review of medical records for these hospitalised patients verified the accuracy of infection-related diagnosis codes and confirmed that in the controls no hospital admissions were missed for post-biopsy infections. None of the patients required intensive care treatment for their infections.

The study identified several moderately strong risk factors for any post-biopsy infection, with odds ratios (ORs) ranging from 1.5 to 2.5 (Figure 13). These include diabetes mellitus, prior antibiotic treatment for UTI, past

fluoroquinolone use, and a history of positive urine cultures. Risk factors with lower ORs (1.3-1.5) were fluoroquinolone treatment, previous non-UTI antibiotic treatment, medication for benign prostatic enlargement and having negative urine cultures in the period from 2 years to 6 weeks before the prostate biopsy (a proxy for symptoms of lower urinary tract).

The association between age and any post-biopsy infection was of borderline statistical significance (p=0.07).

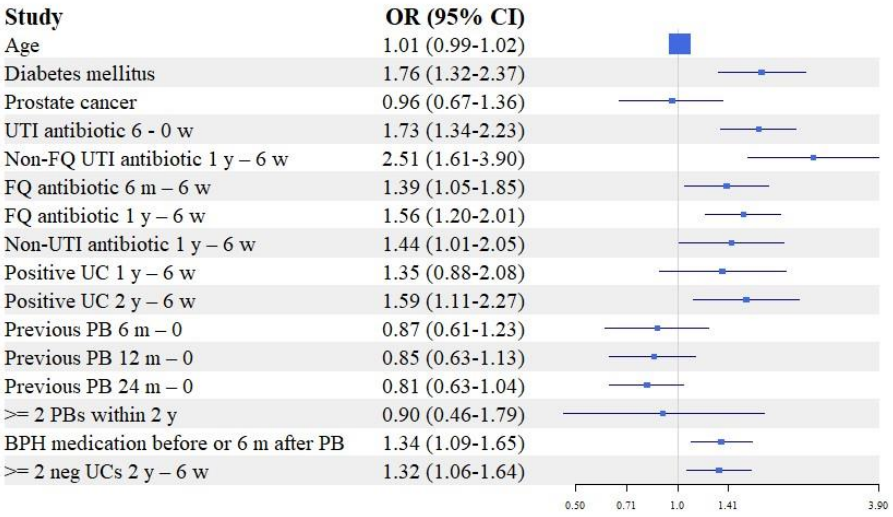


Figure 13: Forest plot of univariable analysis of risk factors for any post-biopsy infection with 30 days after transrectal prostate biopsy.

For infection leading to hospital admission within 30 days after biopsy, the strongest risk factors were previous non-fluoroquinolone UTI antibiotic treatment (OR 2.5, 95% CI 1.3-4.7) and diabetes mellitus (OR 2.3, 95% CI 1.6-3.3). Weaker but statistically significant risk factors (ORs 1.4-1.5) included fluoroquinolone treatment, benign prostatic hyperplasia medication, and having multiple negative urine cultures from 2 years to 6 weeks before the biopsy.

Paper IV

The study included 139,056 prostate biopsy procedures. 64,217 procedures from men diagnosed with prostate cancer, and 74,839 procedures were on men without prostate cancer at time for biopsy. 6,608 (4.8%) of the procedures resulted in any post-biopsy infection, and 2,979 (2.1%) of the procedures led to an inpatient care episode due to a post-biopsy infection within 30 days.

The rate of post-biopsy infections increased over time, from 3.4% in 2006 to 5.9% in 2020. The rate of inpatient care following a post-biopsy infection increased from 1.0% to 2.7%.

After analysing the result from the univariable, a model multivariable analysis prior to calculating the cumulative risk for infection was designed with diabetes mellitus, and the merged variable previous UTI (including both non-fluoroquinolone UTI antibiotics and fluoroquinolones), immunosuppressive treatment (both systemic glucocorticoids and immunosuppressives) and LUTS (both treatment for benign prostatic enlargement and overactive bladder). The risk for any post-biopsy infection for men with no risk factor was 4.0%, (95% CI: 3.8-4.1%), for those with one risk factor it was 6.1% (95% CI:5.9-6.4), with two 10% (95% CI: 9.3-10.7%), and with three 12% (95% CI: 9.8-14%). In the final analysis LUTS was not included in cumulative risk due to the assumed less causative effect of medical treatment for LUTS.

For inpatient care the corresponding cumulative risk ranged from 2% (95% CI: 1.9-2.1%) with none to 3.1% (95% CI: 2.2-4.4%) with three risk factors.

Figure 14 present a Forest plot showing the univariable analysis of risk factors for primary (any post-biopsy infection) and secondary endpoints (inpatient care for post-biopsy infection).

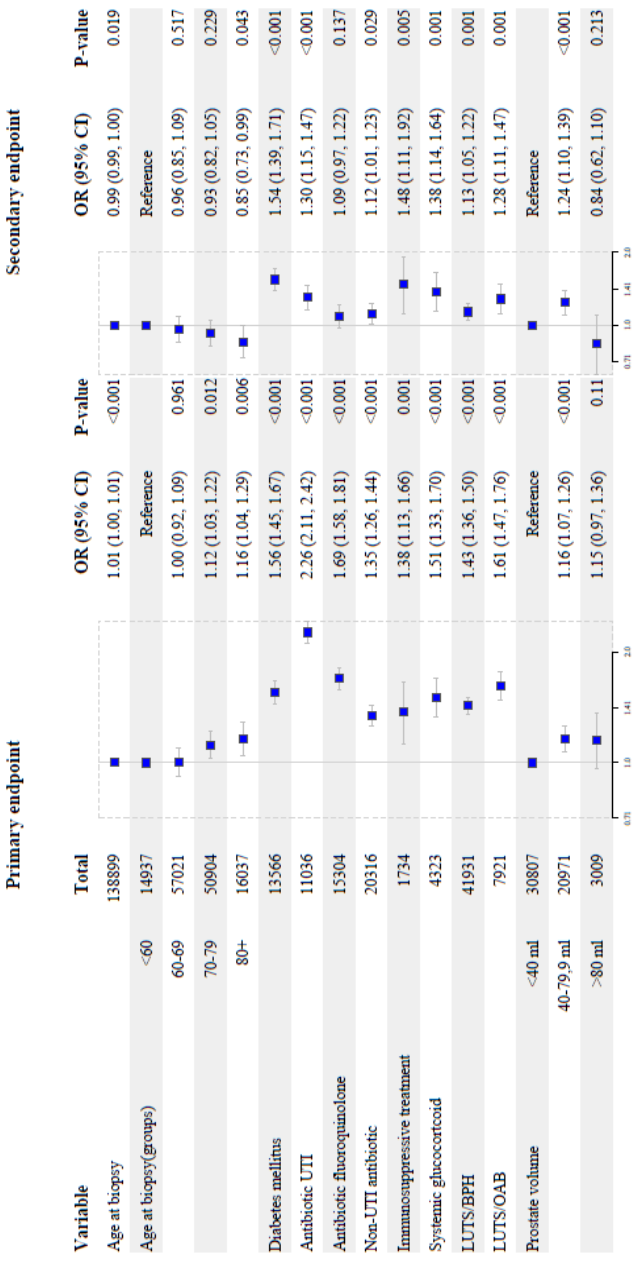


Figure 14 Forest plot on univariate analysis of factors for primary endpoint any post-biopsy infection and secondary endpoint inpatient care for infection.

The multivariable analysis on the merged variables showed antibiotic treatment for UTI (OR 1.72, 95% CI: 1.62-1.82), diabetes mellitus (OR 1.45, 95% CI: 1.35-1.55), LUTS (OR 1.34, 95% CI: 1.27-1.41), immunosuppressive treatment (OR 1.27, 95% CI: 1.13-1.42) and non-UTI antibiotics (OR 1.22, 95% CI: 1.14-1.30), all statistically significant as independent risk factors for any post-biopsy infection.

We performed a sensitivity analysis for the factor LUTS including only procedures where treatment for LUTS was started after the biopsy. This analysis resulted in identical proportions of infection compared with the main analysis (5.9%/5.9% and 7.2%/7.2%, respectively).

6 DISCUSSION

This thesis investigated the diagnostic value of adding anterior biopsies in first re-biopsy for investigating prostate cancer, evaluated a routine with urine culture prior to prostate biopsy, and finally in one regional and one national register study investigated risk factors for infection after transrectal prostate biopsy and the cumulative effect of having multiple risk factors.

Paper I

When **Paper I** was in design phase, systematic biopsies were standard of care (171) and the clinical routine was to re-biopsy if a clinical suspicion of prostate cancer remained after one set of benign biopsies. In everyday clinical work focus was on not missing a prostate cancer, and in most diagnosed men a treatment was recommended in most grades. Some studies suggested adjusting the number of biopsy cores to prostate volume (172) and some suggested maximizing the number of cores with a "saturation biopsy" (173). Repeat biopsies were performed due to the lacking of other diagnostic modalities (174) to detect a previously potentially missed cancer (175). We chose to study the first repeat biopsy due to the more technically challenging biopsies with the end-fire probe when working without the triplane mode when using side-fire. Since the peripheral zone is of main interest in first lateral biopsy, it seemed reasonable to carry out further investigation to other parts of prostate. At the planning phase for the study design, we chose to use previously published data on cancer detection at first repeat biopsy at 15% from the REDUCE study by Andriole et. al (158), but there were other publications with different cancer detection rates (173). For a relevant increase in cancer detection, we estimated an absolute increase of 10-15% and decided that 12% was a reasonable increase for a technically more difficult technique and an increase that could motivate a change of technique. In the study, cancer detection in the experimental group with anterior biopsy cores was 25% and in the standard biopsy group 21%, which was a not statistically significant difference. Gleason Grade Group ≥ 2 cancer detection was 12% in the experimental group and 7% in the standard biopsy group, also not statistically significant.

If, at the study design phase, we had argued that a 5% increase in cancer detection, from 21% to 26%, was reasonable, 1128 participants would be

required in each group to achieve a power of 80% with a two-sided alfa of 0.05. As noted in the methods section, in retrospect and for future studies, it would be preferrable (if possible) to use internal data for study planning.

The finding that anterior end-fire biopsies led to a higher number of complications, both infectious and non-infectious, was a surprise. Possible explanations are that to be able to reach the anterior parts of prostate the needle needs to advance further in prostate gland, which might reduce puncture safety and the precision at the tip, and the longer the path into tissue, the higher the risk of severing a blood vessel or introducing bacteria into blood stream.

A risk with an underpowered study is that a chance finding leads to a Type I error: falsely rejecting the null hypothesis. Since the study was prematurely stopped, it was underpowered. This might have led to a larger variance in the outcomes with subsequent misinterpretation of results.

Studies both from prostatectomy specimens (176) and retrospective biopsy studies (80) show that anterior cancers may be significant and that the anterior part of the prostate therefore needs to be assessed. This is nowadays achieved with pre-biopsy MRI and targeted biopsies.

Transperineal biopsy may detect more anterior and apical cancers (177), but a well-designed randomised trial showed similar cancer detection for transperineal and transrectal biopsies (90). Even so, it supports the retrospective findings and our hypothesis prior to the study design that anterior biopsies are important in prostate cancer diagnostics. Since the introduction of MRI, the use of systematic biopsies has decreased, and target biopsies are more commonly performed. The transperineal route offers better access to the anterior parts and the discussion of transrectal biopsy techniques based on probe design is less current.

Paper II

A routine urine culture prior to prostate biopsy was considered one possible way to decrease risk for men to acquire serious infection after transrectal prostate biopsy, and an attempt to change antibiotic prophylaxis from broad spectrum antibiotics like quinolones (82) to narrow spectrum treatment in cases where urine culture results could support targeted antibiotic prophylaxis

(178). The routine with urine culture prior to biopsy was not primarily intended to form the basis for a clinical study. In planning the study, the ambition to evaluate the routine was important, and the clinical value in everyday urological care of routine urine culture was not previously well studied.

Although the coverage of our regional routine with urine culture prior to transrectal prostate biopsy was high (90%), it did not result in fewer infections. The routine was abandoned after the publication of the results of this study.

A prescription of a UTI antibiotic within 10 days was registered in 5.0% during the routine with urine culture and 4.3% in period without urine culture. During the urine culture period, patients with cultures showing fluoroquinolone resistant bacteria were successfully treated and had no post-biopsy infections. On the other hand, in the group with asymptomatic bacteriuria and any other microbiological pattern 6.9% had an infection after biopsy according to the study's definition. It is thus possible that treatment of patients with a positive urine culture may led to selection of antibiotic-resistant bacteria with a subsequently increased complication risk. It might have been better to use prophylactic measures such as preprocedural rectal povidone-iodine cleansing (109) or a change to a transperineal prostate biopsy.

In the study reported in Paper III and IV we extended the time of follow-up to 30 days. After the publication of **Paper II,** we re-analysed the data with this longer follow-up. With a 30-day follow-up period, the proportion of patients categorized as having a post-biopsy infection during the urine culture period increased from 5.0% to 7.0% and during the control period from 4.3% to 7.0%. This may demonstrate that serious infections (inpatient care) occur earlier in follow-up, and that a shorter follow-up tends to miss some infections. On the other side, a risk of extending the follow-up time is that infections not related to the prostate biopsy are categorized as infections.

A possible measurement error was that in some cases the antibiotic prescription was for another reason than an infection after the prostate biopsy.

As an attempt to reduce misregistration and to validate the data, we identified all patients with inpatient care within 10 days from the biopsy procedure and randomly selected 20 patients with a post-biopsy prescription of UTI antibiotics and reviewed their medical records to assess that cause of the

antibiotic's prescription; in all these patients the prescription was for an infectious complication.

Paper III

The study population for **Paper III** was included during the same study period as **Paper II**; it was a population-based register study in Region Kronoberg of all prostate biopsy procedures 2010 through 2019.

Diabetes mellitus and a previous UTI are previously reported risk factors, and in our results, these two factors increased the odds almost two-fold for any post-biopsy infection.

In previous studies the association of different antibiotic exposures affecting the risk for post-biopsy infection was not well described. The study design enabled us to investigate different antibiotic exposures separately. We found that a prescription of a non-UTI antibiotic within 1 year prior to prostate biopsy was associated with a greater risk for infection. This finding may be explained by either patient specific increased risk for any infection (older, co-morbidity) in line with findings by Lundström et. al (104) and Anastasiadis et. al (179). Alternatively, any antibiotic treatment is causatively related to post-biopsy infections and, if so, the finding by Lundström et. al is explained by that comorbidity is a confounder rather than a causative risk factor. Previous studies on antibiotic use within a year has shown to be associated with resistant bacteria in rectum: in a study from Iran with a prevalence of 46% *E.coli* resistant to fluoroquinolones (180), but not associated with resistance in a Swedish study with around 10% resistant *E.coli* in the population (138).

The finding that treatment with medication for benign prostatic enlargement and previous negative urine cultures is associated with infection is likely explained by that having symptoms from the lower urinary tract rather than the treatment per se increased the risk of a post-biopsy infection.

In **Paper III** we chose to extend the time for registration of complications to 30 days after date of the biopsy procedure. This decision was based on a discussion at the half-time seminar. I have tried to track back and discover where the "30 days follow up after surgery" comes from, but I have not found the origin. It is reasonable to believe that it is related to the number of days in

an average month and assumed to be a reasonable period after intervention for a patient to recover. It is a clarification for future research to try to standardize the follow-up time after an intervention for recording complications, to enable standardised reports and comparable results. As discussed earlier, a longer follow-up time may register antibiotic prescription for other reasons and shorter follow-up time may miss significant morbidity and underestimate the actual problem. It is also desirable that EMRs are comprehensive so that follow-up of patients after interventions is simplified in health care organisations.

Paper IV

In this large population-based register study, the proportion of post-biopsy infections with an infection following a transrectal prostate biopsy doubled between 2006 and 2020. The likelihood of an infection increased with the number of risk factors, from 4.0% in patients with no risk factor to 12% in those with three risk factors.

One secondary aim of the study was to investigate the relationship between prostate enlargement, LUTS and a post-biopsy infection. Previous reports have indicated that both prostate enlargement and treatment for benign prostatic enlargement may increase the risk of infection after transrectal prostate biopsy. However, the association is likely mediated by factors such as residual urine, bacteriuria and bacteria in the prostate rather than the enlargement itself. In our study, treatment for overactive bladder was more strongly associated with infection than treatment for benign prostatic enlargement. This, along with the weak and inconsistent association between prostate volume and infection, suggests that the pathophysiological changes related to LUTS are the causal link to infection, rather than prostate enlargement as such.

Another secondary aim was to clarify the role of different antibiotic exposures as a risk factor for infection. Both previous fluoroquinolone and non-fluoroquinolone UTI treatment increased the risk for post-biopsy infection, but only the latter increased risk for inpatient care. This may be due to persistent bacteria in the prostate or urine associated with previous UTI. Fluoroquinolone treatment can lead to microbial resistance in the rectum, increasing the risk for infection if fluoroquinolone is used for prophylaxis. That a previous non-fluoroquinolone UTI treatment had consistently higher ORs than previous

fluoroquinolone treatment suggests that a prior UTI may be more significant risk factor for post-biopsy infection than fluoroquinolone resistance, is contrary to the previously mentioned study from Sweden (138). Importantly, while post-biopsy infections caused by microbial resistance in the rectal flora can be mitigated using the transperineal biopsy route, the risk associated with previous UTI likely remains.

Limitations in studies II, III and IV in this thesis included the difficulty in defining a post-biopsy infection and defining some of the risk factors that we intended to investigate. Some variables such as age and diabetes mellitus were valid, but antibiotic prescriptions, prior urinary tract infection and post-biopsy infections were not directly assessed. We used a prescription of an UTI antibiotic as the definition of post-biopsy infection and for risk factor defining a previous UTI, and some of these prescriptions may been for other infections not related to the biopsy.

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7 CONCLUSIONS

- Sampling the prostate with 6 posterior and 6 anterior biopsy cores at first repeat biopsy did not increase prostate cancer detection compared with 12 posterior biopsy cores.

- The clinical routine with a urine culture prior to transrectal prostate biopsy did not lead to a decrease in post-biopsy infections.

- Diabetes, a previous urinary tract infection, a previous treatment with glucocorticoids or immunosuppressives, and lower urinary tract symptoms all increase the risk for a post-biopsy infection.

- The risk of infection after transrectal prostate biopsy increases incrementally with the number of risk factors.

- The pathophysiological mechanisms behind lower urinary tract symptoms are likely the true cause for increased risk for post-biopsy infection, not prostate enlargement as such.

8 FUTURE PERSPECTIVES

A prostate biopsy remains an essential diagnostic tool for prostate cancer. The landscape of prostate biopsy has undergone considerable changes in the recent decades, shifting from finger-guided techniques to advanced MRI-targeted strategies, but post-biopsy infections continue to be a significant concern for both patients and clinicians ranging from mild urinary tract infections to serious conditions. As techniques and technologies evolve, there are several promising ways for reducing infection rates and improving patient outcomes. The transition to transperineal prostate biopsies show potential in reducing infectious complications and the feasibility to do biopsies without prophylactic antibiotics may also aid in improving antimicrobial stewardship (181).

Future research and the development of measures to prevent infectious complications may lead to the choice between the transrectal and transperineal route for prostate biopsy being based on the individual patient's risk factors for infection. A future randomised clinical trial may compare standard of care (a defined local routine for biopsy route and preventive measures) with a risk-adapted strategy based on the number of risk factors guide the choice of biopsy route and preventive measures. With no risk factors, transrectal with povidone-iodine and oral antibiotic prophylaxis. If one or more risk factors transperineal route and with all three risk factors transperineal with antibiotic prophylaxis. In a theoretical model with an assumed rate of infection in the standard group of 4% (depending on the proportion of transperineal in standard care group) a total of 2282 study subjects would be required to with 80% power to detect an absolute reduction of 2% with risk factor guided choices of biopsy route and preventive measures.

In a few years, when the Swedish national registers have sufficient data on transperineal prostate biopsy procedures, a study on risk factors for infection after transperineal prostate biopsies would also be valuable. The study may be designed similarly to Study 4 in this thesis.

One way of reducing post-biopsy infections may be by limiting the bacterial translocation by the biopsy needle. A international prospective trial is planned to compare a novel needle design (the Forsvall needle) with the standard Tru-cut needle for prostate biopsy via the transrectal route (182).

What is a reasonable post procedural infection rate? With post-biopsy infections around 1-1.5 % in areas with known low levels of microbial resistance this may be a reasonable acceptance rate. In healthcare settings where the EMR is comprehensive and covers all aspects of health care, a prospective complication surveillance function would be valuable. Today many complications are retrospectively noted in PROM or at follow-up visits. It would be beneficial to prospectively register unexpected events within 30 days after an intervention. Many Swedish regions use an output program (QlikView) that acts as pseudonymized register applicable for searching for diagnosis codes and specific key words for retrospective analysis. This program was used in both **Paper II** and **Paper III.** A program like this could be supported by artificial intelligence and programmed to prospectively register complications and unexpected events after interventions. This would allow clinicians and healthcare providers to continuously monitor the complication rate of various interventions. An alarm function could alert when a complication rate exceeds a predefined limit. Such a model could be applicable to all kinds of interventions with well-known complications and is appealing in current times when administration for clinicians is increasing.

Based on the findings in this thesis and the limitations of performed studies future work may provide a more comprehensive understanding of incidence and risk-minimizing of post-biopsy infections improving patient outcome.

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APPENDIX

*Patient information for study participation and randomisation in **Paper I**:*

Studie där end-fire biopsier jämförs med side-fire biopsier för detektion av prostatacancer.

Patientinformation

Bäste _____!

Du har fått en kallelse för att utreda din prostatakörtel pga stegrat PSA-värde på Urologmottagning Kirurgicentrum Kronoberg i Växjö eller Ljungby.

I utredningen av stegrat PSA-värde ingår en palpationskontroll av körteln och att man utför ultraljudsledd undersökning av körteln samt vävnadsprovtagning via ändtarmen. Man kan använda två olika tekniker för att få ut vävnadsprover från prostatakörteln. De kallas side-fire och end-fire teknik.

Vår studie avser att jämföra dessa två tekniker med varandra för att se om någon av dem är säkrare på att hitta prostatacancer.

Vi använder redan idag båda teknikerna men har inte mer i detalj studerat skillnaderna. Du kommer att slumpmässigt väljas till någon av de två.

Vävnadsprovet kommer att handhas precis som vanligt och skickas för mikroskopiundersökning.

I studien/projektet kommer personuppgifter om Dig att behandlas med datorregistrering. Landstinget Kronoberg är personuppgiftsansvarig enligt PuL för denna personuppgiftsbehandling. Om Du samtycker till att delta i studien samtycker Du också till att personuppgiftsbehandling sker. Du har rätt att ansöka om information från denna personuppgiftsbehandling enligt Pul § 26 och detta gör Du genom att skriva till Personuppgiftsombudet, Lanstinget Kronoberg 351 88 Växjö. Din ansökan måste vara egenhändigt undertecknad. Du har också rätt att få eventuella felaktiga personuppgifter rättade.”

Uppgifterna kommer endast att finnas hos projektansvariga (Fredrik Liedberg, överläkare och Joakim Karlsson, ST-läkare). Insamlad information kommer att hanteras enligt gällande sekretessbestämmelse. Uppgifterna kommer att lagras under studiens gång och därefter avidentifieras.

Deltagande i studien är helt frivilligt. Skulle Du välja att ej delta i undersökningen kommer Du genomgå utredning enligt normala rutiner. Om Du väljer att delta i studien kan Du när som helst avbryta utan närmare förklaring. Eventuell kommande behandling efter utredningen kommer inte att påverkas av Ditt beslut.

Någon ekonomisk ersättning utgår ej.

Vid frågor beträffande studien kontakta ÖL Fredrik Liedberg eller ST Joakim Karlsson, Urologsektionen, Centrallasarettet Växjö tel: 0470-588000.

Informerat samtycke

Jag medger härmed deltagande i studien

_____Växjö /

_____ patientansvarig läkare

Joakim Karlsson

Urologsektionen

Centrallasarettet Växjö

351 88 Växjö Tel 0470-588000