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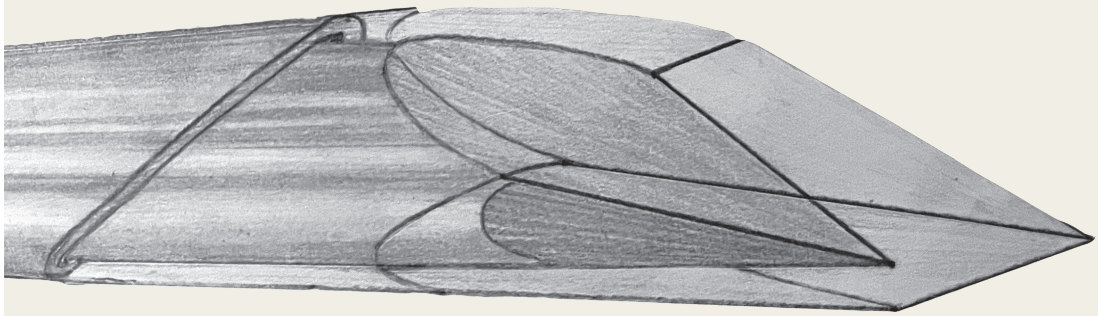

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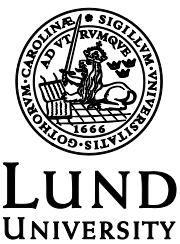

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 18th of November 2022 at 09.00 in Belfragesalen, BMC, klinikgatan 32, Lund

Faculty opponent

Associate Professor Mikael Häggman,
Uppsala University

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Improved needle design to reduce the risk of infection in transrectal prostate biopsy

Abstract

Prostate cancer is the second most common cancer in men with 1.4 million cases/year. Clinical examination, Prostate Specific Antigen (PSA) and Magnetic Resonance Imaging (MRI)-scans can all raise suspicion of cancer. The prostate cancer diagnosis is then made from examination of prostate tissue, almost always obtained by a prostate biopsy. The prostate is located next to the rectum and most commonly a transrectal prostate biopsy is performed. Transrectal prostate biopsy transfers colonic bacteria into prostatic tissue, potentially causing infectious complications, including sepsis. Antibiotics are used as prophylaxis but risk of infection is rising in parallell with rising antibiotic resistance. About 3.2 million prostate biopsies are performed and about 95.000 men are expected to be hospitalized due to infection each year.

It is known that reducing bactieral contamination at the puncture site reduces the risk of infection. Antibiotics, cleaning the rectal wall or avoiding puncturing the rectal wall are current methods to reduce the risk of infection. Even though the infections are caused by bacteria transferred by the biopsy needle, to our knowledge no efforts have been made to improve the very instrument that causes bacterial transfer – the needle.

This thesis addresses the medical needle design in relation to the risk of infection in transrectal prostate biopsies. Paper 1 explains the mechanism of bacterial transfer with the current needle technology and introduces the Forsvall needle, a novel needle design aiming to reduce bacterial transfer. In a simulation of prostate biopsy, using human colon tissue, the novel needle reduced bacterial transfer by 96.0% (95% confidence interval 93.0-97.7%; $p < 0.001$) compared to the currently used Tru-Cut needle.

Paper 2 is a pilot clinical trial where 20 patients were randomized to undergo prostate biopsy using either the Forsvall needle or the standard Tru-Cut needle. Altogether, 119 and 130 biopsies were taken with each needle respectively. Patients and pathologist were blinded to instrument used. The Forsvall biopsy needle was non-inferior compared to the standard Tru-Cut needle in terms of mean pathologist-measured biopsy length (0.02 mm longer, 95%CI-0.73 to 0.76 mm). Biopsy quality and patient discomfort were not significantly different between the two groups. Biopsy fragmentation was more common in the Forsvall group.

Paper 3 is a retrospective medical records review of 670 prostate biopsies in Helsingborg/Ängelholm during 18 months 2017-19. 5.4% of patients had an infection, 3.9% were hospitalized. The study also highlights costs of infection and the lack of an ICD-10 code for the diagnosis of infection after prostate biopsy.

Paper 4 is a manuscript for the protocol for a large trial. The purpose of the trial is dual, aiming to evaluate both whether the Forsvall needle reduces the risk of infection in transrectal prostate biopsy and whether cancer detection is improved in targeted biopsies.

Prostate biopsy, infection, sepsis, biopsy needle, innovation, Tru-Cut, prostate cancer

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To Cecilia, Oscar, Olivia and Linnea,
who have given up much family time to make this possible

Table of Contents

Abbreviations

AMR	Anti-Microbial Resistance
CT	Computed Tomography
DRE	Digital Rectal Examination
EAU	European Association of Urology
ED	Erectile dysfunction
HIFU	High-Intensity Focused Ultrasound
ISUP	International Society of Urological Pathology
LB	Liquid Biopsy
MRI	Magnetic Resonance Imaging
PET-CT	Positron Emission Tomography–Computed Tomography
PSA	Prostate Specific Antigen
RCT	Randomized Controlled Trial
SVP	Subcutaneous Venous Port
TPbx	Transperineal prostate biopsy
TRbx	Transrectal prostate biopsy
TRUS	Transrectal Ultrasound
TURP	Transurethral Resection of the Prostate
US	Ultrasound

Popular science summary (Swedish)

Prostatacancer är Sveriges vanligaste cancer, och en av världens vanligaste cancerformer med 1.4 miljoner fall/år. Blodprovet PSA kan ge misstanke om prostatacancer. Magnetkameraundersökning kan ytterligare stärka misstanken. För att ställa diagnosen prostatacancer krävs dock ett vävnadsprov – en biopsi.

Biopsin erhålls nästan alltid av en biopsinål som med hjälp av ultraljud riktas mot områden i prostata. Sedan ungefär 50 år tillbaka används en Tru-Cut biopsinål. Då prostatan ligger an mot ändtarmen tas vävnadsprov oftast genom ändtarmsväggen (transrektala prostatabiopsier). Nålen kan då föra med sig bakterier från ändtarmen in i kroppen, med risk för infektion.

Antibiotika används som skydd men med ökande antibiotikaresistens ses nu en ökande risk för infektion.

Idag får 5–7% av patienter en infektion varav ungefär 3% blir så svårt sjuka att de behöver sjukhusvård. Med 3.2 miljoner tagna prostatabiopsier per år i världen hamnar nästan 100.000 män på sjukhus årligen. Olika åtgärder görs för att minska infektionsrisken, men trots att infektionerna direkt orsakas av den medicinska nålen finns inga studier som undersöker hur bakterietransporten går till. Det finns därför heller inga nålar som syftar till att minska bakterietransport och därmed minska infektionsrisken.

Denna avhandling syftar till att beskriva biopsinålens roll i infektionsrisken vid transrektala prostatabiopsier, presentera hur bakterier överförs in i kroppen av nålen och presentera en alternativ nåldesign för att minska bakterietransporten samt i studier jämföra den med dagens biopsinål (Tru-Cut nålen).

I studie 1 beskrivs den nya nåldesignen (Forsvall-nålen) och jämförts med dagens nål (Tru-Cut nålen) i en studie på human tarm efter operation. Studiedesignen ämnar efterlikna prostatabiopsi så realistiskt som möjligt. Studien visar att Forsvall-nålen minskar bakterieöveröringen med 96% jämfört med Tru-Cut nålen.

Studie 2 är en pilotstudie på 241 prostatabiopsier hos 20 patienter som visade att Forsvallnålen tog lika långa vävnadsprover som Tru-Cut nålen. Patienterna tolererade Forsvallnålen väl och inga nya komplikationer inträffade.

I studie 3 eftergranskades journaler hos alla patienter som genomgått prostatabiopsi på Helsingborgs Lasarett och Ängelholms sjukhus under en 18 månaders period 2017-19. 5.4% fick en infektion, 3.9% behövde sjukhusvård för infektionen och 1.3% var så sjuka att de behövde intensivvård eller hade en infektion som inte läkte ut vid första behandlingen och behövde därför upprepad sjukhusvård eller besök på akutmottagning.

Kostnaden för de sjukhuskrävande infektionerna är hög; för varje patient som genomgår en biopsi måste sjukvården budgetera 3000kr bara för akut vård för infektioner. Som jämförelse kostar nålen som orsakar infektionen ca 150kr.

Det saknas även en diagnoskod för infektion efter prostatabiopsi, trots att det är så vanligt. I studien konstaterade vi att de 26 patienter som vårdats för infektion efter prostatabiopsi fått 15 olika diagnoser. Bristen på en bra diagnoskod gör det svårare att ha översikt på hur många som drabbas av dessa infektioner.

För att utvärdera hur mycket infektionsrisken minskar vid en 96% minskning av bakterietransporten behöver man göra en stor studie där patienter lottas till biopsi med Forsvall-nålen eller Tru-Cut nålen. Studie 4 är ett protokoll för hur en sådan studie kan göras. I arbetet med biopsinålen har vi även gjort designjusteringar som gör att Forsvall-nålen förväntas gå rakare i vävnad än dagens Tru-Cut nål. Vi tror att det kan göra att vi lättare kan träffa tumörmisstänkta områden i prostata. Protokollet i studie 4 beskriver därför även hur man kan undersöka om Forsvallnålen kan vara bättre att diagnostisera cancer än dagens Tru-Cut nål.

Avhandlingen beskriver även den tekniska utvecklingen, ny nålteknik för infektionsprevention även utanför urologin, framtida studier samt strävan att göra Forsvallnålen tillgänglig för patienter.

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Forsvall A, Fisher J, Cardoso JFP, Wagenius M, Tverring J, Nilson B, Dahlin A, Bratt O, Linder A, Mohanty T. Evaluation of the Forsvall biopsy needle in an *ex vivo* model of transrectal prostate biopsy - a novel needle design with the objective to reduce the risk of post-biopsy infection. Scand J Urol. 2021 Jun;55(3):227-234. doi: 10.1080/21681805.2021.1921023. Epub 2021 May 17. PMID: 33999753.

Forsvall A, Fisher J, Wagenius M, Broman C, Korkocic D, Bratt O, Linder A. Prostate biopsy quality and patient experience with the novel Forsvall biopsy needle - a randomized controlled non-inferiority trial. Scand J Urol. 2021 Jun;55(3):235-241. doi: 10.1080/21681805.2021.1921024. Epub 2021 May 17. PMID: 33999764.

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Forsvall A, Fisher J, Wagenius M, Bratt O, Linder A. Infectious complications following transrectal prostate biopsy using the novel Forsvall needle vs a standard Tru-Cut needle – study protocol for a randomized controlled trial. Manuscript.

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Introduction

Like most cancers, prostate cancer is almost always diagnosed by a pathologist examining tissue (a biopsy) from a suspected tumour with a microscope. The tissue is in general obtained by a Tru-Cut biopsy needle, a central tool in cancer diagnostics.

The prostate is located in the male pelvis, a few millimetres away from the rectal wall. Prostate biopsy is therefore mainly performed transrectally, with ultrasound guidance. The needle will then pass through the rectal wall on its way into the prostate, but on its way also bring bacteria from the colon into sterile tissue. Antibiotics are used to limit the adverse effects of bacterial transfer, but the effectiveness of antibiotics is decreasing with increasing antibiotic resistance. If the number of bacteria exceeds an individual threshold value the patient will develop an infection. These infections range from mild to deadly and often require hospital care.

Since prostate cancer is so common, so is prostate biopsy and so are unfortunately also infections following prostate biopsy. A lot of science and efforts are of course put into addressing this problem. But I reason that the main cause of infection is the needle.

Bacteria are brought into sterile tissue by the needle and infection arises.

Infection after prostate biopsy is thus a needle-related complication. Still, to my knowledge, no efforts have been made to alter the needle design.

The research presented in this thesis aims to address the role of the biopsy needle in infection after transrectal biopsy, explain how bacteria are transferred from the rectum to the prostate and periprostatic tissue, develop a novel biopsy needle to minimize bacterial transfer, and evaluate the needle's potential to reduce post-biopsy infections.

The thesis is part of what I like to see as the path of "P"s from a clinical problem all the way to a solution for the patient:

Problem - Prototype - Proof of concept - Papers - PhD - Product - Patient

Prostate Cancer

Epidemiology

Prostate cancer is the second most common cancer in men. In 2020, 1.4 million men received this diagnosis[1]. In 2040 this number is expected to rise to 2.4 million with the steepest increase in Africa (+107%) and Asia (+94%) [2].

The incidence of prostate cancer is highest in Northern Europe (178/100.000), Western Europe (176/100.000), Australia/New Zealand (139/100.000), and North America and Southern Europe (both 131/100.000) [3]. The main explanations for the high incidence in these areas are a long life expectancy and high use of serum PSA tests and prostate biopsy [4].

Figure 1 shows most prevalent cancers in males in each country in 2020. Prostate cancer (shown in green) is the most common cancer in 117 countries and the second most common cancer in another 34 countries (not shown in image)[3].

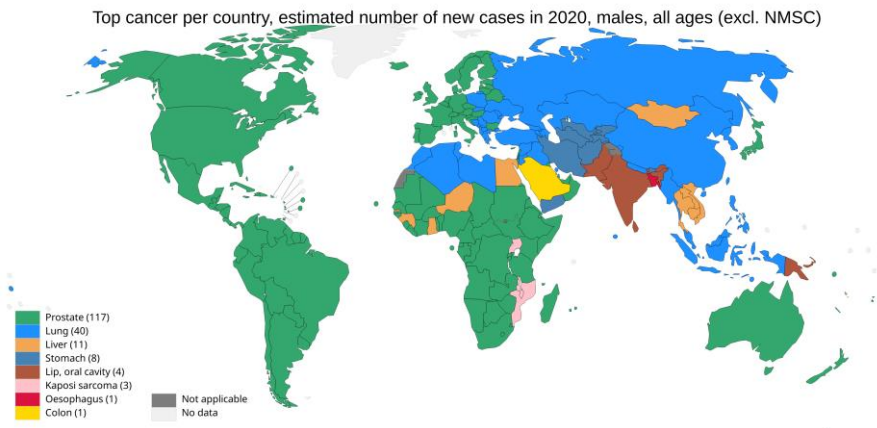


Figure 1 Top cancer per country, World Health Organization estimate of new cancers in 2020, male, all ages, non melanoma skin cancers excluded. Prostate is marked in green.

Sweden has one of the highest incidences of prostate cancer. One in five Swedish men will have a prostate cancer diagnosis during their lifetime [5].

The risk of prostate cancer is also influenced by biological, genetic and lifestyle factors. African descendants living in the Caribbean or North America have the highest risk of developing prostate cancer [3].

Prostate cancer is rare under the age of 40 and very common in older men. Autopsy results indicate a risk of about 35% at 60 years of age and over 60% at 80 years of age [6].

In Swedish men, prostate cancer is both the most common cancer (10949 cases 2020) and the cancer that takes the most lives (2243 deaths in 2020) [7].

Besides being common, prostate cancer is also one of the cancers that has the longest survival times, meaning that it has a high prevalence. This is often measured as 5-year prevalence, meaning the number of people alive in the reference year who had been diagnosed with cancer within the previous 5 years.

Figure 2 shows 5-year prevalence of prostate cancer, the darker the green the more men living with diagnosed prostate cancer.

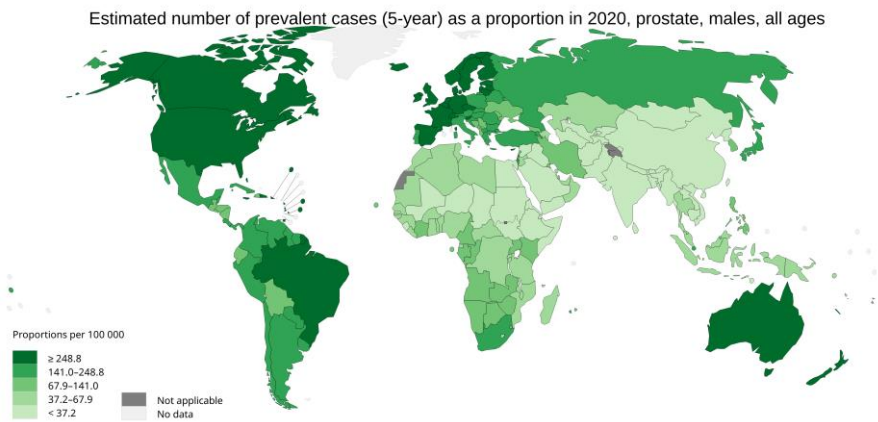


Figure 2 World Health Organization estimate of prostate cancer 5 year prevalence in 2020, male, all ages. IARC, Cancer today, World Health Organization.

The reported prevalence includes men with prostate cancer who have had curative treatment, men with non-curable metastatic disease and men with low and intermediate risk disease who are only monitored but may receive deferred treatment if the cancer progresses.

Prostate biopsies are used both to diagnose prostate cancer and to monitor low risk disease.

Anatomy and physiology

The prostate is located in the male pelvis and part of the reproductive organs.

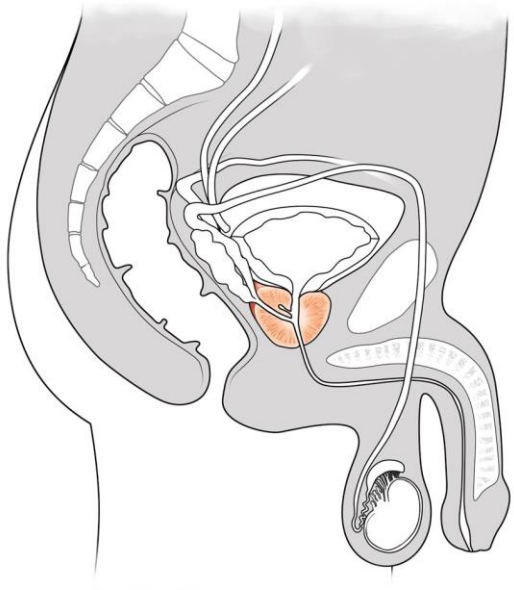


Figure 3 Male anatomy. The prostate in colour. Image :Shutterstock, used with permission.

As seen in image 3, the prostate is at the lowest point of the male pelvis, surrounding the proximal urethra. It is located just below the urinary bladder, and very close to the rectum. The prostate produces fluid for ejaculation, which supports the sperm cells once inside the female.

Diagnosis of prostate cancer

PSA

Prostate Specific Antigen (PSA) is a protein produced by epithelial cells of the prostate. The PSA-test measures PSA in the blood serum, and its usefulness in diagnosing prostate cancer was described in 1987 [8].

The PSA concentration in the prostate cells producing PSA is about one million times higher than in the blood serum. PSA levels in serum are a result of leakage of PSA from prostate cells. This means that an elevated serum PSA is unspecific.

Elevated PSA may for example occur from a large prostate (more cells with normal leakage), urinary tract infection or prostatitis (increased cell damage due to infection/inflammation) and prostate cancer (abnormal leakage from many cancer cells).

Although unspecific, the blood test PSA is an excellent cancer marker, used to raise suspicion of prostate cancer as well as follow up the effect of both curative and non-curative treatments.

Prostate cancer is very prevalent in elderly men, and most will live their life without any symptoms of the prostate cancer. Small, slow growing cancers are therefore not be over-treated. Thus age-specific cut-off values are used to initiate further diagnostic steps.

In men without symptoms or positive digital rectal exam (DRE), the following age specific PSA-values are used for suspicion of prostate cancer in Swedish guidelines:

Table 1. Age specific PSA values, as a recommendation for further diagnostic steps.

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

Further information is given by the relating the PSA level to the prostate gland volume (measured by ultrasound or magnetic resonance imaging (MRI)) - the PSA density, and the level of binding of PSA to macromolecules in plasma (free/total PSA ratio), as well as the rise of PSA over time (PSA velocity). Although unusual, some very aggressive cancers may differ so much from normal prostate cells that they lose the ability to produce PSA.

The standard PSA-test is challenged by other blood tests such as Stockholm3, 4K score test (4KS) and Prostate Health Index (PHI) as well as urine tests such as Prostate Cancer Antigen-3 (PCA3) and Select MDx, all aiming to improve selection of patients for prostate biopsy.

DRE

Digital rectal examination (DRE) is when the doctor palpates the prostate from the rectum with a finger. Many cancers are palpable but a suspicious finding on DRE may have a non-malignant cause.

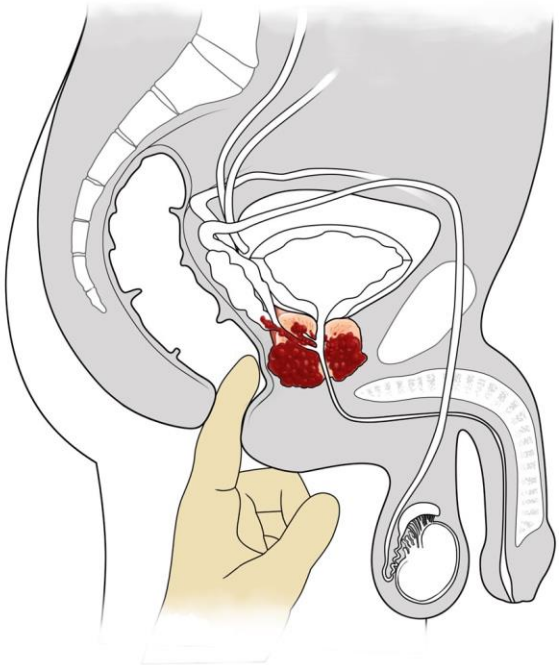


Figure 4 image shows a large, very locally advanced tumour, growing outside the prostate and easily palpable. Image :Shutterstock, used with permission.

Diagnostic pathways

Asymptomatic cancer, standard

Suspicion of prostate cancer in the early, asymptomatic, stages of the disease usually arise by DRE findings or a high PSA value. PSA by invitation (organized PSA testing) is currently evaluated in pilot projects in some areas in Sweden, including Scania.

If PSA and/or DRE raise suspicion of cancer, the next step in current practice is diagnostic imaging by MRI followed by ultrasound guided prostate biopsies using a Tru-Cut biopsy needle system. If the MRI shows a suspected tumour, biopsies are aimed for that area (targeted biopsies). If not, or if the suspected tumour cannot alone explain the PSA level or DRE finding, the prostate is sampled in a systematic way including the areas of the prostate with the statistically highest risk of tumour (systematic biopsies).

The diagnosis of prostate cancer is set by the pathologist when examining the biopsy samples in a microscope. This pathway is by far the most common in countries with a high standard of health care. In regions of the world where MRI is less available,

biopsies are targeted based on ultrasound findings or DRE. Consequently, systematic biopsies are more common there.

Asymptomatic cancer, unusual

Prostate cancer is sometimes diagnosed in histology specimens from surgery for benign prostatic hyperplasia. Surgery is made for voiding problems, usually by a transurethral resection of the prostate (TURP).

Other unusual routes of diagnosing prostate cancer include when the prostate is removed as part of a larger operation for bladder cancer (cystectomy) or biopsy of an incidentally detected lymph node or skeletal metastasis in a patient who has had a computed tomography (CT) scan for an unrelated reason.

Symptomatic cancer

Symptomatic prostate cancer is often locally advanced and/or metastasised.

Local symptoms include increasing voiding symptoms and pelvic pain. Metastatic disease is most often characterized by skeletal pain, often from the spine, pelvis, or hips. Advanced prostate cancer may also present with general cancer symptoms such as weight loss, malaise, and loss of appetite. PSA and DRE often gives a very high suspicion of prostate cancer in these cases.

In rare cases of elderly men with highly elevated PSA, cancer-suspicious DRE, typical metastasis on CT/MRI, and a life expectancy below 5 years, a clinical diagnosis of prostate cancer can be made without prostate biopsy. All others are diagnosed using tissue collected by a Tru-Cut biopsy system.

Prostate cancer may also be diagnosed on a biopsy from a lymph node metastasis, skeletal metastasis, or other metastasis with unknown primary tumour.

Diagnostic pathways – Summary

In almost all cases, the prostate cancer diagnosis is established by a pathologist using tissue obtained from the prostate using a Tru-Cut biopsy system.

The use of the Tru-Cut biopsy needle is so self-evident that its rarely even described in scientific reports on prostate cancer diagnostics. When a prostate biopsy is mentioned, it is implicitly understood that a Tru-Cut biopsy system has been used.

Classification of Prostate Cancer

Prostate cancer is not one disease; some prostate cancers are almost harmless, and some are highly malignant. To differentiate these extremes and everything in between, the Gleason system is used to describe the grade of the cancer. Published

by Donald Gleason in 1966 it sorts prostate cancer growth patterns, as seen in the microscope, into five categories: Gleason grade 1-5 [9]. Each Gleason grade has a complicated description due to it including many morphologies (figure 5). A shorter, and for this setting more pragmatic, description is given below:

Gleason grade 1 is no longer considered malignant.

Gleason grade 2 is no longer reported for prostate biopsies and only rarely in radical prostatectomy specimens.

Gleason grade 3 is small, well differentiated invasive glandular structures.

Gleason grade 4 includes several different tissue morphologies (figure 5), but in short is poorly formed glandular structures.

Gleason grade 5 does not form any glandular structures at all, some not PSA producing.

For simplicity, when explaining biopsy results to a patient, Gleason grade 3 may be described as low risk cancer cells, Gleason grade 4 are intermediate (but often requiring treatment) and Gleason grade 5 as high-risk cancer cells.

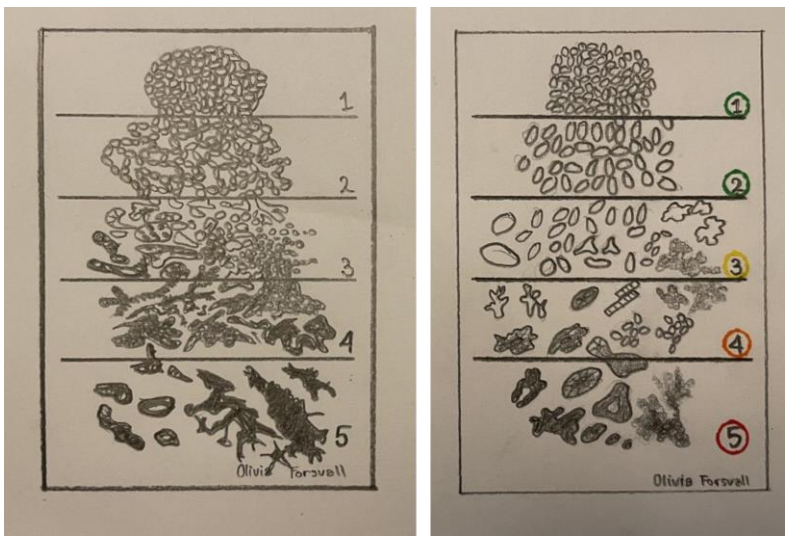


Figure 5 Gleason grading. To the left: Gleason grade as originally described by Donald Gleason in 1966. To the right:The latest Gleason classification from 2014. Gleason grade 1-2 are here marked in green as they are not clinically significant and not reported in prostate biopsy. Gleason grade 3 is yellow, 4 orange and 5 red, symbolizing the worse prognosis with increasing gleason grade. Drawings by Olivia Forsvall

The prognosis of patients with prostate cancer is highly dependent on the Gleason grade; the higher the grade, the more aggressive cancer. The tumour is in most cases heterogenous, containing parts with different Gleason grades.

Since 2005 reporting of Gleason score for biopsy specimens is done as the sum of the most common Gleason grade + the highest of the remaining Gleason grades. For example, if the biopsy shows both Gleason grade 3 and 4 but more Gleason grade 3, it is reported as Gleason score 3+4=7. If Gleason grade 4 is more common, it is reported as Gleason score 4+3=7.

If the tumour is homogenous and only one Gleason grade is present it is still presented in the same way. For example, if the biopsy shows only Gleason grade 3 it is reported as Gleason score 3+3

A Gleason score 6 (3+3) is thus the least malignant form of prostate cancer. Gleason score 10 (5+5) is the most malignant, with the worst prognosis.

Both Gleason score 3+4 and 4+3 equals 7, but Gleason score 4+3 has worse prognosis. Also, Gleason score 6 is a low risk cancer and should not be routinely treated. These clinical implications have been addressed in the 2014 International Society of Urological Pathology (ISUP) grade groups. The ISUP grade groups are also on a scale from 1-5.

Table 2 ISUP grade groups

Gleason Score	ISUP grade group
≤6	1
3+4=7	2
4+3=7	3
4+4, 3+5, 5+3 all = 8	4
9-10	5

The section above relates to adenocarcinomas in the prostate, the by far most common form of prostate cancer. Adenocarcinomas develop in the gland cells that line the prostate gland and the tubes of the prostate gland. Some non-adenocarcinoma cancers may also develop in the prostate, for example small cell cancers (neuroendocrine tumours) and sarcomas (cancers arising from supportive tissue). In general, non-adenocarcinomas have worse prognosis. Gleason grade is used for adenocarcinomas only.

Risk groups of non-metastatic Prostate Cancer

There are several ways to categorize non-metastatic prostate cancer [10]. One commonly used way is the D'Amico system, in which DRE findings, PSA and ISUP grade are combined into three risk groups.

Table 3 D´Amico risk classification of prostate cancer

Low Risk	Intermediate Risk	High Risk	High Risk
PSA<10 ng/mL	PSA 10-20 ng/mL	PSA >20 ng/mL	Any PSA
and ISUP 1	or ISUP 2-3	or ISUP 4-5	Any ISUP
and T1-T2a	or T2b	or T2c	T3-4 or N+
Localised	Localised	Localised	Locally advanced

Where and how much prostate cancer– the TNM-system

The TNM system is used to categorize the extent of local growth and spread of cancer. The structure is the same for all cancers, but it's adapted to specific cancer types.[11] Table 4 describes the TNM-system for prostate cancer. The T means local **t**umour stage, i.e. how big and advanced the primary tumour is in the prostate. The N means lymph **n**odes, i.e. whether there is lymph node metastasis. The M means distant **m**etastasis.

Table 4 TNM staging of prostate cancer

T stage	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically unapparent tumour, not palpable or visible on imaging
T1a	Tumour incidental histologic finding in ≤5% of tissue resection
T1b	Tumour incidental histologic finding in >5% of tissue resection
T1c	Tumour identified by needle biopsy
T2	Tumour confined within the prostate
T2a	Tumour involves no more than half of one lobe
T2b	Tumour involves more than one half lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades the seminal vesicle(s)
T4	Tumour is fixed to or invades adjacent structures other than seminal vesicles (e.g. bladder, levator ani muscle, pelvic wall or rectal wall)
N stage	
Nx	Regional lymph nodes not assessed
N0	No lymph node metastasis
N1	Metastasis in regional lymph node(s)
M stage	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

For example, a locally advanced prostate cancer with localized extracapsular extension without lymph node or distant metastasis on imaging would be categorized as T3aN0M0.

When there is a reasonable risk of metastasis, imaging is used to locate or exclude cancer spread. Imaging includes technologies such as CT, Positron Emission Tomography–Computed Tomography (PET-CT), scintigraphy and MRI.

We will now leave diagnosis of prostate cancer for a while and briefly go into treatment options, before returning to prostate biopsy.

Treatment of Prostate Cancer - curative intention

Surgery

Radical prostatectomy means removal of the entire prostate gland and the seminal vesicles. The bladder is sutured to the urethra to restore outflow of urine. The surgery may be done openly, by making a skin incision between the symphysis and the umbilic and manually removing the prostate. Minimally invasive surgery includes laparoscopic prostatectomy with or without the use of a surgical robot. Robotic surgery has no automated movement, the robotic arms do exactly what the surgeon's hands do in the control console.

Side effects of surgery include a risk of incontinence (insufficient sphincter muscle function) and erectile dysfunction (damage to erectile nerves).

Radiotherapy

External beam radiation therapy (EBRT) is as effective as surgery in curing prostate cancer but has other side effects [12]. Irritable rectal and bladder symptoms as well as bleeding are side effects that may be permanent. Erectile dysfunction often develops slowly due to damage to erectile nerves and their fine vascular system. The radiation also slightly increases the risk of secondary malignancies in the bladder and rectum decades later.

Internal radiotherapy (brachytherapy)

Temporary brachytherapy, or high dose radiation, means a transient placement of radioactive rods inside the prostate under general anaesthesia. It may achieve very high focal doses of radiation to a tumour. This treatment is usually combined with external radiation to give a local boost to high-risk tumours, but it may be used as a standalone treatment.

Permanent brachytherapy means the implantation of multiple small radioactive seeds inside the prostate. It is recommended by the European Association of Urology (EAU) in low-risk disease and in combination with ERBT in intermediate and high-risk disease.

Investigational therapies

The rationale for focal therapy is to reduce the side effects of surgery and radiation by focally treating only the area of the prostate with proven cancer (the index tumour). These alternatives are evaluated in clinical trials mainly with patients with one distinct area of cancer. The flip side is that prostate cancer often is multifocal and there is a concern that minor cancer sites in other parts of the gland may grow over time, requiring repeat treatment by use of the same or another modality.

Temperature changes are widely used to kill prostate cancer cells in focal therapies. In cryotherapy, needles are introduced into the tumour and used to lower the temperature to -40ºC. Half or whole gland-treatments are used. In High-Intensity Focused Ultrasound (HIFU) ultrasound waves are aimed at the tumour and by a combination of heat (65ºC) and mechanical effects tumour tissue is destroyed.

Heat may also be used in laser treatment, where laser energy is pinpointed to a very small area to burn away cancerous tissue. Some laser ablation has the advantage of being able to be performed at the same time as MRI, allowing very specific targeting and also real-time views of results.

None of these therapies are without side effects but focal therapy of prostate cancer has potential in low and medium risk disease, considering that it has less impact on continence and potency than radical prostatectomy. It still lacks long term oncological follow up [13].

Active Surveillance

As noted above, side effects of prostate cancer treatment are a major concern. Delaying and potentially avoiding treatment it is an attractive way to reduce the risk of treatment-related complications. Active surveillance (AS) usually means that the prostate cancer is monitored by yearly DRE, biannual PSA, and MRI and/or repeat biopsy with a few years' interval. Repeat biopsy is invasive and comes with the risk of side effects. A possible pragmatic path is that, if DRE/PSA/MRI shows progression, repeat biopsy is recommended and if the cancer is upgraded then curative treatment is offered [14]. AS is mainly used in patients with ISUP grade group 1 or low volume group 2 who have an estimated life expectancy of >10 years [15]. There is, of course, a risk of missing the window of opportunity to cure the cancer. EAU guidelines recommend a confirmatory set of biopsies at 6 months post inclusion in AS if no systematic biopsy has been done upfront. The authors of a

recent study recommend at least 3 repeat biopsies in the following 10-year period, even in the absence of DRE/PSA/MRI progression [15]. The future use of MRI, novel biomarkers, genetic tests, and new trials results may change these recommendations. As seen later, active surveillance results in many prostate biopsies.

Prostate Cancer - Non-curative treatments

Watchful waiting

Watchful waiting is a similar setting to AS but in patients with life expectancy <10 years. If prostate cancer progresses during watchful waiting, then non-curative treatment is initiated. Treatment is preferably started prior to onset of cancer symptoms. Watchful waiting is used as a way of limiting the side effects of both curative and non-curative treatments in patients with limited life expectancy due to age or other diseases that poses a greater threat to their health.

Treatments for longer life expectancy with better quality of life

Non-curative treatments are used in situations where curative treatment is not possible. This includes all situations with bone metastasis and many with lymph node metastasis. This situation may be present at the time of diagnosis of prostate cancer or as a result of a failed curative treatment or active surveillance.

While the development of curative treatments is mostly driven by developments in MedTech and surgical techniques, new non-curative treatments are mainly based on pharmacological research related to sex hormones.

The basis of hormone treatment is the removal of testosterone from the cancer, a principle based on research for which Charles Huggins was awarded the Nobel Prize in 1966. This may be achieved surgically by bilateral orchiectomy (surgical removal of both testicles) or pharmacologically.

The pharmacological treatment in these situations has seen a remarkable evolution in the last 10 years. We currently have a wide range of treatments that use different intracellular pathways to significantly improve life expectancy in these patients. This enormous field is out of scope for this thesis.

Non-curative prostate cancer treatment also includes chemotherapies, AKT inhibitors, Radium-223, PARP-inhibitors and Lu-PSMA-177, all using different approaches to palliatively treat prostate cancer. It is a huge field of research with many very large trials, but again outside the scope of this thesis.

Prostate biopsy

A brief history of prostate biopsy

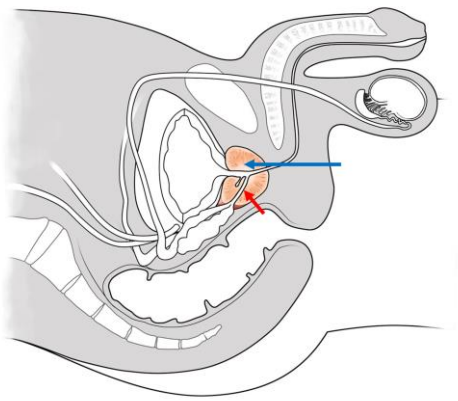


Figure 6 Prostate biopsy. Red arrow indicates needle travel in transrectal prostate biopsy, blue arrow indicates needle travel in transperineal prostate biopsy Image :Shutterstock, used with permission, modified by Andreas Forsvall.

Prostate biopsy started out 100 years ago using a transperineal (TP) approach. In 1922 Barringer described the use of a screw tip needle to obtain a perineal punch biopsy and was successful in obtaining prostatic tissue in 16 out of 33 patients (49%) [16]. Interestingly an improvement of this technique is currently used by Lund MedTech company BiBB instruments in endoscopic biopsies (Endodrill Model X).

In 1930 Ferguson published a series of 280 patients who had prostate needle aspiration biopsy using a standard hollow 18-gauge needle, also via the TP approach. He was able to remove prostate tissue in 78 to 86% of patients [17].

Kaufman, Parry and Finelly were some of the urologists in the 1950-60s to introduce TP biopsies where the needle was stabilized by the index finger in the rectum in combination with a trocar needle. Adequate prostate tissue was obtained in 88% of patients. Rates of erectile dysfunction, incontinence and rectal damage were lower than previously and local anaesthetics were now predominantly used [18] [19].

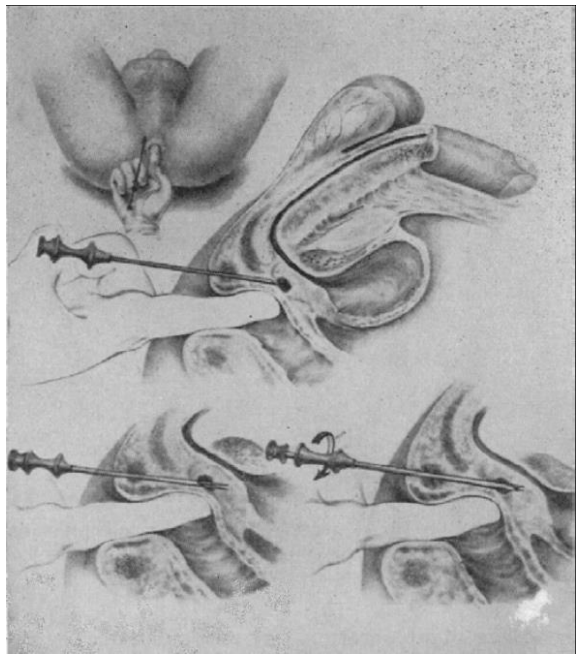


Figure 7 Kaufman 1954, the needle and index finger moves in parallel, guiding the needle towards the palpable tumour. Silverman needle.

Transurethral biopsy, through Trans Urethral Resection of the Prostate (TURP) has been described as successful in the early 1900s [20] but in mid 1900s reserved for very advanced cases [21] and, with non-convincing results, evaluated in smaller studies in later years (pre-MRI) where cancer suspicion prevailed even after repeated negative needle biopsies [22].

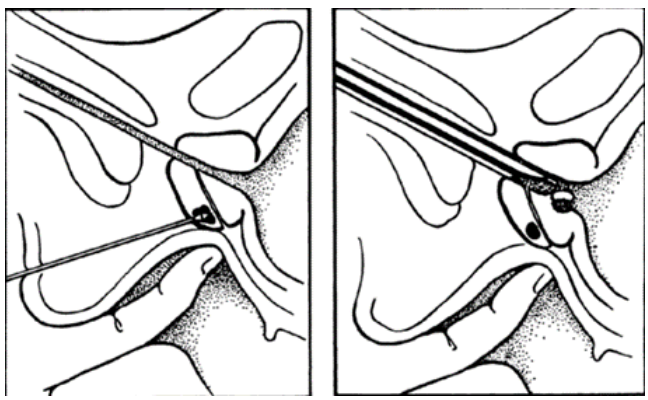


Figure 8 Grabstald 1965; Left: Trans perineal prostate biopsy ; Right Transurethral prostate biopsy. Both with guiding finger in the rectum fixating the tumour.

Transrectal biopsy (TRbx) was first introduced in 1937 by Astraldi [23]. By the 1950s it was considered safe and yielded a higher diagnostic accuracy than Trans Perineal prostate biopsies (TPbx).

The Franzén and Silverman needles

Two types of needles were used:

Franzén

The Franzén needle was used for cytologic diagnosis. The invention was not actually the needle but a needle holder guiding a standard thin needle towards palpable lesions in the prostate. The Franzen needle holder consists of a metal tube, supported by two metal rings as seen in figure 9.

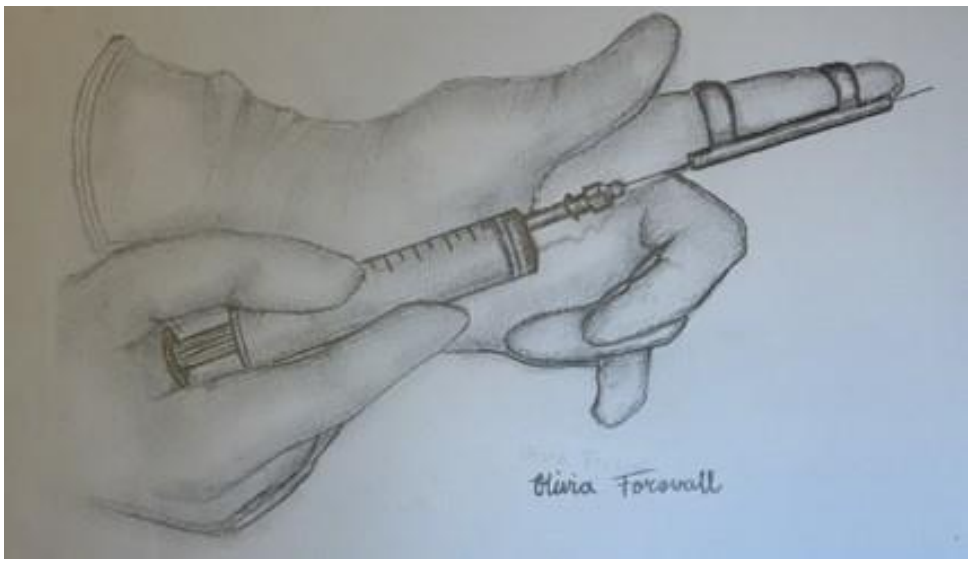


Figure 9 Franzen needle holder. Drawing by Olivia Forsvall.

By placing the needle guide in the palm of the finger inserted in the rectum the lesion could be palpated and the end of the thin guiding tube placed towards the target. Cells were obtained by moving a thin standard injection needle back and forth in the prostate while obtaining a negative pressure in the needle using the syringe. The Franzén needle holder was invented by the Swedish Scientist Sixten Franzén (1919-2008), active mostly at Radiumhemmet and Karolinska Institutet. Initially criticized for performing pseudoscience Franzén developed instruments to help his everyday practice and eventually got internationally recognized [25] [26].

Silverman

The competing needle technique was the Silverman needle, developed in 1938 by Vim-Silverman. It was able to obtain tissue pieces – soft tissue biopsy.

It consists of three parts; a trocar, a hollow needle and a split inner needle.

The trocar and hollow needle is inserted proximal to the lesion and the trocar removed. The split needle is introduced inside the hollow needle. The inner needle parts will split in tissue allowing tissue to be trapped between the needle parts. The hollow needle is then forwarded to close the split parts of the needle. Tissue is trapped and can be torn off by rotating the inner needle. The inner needle is then removed along with the collected biopsy (figure 10).

Pierson and Nickerson were the first to use the Silverman needle in TRbx, in 1943 [27].

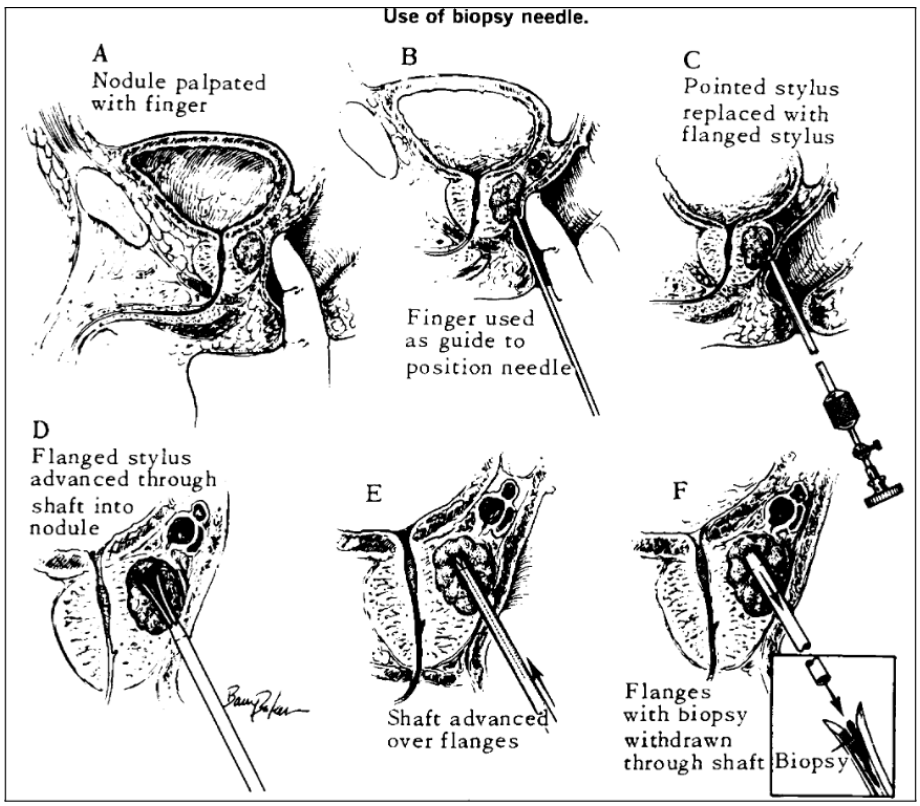


Figure 10 Digital guided TRbx using the Silverman needle, described by Pierson and Nickerson in 1943.

In 1971 Henry and Williams found a reliable diagnosis in 82% of patients with Franzen needle biopsy and 95% using the Silverman needle. The Franzen needle

could be used in an outpatient setting, the Silverman needle required general anaesthesia. It was suggested that the Franzen needle aspiration should be used twice and if diagnosis was still inconclusive the urologist should proceed to use the Silverman needle biopsy [28].

The ultrasound, the prostate anatomy and the Tru-Cut needle

1) 1963 Takahashi and Ouchi were the first to describe the use of transrectal ultrasound (TRUS) to evaluate the prostate [29].
2) 1968 McNeal described the three glandular zones of the prostate (transitional zone, peripheral zone, central zone) [30]. Important since 70-80% of prostate cancer arises in the peripheral zone[30].
3) 1969 Griffith was awarded a patent for his new biopsy instrument – the Tru-Cut biopsy needle. (Filed on Jan 9th 1967 for Baxter laboratories Inc)

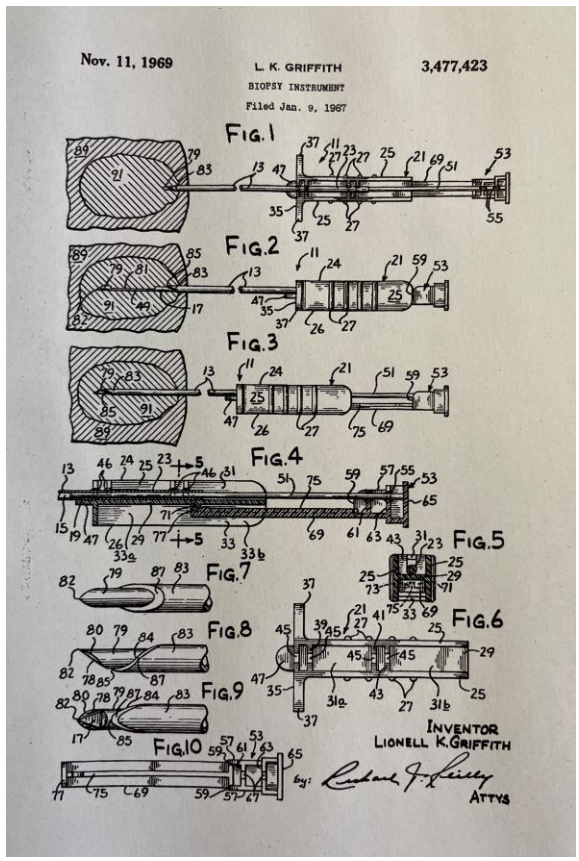


Figure 11 Griffith's patent for the Tru-Cut needle (still the standard biopsy needle today)

The Tru-Cut needle design and basic mechanism of action has remained the same to date. In Griffith's patent a plunger was used to mediate the needle movement.

In 1987 Swedish engineer Per G Lindgren (Uppsala) developed an actuator to automate the Tru-Cut needle movement – the biopsy gun. (US patent 4.699.154). The modern biopsy instrument was born. The biopsy instrument has been used to diagnose almost all prostate cancer since.

Lindgren's mechanism is since used in both multiple-use and single-use biopsy instruments.

Its use is so ubiquitous that its mention in modern scientific literature since is very scarce. When the term prostate biopsy or needle biopsy is used it refers to the combination of Griffith's needle and Lindgren's gun.

Lindgren's patent was sold to CR BARD, now the world's leading manufacturer of biopsy instruments (BARD was later bought by Becton Dickinson Company in 2019).

We will come back to this instrument as it is very central in this thesis, but first a short return to the history books.

In 1974 the first useful TRUS images were described [31] and during the 1980s the technology was made useful in clinical practice. In 1987 the clinical use of PSA was described[8], and PSA was approved by the US Food and Drug Administration (FDA) for prostate cancer screening in 1995[32].

Up until this point all biopsies had been targeted towards a DRE finding. Hodge et al introduced the sextant biopsy in 1989 by proving a higher hit rate systematically than when using target biopsy. [33]. In the following years several studies were published evaluating different biopsy schemes and number of biopsy cores. Eventually Levine published the double sextant biopsy scheme on which modern systematic template is based [34].

Ultrasound guided transperineal biopsies was demonstrated in Copenhagen by Holm and Gammelgaard in 1981 [35]. The needle guiding equipment they describein the article is strikingly similar to what is shown as novelties by Medtech companies in 2022.

In 1999 Djavan et al. suggested to adapt the number of biopsies to prostate size [36]. In 2001 the era of saturation biopsies was supported by a study from the same group: a 24-core transrectal biopsy template demonstrated a 41% cancer detection rate in 116 patients with suspicious findings for a missed tumour yet a previous negative biopsy [37].

However all was not well. Infections in TRbx started to become a clinical problem. As a result, TPbx is making a come-back due to its avoidance of puncturing the rectal wall.

But before moving on to this central part of this thesis, let's have a look at some more modern attempts to improve the biopsy instrument. The aim has never been infection reduction. Tissue collection – and thus improved diagnosis – is the holy grail of biopsy needle development. No difference is made between needles for TRbx or TPbx.

How to increase tissue collection in prostate biopsy?

Without adequate tissue collected by the biopsy needle a cancer diagnosis may still be missed in spite of all the previous diagnostic workup (DRE,PSA,MRI). It is obvious that the more tissue the needle collects from the target area, the higher the chance of a correct diagnosis. Several studies have attempted to find the minimum amount of tissue and some an "optimal" amount of tissue collected by the biopsy needle[38-40]. The user, however, is interested in collecting all the tissue from the target he/she aims for. Biopsy core length is one of the most important parameters that determines the quality of biopsy and detection of prostate cancer[40]. I would argue it is the most important parameter.

In his 1965 publication on biopsy techniques, Grabstald described an open transrectal biopsy. Surgery was made transrectally. An incision was made in the rectal wall and tissue was collected using biopsy-pliers. The advantage was that more tissue was collected [41].The technique was short-lived due to the risk of fistulas and a high rate of complications in subsequent prostatectomy.

Attempts have been made to increase the amount of tissue collected by biopsy needles and thus reduce the number of biopsies needed.

One attempt developed in the early 2000s is the bio-pince needle (Argon Medical). It has a theoretically interesting approach by obtaining full core biopsy samples and featuring three different biopsy lengths (13,23,33mm)

It's an open tip needle using three needle parts. However, it has not become the success it was expected to be. Biopsy length has not impressed, and it has a higher failure rate than the Tru-Cut needle. In a head to head study in TRbx it had a high fail rate and collected shorter biopsies in the 23 mm setting than did Tru-Cut needles with a 19 mm notch [42]. In another study it showed a 27% failure rate and a higher rate of pain and post biopsy fever [43]. It seems to be used today mainly in liver biopsy, preferred because of the 33 mm setting, as long biopsies are very important in liver biopsy [44].

Another ongoing attempt to increase biopsy length is done by the American company Triopsy (formally 3DBiopsy Inc). They have evolved the Tru-Cut biopsy

needle and made it bigger. It is a massive Tru-Cut type needle, 15 Gauge (1.8 mm in diameter) and has an adjustable stroke length up to 60 mm with a unique design to the bottom of the biopsy chamber. It aims to be used in TPbx to collect apex-to-base biopsies in a single shot [45]. The concept looked promising around 2018, but development seems to have halted.

Vacuum-assisted biopsy is a well-known technique in breast biopsy for 20 years, used for both diagnostics and in some cases treatment [46]. The vacuum sucks tissue into the biopsy chamber in an aim to increase the amount of tissue collected per biopsy. The needles used are large (13-7G = 2.5-4.5 mm in diameter) and cost/procedure is fairly high. I have found no published studies describing their use in prostate biopsy.

All in all there are surprisingly few studies and very limited technological development done to the biopsy instrument in relation to its importance. After all, prostate cancer is almost always diagnosed using a biopsy needle.

If the biopsy needle does not collect the right amount of tissue from the right location it breaks the chain of events leading to treatment of the patient.

There is always a weakest link in every chain. I argue that the weakest link is the biopsy needle when it comes to diagnosis of prostate cancer. More on this later.

I also argue the needle used today has the potential to be the main reason for infections in TRbx.

Let’s have a look at the Tru-Cut needle.

Tru-Cut biopsy needle design and function

Figure 12a Open Tru-Cut needle, displaying the biopsy chamber in the inner needle. Photo by Charlotte Carlberg Berg

Figure 12b Closed Tru-Cut needle with the larger hyperechogenic zone and centimetre markings Photo by Charlotte Carlberg Berg

The Tru-Cut needle has a simple design. Is easy and cheap to produce and provides decent tissue samples from most soft tissues. It's used in all types of soft tissue biopsy and comes in different lengths and diameters. In prostate biopsy an 18 Gauge (1.26 mm diameter) 20-25 cm long needle is used. The needles are long since they pass a long steel canal in the ultrasound handle in TRbx, and only the distal part is introduced in the patient (figure 12).

Design

The needle consists of an inner and outer needle part, both connected to a biopsy gun. The needle and gun combined is a biopsy system.

The inner needle has a wedge shape tip and a biopsy chamber of often 20 mm. The biopsy chamber starts about 5 mm from the tip of the needle.

The outer needle is a steel tube with an angled and sharpened edge, like a circular knife. It often contains a hyperechogenic zone close to the distal end and centimetre markings along the needle. The hyperechogenic zone and centimetre markings facilitates location of the needle when using free hand ultrasound, and neither has any use in TRbx.

The Tru-Cut system may consist of a multiple-use gun with single-use needles (one needle/patient), or as a single use product (one system per patient)(figure 13).

Figure 13 Top: Example of single use biopsy instrument (BD/BARD). Middle/bottom: Example of multi-use biopsy gun with single use needle (Argon medical devices). Photo Andreas Forsvall.

The biopsy system uses a two-step movement to obtain a biopsy (figure 14). When the user has positioned the needle tip towards the target the gun is fired by pressing a button. The biopsy sampling procedure takes 1/50 second. Even though it is two separate movements making two sounds, the user and patient only hear it as one sharp sound from the mechanism.

Tru-Cut needle movement

Please see illustration below, describing the needle movement when obtaining a biopsy.

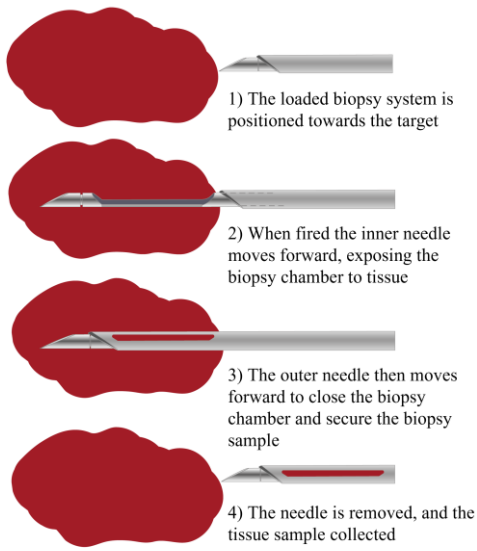


Figure 14 Tru cut biopsy needle movement. Total time for step 2-3 is 1/50 second. Illustration by Catarina Jandér

Development of the Tru-Cut needle 1969-2022

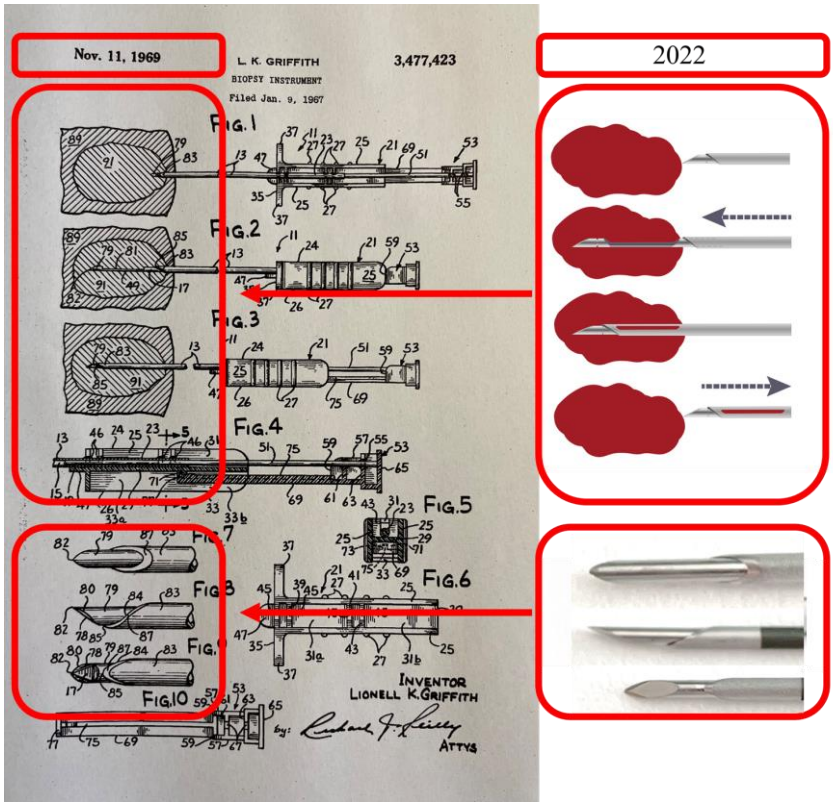


Figure 16 Griffiths patent from 1969 (left), the current Tru-Cut biopsy needle movement (top right) and the current Tru-Cut biopsy needle tip design (bottom right). Please compare and note the lack of difference. Illustration by Catarina Jandér, photo by Andreas Forsvall

he top panels compare the needle movement today with Griffith's patent from 1969. The only difference is that Griffith used a plunger and now we use Landgren's gun to automatically mediate the movement. The needle movement sequence remains the same.

In the bottom panels, note the needle tip design shown from 3 angles in Griffith patent. It consists of an inner needle with a wedged edge and two facets. The outer needle is angled and sharpened on the outside. These exact features continue to be used in the Tru-Cut needle today (bottom right)

Infections in Transrectal Prostate Biopsies (TRbx)

Antibiotic resistance and the increase in infections

When Astraldi published his paper on TRbx in 1937 there was a debate regarding the risk of faecal contamination in TRbx, but still it became widely used in the 1950s. I have not been able to confirm the exact details but I assume it was facilitated by the evolvement of large scale production of antibiotics during the later stages of the second world war. This allowed chemical protection against infection, enabling biopsy through a bacteria-rich area such as the rectum. With antibiotics, TRbx became reasonably safe and, at the time, provided better diagnostics. Randomized trials have since confirmed the effectiveness of antibiotics [47] [48] and they are now standard of care.

Smaller studies[49] had reported risk of infection earlier but the study by Nam et al of 75.000 prostate biopsies from Ontario, Canada was the first real warning sign in 2013. It demonstrated that the rate of hospital admissions related to infection had increased from 0.6% in 1996 to 3.6% in 2005. A sixfold increase. The authors attributed it to rising rates of antimicrobial resistance (AMR)[50]. A similar, although less dramatic, increase was later recorded in Stockholm with a rate of positive blood cultures within 30 days of biopsy increased 3-fold from 2003-2012 [51].

The increase in infection rate has been described in multiple studies since [52-54]. As always in science not all results align and there are studies showing very low infection rates in TRbx [55-57]. Still the evidence for an increase is overwhelming and it is an accepted fact in major guidelines (European Urology Association/American Urology Association). The exact level of infection is hard to stipulate since studies use comparisons between different times and geographical locations, using different definitions of infection. This field of research also suffers from the lack of an ICD-10 code describing post biopsy infection.

ICD-11 is slightly better, using the combination of an infection code with PK81.5 “Biopsy procedure, not elsewhere classified, associated with injury or harm in therapeutic use” or (for the little more daring) PK98 “Radiological devices associated with injury or harm”. These classifications are still unintuitive and in my mind not good enough.

I argue that there should be a specific infection code related to prostate biopsies.

Magnitude of the problem

I estimate that about 3.2 million prostate biopsies are performed each year. The estimate is based on a combination of sources. WHO estimates that 1.4 million men are diagnosed with prostate cancers annually. Biopsies are also used in active surveillance of prostate cancer. My estimation is described below.

An estimation of the number of prostate biopsies

At the time of calculation (1 June 2022) Swedish National Prostate Cancer Register, NPCR Ratten reported 4481 biopsies in 2021[58]. About 11.000 cancers are expected to be diagnosed 2021. (Far from all the 4481 biopsies diagnose a new cancer so well below 50% of biopsies taken were reported). In 75% MRI was used pre-biopsy.

NPCR Ratten shows 692/4481 biopsies reporting Gleason 6 (low risk cancer, suitable for Active Surveillance (AS)). 1516/4481 reports medium risk (Gleason 7) – a mixed group of patients where some will be treated, and some go into AS.

If 1/4 of the Gleason 7 cancer patients are estimated to be recommended AS then 1071/4481 (24%) of biopsies results in an AS.

Of 11.000 cancers then 2630 (24%) are recommended AS/year in Sweden.

There are several follow-up programs for AS, but most include a set of 3 re-biopsies within 10 years. If we calculate that the average patient stays in AS for 10 years, the pool of patients in AS is 2630 x10 (26300) in Sweden.

If we calculate a re-biopsy every 3 years, then AS results in 26300/3=8767 (9000) biopsies/year in Sweden.

Using MRI pre biopsy the percentage of cancer findings in prostate biopsy has increased (Personal estimate 70%) With 11000 cancers then 16000 biopsies are needed to find them.

Total number of biopsies is then 16000+9000=25000. Thus 44% of the total amount of biopsies diagnose a cancer.

World Health Organization reported 1.4 million new cases of cancers in 2020[3]. With a 44% of biopsies diagnosing a new cancer, then 3.2 million biopsies are taken each year with a high usage of the MRI-first approach.

Factors increasing this number are increasing numbers of prostate cancers due to more elderly people and increasing use of PSA as well as increasing use of AS. All of the world is not using MRI first, decreasing the hit rate of cancers, thus requiring

more rebiopsies. It also increases findings of Gleason 6 cancers, further increasing the use of AS and rebiopsies in this setting.

Factors decreasing the number of biopsies is the future likely possibility of using PSA+MRI as a tool in AS and unknown adherence to AS recommendations of re-biopsy.

Number of biopsies in literature

EAU estimated that 3.7 million biopsies were taken in USA and Europe alone in 2017[59]. Many studies claim that 1 million biopsies are taken annually in the US each year, however without reference to data. In 2022, Bratt estimated the number of biopsies to be over 3 million annually[60].

Cost of infection

The risk of infection is mainly reported as 5-7%[53, 61, 62] and hospitalization due to infection around 3%[53, 61-63]. The re-introduction of TPbx will lower these numbers.

With 3.2 million biopsies and an infection rate of 5-7%, 160.000-224.000 men suffer an infection and, at a hospitalization rate of 3%, 96.000 men are hospitalized each year following prostate biopsy. Cost of hospitalization due to infection is discussed in paper 3[62] and estimated to $US 8672-19100 per patient [64].

A gross estimate using 96.000 hospitalizations at an average cost of $US 11000, indicates a global direct hospital cost of $US 1.050.000.000/year. Using the current exchange rate (10.7 SEK/USD) that translates to 11.3 billion SEK/year. This is a significant economic stress on health care systems.

Risk factors for infection

A vast number or risk factors for infection have been described: Age, obesity, diabetes, chronic obstructive pulmonary disease, corticosteroids or other immunomodulating drugs, ongoing urinary tract infection, travel to areas with higher level of antibiotic resistance, antibiotic use within 6 month, non-white race (USA) and antibiotic resistant bacteria in the stool [52, 65-68]. Others are not so commonly described, for example chronic idiopathic constipation [69].

Conflicting results

Positive urinary culture without clinical signs of infection has been discussed as a risk factor for infection. Level of evidence is low, and a recent expert opinion did not see it as a risk factor for infection [70]. It is however reasonable to believe that

the trauma and tissue destruction by the needle may transform asymptomatic bacteriuria or focal bacterial growth in the prostate into a clinical infection.

Transrectal infiltration of local anaesthetics has shown to increase the risk of infection in a large trial [71] but not in a metaanalysis of 26 studies (although authors state very low certainty of evidence) [72]. Anectodical patient cases include a patient who aborted TRbx after local anaesthetics were administered and did not have TRbx, but still developed infection [73].The pathophysiology of infections in TRbx (bacterial transfer by the needle, please see later sections) supports the role of transrectal punctures for local anaesthetics as a risk factor for infections.

Current methods to reduce the risk of infection

Choice of antibiotic prophylaxis

As the increase in antibiotic resistance in bacteria has been the logical explanation for the increase in infections multiple studies have compared different antibiotic prophylaxis regimens [74].

Increasing antibiotic resistance as the only explanation for the increase in infections has been questioned in a recent study from Malmö: The Proqur study showed an increase of positive urine or blood cultures within 14 days of biopsy from 1.5% in 2003-07 to 2.6% in 2013-17. So far results are in line with most other publications. Fluoroquinolone (ciprofloxacin) were given as prophylaxis in 98% of patients. However, resistance rates for fluoroquinolones in infected patients did not increase during the study period, the trend on the contrary was the opposite, and decreased from 54-44% during the study period. Conclusions for the increase of infections could not be made due to limitations in the study design but an increased fragility in patients accepted for TRbx later in the study interval is one hypothesis[75]. A complementary explanation to the rising global rates of infection may thus be TRbx of more fragile patients in later years.

In the greater picture, the increase in risk of infection is in parallel and strongly associated with increasing antibiotic resistance. As a response, the number of antibiotics used as prophylaxis has thus increased.

There is however a line between antibiotics intended to be used as prophylaxis and those used for treatment. If we start to use more and more sophisticated antibiotics as a prophylaxis we will have less alternatives for treatment later. An overuse of potent antibiotics in prophylaxis thus drives antibiotic resistance also in our “last line of defence”. Ertapenem is a treatment drug in Sweden. In line with lower rates of antibiotic resistance it has shown promising results as a prophylaxis reducing infections from 2.65 to 0.34% compared to ciprofloxacin [76]. Fosfomycin has

shown superiority to ciprofloxacin in 2 meta-analyses[74, 77] but again local resistance situation should be taken into consideration in the choice of prophylaxis as the study results may not be generalized.

The situation is further complicated by the fact that only a minor number of antibiotics achieves minimal inhibiting concentration (MIC-values) in the prostate and provides protection towards the faecal pathogens that causes infections in TRbx.

Fluoroquinolones (e.g. ciprofloxacin) have been the drug of choice, but overuse has increased antibiotic resistance in *E. Coli* and in combination with an increased awareness of side effects they are now not recommended by the EAU. In Sweden AMR is still low and they remain the drug of choice along with Co-trimoxazole.

Globally *E. Coli* resistance to fluoroquinolones and co-trimoxazole are currently both 43.1% with high regional differences [78]. India and Sweden are examples of high and low AMR regions underlining the need to adapt antibiotic prophylaxis to local resistance patterns.

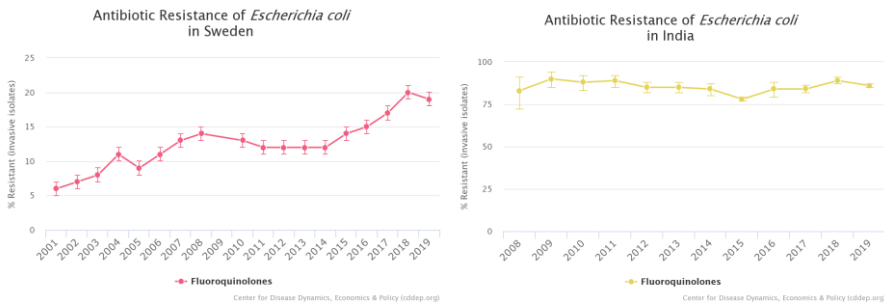


Figure 17 Antibiotic resistance of *E. Coli* in Sweden and India. Graphics from Center for Disease, Dynamics, Economics & Policy. Please note the differences in scale.

If knowing your local resistance rate is superior to following general guidelines for antibiotic prophylaxis, then knowing the individual patient's resistant pattern should be even better. That is the rationale for targeted prophylaxis.

Targeted prophylaxis

Targeted prophylaxis is performed by analysing AMR in a stool sample prior to biopsy and adapting antibiotic prophylaxis to the result. The aim is to avoid using a prophylaxis to which the patient's gut bacteria are resistant, as they are likely to be involved in a post-biopsy infection.

Logically it would work better in areas with high rates of AMR. In a 2018 meta-analysis by Scott et al. the rate of infection was 0.8% in the target antibiotics group compared to 3.4% using standard prophylaxis [79]. An RCT from a high AMR area (Nigeria)[80] showed similar results[81]. A large RCT from London (a low/medium

AMR area) [82] on the other hand showed no effect of target prophylaxis [83]. A 2020 metanalysis again showed an effect of target prophylaxis, although less prominent than in the 2018 Scott et al. study with a 55% lower risk of infection compared to standard prophylaxis. [74].

Investigated non-antibiotic methods to reduce infections in TRbx

Rectal cleansing

In line with the hypothesis that cleaning the colon from bacteria prior to TRbx reduces infection, different cleaning methods have been examined, with very different results.

Enema – No effect [72], probably due to a macroscopic cleaning but an ineffective microscopic cleaning. As the bowel moves and bacteria with it, timing may also affect results.

Povidone-iodine or chlorhexidine – Effective and reduces infectious complications by 50% in meta-analyses [72, 84] and reduced hospitalization due to infection from 7% to 1% in a Turkish RCT of 222 patients [85]. Raman et al developed a very thorough method of cleaning the rectal vault, using either povidone-iodine or chlorhexidine. The method is described in a video-publication from 2015 [86] but the graphic excessive scrubbing of the rectal vault demonstrated in a sedated patient might have discouraged some colleagues from using the method.

A cohort study of 1181 men this from the same group (Penn state), using the same rectal cleaning method, showed very interesting and for this thesis very relevant results [87]. Both povidone-iodine and chlorhexidine was used, with no relevant difference in effectiveness. The interesting part is that they also quantified the effect on bacterial load by cultures before and after rectal cleansing.

Their method of cleaning the rectum reduced the bacterial load by 98.1%

Total infectious complications were reduced by 50% (2.4 to 1.2%) although not statistically significant (p=0.14).

Serious infections were significantly reduced by 78% (2.3 to 0.5% p=0.013).

ICU treatment was rare but, not significantly, reduced by 75% (0.8 vs 0.2%, p=0.22).

A 98% reduction in bacterial load

reduced the risk of serious infection by 78%

The cohort design has inherent risk of bias but to my knowledge it's the only study that quantifies bacterial load and correlates it to a clinical result in infections following TRbx.

The method has some strengths and limitations:

Strength: Povidone-iodine and chlorhexidine are cheap. The effect is proven in multiple trials. It may also be combined with our novel needle with a possible additive effect.

Limitation: It takes 5 minutes or so and is uncomfortable for the patient. As performed in the study it is user dependent and povidone-iodine has a minor risk of allergic reactions. If sedatives are used, total patient care time is significantly prolonged.

Rectal cleansing using povidone-iodine prior to TRbx is currently recommended in the EAU guidelines.

Single use instruments

The infection is caused by bacterial transfer from the tip of the biopsy needle. Instrument parts not entering the body cannot inoculate bacteria. Changing the handle from multi-use to single use reduces cleaning time of the biopsy gun but increases cost and environmental effects. Even though the market is switching more and more towards single use instruments, I have not found any infection-related studies supporting their use.

Single use biopsy needle guide

A small Turkish RCT with 55 patients did not show an effect of single use needle guides [88], but another Turkish RCT of 198 patients showed significantly lower rates of infection [89]. A case report from 2013 showed a possible transfer of hepatitis C [90] and a US article has described an outbreak of pseudomonas infections following uncomplete cleaning of reusable needle guides [91]. My conclusion is that if adequate equipment for sterilization of the needle guide is not available, single use guides do have an advantage.

Limiting the number of biopsy cores

Theoretically limiting the number of biopsy cores would reduce the risk of side effects as fewer transrectal punctures are made. There is conflicting evidence regarding the effect.

In large materials and meta-analyses, the number of cores has not been shown to reduce the risk of infection. In a recent meta-analysis by Pradere et al [92] in the Journal of Urology, the number of biopsy cores was again not associated with hospitalization due to infection. However, the conclusion was based on 5 studies with in total 5 hospitalizations (4 in the extended biopsy scheme and 1 in the standard). Hence the authors' conclusion that there is no evidence supporting that more cores increase the risk of infection.

Based on the study above and a meta-analysis of antibiotic prophylaxis[74] the EAU stated [93] that "Furthermore, the number of biopsy cores, use of local anaesthesia in the form of periprostatic nerve block (PPNB), number of injections for PPNB, needle guide type, needle disinfection, and needle type had no influence on the rate of infectious complications". Though this is true based on their result a lot of comments can be made on these conclusions, mainly that a mix of TRbx and TPbx studies was used and the number of included papers and patients was low compared to available literature. Although easily misinterpreted, there were no different needle types used (all were Tru-Cut needles), the wording "needle type" refers to the use of an extra coaxial needle or not in TPbx.

However, looking at newly published individual trials there is evidence emerging supporting that limiting the number of cores may reduce infectious complications in TRbx. With the introduction of target only biopsies this has now been more extensively studied.

A Dutch study of 4322 biopsies, published in July 2022 [94] compared infectious complications after TPbx biopsy with TRbx and also grouped them into systematic + target (>10 biopsy cores) or target only (<4 biopsy cores).

At 30 days 4.8% (>10 biopsy cores) and 2.3% (<4 biopsy cores) of patients in the TRbx group had infectious complications. The results were mirrored in TPbx, but at a lower rate; 2.6% in >10 biopsy cores and 1.3% in <4 biopsy cores had infectious complications at 30 days.

In August 2022 a group from Helsinki [95] published a comparison of TRbx between 12 systematic biopsy cores and target only (3.7 biopsy cores on average) in a total of 5288 biopsies (54% of patients had 12 biopsy cores). Urine cultures within 30 days were positive in 2.7% in the 12-core group and 1.7% in the target group (not statistically significant). CRP >100 was found in 4.2% of the patients with 12 cores and 3% of target biopsy patients (p=0.015). Blood/urine cultures and CRP was taken more frequently after 12 cores.

Recent, larger, studies are thus starting to support the theory that reducing bacterial transfer by limiting the number of biopsies may also reduce the risk of infection. Future meta-analysis may thus come to different conclusions than currently available.

Limiting the number of cores increases the need for needles designed to hit the target.

Transperineal biopsy (TPbx)

In line with the bacterial reduction theory of this thesis TPbx aims to reduce bacterial transfer by avoiding the puncture of the rectum altogether. It is successful and is currently recommended by the EAU [93]. Multiple large trials have been published, in general infection is much less frequent than in TRbx, and infections also tend to be less severe[96-98]. It seems likely that antibiotic prophylaxis can be omitted [60]. I have not found any studies indicating a higher risk of infection in TPbx than TRbx.

A British study of 73 630 patients undergoing prostate biopsy retrospectively compared complications between TRbx and TPbx. Those undergoing TPbx (n = 13 723) were more likely to have an overnight hospital stay (12.3% vs 2.4%), were less likely to be readmitted because of sepsis (1.0% vs 1.4%) but were more likely to be readmitted with urinary retention (1.9% vs 1.0%) than those undergoing a TR biopsy (n = 59 907). There were no significant differences in the risk of haematuria or mortality [99].

As noted, although sepsis rates are lower, total complication rate and logistical issues balance the comparison somewhat. With the current introduction of local anaesthetics in TPbx, the rate of overnight stay is expected to be reduced in the TPbx group. Although intuitive, the reduction in bacterial transfer in TPbx has been evaluated by 2 extra biopsies solely for culture purposes after either TRbx or TPbx, showing 66% lower total bacterial counts after TPbx. The rate of *E. Coli* (the bacteria causing >80% of infections) in biopsy-based cultures were 45% in TRbx and 0% in TPbx [100]. A possible bias is that the skin was cleaned with povidone-iodine prior to TPbx but no similar measures were made prior to TRbx.

Trans gluteal biopsy

Instead of, as in TPbx, puncturing the perineum to access the prostate, the needle is inserted through the gluteus muscle and in an angle aimed towards the prostate. It more complicated than TPbx and provides a longer travel of the needle. Usage is currently very limited and mainly an alternative for patients without a rectum, trans gluteal biopsy is then performed with CT guidance [101]. From an infection point of view, I estimate it should be comparable to TPbx.

Methods under investigation in TRbx

Intraprostatic injection of amikacin directly after TRbx in combination with per oral ciprofloxacin has showed a reduction of infections compared to per oral ciprofloxacin alone (0% vs 8,6%) in a study of 210 patients [102]. All infected patients had ciprofloxacin resistant, amikacin sensitive *E.Coli* in cultures. It is unclear if the results are due to the intraprostatic injection or just the use of an adequate antibiotic.

Formalin disinfection of the needle between biopsies; Issa et al showed a reduction from 0.8 to 0.3% infections [103] but the results was not as favourable in an Indian study comparing the method head-to-head with povidone-iodine. Bajpai et al showed a 7.6% infection rate with formalin needle disinfection and 2.3% using povidone-iodine rectal cleansing, both in combination with antibiotics [104]. Adding formalin disinfection of the needle to povidone-iodine and antibiotics reduced the risk of infection from 6.4% to 3.9% compared to antibiotics alone in a recent 1250-patient Brazilian RCT, posted as a preprint at the time of writing. [105]. The result shows a lower effect than most studies have seen for povidone-iodine alone. However, the rectal cleansing was not as extensive as in many trials, here made by swiping the rectal wall with a povidone-iodine gauze around the index finger, possibly affecting results.

As discussed later in paper 1, cleaning of the needle between punctures did not affect bacterial transfer in our study [106] as the needle collected new bacteria with each puncture. Auffenberg et al studied 17.954 TRbx, of whom 5.321 received cleaning the needle tip with formalin or alcohol. Needle tip cleaning reduced hospitalizations from infections from 1.12% to 0.85% [107]. In conclusion cleaning needles or formalin dip between punctures does not seem to have a great effect on infection risk. In Issas [103] study the needle was opened in formalin and then closed so formalin was trapped inside the needle.

I hypothesize that the main effect of formalin in this study may be that it, by capillary force, in part helps block bacteria from entering the forward-facing opening of the Tru-Cut needle as well neutralizing any bacteria trapped here.

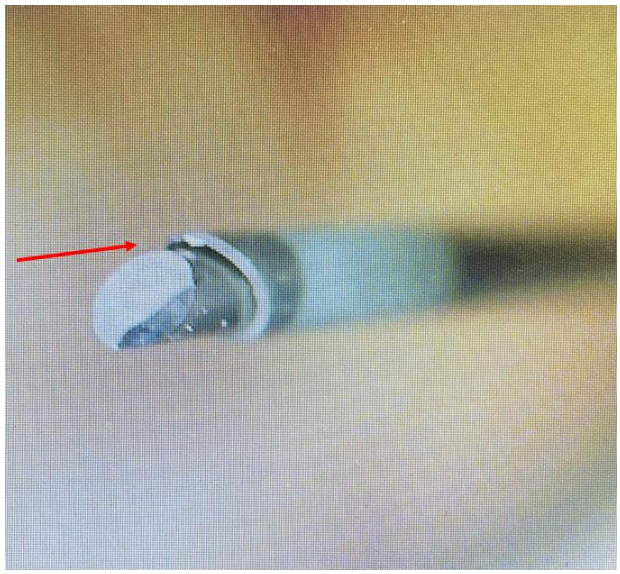


Figure 18 The Forsvall hypothesis – Formalin may partly block the forward facing opening of the Tru-Cut needle and helps neutralize trapped bacteria.Photo by Andreas Forsvall

Liquid biopsy

The term liquid biopsy (LB) refers to a blood or urine test aiming to diagnose cancer. It's technically not a mechanical biopsy at all, but the technology aims to solve the same problem as a biopsy needle.

The dream is to diagnose, or screen for, cancer by analysing body fluids instead of solid cancer tissue. The term LB is also used for genetic tests to guide targeted oncological treatments (e.g. PARP-inhibitors) and some LB in this field has been approved[108].

There are numerous scientific groups and Life Science companies in the LB and biomarker field in Lund alone, indicating the massive interest and potential. Although it is likely to be the future of cancer diagnostics, the path from idea to a proven and approved product is very long and the failure rate is very high. For the foreseeable future medicine will have to rely on a mechanical biopsy for solid cancer diagnostics.

Infections in TRbx- the new angle

The current view – infections in transrectal prostate biopsy are caused by bacterial transfer from the rectum into sterile tissue.

My view - infection in transrectal prostate biopsy is a needle-induced infection. The focus should be the needle. And this is where this story begins.

Overview of the project

This project, of which this thesis is a central part, can be described as a series of Ps. It all started with a clinical **P**roblem to which the solution seemed to be technical. **P**rototypes were made and **P**roof of concept achieved. The **P**hD-studies have aimed to test the **p**rototypes against the current gold standard (the Tru-Cut needle). To come all the way to the **p**atient one must move outside the university world and into the company world to produce a **P**roduct. Hence Xaga Surgical AB was founded in 2016. Using parallel funding and having an extra leg to stand on has really been essential for the scientific results, the same way the scientific results have been important for the company. The unique possibility of having one foot in the clinical world (Region Skåne), one in the scientific world (LU) and one in the company (Xaga) has enabled me to attract finance and co-workers to make this project a reality. Without all these three and all the people who has helped along the way this would not have been possible. **P**atents are also essential to secure finance. Following this **P**hD the goal is to bring the **p**roducts to the market (via regulatory approved **P**roduct) and thus reach the final goal – to make the technology available to **P**atients.

Early work, a background to published articles

This section contains unpublished data that serves as a background for the technical development and the published articles.

Two of my patients were almost simultaneously readmitted with sepsis after TRbx in 2014. I started reading up on the subject, around the same time as the Nam publication [50] which showed a rapid increase in infections with a logical connection to increasing antibiotic resistance.

My wife, Cecilia, and I had just sold her silver jewellery business (sagaofsweden.se). My part of the business was mainly to engrave names in Cecilia's silver jewellery. The eye is very sensitive to small details and if I missed by 5/100 of a millimetre it did not look right, and the jewellery had to be redone. I got an eye for small details in metal.

I started looking at the biopsy needles we used and realized that they have a forward-facing opening. And that opening is quite large, clearly visible with the naked eye. This large opening could collect bacteria and "scoop" it into the prostate. The design seemed utterly unfit for transrectal use. (As described later, the opening is at least a staggering 200.000 times the size of the infection-causing *E. Coli* bacteria)

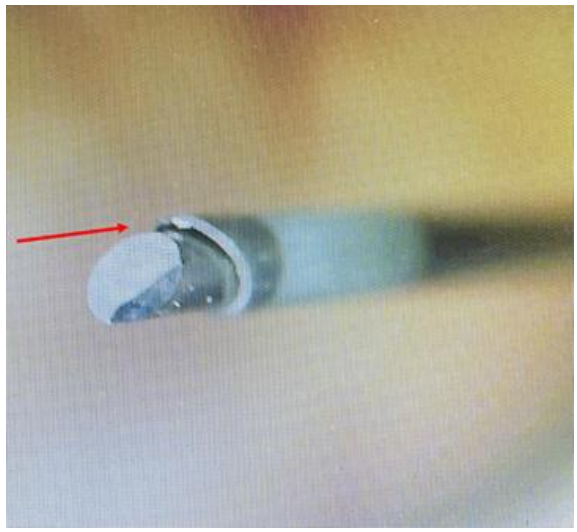


Figure 19 Tru-Cut needle: please note the forward facing opening between the needle parts. Arrow indicates the suspected (and later confirmed) main location of bacterial collection, between needle parts. Photo by Andreas Forsvall.

I then started to look for other needle designs to buy for the clinic, to reduce the risk of infection. There were none. I asked my colleagues if they knew of any alternative needles to use. They knew of none.

During the following year I started drawing different needle models, all aiming to reduce the risk of infection. I then had 14 versions, all intended to be better than the Tru-Cut needle.

Using simple tests, deduction, and head-to-head comparisons, I came to the conclusion that a heated needle must be the optimal choice. Bacteria can not develop resistance to heat, and heat kills all bacteria. Heat is also technically easy to produce and already used in killing cancer cells (see investigational therapies).

The next great technical challenge was the balance of making the needle hot enough to kill all the bacteria on the outside of the needle but limit the heat transfer to the patient and to the biopsy chamber.

The forward-facing opening was still a big problem and after a lot of work and help from LU Innovation I developed a closed needle, the early version of the needle we will later use in the studies of this PhD.

The closed needle tip had a dual purpose, to prevent the “scoop” effect of the Tru-Cut needle (i.e. prevent bacteria from being collected inside the needle) and spread any collected bacteria evenly along the outside of the needle by tissue friction. Using very simple tests (punctures of Nutella covered banana peels with a sharp rod) it was clear that it worked. The collected simulated bacteria (Nutella) formed only an

almost non-existent thin layer along the needle. Similar tests were used to determine simulated bacterial transfer with different needles.

I started experimenting with how to heat the needle. One of the needle versions was based on that infrared laser light passes through the human body without delivering its energy, but if it hit metal it would heat the metal[109]. The technology is used in treatments of thyroid cancers where gold nanoparticles are injected into the blood stream and then leak through capillary defects in the tumour. Targeted laser light heats the gold and the heat destroys the tumour[110]. I heard Maria Stömme, professor of Nanotechnology in Uppsala, talk about the technology and got inspired. My theory was that if we equipped the ultrasound handle with a laser pointed at the where the needle entered the prostate we could heat the needle as it passed and sterilize it.

With the help of Andreas Dahlin, professor of nanotechnology at Chalmers, we set up an experiment using lasers. The first part went excellently, the needle heated up as planned when exposed to the laser energy. But when adding tissue (simulated by an entrecôte) the laser light scattered and 95-98% of the energy was lost. A strong enough laser was not technically feasible, and the laser version was put on ice.

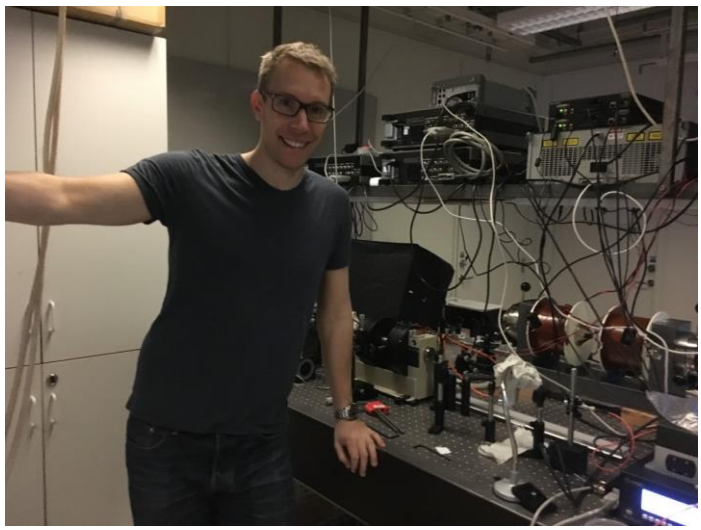


Figure 20 Andreas Forsvall and the laser setup, Chalmers School of Engineering, Gothenburg 2015.

After other failed needle versions, I constructed a needle heated by electric resistance. It looked really promising.

With money from the Gorthon foundation and Sten K. Johnson we built the first prototypes for a preclinical trial in 2015 and by 2016 I was accepted as a PhD student at Lund University.

The first needle study (unpublished)

The first study at LU was promising but with an important lesson – do not create a solution that cannot be put into practice.

The aim of the study was to evaluate if the construction of the heated needle may work and what temperatures were needed to sterilize the outside of the needle.

The first half of the study was to evaluate at what temperature *E Coli* was not able to survive on the outside of a biopsy needle, and a heatable prototype needle was set to different temperatures and an *E. Coli* solution was applied to the needle. The needle was then rolled on an agar plate.

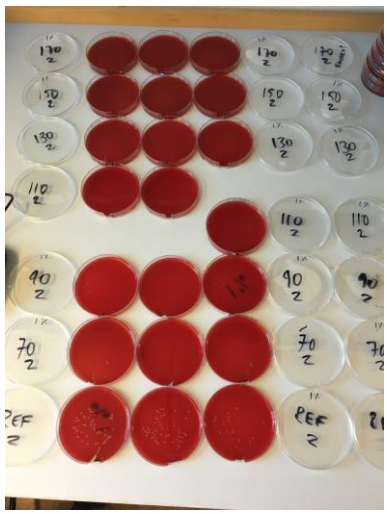


Figure 21 Image from the study: The top section (130+ degrees) with zero growth of *E. Coli* on the outside of the heated biopsy needle. Temperatures 70-90-110-130-150-170-190 degrees Celsius and exposure time 4 seconds was used. Bottom section with lower temperatures and growth on the agar plates, 110 degrees had growth on 1 of 3 agars. Photo by Andreas Forsvall

The other half of the study was a simulation of the heat in a computerized model of the needle in tissue made in collaboration with FS Dynamics in Gothenburg. I had constructed a very complicated needle model. It had a closed tip, an electrical circuit and a nanocoating.

Both the inner and outer needle parts of the simulated needle were made from Kevlar with an electrical leading part made of silver. The most distal 6 centimetres of the needle had a 50 nm gold coating. At the base of the needle there was two electrical connectors (+/-).

The simulation was a success. Using 0.75V for 0.15 seconds the needle heated up to 200 degrees along the outside of the needle with peak temperatures of over 800

degrees at the tip (where most bacteria were expected). The nanocoating heated up very quickly but due to the very small mass of the 50 nm coating it also cooled very fast. It also caused very limited head spread into tissue with only 100 degrees of tissue temperature 0.1 mm from the needle and normal tissue temperature 0.5 mm from the needle.

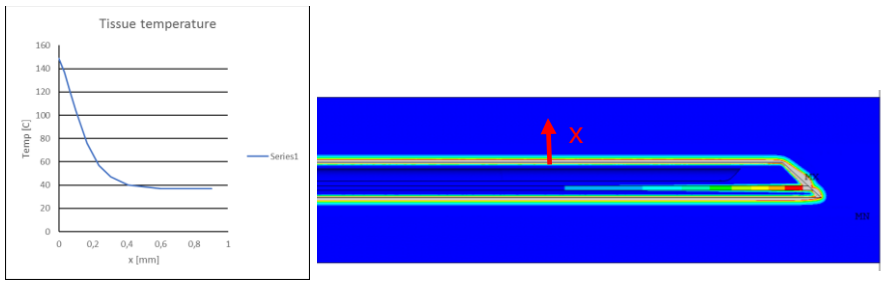


Figure 22 Limited heat transfer into tissue by the heated needle. X marks distance (mm) from needle surface. Graphics by FS Dynamics AB

The construction also insulated the biopsy chamber from the heat and by using a 16 gauge needle the insulation by the Kevlar was good enough to allow for another heat pulse after the biopsy was taken

Thus, we had a theoretical needle that could kill any bacteria collected, first at the time of passage through the rectal wall and then again, by adding another heating, at the most distal location in the prostate, directly after biopsy sampling. The construction caused very limited heat transfer to the tissue, thus we did not expect any serious side effects. And it only needed half the energy of a 1.5V standard battery to achieve this.

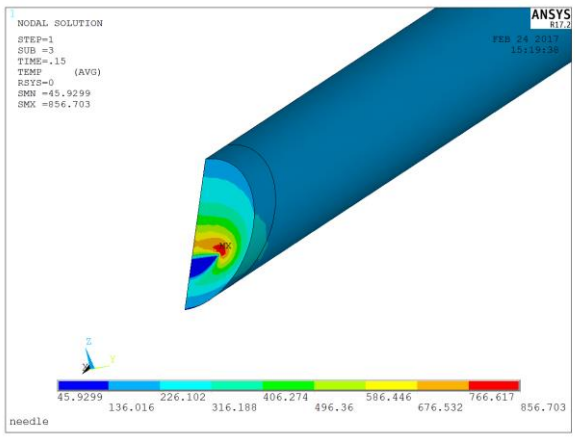


Figure 23 Computer simulation of a closed needle with heating of the needle exterior while in prostate tissue. Image at 0.15 seconds from the start of heating. The tip is >800 degrees. At 0.175 s the whole outside of the needle is 200 degrees Celcius (not shown). Graphics by FS Dynamics AB

It all looked very promising.

Until I started searching for someone to produce the needle for a preclinical trial. After a lot of work and industry contacts we realized that it was too complicated to produce to be made available to patients.

Without a construction that was profitable, no company was interested, and the needle would not be made available to patients. The same applied to investors, without a possible profit – no investments. The same moral applies to scientific grants – without a chance of reaching a final product to realize the research results, it's immoral to apply for research money. An important lesson.

It was a dead end. We chose not to complete the study, remove it from the PhD plan, and once again go back to the drawing board.

It took some time to realize that perhaps the shape of the needle was enough, even without heat. If the needle was completely smooth, perhaps tissue friction would be enough to clean it? After all many procedures are made clean but not sterile and still provide sufficient infection protection. Examples include urinary catheterization, skin wound care, and the use of face masks to prevent infection in the operating room and later in the covid pandemic.

Proof of concept, leading up to Paper 1

The first test was a proof of concept comparing a smooth needle to the Tru-Cut needle. A 3 mm-thick piece of veal meat covered with faeces from a healthy human was used to simulate the rectal wall. The meat was punctured with three brands of Tru-Cut needles and a closed needle, now called Forsvall needle prototype. The bacterial culture results are visible in figure 24.

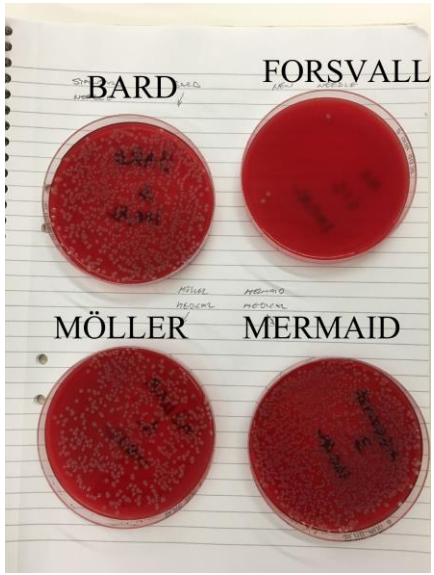


Figure 24 Agar plates representing bacterial transfer across a simulated colon wall. The steel rod simulating a closed tip needle (Forsvall) reduced the bacterial transfer by 99% compared to three brands of Tru-Cut needles (Bard, Möller medical, Mermaid medical) All needles are 18 gauge in diameter. Photo by Andreas Forsvall

Microscopy of the needles after puncture confirmed that faecal matter was collected between the Tru-Cut needle parts, details in paper 1.

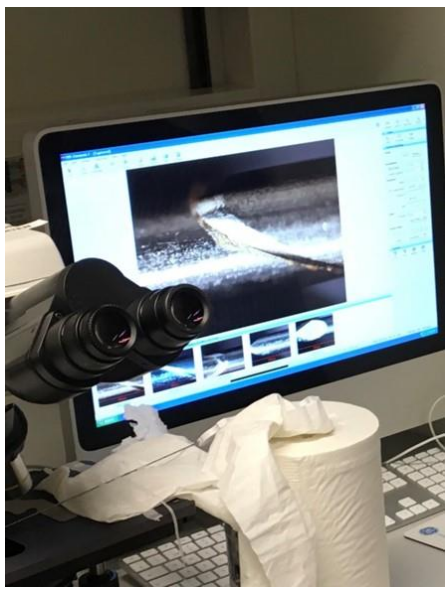


Figure 25 Photo from the first microscopy. The needle is located in the microscope and the enhancement is on the screen. Please note the visible fecal matter collected between the Tru-Cut needle parts.Photo by Andreas Forsvall

Know your enemy – the size of bacteria causing infections in TRbx

About 85% of infections after TRbx are caused by *E. Coli* [62, 111]. *E. Coli* is part of the normal faecal flora and is also the most common pathogen in common urinary tract infections [112]. *E. Coli* is a gram-negative rod 0.5x2 micrometres in size. One gram of normal human faeces is estimated to contain 10^7-10^8 *E. Coli* bacteria [113].

Other causes of infection include other parts of faecal flora, such as *K. Pneumoniae* and *E. Faecalis*, all approximately the same size as *E. Coli.*

Bacterial size vs the Tru-Cut needle forward facing opening

The bacteria are thus 0.0005 x 0.002 mm in size. The 18-gauge Tru-Cut biopsy needle is 1.26 mm with a 0.05 mm gap between the needle parts (figure 19).

The area of the forward-facing opening in a closed Tru-Cut needle is at least 200.000 times the size of an *E. Coli* bacterium

What happens with bacterial transfer if that opening is closed was studied in paper 1

Abstract Paper 1

Background: Transrectal prostate biopsy (TRbx) transfers colonic bacteria into prostatic tissue, potentially causing infectious complications, including sepsis. Our objective was to determine whether biopsy needle shape, surface properties and sampling mechanism affect the number of bacteria transferred through the colon wall and evaluate a novel needle with improved properties.

Methods: The standard Tru-Cut biopsy needle used today was evaluated for mechanisms of bacterial transfer in a pilot study. A novel Tru-Cut needle (Forsvall needle prototype) was developed. TRbx was simulated using human colons ex-vivo. Four subtypes of the prototype needle were compared with a standard Tru-Cut needle (BARD 18 G). Prototype and standard needles were used to puncture 4 different colon specimens in 10 randomized sites per colon. Needles were submerged into culture media to capture translocated bacteria. The media was cultured on blood agar and then the total amount of transferred bacteria was calculated for each needle. The primary outcome measure was the percent reduction of bacteria translocated by the prototype needles relative to the standard needle. Secondary outcome measures were the effects of tip design and coating on the percent reduction of translocated bacteria.

Results: Prototype needles reduced the number of translocated bacteria by, on average, 96.0% (95% confidence interval 93.0-97.7%; $p < 0.001$) relative to the standard needle. This percent reduction was not significantly affected by prototype needle tip style or surface coating.

Conclusions: The Forsvall needle significantly reduces colonic bacterial translocation, suggesting that it could reduce infectious complications in prostate biopsy. A clinical trial has been initiated.

The work between paper 1 and 2

Collecting tissue – a lot harder than expected.

A biopsy needle is useless if it does not collect tissue at the site of the suspected tumour. This means that it must first **hit the intended target area** and then **collect enough tissue**.

We had problems with both and it took a long time and many designs and tests to understand the mechanisms in tissue collection and over a year to get it right.

Needle deviation and “The Diving Board Effect”

My clinical experience was that the Tru-Cut needle deviated off-target in tissue, something well known and described in literature,[114-116] and sometimes called “ needle skidding” or “needle drifting”. The wedge shape of the Tru-Cut needle pushes tissue up towards the chamber aiming to increase the amount of tissue collected. By the laws of physics, it then also forces the needle tip downwards when it travels in tissue, causing deviation.

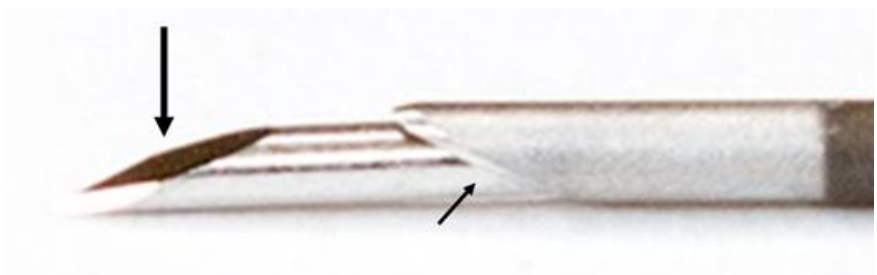


Figure 26 A Tru-Cut needle. The arrows indicate the forces on the needle upon movement in tissue, causing needle deviation. Photo by Andreas Forsvall

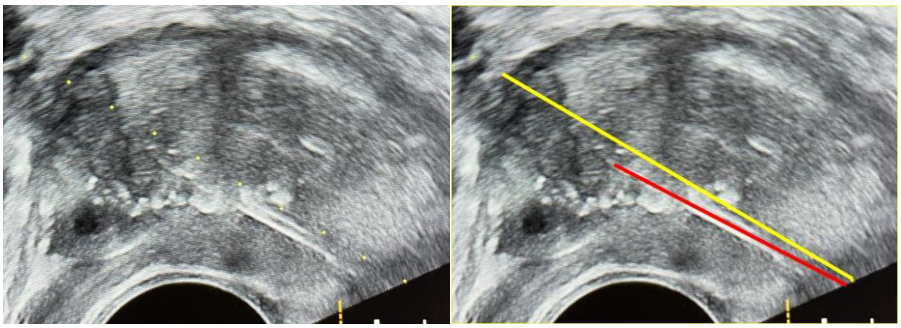


Figure 27 Tru-Cut needle deviation. Ultrasound image of TRbx of a normal size prostate. In the left image is a yellow dotted line guides the user in aiming at cancer suspicious targets, hence the dotted line is the expected needle path. The Tru-Cut needle can be seen deviating below the yellow dots. In the right image the expected needle trajectory has been highlighted by a yellow line and the location of the Tru-Cut needle by a red line. This type of deviation is well known and caused by the wedge design as the closed Tru-Cut needle is forwarded in tissue prior to biopsy. Photo by Andreas Forsvall

However, I found no studies on what happens in the exact moment of tissue collection. Since the force that is causing the needle to deviate is due to the wedge shape of the inner needle tip and that needle has a very thin chamber, deviation may be even greater at the exact time of biopsy, when the inner needle part is not supported by the rigid outer tube. However, I have seen no description of it. I call this The Diving Board Effect.

Figure 28 The same force that causes the closed needle to deviate is applied to the flexible inner needle part at the exact time of biopsy. Photo by Charlotte Carlberg Berg

Figure 29 The diving board effect. An other example of a similar force placed at the end of a thin flexible structure. Photo of Alexandre Despatie at the London Olympics 2012, Getty Images, used with permission.

A simple test in a melon (figure 30) showed the deviation of the inner needle as a proof of concept of the diving board effect. The green line shows the expected needle path. This is not visible for the user, as the tube is forwarded the inner needle is straightened faster than visible ultrasound (Biopsy needle movement takes 1/50 s, while ultrasound screen frequency is 50Hz). I have not found any studies examining the needle movement divided by inner and outer needle at the time of biopsy or description of the diving board effect.

It is thus unclear from where exactly the tissue collected by the biopsy needle is sampled. A minor deviation may cause a very different biopsy result in targeted biopsy.

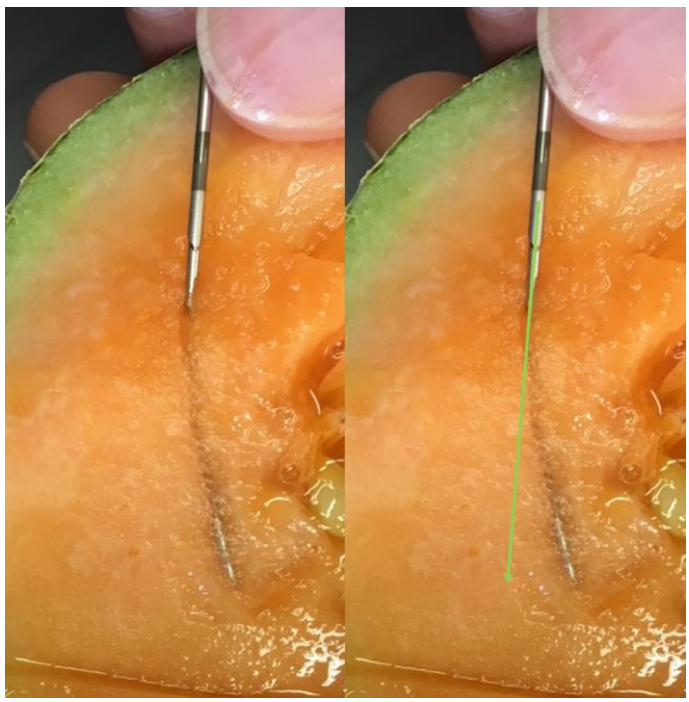


Figure 30 A Tru-Cut needle in a melon demonstrating the diving board effect of the inner needle part. The user believes tissue collection is made along the green line, while it is unclear where it actually is made (to be evaluated in the planned Wilhelm Tell study, please se section Future work) Photo by Andreas Forsvall

Redesigning the needle by making the needle parts support each other created a much sturdier needle and, in combination with a balanced grinding of the needle head, we could create a needle aiming to eliminate deviation in tissue and the diving board effect. Thus, we were aiming to improve accuracy in biopsy sampling by collecting tissue from the actual area the user aims for. A needle suitable for targeted biopsies.

Constructing a novel biopsy gun

Since the Forsvall needle has a novel closed tip it does not work with ordinary biopsy guns. An ordinary gun has two movements, it fires the inner needle part and then the outer needle part (figure 14).

The Forsvall biopsy mechanism needs to force the needle parts together when the gun is loaded to ensure that the outer surface of the needle is smooth and no foreign matter is collected between the needle parts. Once past the rectal wall: Upon firing it must eject the inner needle part, and make it come to a complete stop. It then fires the outer sheath but makes it stop 1 mm before hitting the closed needle tip. It then soft closes the needle, like a modern kitchen drawer. Finally, it reapplies the closing pressure between the needle parts, so the needle is once again smooth and bacteria is not collected on the way out. It is thus a slightly more complicated mechanism than current biopsy guns. It must also move the needle parts so it optimizes tissue collection, a delicate interaction between the needle design and the mechanism of the gun.

Collecting enough tissue

After several discarded technical solutions and several different in-vitro models to simulate TRbx we were unsure if the models reflected real prostates. Thus, we got ethical permission to take biopsies from prostatectomy specimens directly after prostatectomy. Using trial and error we compared the biopsy results with our needle design to that of the Tru-Cut needle and adapted the design to improve the biopsy results.

This was followed by rigorous safety tests.

When we finally believed we had a system that seemed to hit the target, collect equal amounts of tissue as the Tru-Cut needle and was safe to use, it was time for the study described in paper 2. Please note that paper 2 does not discuss needle movement/target accuracy in tissue, for this - please see the planned Wilhelm Tell study.

Figure 31 Needle tips: Top: The Forsvall biopsy needle prototype 2 used in Paper 2. Bottom: A Tru-Cut biopsy needle. Photo by Charlotte Carlberg Berg

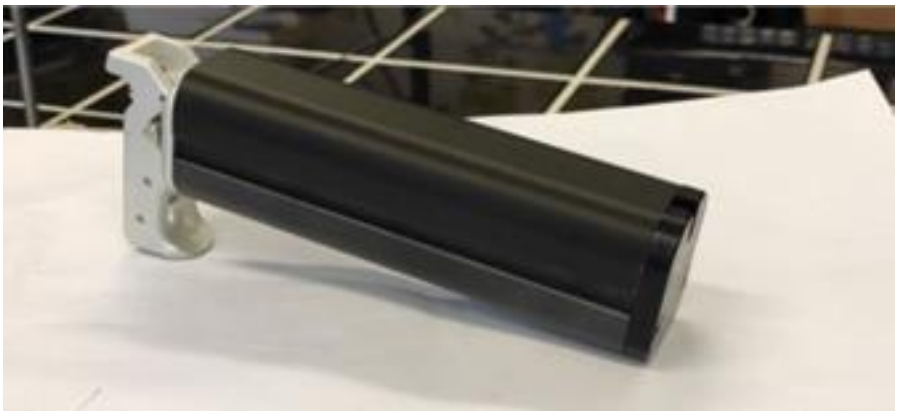


Figure 32 A Forsvall biopsy gun prototype, the mechanism built into a shell from a standard biopsy gun. Photo by Andreas Forsvall

Abstract paper 2

Background: Transrectal prostate biopsy (TRbx) carries an increasing risk of infection. The Forsvall Needle Prototype (FNP) is a novel biopsy needle that reduces bacterial load brought across the rectum and may therefore reduce infection risk. The objective of this study was to compare biopsy length, quality and patient experience for the FNP Version 2 (FNP2) versus a standard Tru-Cut needle.

Methods: We conducted a randomized, parallel-group, non-inferiority trial with twenty consecutive patients eligible for TRbx. Participants were randomized to undergo TRbx using either FNP2 or a standard Tru-Cut needle. The primary outcome was difference in mean biopsy lengths measured by the pathologist. FNP2 biopsy lengths $\leq$1.35 mm of the standard needle length were considered non-inferior. Secondary outcomes were biopsy length in the needle chamber and immediately after removal, biopsy quality, biopsy fragmentation, patient discomfort/pain, and complications (immediate and after 14 and 30 days).

Results: Mean pathologist-measured FNP2 biopsy length was non-inferior compared to the standard Tru-Cut needle (0.02 mm longer, 95%CI-0.73 to 0.76 mm). Biopsy length in the needle chamber and immediately after removal were also non-inferior. Biopsy quality and patient discomfort were not significantly different for the FNP2 and the standard Tru-Cut needle. Biopsy fragmentation was more common in the FNP2 group.

Conclusions: The FNP2 biopsy needle is non-inferior to the Tru-Cut needle in terms of biopsy length and not significantly different in terms of biopsy quality and patient experience. Future studies will evaluate the Forsvall needle design's effect on post-biopsy infection risk.

The rationale for paper 3

Available literature at the time showed infection rates that were very hard to interpret. Some studies showed very high infection rates, others very low. There was no clear definition of infection following TRbx. The term sepsis was used extremely broadly. There was not even an ICD-10 diagnosis code for infection after prostate biopsy. Results were dependent on the local antibiotic resistance rates. Some studies used patient-reported data (with risk of overexaggerating the results as other symptoms after TRbx may mimic infection). Others used positive blood or urine cultures (with risk of underexaggerating the results as not all infection are culture positive).

We needed a basis for a power analysis for the large trial described in paper 4. But whose results were relevant to us? Since Helsingborg/Ängelholm was the planned first site of such a study, and easily accessible, we did the analysis there. We also used a time-consuming manual chart review to avoid using ICD-codes, antibiotic prescriptions or culture results as a method of identifying infections. This also allowed us to get a deeper understanding of the individual patient's clinical path.

Calculations of cost of infection was based on few studies, mostly from the English-speaking world. Would the results from these studies be relevant in a Swedish setting? Would we get a totally different result?

Lastly, we aimed to highlight the (very annoying) problem with the lack of an ICD-10 code for TRbx infections.

Abstract Paper 3

Objectives: The aim of this study was to assess the incidence of infection after transrectal prostate biopsy (TRbx). Secondary objectives were to describe infection characteristics, antibiotic resistance patterns, ICD-10 coding, and costs.

Methods: TRbx carried out at the hospitals of Ängelholm and Helsingborg, Scania, Sweden, between October 2017 and March 2019, were identified based on the NOMESCO Classification of Surgical Procedures code for TRbx, TKE00. All patients received per oral antibiotic prophylaxis, usually 750 mg ciprofloxacin at biopsy. Other preventative measures were not used. Medical care within 30 days of the biopsy was evaluated through a manual retrospective medical chart review. Data on patient and infection characteristics were collected. The costs of infections causing hospitalization were estimated.

Results: After 36 (5.4%) of 670 biopsies, the patient developed post-biopsy infection within 30 days after TRbx. Twenty-six patients (3.9%) required hospitalization for an average of 6 days, at an estimated direct cost of USD 9174 (EUR 8031) per patient. Nine patients (1.3%) had a complicated infection leading to intensive care, multiple hospitalizations or emergency department visits. The inpatient care episodes for the 26 hospitalized patients were categorized with 15 different ICD-codes. In 6 episodes no ICD-code related to infection was used.

Conclusions: In this study, we found an infection rate of 5.4% after TRbx; 3.9% of the patients were hospitalized for a post-TRbx infection and 1.3% had complicated infections. A specific ICD code for post-TRbx infections would facilitate evaluation and monitoring of this common, costly, and sometimes serious complication.

Rationale for paper 4

As described in the previous texts, there are clear indirect proofs that reducing bacterial transfer in TRbx will reduce clinical infections.

There are also strong reasons to believe that a needle that moves straight in tissue may hit a cancer suspicious target more centrally than a needle that deviates away from the target[115].

In a diagnostic chain where a biopsy needle is the tool used to collect the tissue used for cancer diagnostics, it is rather uncontroversial to state that hitting the target or not may affect cancer diagnostics.

To validate these statements, a randomized trial is needed. It is based on the findings in studies 1-3. The protocol for such a study is presented in paper 4. Results from ongoing trials may give reasons to amend the protocol (please see section: Future developments - A glance into the future).

Abstract paper 4

Introduction: High-quality biopsies of cancer tissue are required for diagnosing and assessing the severity of most cancers. The biopsies are usually obtained by a Tru-Cut needle. Prostate biopsies are usually obtained transrectally, which confers a risk of infection as the biopsy needle passes through the rectal lumen where it is contaminated with faecal bacteria. Each year, over 100.000 patients worldwide experience a febrile post prostate biopsy infection. The Forsvall biopsy needle is designed to minimize transfer of rectal bacteria. This study aims to investigate whether the Forsvall biopsy system can reduce biopsy-related infectious complications after transrectal prostate biopsy, compared with a standard Tru-Cut biopsy system.

Methods and analysis: This is a randomized (1:1 allocation), controlled, multicenter, superiority trial with blinding of patients and outcome assessors. Men eligible for transrectal prostate biopsy will be randomized to having the biopsy done by using either the Forsvall or the standard Tru-Cut biopsy system. The primary outcome measure is the proportion of patients who receive intravenous antibiotics or are hospitalized for infectious complications within 14 days after biopsy. Secondary outcome measures are any infectious complication and sepsis within 14 days. Patient experiences of the biopsy procedure will be assessed by patient-reported pain score and of complications within 14 days. The diagnostic outcomes from the two biopsy systems will also be analyzed.

Ethics and dissemination: The study will be performed in accordance with the ethical requirements defined in the Declaration of Helsinki, the ISO 14155 standard, and national regulations. The results will be published in peer-reviewed journals and presented at national and international conferences.

Strengths and limitations of this study

To our knowledge, this is the first study of an intervention aiming to reduce biopsy-related infections by a new biopsy needle design rather than by preventative measures such as antibiotics.

The investigated biopsy system has the potential to reduce biopsy-related infectious complications and improve sampling of millions of tumor biopsies performed each year.

The study is designed to minimize bias and provide conclusive results. The allocation will be randomized and both study subjects and outcome assessors blinded to the type of needle used.

The study focuses on prostate biopsy, limiting the ability to make conclusions about whether the Forsvall biopsy system can reduce biopsy-related infections after biopsies taken from other organs.

Further developments and a glance into the future

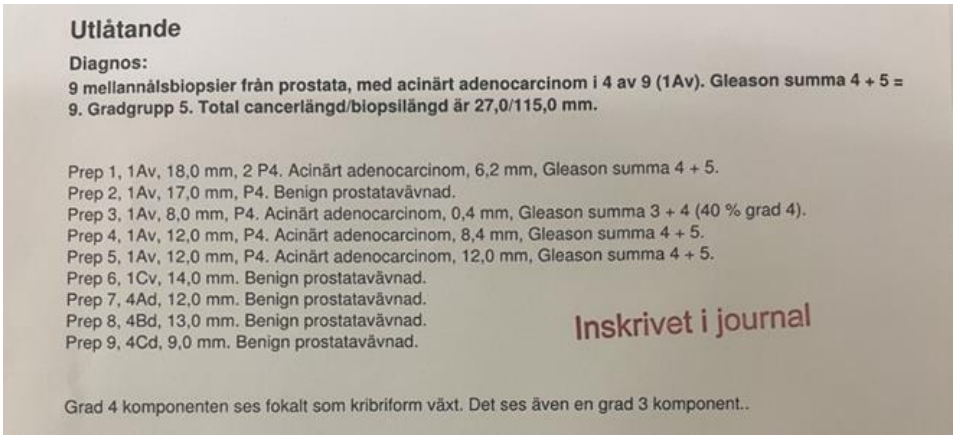
This section is a glance into ongoing work, not included in the papers in this thesis.

Aiming to improve cancer diagnostics – the development of the Forsvall double needle

The biopsy needle in Paper 1 and 2 aims to reduce the risk of infection in TRbx. The development of the needle used in paper 2 also aims to improve the needle's movement in tissue to increase the accuracy in MRI-first target biopsy in both TRbx and TPbx. Needle movement in tissue has been evaluated in smaller experiments achieving proof of concept. The needle movement is to be compared to the Tru-Cut needle in a preclinical gelatine-based study (The Wilhelm Tell study), and indirectly in the study described in paper 4.

There is, however, a third issue with the Tru-Cut needle: it only collects tissue specimens representing 2/3 of the chamber length. In a 20 mm chamber, on average 13 mm is collected. Thus, we only collect about 66% of the tissue we aim to, 33% of the information is missing. A clinical reflection is that the length of tissue varies a lot, sometimes a biopsy is 20 mm, sometimes only 5 mm. This happens in the same patient, aiming at a similar location, at the same time, using the same instrument (figure 33). Tissue length in biopsy is (of course) strongly correlated to cancer detection.

Why is the chamber not always full? And why do the results vary so much? We have tried to investigate this ever-changing difference in biopsy length, testing basically anything available at the grocery store as a surrogate for prostate tissue.



Utlåtande

Diagnos:

9 mellannålsbiopsier från prostata, med acinärt adenocarcinom i 4 av 9 (1Av). Gleason summa 4 + 5 = 9. Gradgrupp 5. Total cancerlängd/biopsilängd är 27,0/115,0 mm.

Prep 1, 1Av, 18,0 mm, 2 P4. Acinärt adenocarcinom, 6,2 mm, Gleason summa 4 + 5.
Prep 2, 1Av, 17,0 mm, P4. Benign prostatavävnad.
Prep 3, 1Av, 8,0 mm, P4. Acinärt adenocarcinom, 0,4 mm, Gleason summa 3 + 4 (40 % grad 4).
Prep 4, 1Av, 12,0 mm, P4. Acinärt adenocarcinom, 8,4 mm, Gleason summa 4 + 5.
Prep 5, 1Av, 12,0 mm, P4. Acinärt adenocarcinom, 12,0 mm, Gleason summa 4 + 5.
Prep 6, 1Cv, 14,0 mm. Benign prostatavävnad.
Prep 7, 4Ad, 12,0 mm. Benign prostatavävnad.
Prep 8, 4Bd, 13,0 mm. Benign prostatavävnad.
Prep 9, 4Cd, 9,0 mm. Benign prostatavävnad.

Inskrivet i journal

Grad 4 komponenten ses fokalt som kribriform växt. Det ses även en grad 3 komponent..

Figure 33 A typical example of a pathology report after prostate biopsy. Nine biopsies were taken and biopsy core 1-5 were targeted biopsies aimed at a Pirads 4 target found by MRI. Four of five targeted biopsies showed cancer. Aimed at the same target at the same time, still the length of the biopsy cores were 18-17-8-12-12 mm long. Systematic biopsy cores (number 6-9) were benign with length ranging 9-14 mm. On average biopsies were 12.7mm long. The Tru-Cut biopsy chamber was 20mm, a 64% coverage. Please also note that the length of cancer in the positive cores (1,3,4,5) ranges from 0.4mm to 12 mm, and Gleason score varies from 3+4 to 4+5.

For example – is the partial filling of the biopsy chamber only due to compression of the specimen, meaning has the needle sampled the entire length of the biopsy chamber but the biopsy has been compressed and only looks shorter? We have evaluated this in different models, for example like in the figure 34, and by weight.

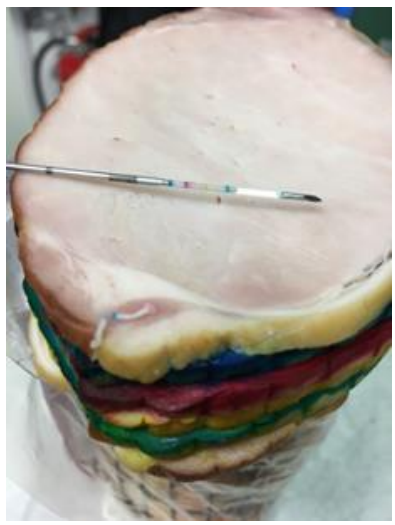


Figure 34 Cassler cut in 5 mm slices with coloring between slices. A model to evaluate compression of biopsy samples. This biopsy looks short (the tissue does not fill the chamber) but the coloring shows that the sampled tissue is indeed is 20 mm since it has 4 colours (blue, red, yellow and green). The image shows a rare example of compression actually explaing the short length of biopsy, in most cases it does not. Photo by Andreas Forsvall

Working with a conflict diagram the technical team found one factor that kept coming back as an individual factor theoretically affecting biopsy core length.

It took a long time to realize but a reason for the chamber not filling may be because:

The biopsy chamber is not empty to start with – its filled with air.

Figure 35 The biopsy sample mechanism is very fast (1/50 second) and the biopsy chamber is only open about 1/100 of a second, possibly not allowing the air to evacuate. One reason for the uneven and uncomplete filling of the biopsy chamber may thus be air-blocking. Photo by Charlotte Carlberg Berg

To evaluate and address this we have developed a next generation of the needle used in paper 2. Since it has two inner needles it has the working name Forsvall double needle. Design and mechanism of action below.

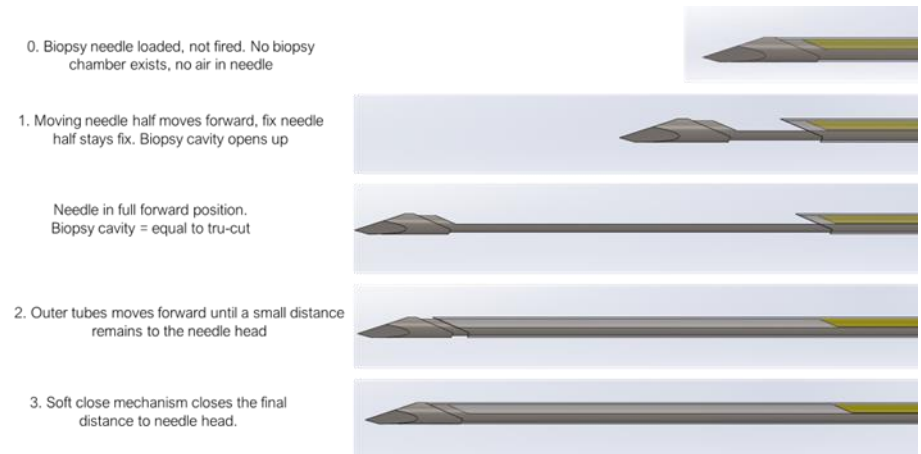


Figure 36 The Forsvall double needle, please note that prior to firing of the biopsy gun, there is no biopsy chamber, thus air is eliminated. The yellow needle part differs from previous needles. Graphics by Ola Carmonius

To evaluate the effect, the biopsy gun was rebuilt and adapted for the double needle. After multiple tests in meat, preclinical *ex vivo* tests in prostate were made comparing the biopsy length head-to-head with the Tru-Cut needle in prostate tissue directly after prostatectomy.

Since I performed all the biopsies, and I must technically be considered biased (even if I tried my very best not to be), we have not published the results.

They were however very promising and considered as proof of concept for the double needle. Based on 30 consecutive *ex vivo* punctures with each needle, on average the double needle produced 26% longer biopsies than the Tru-Cut (19.2 vs 15.0 mm) and the double needle biopsy cores had a 20% higher weight. It however also collected more fluid than the Tru-Cut needle.

Figure 37 Example of an *ex-vivo* prostate biopsy using the double needle prototype. Photo by Andreas Forsvall

Thus, proof of concept looks promising. A clinical trial has been initiated, (clinicaltrials.com NCT04880681). If successful, the technology may help improve tissue collection and thus cancer diagnostics in biopsy of other soft tissue cancers as well.

The needle design and function remove the air-blocking. The mechanism also causes a negative pressure inside the biopsy chamber, without using currently available large and expensive suction systems used in breast biopsy (please see section “how to increase tissue collection in prostate biopsy”), but with an 18-gauge needle using a simple mechanical motion.

The development of fluid needles

In most patients local anaesthetics are injected periprostatically at 2-4 locations prior to obtaining transrectal prostate biopsies. Thus, the rectal wall is not only punctured by the biopsy needle but also multiple times by a cannula.

The modern medial needle (a steel tube with a sharp end and a connector in the other end) was probably invented and first used by Francis Rynd, Dublin in 1844 [117].

A cannula, or hypodermic needle, is hollow with a cutting edge, enabling tissue collection inside the needle.

Figure 38 A hypodermic needle tip,the arrow indicates mechanism of collection of tissue and bacteria inside the needle. Illustration by Andreas Forsvall

A hypodermic needle is thus likely to collect tissue inside the needle. This fact, in combination with a negative pressure, was used in early TPbx and is still clinically used in fine needle aspiration cytology.

To test if the hypodermic needle collects tissue inside the needle, without negative pressure, several pieces of meat were punctured by a hypodermic needle connected to a syringe, and, in most punctures, meat was collected inside the needle and ejected when injecting the fluid from the syringe.

Thus, a puncture through the rectal wall means that a stance biopsy of the rectal wall may be taken and injected into periprostatic tissue prior to biopsy. This tissue contains rectal bacterial flora and devitalized tissue, just like the Tru-Cut biopsy needle – in theory a perfect combination for a clinical infection.

So just making the biopsy needle reduce bacterial transfer might not be enough since the injection needle might continue to cause the same problem. Therefore I started developing a fluid needle using the same closed needle tip design as the biopsy needle.

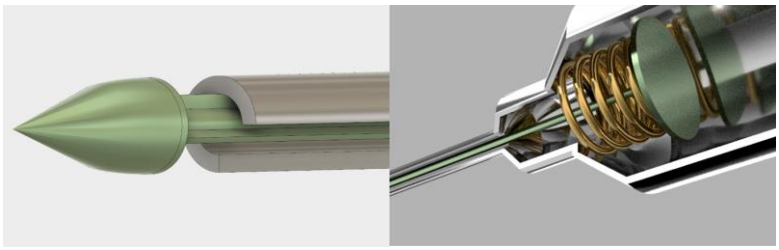


Figure 39 Simplified mechanism of the Forsvall injection needle. Graphics by RAPS.

The basic principle of the fluid needle is seen in figure 39 (simplified). The left image shows the needle tip in an open state. It consists of two parts, an outer tube (grey) and an inner needle with a closed tip (green). The inner needle is forced closed by a spring in the proximal end of the needle (right image). The proximal end is connected to a standard syringe. The needle tip is opened by the flow of fluids from the syringe and automatically closes when the flow stops.

The infection prevention theory is the same as in the biopsy needle: a completely smooth needle is likely to bring significantly less bacteria into sterile tissue than a standard hypodermic needle.

The fluid needle has been optimized in several iterations during several years of work.

Figure 40 One of the first working prototypes of injection needles, connected to a syringe. Photo by Andreas Forsvall

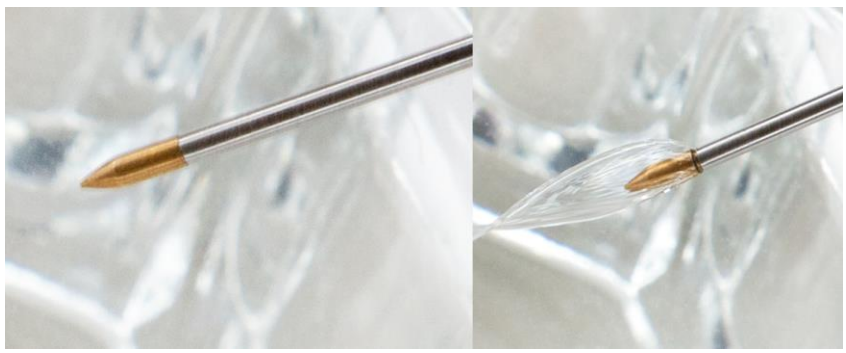


Figure 41 Enhancements of the needle tup. Different metals are used in the inner and outer needle for demonstrational purposes. Left image: Needle not in active use, closed. Right: The needle opens and allows for injection of fluids. As soon as the manual pressure on the syringe is released the needle goes back to its closed state. Please note that the flow of fluids are in the direction of the needle despite the closed tip.Photo by Andreas Forsvall

Injection of fluids was the first challenge. The real technical challenge was how to make the needle fully comparable to the hypodermic needle. How to add aspiration? The mechanism needed to be built so the needle opened both for injection of fluids (the user pushes the syringe) AND aspiration (the user pulls the syringe). This teamwork took some time, but again, after several iterations we have been able to produce a fully functional injection and aspiration needle. It thus allows the urologist to aspirate prior to injection of local anaesthetics, to ensure injection is not made into a blood vessel. It also aims to be able to be usable as an alternative to the current cannula in other fields of medicine.

Figure 42 The closed needle tip of the Forsvall injection/aspiration needle and a standard hypodermic needle for reference. Image from microscope. Photo by Andreas Forsvall

Figure 43 Forsvall injection and aspiration needle prototype for transrectal injection of local anaesthetics prior to TRbx. Photo by Andreas Forsvall

Needle related infections are unfortunately not limited to urological patients after prostate biopsy – the Voodoo and Port studies.

Needle-related infections theoretically may occur at higher risk in any situation where:

- The needle passes an area that cannot be sterilized (e.g. mucosa, damaged skin)
- The patient is very sensitive to infections (e.g. diabetes, chemotherapy, corticoids, immunomodulating treatments
- The puncture enters or passes through a foreign body which the immune system has access but may not clear an infection due to the presence of the foreign body (e.g. prosthetic joints, subcutaneous infection around subcutaneous venous ports)
- The puncture enters a foreign body where the immune system has no access (e.g. subcutaneous venous ports, intrathecal containers)
- The risk of infection is low/very low but the consequence of an infection is so dear that any measures to prevent it may be used (e.g. amniocentesis)

A standard hypodermic needle is currently used in these situations, with some exceptions.

The main exception is in subcutaneous venous ports (SVP) where a Huber needle is used. The Huber needle was patented in 1946 and is a hypodermic needle with an angled tip. It was invented to reduce pain but is now used in SVP as it avoids coring of the port silicon septum.

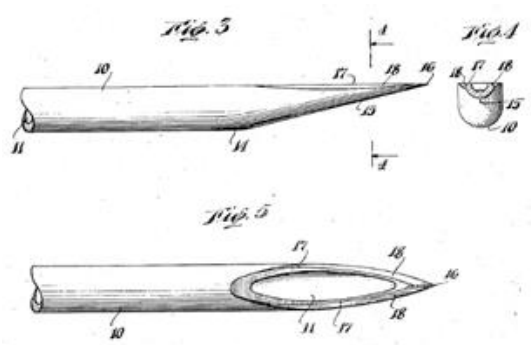


Figure 44 From Hubers patent (US2409979), the Huber needle seen from three angles

From an infection point of view it still has an open tip, although angled, and is not built for infection prevention. We therefore set off to build prototypes of a needle that could be used in subcutaneous venous ports, based on the closed tip technology.

Approximately 2 million SVP are placed annually. There is an early infection risk related to the procedure and a late infection risk mainly relating to usage of the SVP. A recent meta-analysis of gynaecological cancers showed a 9.9% risk of total (early+late) SVP infections [118]. The risk of a late infection, arising more than 30 days after placement is around 5% in large materials of different cancers [119]. The most likely cause of the late infections are bacterial transfer by the Huber needle into the SVP. Note that the SVP is a foreign hollow body with an interior out of reach for the immune system. The theory is strengthened by the research showing skin bacteria and skin fungi as the main cause of infections [119-122].

Access to central venous circulation is mandatory for most chemotherapy cancer treatments, hence many of patents with SVP have a serious cancer diagnosis. An infected SVP must in most cases be surgically removed. A cancer patient who suffers a serious SVP infection thus risks the following sequence of events:

Sepsis – hospitalization – emergency removal of port – long antibiotic treatment – hopefully recovery – reimplantation of a new port.

After a long and difficult recovery at a high human and economic cost during which the cancer has remained untreated – the chemotherapy may hopefully be resumed.

With an estimation of 2 million ports and 5% risk, 100.000 patients are affected annually.

My theory is that bacteria and fungi are collected by the Huber needle and injected into the SVP. Even though sterile cleaning is used prior to puncture, the skin might be damaged by the repeated punctures impairing sterilization along the needle tract.

Alternative possibilities include the introduction of bacteria into the medication/injected fluid at any time prior to the fluid reaching the Huber needle, or colonization of the port through hematogenic spread of bacteria from another infection.

We aim to investigate the effect of bacterial reduction in punctures through skin and ports in the ongoing Voodoo and Port studies, *ex-vivo* comparisons of bacterial transfer using the Forsvall fluid needle vs the hypodermic needle in skin punctures (Voodoo study) and the Forsvall port needle vs the Huber needle in punctures of skin over a port membrane (Port study). Study setups and methods are similar to the colon punctures in paper 1. The Voodoo study name comes from the study method of puncturing human skin with needles.

Future work

Needle tract seeding – “The open backdoor hypothesis”

Figure 45 A van dropping boxes fom an open back door, a metaphor to my theory of needle tract seeding when using a Tru-Cut needle. Image used with permision from Shutterstock.

Biopsy of some types of tumours using a Tru-Cut needle poses a small risk of needle tract seeding (NTS). NTS means tumour spread along the biopsy canal. NTS is described as a very rare complication (<1%) in prostate biopsy, with higher risk in TPbx than TRbx [123]. In one study NTS in TPbx was as high as 1% [124], so it’s a rare but due to the large number of biopsies taken annually, not a totally negligible problem as TPbx are increasing.

Other examples include liver biopsy for hepatocellular cancer (2.7% risk)[125], liver biopsy for colorectal metastasis (16% risk)[126], and sarcomas (0.37% risk)[127]. In sarcomas the biopsy canal is often surgically removed *en-bloc* with the tumour due to the risk of NTS.

NTS may have several explanations, for example tumour spread by bleeding from the tumour allowing for a flow of tumour cells in the needle tract. However, one explanation may be the Tru-Cut needle design. The chamber of the Tru-Cut needle is not completely closed following biopsy. The same gap between needle parts that collects bacteria when the needle is moving forward may possibly cause parts of the collected tumour tissue to dislodge from the needle as it is retracted. The novel

needle has a closed biopsy chamber, possibly reducing the risk of needle tract seeding.

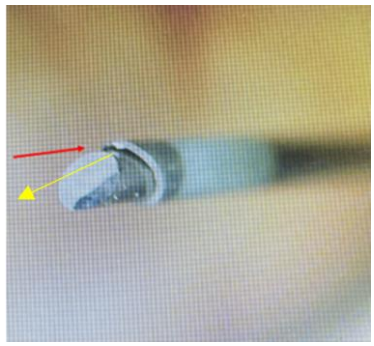


Figure 46 Tru-Cut biopsy needle. Red arrow indicates area of bacterial collection in TRbx. Yellow arrow sympolizes the “open backdoor hypothesis” of needle tract seeding upon retraction of the needle. Photo by Andreas Forsvall

Erectile dysfunction after biopsy – The “Hole Puncher Hypothesis”

The erectile nerves pass on the outside of the prostate towards the base of the penis. Several studies have shown increased erectile dysfunction (ED) following prostate biopsy, often transient [128, 129], although I have not found studies examining long-term data. In general, the results are hard to interpret as psychological factors related to both biopsy and cancer diagnosis may also affect the risk of ED. However, neural trauma from the biopsy or the injection needle is a possible reason for erectile dysfunction after prostate biopsy.

It is well known that the erectile nerves may be damaged in prostatectomy, prostate cancer surgery. If the cancer does not threat to grow into the nerves, a great deal of effort is made to prevent them during surgery in order to preserve erectile function. But what if the nerves were in part damaged already by the biopsy? Then, theoretically, the additive negative effect of both procedures could determine the final outcome of erectile function after surgery. Anatomically the risk of nerve damage is likely higher in TPbx than TRbx, as all needles pass through the lower apex of the prostate, where the erectile nerves converge and are dense. Theoretically the highest risk would be using the now more common freehand TPbx with one skin puncture for each of the two prostate lobes, as these puncture sites are basically pointing at the dense area of nerves at the apex of the prostate. This type of TPbx is often performed in local anaesthetics with a coaxial and Tru-Cut needle.

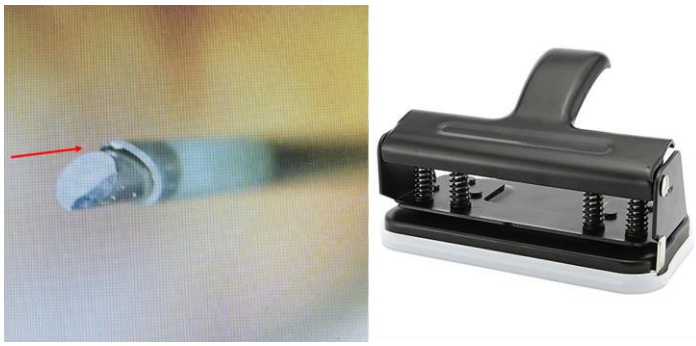


Figure 47 The outer tube of the Tru-Cut needle is a circular knife (left) that may act as a hole puncher (right) when passing erectile nerves. Photo by Andreas Forsvall

Referring to the left image above; Again looking at the Tru-Cut needle design, please note that the outer needle sheath is sharpened like a circular knife. As the Tru-Cut needle passes through the neurovascular bundle, nerves are theoretically partly pushed aside by the inner needle tip but then cut by the sharp outer needle sheath. The red arrow indicates where the nerve may be cut by the sharp outer needle sheath. The final result may be similar to that of a hole puncher, cutting circular holes in paper (right image above).

In theory the smooth needle design may thus help reduce the risk of damage to erectile nerves if it is not fired prior to the anatomical location of the nerves. Anatomically the effect should be greatest in TPbx.

It has been very hard to find a model to test this theory and it is possible that it cannot be investigated other than in a large RCT comparing the Tru-Cut needle to the Forsvall needle in TPbx.

The Wilhelm Tell study – hitting the target?

Hitting the target and collecting tissue from the exact intended area – is there a difference between the Forsvall and Tru-Cut needle?

By making the needle move straight in tissue and avoiding the diving board effect, in theory, the Forsvall needle should sample tissue exactly from the intended area while the Tru-Cut needle may not. This may influence cancer diagnostics. We aim to examine the exact location of tissue sampling in a preclinical study using gelatine as a model for tissue. In the study the Forsvall and Tru-Cut needles are to be aimed at coloured globe-shaped gelatine targets embedded in the simulated transparent gelatine tissue. Outcomes will include high speed camera filming of the needle

trajectory and analysis of the colour of the collected biopsy sample to quantify how much of the coloured target is collected.

Previous studies have evaluated the needle deviation by comparing the location of the needle after biopsy with the expected trajectory [114-116]. To my knowledge, the Wilhelm Tell study will be the first study aiming to evaluate the actual biopsy needle movement during biopsy and hopefully shed a light on exactly were a biopsy specimen is sampled.

Closing the loop – bringing the technology to the patient

The aim of the project is to go from Problem to Patient. The scientific work presented in this thesis is a part of that work. The project however expands beyond that and requires a company part. Instead of relying on an external part I founded Xaga Surgical AB in 2016.

The short story of this project is to go from idea and vision through: soft money/grants finance, prototype, several revisions of prototypes, pre-product (safe, producible and accepted for use in pre/clinical trials), preclinical and clinical trials (this PhD and future trials), improved product (cost-effective, user friendly, environmentally friendly, and producible in larger scale), patents to protect IP and attract investors and government/EU funding, set up production, regulatory approved product and finally market entry. Then find someone who is willing to do business and have the infrastructure to (help) start mass-production and make the needles readily available. Then gain market acceptance, patient acceptance and acceptance in colleagues and get recommendations in guidelines. Finally post market follow up to ensure safety and that the results from studies can be reproduced outside clinical trials.

Most steps up to PhD can be made within the University and financed by research grants and soft money. All steps after studies/PhD needs a company and investments. All preclinical and clinical trials need contacts with patients or patients' tissue.

Hence this project would not be possible without standing on three legs.

Hospital (Region Skåne), University (LU) and company (Xaga Surgical AB)

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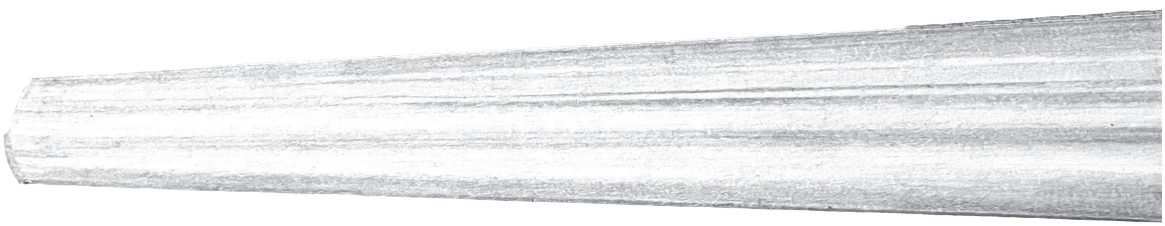
Improved needle design to reduce the risk of infection in transrectal prostate biopsies

Photo: Tove Smeds

The author, Andreas Forsvall, is a specialist in surgery and urology, working with prostate cancer at the urology department at Helsingborg hospital. He has a technical interest and experience in entrepreneurship, metal working, and MedTech research.

This thesis addresses infections in prostate biopsy – a global problem. Over 3 million prostate biopsies are performed annually and 3% of men suffer a severe infection. The risk of infection is increasing in parallel with rising antibiotic resistance.

By combining clinical knowledge with technical development, this thesis aims to address the risk of infection in a novel way – by redesigning the medical needle that causes the infections.



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