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SAHLGRENSKA AKADEMIN

Infectious complications after transrectal ultrasound guided prostate biopsy in a prostate cancer screening trial.

Degree Project in Medicine

Karl Eriksson

Programme in Medicine

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Supervisor: Kimia Kohestani, MD, PhD

Department of Urology, Sahlgrenska University Hospital

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Abbreviations

PSA: Prostate specific antigen

LUTS: Lower urinary tract symptoms

UTI: Urinary tract infection

MRI: Magnetic resconance imaging

TRUS: Transrectal ultrasound

TRUS-BX: Transrectal ultrasound guided biopsy

TPBx: Transperineal biopsy

Abstract

"Infectious complications after transrectal ultrasound guided prostate biopsy in a prostate cancer screening trial"

Author:	Karl Eriksson
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Supervisor:	Kimia Kohestani
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Background: Globally, prostate cancer is the second most diagnosed cancer among men. Prostate biopsies are necessary to obtain a histological diagnosis. Prostate biopsies can lead to different complications. Minor complications include hematuria, hematochezia, hematospermia and urinary tract infections. Major complications are uncommon and consists mainly of rectal bleeding and sepsis. This study investigates the infectious complication rate after transrectal prostate biopsy in a screening population.

Materials & Methods: For this study, data was taken from the Göteborg prostate cancer screening 2 trial study. The study population consisted of 810 men aged 50-60 years. All men were asked to answer questionnaires prior and post prostate biopsy. Questionnaires consisted of questions regarding basic health charecteristics and whether the patient had suffered any complications post biopsy. Some questionnaires lacked information, therefore a total of 207 medical charts were reviewed. The primary outcome for this study was to evaluate the infectious rate post biopsy. The secondary outcome was to investigate whether there was a difference in infection rates between systematic and targeted biopsies and furthermore the cause for the infections. This study is approved by the Regional Ethical Review Board in Gothenburg, January 2015 (registration number 890-14).

Results: A large proportion of men in the questionnaire group were asymptomatic (7.8%) or had mild lower urinary tract symptoms (34.5%). Median age was 58.7 years. Out of the total study population of 810 men, infectious complications rate after transrectal biopsies in the population-based Göteborg prostate cancer screening 2-trial resulted in 1.7% patients with urinary tract infection (UTI) and 0.5% needing hospital care due to UTI. There was no significant result regarding biopsy approach and infection rates.

Conclusion: Infectious complications post transrectal biopsy are rare in a screening population in men aged 50-60 years. These results can be used as a reference for further screening studies as well as in clincal practice.

Background/Introduction

Prostate cancer

Globally, prostate cancer is the second most frequent cancer diagnosed in males.

In Sweden, prostate cancer is the most common cancer and is the leading cause of cancer deaths among men. In the 21st century, the incidence of prostate cancer has increased worldwide with approximately 1.4 million new cases and 375,000 deaths in 2020. Current research suggests that the increase in prostate cancer prevelance may be due to increased awareness in the general population regarding prostate cancer and increased Prostate specific antigen-testing (PSA). Furthermore prostate cancer treatment has evolved, resulting in the possibility to a longer life among those with advanced stages of prostate cancer. (1, 2)

Prostate anatomy and physiology

The prostate has the size of a walnut and is situated under the urine bladder. Vas deferens and the seminal vesicle connect into the prostatic urethra that eventually becomes the urethra. The prostate is a gland that produces a thin liquid-like fluid that fuse together with semen during ejaculation. Growth and function of the prostate is regulated through testosterone mainly produced in the testicles. (3)

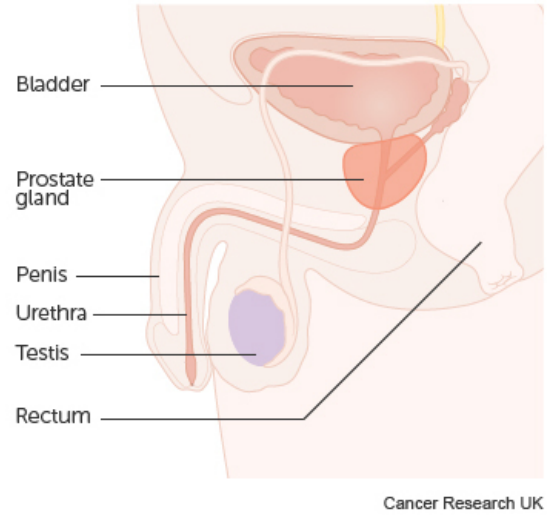


Fig 1. Location of the prostate

Cancer Incidence from Cancer Intelligence Statistical Information Team at Cancer Research UK (2015 - 2017 UK average)

Accessed September 2021

Prostate Specific Antigen

PSA is produced in the prostate and is normally transported out via semen. The main purpose of PSA is to facilitate the passage of the sperm through the cervix canal. In different diseases such as prostatitis and cancer, PSA leaks out from the prostate and into the bloodstream. PSA taken via a blood sample can therefore be used as a diagnostic test when investigating prostate cancer or other diseases in the prostate. The measure limit for further investigation regarding prostate cancer is set to 3 ng/ml, however due to individual diversification the diagnosis depends on several factors, such as biopsy and palpation. PSA is not related to a specific disease.(4) (5)

History of prostate biopsy

Prostate biopsy was introduced in the beginning of the 20th century and has been evolving ever since. The first prostate biopsy was performed transperineally via an open incision and small parts of the prostatic tissue was surgically removed and examined. If there were signs of cancer, the patient then directly underwent prostactectomy. Transperineal prostate biopsy later developed into a minimally invasive technique by using a biopsy needle for sampling. The biopsy needle was manually guided by the surgeons finger with an accuracy success rate of 88%. Following research resulted in transrectal biopsies and in the 1970s transrectal ultrasound (TRUS) guided biopsy began to show clinical usefulness. In the 1980s the biopsy needle was attached to the ultrasound probe for enhanced accuracy. The continuous development of prostate biopsies has resulted in more efficient ways concerning anesthesia, sampling of more cores and the use of MRI in present day.(6, 7)

Diagnosis of prostate cancer

In the diagnosis of prostate cancer, digital rectal exam is a standard clinical procedure, however tumours in the prostate gland are not always palpable. TRUS is utilized to acquire information such as the prostate volume and to guide the needle in biopsy. Prostate biopsies are required to obtain histopathological diagnosis (4) Multiparametric magnetic resonance imaging (MRI) has become an important tool when detecting prostate cancer. MRI can detect clinically significant cancer while also eliminating insignificant findings on a higher level than ultrasound. (8, 9) Prostate Imaging-Reporting and Data System (PI-RADS) is a standard classification scale for radiological evaluation of lesions in MRI.(10)
The standard procedure for histopathological diagnosis has for a long time been systematic biopsies. A technique where many samples of tissue is taken systematically from different areas of the prostate. With the use of prostate MRI in the diagnostic pathway for prostate cancer, the procedure of targeted biopsy has emerged.(11) There are three different techniques in presence for targeted biopsies: in-bore MRI target biopsy, MRI-TRUS fusion target biopsy and cognitive registration TRUS target biopsy. (12)
In-bore MRI targeted biopsy is conducted with MRI-guidance within the MRI scanner, usually under general anaesthesia. (13) In MRI-TRUS fusion biopsy, MR-images are first taken and the suspected lesions are marked and then fused with the ultrasound image to guide the targeted biopsy. (14, 15) In MRI cognitive-targeted biopsy, lesions are identified with MRI and urologists can then study the localization of the suspected lesion on the images and target the zones of interest with help of TRUS.(16)
Although these three techniques for MRI targeted biopsies have been developed, there is still no standard procedure for targeted biopsies. Further studies are necessary to evaluate whether one of the techniques are preferred. (17)

Several studies that compare MRI with targeted biopsies to systematic biopsies have shown that excluding systematic biopsies from MRI with targeted biopsies reduces diagnosis of clinically insignificant prostate cancer. This, without exposing patients of undiagnosed clinically significant or high grade prostate cancer. (18) On the other hand a meta analysis by

Sathianathen et al showed a 7-10% risk of missing significant cancer if not a systematic biopsy was conducted. The authors suggested that the decision regarding proceeding with systematic biopsies or not, need to be overlooked at each clinical case. (9)

Prostate biopsies can be obtained by two approaches, either transrectally (TRUS-Bx) or transperineally (TPBx). TRUS-Bx has been used worldwide for decades to enable detection of prostate cancer. The technique of TRUS-Bx has evolved considerably over time and has become the gold standard for prostate biopsy. (19, 20) TPBx has however increased in use as an attempt to reduce the risk of sepsis and major rectal bleeding. Both techniques have the same cancer detection rate, however, TRUS-Bx is more efficient in terms of hospital resources, e.g. time and staff. (21)

To avoid infections, mainly caused by E.coli, prophylactic antibiotics are given prior to biopsy. Fluoroquinolones are generally preferred because of their prostatic tissue penetration capabilities. (22) If the patient has any risk factors regarding complications post biopsy, prolonged prophylactic antibiotic treatment is given. Diabetes, immunosuppression, positive urine culture, urinary tract infection (UTI) prior post biopsy, several prior UTIs or prostatitis and urinary catheter are risk factors that require prolonged prophylactics. Anticoagulantia treatment are withdrawn prior to biopsy. In addition to prophylactic antibotics, rectal preparation with Povidone-iodine is sometimes used to reduce the risk of febrile infection post prostate biopsy. Local anesthesia is given before the initiation of biopsy. (5)

The Gleason score is a histological grading scale that is used to evaluate and determine the severeness of the tumour from a prostate biopsy. (23) The Gleason score has developed since its introduction in 1966 hence why the original grading scale deviates from the scale that is used today. (24) The modern Gleason grading scale starts at 3 (slow-growing tumor) and extends to 5 (aggressive tumor). Gleason score consists of the most dominating pattern combined with the highest (worst) pattern. (5)

Fig 2. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol. 1974;111(1):58-64.

Prostate biopsy Complications

Minor complications such as hematuria, hematospermia, impairment of lower urinary tract symptoms (LUTS) are common but mostly transient. There is no strong etiological evidence regarding erectile dysfunction and prostate biopsy. More severe but rare complications are rectal bleeding and sepsis. The rate of infectious complications varies in several studies and ranges between 0-6.3%. (25) A nationwide study by Lundström et al. in Sweden showed that although the risk of infection is around 6%, the need of hospital care due to infectious complications has increased over time to 1% in year 2011. Furthermore, Forsvall et al. published a study in 2021 showing that infection rates after prostate biopsies was 5.4% whereas 3.9% of those patients needed hospital care. However, mortality rates due to infectious complications are still low.(26, 27) The rise in antibiotic resistance among colonic bacteria is the main cause for the increase in infectious complications.(28)

Prostate Cancer Screening

PSA testing is nowadays utilized as a form of screening implement for prostate cancer and varies in usage among healthcare facilities worldwide.(29) Sweden still lacks a screening program for prostate cancer and only a few countries in the world has their own national screening program.The propagation of PSA-testing has led to increased diagnosis and treatment. Although most patients can be cured through treatment, quality of life can be greatly affected and thus not always beneficial. (30) This corresponds with findings from a systematic review, that potential benefits include fewer patients dying and fewer patients experiencing metastasis. However, patients face potential overdiagnosis, overtreatment, unnecessary worry and treatment side effects. (29)

There are large studies published with data that suggests different possibilities to commence a screening program, however it takes time to implement studies to clinical work and there is still insufficient evidence for a population based prostate cancer screening. The European Randomized study of Screening for Prostate Cancer (ERSPC) including 162 388 men is the worlds largest multi-center randomized screening trial that evaluates PSA as a screening tool. The study has shown up to 44% reduction in prostate cancer mortality.(31) Another large study in the United States named Prostate, Lung, Colorectal and Ovarian (PLCO) cancer trial with 76.685 men showed no difference in mortality reduction in PSA-testing. A re-analysis later confirmed a significant reduction in mortality such as the ERSPC study.(32) A screening study from Karolinska university hospital published in 2018 showed that using PSA together with MRI and several biomarkers, reduces the risk of unnesscary prostate biopsies by one third.(33) The Göteborg prostate cancer screening 2 trial will contribute with new data by evaluating the addition of MRI to PSA in screening.(34)

There are several articles describing prostate biopsy complications, however data from the Göteborg-2-trial is unique, as the study includes men of ages 50-60 years and examines data regarding infectious complications from a screening population. (34) Since infections post transrectal prostate biopsies is seen as an increasing complication based on general

population, a study that focuses on a screening population is highly relevant. Knowledge concerning the rate of infectious complications in a screening population is important when establishing a potential screening program in the future.

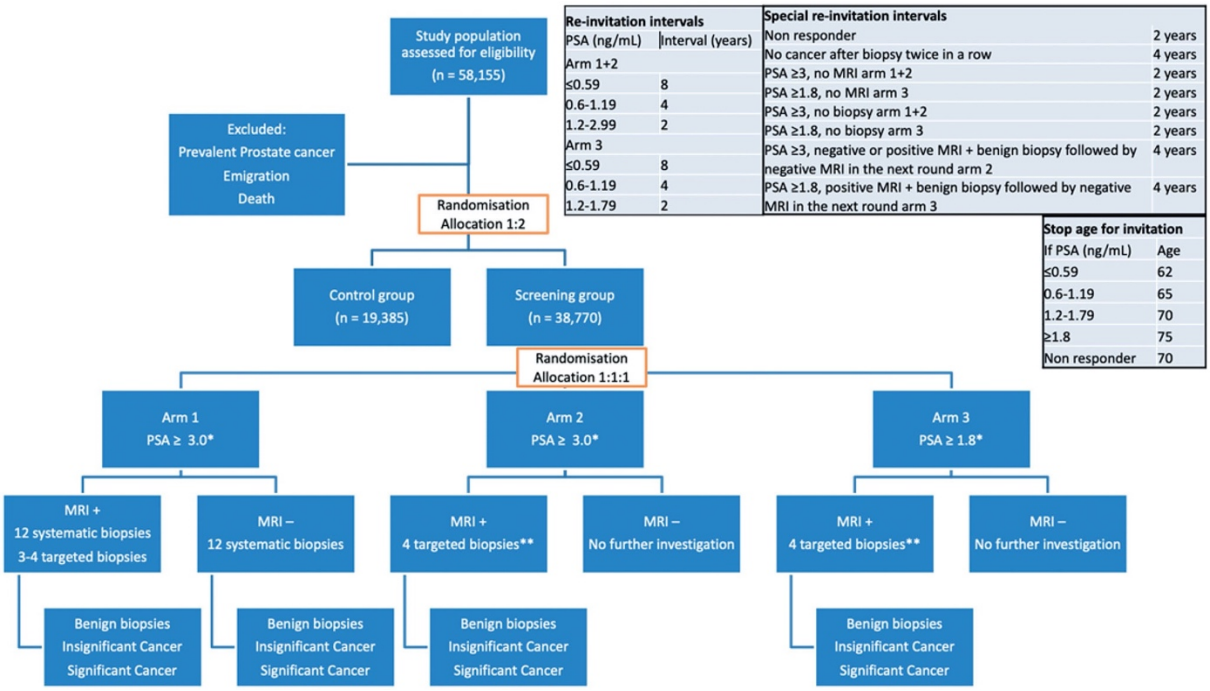
Aim

The primary aim of this study was to investigate the infectious complication rates after transrectal ultrasound guided transrectal prostate biopsies in the population-based Göteborg prostate cancer screening 2-trial. The secondary aim was to investigate whether the biopsy approach, transrectal targeted biopsies versus transrectal systematic biopsies, could have an impact on the infectious complications rate.

Material and Methods

This study is based on data from the Göteborg prostate cancer screening 2 trial. The Göteborg prostate cancer screening 2 trial is a prospective, randomized, population-based prostate cancer screening trial which started in 2015. The primary objective of this study is to evaluate whether changing the screening algorithm in men with PSA≥3 ng/ml from systemic biopsy to pre-biopsy MRI and MRI-targeted biopsy can reduce the risk of detecting clinically insignificant cancers. The result of the primary objective is expected shortly. The study was designed as a 2-step 3 arm randomized screening study with a study population of 62 117 men. The first step consisted of taking a random sample of men from the Total Population Register of men aged 50-60 years in Gothenburg and its surroundings. The study population of 62 117 men were then randomized to a screening group or a control group. Men in the screening group were invited for PSA-testing. Men who accepted participation were then dividied into one out of three screening-arms. Men in arm 1 with PSA≥3 ng/mL were invited

to prostate MRI followed by systematic biopsies irregardless of the MRI results. Targeted biopsies were added if there were suspicious lesions on MRI. Men in Arm 2 with PSA≥3 ng/mL were invited to prostate MRI followed by targeted biopsies towards suspected lesions on MRI. Negative MRI results lead to no further investigation. Men in Arm 3 were identical to Arm 2, however with a lower limit of PSA≥1.8 ng/mL. Layout is presented in figure 3.



Re-invitation intervals	
PSA (ng/mL)	Interval (years)
Arm 1+2	
≤0.59	8
0.6-1.19	4
1.2-2.99	2
Arm 3	
≤0.59	8
0.6-1.19	4
1.2-1.79	2

Special re-invitation intervals	
Non responder	2 years
No cancer after biopsy twice in a row	4 years
PSA ≥3, no MRI arm 1+2	2 years
PSA ≥1.8, no MRI arm 3	2 years
PSA ≥3, no biopsy arm 1+2	2 years
PSA ≥1.8, no biopsy arm 3	2 years
PSA ≥3, negative or positive MRI + benign biopsy followed by negative MRI in the next round arm 2	4 years
PSA ≥1.8, positive MRI + benign biopsy followed by negative MRI in the next round arm 3	4 years

Stop age for invitation	
If PSA (ng/mL)	Age
≤0.59	62
0.6-1.19	65
1.2-1.79	70
≥1.8	75
Non responder	70

Figure 3. Study Schema of the Göteborg-2 trial. Figure 3 shows the study layout of the Göteborg-2 trial. MRI interpretation is performed according to Prostate Imaging-Reporting and Data System (PI-RADS), v.2.1. MRI þ: positive MRI defined as PI-RADS 3, 4 or 5. MRI: negative MRI defined as PI-RADS 1 or 2. All men with PSA > 10.0 ng/mL are recommended 12-core systematic TRUS biopsy plus additional targeted biopsy if positive MRI. **All men with an MRI showing PI-RADS 5 are recommended 12-core systematic TRUS biopsy. Reprinted with permission from (34)

Table 1. Göteborg 2 Trial Inclusion and exclusion criterias. Reprinted with permission from (34)

Eligibility criteria:	Inclusion criteria	Exclusion criteria
	-Alive on randomisation date -Registered address in the county of Gothenburg or any of six specified municipalities in Sweden -Age 50-60 years	-Previous diagnosis of prostate cancer Emigration during period between randomization and update of the total population register, to which the G2-Trial-study participants unique personal identification numbers are linked. -Death during the period between randomization and update of the total population register, to which the G2-Trial-Study participants unique personal identification numbers are linked.

For this study, participants in the screening group of the Göteborg prostate cancer screening 2 trial who underwent their first prostate biopsy (October 2015-March 2021) were considered. Therefore the selected study population consisted of 810 men from the main study population of 62 117. When the complete cohort of the Göteborg prostate cancer screening 2 trial were randomised in spring 2020, 38 770 men were invited to the screening group. Among the invited men, 50 % participated and 94 % attended further evaluation with MRI. Of these men, 908 were invited for urological examination and first time biopsy. A total of 98 men were excluded due to transperineal biopsies, patients not participating and metastasis. Flowchart of the final study population is shown in figure 4.

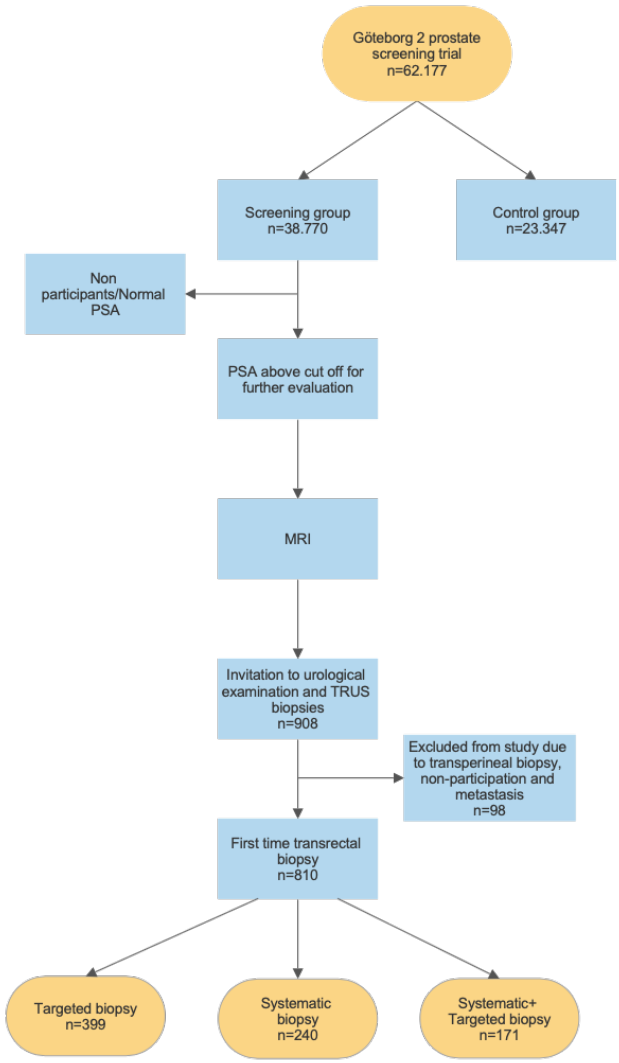


Figure 4. Shows the selection process of data to be analyzed in the study. Patients with normal PSA were transferred to the screening group for a new PSA subsequently. Patients with a negative MRI were both subject to biopsy (Arm 1 Göteborg 2 trial) and transferred back to the screening group (Arm 2 and 3, Göteborg 2 screening trial). Biopsypopulation in this study is from patients fist time biopsied in the Göteborg 2 Trial study.

Data was collected from questionnaire 1 and 2 from the Göteborg prostate cancer screening 2 trial. Men were asked to answer the first questionnaire when accepting invitation and consisted of basic health characteristics. All men were asked to answer the second questionnaire at a follow up visit 3-6 weeks after prostate biopsy. The second questionnaire consisted of questions regarding experiences with the diagnostic investigation and wether the patient had suffered any side effects post biopsy, such as bleeding from the rectum, fever or

UTI. Not all questions from the Göteborg prostate cancer screening 2 trial questionaires were used as data for this study since there were several questions not associated with infectious complications. Questions that were chosen are shown in table 2.

Table 2, shows questions investigated from the Göteborg 2 Trial study questionnaire 1 and 2. Not all questions were taken from questionnaire 1 and 2. IPSS questions were taken directly from the original IPSS-inquiry and are not presented in this table.

Questions survey 1	Swedish	English translation
1.7	Jag har genomgått vävnadsprovtagning av prostata (”biopsier”) (Ja/Nej/Vet ej)	I have undergone prostate biopsy (Yes/No/ don’t know/ decline to respond)
13.1	Har du fått diagnosen diabetes? (Ja/Nej/Vet ej)	Do you have diabetes? (Yes/No/ don’t know/ decline to respond)
13.2	Om ja, När fick du diagnosen diabetes? (0-5 år sedan/6-10 år sedan/ 11-20 år sedan/ >20 år sedan/Vet ej)	If yes, when did you get your diagnosis? (0-5 years ago/6-10 years ago/ 11-20 years ago/ >20 years ago/ don’t know)
13.3	Om ja, hur behandlar du din diabetes? (Kost/Tabletter/Insulin/Vet ej)	If yes, do you have any diabetes treatment? (Medications/diet/don’t know)
IPSS		
Questions survey 2		
13.1	Efter vävnadsprovtagningen, fick du urinvägsinfektion? (Ja/Nej/Vet ej)	Following the prostate biopsy, did you experience urinary tract infection? (Yes/No/ don’t know/ decline to respond)
13.2	Efter vävnadsprovtagningen, fick du frossa/låggradig feber (37.5-38.5 grader)? (Ja/Nej/Vet ej)	Following the prostate biopsy, did you experience Rigor/low grade fever? (37.5-38.5 degrees Celsius) (Yes/No/ don’t know/ decline to respond)
13.3	Efter vävnadsprovtagningen, fick du frossa/hög feber (>=38.5 grader)? (Ja/Nej/Vet ej)	Following the prostate biopsy, did you experience Rigor/high grade fever? (>= 38.5 degrees Celsius) (Yes/No/ don’t know/ decline to respond)
13.4	Efter vävnadsprovtagningen, fick du blod i urinen? (Ja/Nej/Vet ej)	Following the prostate biopsy, did you experience blood in urine? (Yes/No/ don’t know/ decline to respond)

13.5	Efter vävnadsprovtagningen, fick du blod i sädesvätskan? (Ja/Nej/Vet ej)	Following the prostate biopsy, did you experience blood in semen? (Yes/No/ don't know/ decline to respond)
13.6	Efter vävnadsprovtagningen, fick du blod från ändtarmen, eller i avföringen? (Ja/Nej/Vet ej)	Following the prostate biopsy, did you experience blood from the rectum or in the stool? (Yes/No/ don't know/ decline to respond)
14	Behövde du ytterligare antibiotikatabletter, utöver de du fick i samband med vävnadsprovtagningen, på grund av urinvägsinfektion eller frossa/feber? (Ja/Nej/Vet ej)	Due to urinary tract infection or rigor/fever as a result of the prostate biopsy, did you need to take antibiotic medication in addition to the one you received in conjunction with the prostate biopsy procedure? (Yes/No/ don't know/ decline to respond)
15.1	Behövde du uppsöka vårdcentral eller läkare efter vävnadsprovtagningen? (Ja/Nej/Vet ej)	Did you need to seek care at a primary care facility or a physician following the prostate biopsy? (Yes/No/ don't know/ decline to respond)
15.1.1	Varför behövde du uppsöka vårdcentral eller läkare? (UVI/feber/Blödning från ändtarmen/Annat,vad:/ Vet ej/vill ej besvara)	If yes…Why? (Urinary tract infection/feber/bleeding from the rectum/Other/Don't know/Decline to respond
15.1.2	Fick du någon behandling eller vidtogs någon åtgärd? (Ja, ange vad/ Vet ej/Vill ej besvara)	Did you recieve any treatment? (Yes/No/ don't know/ decline to respond) If yes what?
15.2	Blev du inlagd på sjukhus efter vävnadsprovtagningen? (Ja/Nej/Vet ej)	Were you admitted to the hospital following the prostate biopsy? (Yes/No/ don't know/ decline to respond)
15.2.1	Varför blev du inlagd på sjukhus? (Urinvägsinfektion/feber/Blödning från ändtarmen som krävde åtgärd/Annat, vad:/Vet ej/Vill ej besvara)	If yes…Why? Urinary tract infection/fever/Bleeding for the rectum that required care/other/Don't know/Decline to respond
16	Om du vanligtvis arbetar, behövde du vara hemma från jobbet efter vävnadsprovtagningen? (Ja/Nej/Vet ej)	If you typically go to work, did you need to stay at home from work following the prostate biopsy? (Yes/No/

		don’t know/ decline to respond)
16.1	Ange hur många dagar du behövde vara hemma från jobbet med siffror: (Svar:)	If yes…Please specify the approximate number of days
16.2	Vad var anledningen till att du behövde vara hemma från jobbet: (Svar:/Vet ej/Vill ej besvara)	What was the reason?

In case questionnaires lacked information, medical charts of those men were investigated.

Criterias for review of medical charts among the men who had not answered questionnaires, herforth called non-responders, were: patients that had undergone prostate biopsy for the first time in the Göteborg prostate cancer screening 2 trial study, all within a 30 day period post biopsy. Exclusion criterias were patients not accepting access to their medical charts followed by same exclusion criterias as in the Göteborg prostate cancer screening 2 trial study. The non responders base charecteristics were examined as a security check.

Clinical findings such as TRUL volume, clinical stage, PAD and PSA were taken from the Göteborg prostate cancer screening 2 trial study database acquired from clinical examination. Infectious complication rates were calculated on the total study population of 810 men. Infectious complication rates were analyzed by looking at the UTI rates as well as UTIs requiring hospitalization. In order to be classified as having an UTI, men must have been prescribed with antibiotics. The secondary objective was answered by comparing infectious rates after systematic biopsies versus targeted biopsies. To investigate whether there were any significant differences in biopsy techniques, Fishers test was used between the groups with a significance level of 0.05.

The primary outcome for this study was to evaluate the infectious rate post biopsy. The secondary outcome was to investigate whether there was a difference in infection rates between systematic and targeted biopsies and furthermore the cause for the infections.

All data was collected onto a spreadsheet and analyzed using SPSS version 28 (Statistical Package for the Social Science) to acquire correct results. Results were analyzed through

descriptive statistics and Fisher's test. Results were presented via median, interquartile range and incidence percentage. Secondary objective was presented in P-value through Fisher's Test.

Student's contribution

Analyze and summarize data from the Göteborg-2 trial study. Literature search in databases and review of patient´s journal. Conducting and writing the thesis.

Ethics

The Göteborg-2 trial study is approved by the Regional Ethical Review Board in Gothenburg in January 2015 (registration number 890-14). Those who participated in the Göteborg-2 trial had their identity anonymized through participant ID numbers. To investigate the medical charts, the writer had access to the participant ID numbers and their personal identification number. Anonymity and integrity was ensured by only reviewing medical charts if necessary. Furthermore the men included in this study had left their informed consent when accepting participation. Personal identification numbers with their matching participant ID numbers were stored in a database with limited access. No patients were harmed in this study as the study exclusively investigated a complication from a procedure that already had been done. Results from this study will be used in a later publication originating from the ongoing Göteborg-2 trial study, participants will gain access to the results.

Results

There were a total of 193 questionnaires that were incomplete, which lead to review of

medical charts in these cases. Furthermore there were 14 patients in the questionnaire group that had answered “No” on question 13.1, regarding UTI but “Yes” on question 14 regarding need of extra antibiotics due to UTI. To ensure a valid infection rate, additional 14 extra journals from the questionnaire group were therefore examined. A total of 207 medical charts were reviewed.

Among the 617 men who had answered the questionnaires the median age at biopsy was 58.7 years with a median PSA of 3.8 ug/l. Among the 193 men who had not answered the questionnaires, the median age was 58.2 years with a median PSA of 3.7 ug/l. A large proportion of the men who had answered the questionnaires, were asymptomatic (7.8%) or had mild LUTS (34.5%). Baseline characteristics for the entire study poplation is shown in table 3.

Table 3 Describes baseline charecteristics in questionnaire group (n=617) and journal group (n=193. This table was made to compare base charecteristics as a security check in the two groups.

Study population Total (n=810)	**Men who had answered the questionnaires (n=617)**	**Men who did not answer the questionnaires (n=193)**
Age at biopsy, years Median (IQR)	58.7 (55.6-60.9)	58.2 (54.8-60.7)
Median PSA ug/l, (IQR)	3.8 (3.1-5.3)	3.7 (3.1-5.1)
Median TRUL Volume ml (IQR)	37.3 (29.7-49.1)	37.9 (29.8-47.8)
Clinical stage		
T1c	461 (74.7%)	141 (73.1%)
T2a/b	141 (22.9%)	42 (21.8%)
T2c	4 (0.6%)	0 (0%)
T3-T4	2 (0.3%)	2 (1%)
TX	9 (1.5%)	8 (4.1%)

PAD		
Cancer	301 (48.8%)	79 (40.9%)
No cancer	310 (50.2%)	113 (58.5%)
Suspicous+PIN	6 (1.0%)	1 (0.5%)

Baseline characteristics among the 617 men who had answered the questionnaire, according to biopsy procedure, and supplemented with IPSS-score and history of diabetes are shown in table 4.

Table 4. Baseline charecteristics among the 617 men who had answered the questionnaire according to biopsy procedure.

	Total population of men who had answered the questionnaires (n=**617)**	**Systematic biopsy (n=171)**	**Targeted biopsy (n=319)**	**Systematic+Targeted biopsy (n=127)**
Age at biopsy, years Median (IQR)	58.7 (55.6-60.9)	58.4 (55.4-60.9)	58.4 (55.5-60.8)	59.3 (56.5-60.8)
Median PSA ug/l, (IQR)	3.8 (3.1-5.3)	4.5 (3.4-6.0)	3.3 (2.4-4.3)	4.6 (3.4-6.4)
Median TRUL Volume ml (IQR)	37.3 (29.7-49.1)	43.8 (32.5-57.0)	36.0 (29.0-45.3)	35.0 (28.3-44.6)
Clinical stage				
T1c	461 (74.7%)	146 (85.4%)	242 (75.9%)	73 (57.5%)
T2a/b	141 (22.9%)	21 (12.3%)	73 (22.9%)	47 (37.0%)
T2c	4 (0.6%)	1 (0.6%)	1 (0.3%)	2 (1.6%)
T3-T4	2 (0.3%)	0 (0%)	0 (0%)	2 (1.6%)
TX	9 (1.5%)	3 (1.8%)	3 (0.9%)	3 (2.4%)
Diabetes	19 (3.1%) 152 Missing	5 (2.9%) 38 Missing	11 (3.4%) 79 Missing	3 (2.4%) 35 Missing
LUTS (IPSS score)	228 Missing	56 (32.7%)	125 Missing	47 Missing
0 (asymptomatic)	48 (7.8%)	14 (8.2%)	26 (8.2%)	8 (6.3%)

1-7 (mildly symptomatic)	213 (34.5%)	57 (33.3%)	106 (33.2%)	50 (39.4%)
8-19 (moderately symptomatic)	105 (17.0%)	37 (21.6%)	48 (15.0%)	20 (15.7%)
20-35 (severely symptomatic)	23 (3.7%)	7 (4.1%)	14 (4.4%)	2 (1.6%)
LUTS Treatment	Missing= 517 (84%) 5 (0.8%)	NA	NA	NA
Type of treatment:	Alfuzosin (n=3) RIK (n=1) Omnic (n=1)	NA	NA	NA

Out of the total study population of 810 men, infectious complications rate after TRUS guided TRUS-Bx in the population-based Göteborg prostate cancer screening 2-trial resulted in 1.7% patients with UTI and 0.5% needing hospital care due to UTI. UTI results are presented in table 5. The main cause for UTI requiring hospital care was sepsis, the men had no risk factors prior to biopsy. One of these four men required care in a ICU. Charecteristics regarding UTI/UTI requiring hospitalization are presented in table 6 and 7. A total of 2.8% (23 men) of the study population received prolonged prophylactic antibiotics. Furthermore prolonged prophylaxis was given to 2.0% in the targeted biopsy group, 4.2% in the systematic biopsy group and 2.9% in the targeted with systematic biopsy group. One patient that was given prolonged prophylactic antibiotics suffered an UTI. Out of 23 men, eight received prophylactic antibiotics due to diabetes. Reasons for prolonged antibiotics are presented in table 8. Ciprofloxacin was the most used prophylactic antibiotic.

The biopsy approach, targeted biopsies versus systematic biopsies, had no impact on the infectious complication rate. Results showed no significance with a p-value of 0.093. Crosstable can be seen in appendix 1.

Table 5. The rates of infectious complications after TRUS biopsy presented according to biopsy procedure. Missing patients are due to questionnaires not being answered or patients not wanting access to journals by researchers.

	Overall study population N= 810	**Men who underwent targeted biopsies (2-9 cores) N=399**	**Men who underwent systematic biopsies (10-12 cores) N=240**	**Men who underwent a combination of targeted and systematic biopsies (6-23 cores) N=171**
UTI	1.7% (14) Missing: 9	1.0% (4) Missing: 3	2.5% (6) Missing: 4	2.3% (4) Missing: 2
UTI requiring hospitalisation	0.5% (4) Missing: 1	0.3% (1)	0.4% (1) Missing: 1	1.2% (2)

Table 6. Characteristics of men in the studypopulation who had UTI (urinary tract infections) requiring hospitalization. Reason for admission to hospital, results of cultures and given treatment are shown. As none of these men had increased risk for UTI , no prolonged antibiotics prophylaxis were given. 1 patient required healthcare at ICU (intensive care unit)

UTI requiring hospitalisation	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**
Reason	Sepsis	Sepsis	Sepsis	Fever/Suspected sepsis
Urine/blood culture	E.coli no resistence	Pseudomonas aeruginosa, no resistence	E.coli resistant to ciprofloxacin	Negative
Antibiotics	Pip/taz	Cefotaxim	Pip/taz+Nebcina	Cefotaxim
ICU Yes/No	No	No	Yes	No
Risk factors	No	No	No	No
IPSS-Score	1	Missing	14	0

Table 7, Charecteristics of the men that underwent an UTI (urinary tract infection), culture and given antibiotics are shown. Most of the patients seeked health centers and not hospitals which explains lack of data regarding urine/blood culture. One patient with UTI had been given extended prophylactic antibiotics prior to biopsy due to bladder disorder. Only 1 patient with diabetes.

UTI - Patient:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Reason	UTI	Pelvis pain/Hematuria	Unclear	UTI	UTI	Urinary incontinence/ Low fever	UTI	UTI/Fever	UTI/Fever	UTI	UTI	Epididymitis	UTI	UTI
Urine/ blood culture	N.A	N.A	N.A	N.A	N.A	E.coli, Resisant to ciprofloxacin +Selexid	N.A	N.A	N.A	N.A	N.A	N.A	N.A	E.coli resistance to Trimetoprim+ Ciprofloxacin
Antibiotics	Bactrim forte	N.A	Idotrim	N.A.	N.A	Bactrim forte	Ciprofloxacin	Ciprofloxacin	N.A.	Bactrim forte	N.A	N.A	N.A	Ciprofloxacin change to Penomax
Profylactic Antibiotics	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Diabetes Yes/No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No
IPSS-Score	6	10	3	20	Missing	15	3	25	15	Missing	Missing	Missing	14	Missing

Table 8 Shows charecteristics of the men that were given prolonged prophylactics prior to biopsy with reasons to why and type of antibiotics.

Prolonged profylactics Patients	**Reasons:**	**Diabetes**	**Antibiotics**	**IPSS-Score**
1	Nefrotic syndrome	Yes	Cipro	N.A
2	Prior asymptomatic E.coli UTI	No	Cipro	14
3	Prior Prostatitis	No	Cipro	7
4	Prior UTI	No	Amoxicillin	10
5	Diabetes	Yes	Cipro	8
6	Prior Prostatitis	No	Cipro	24
7	Prior urosepsis	No	Cipro	5
8	Bleeding during biopsy	Yes	Cipro	N.A
9	Immunology treatment	Yes	Bactrim	6
10	N.A	No	Cipro	9
11	Prior UTI	No	Cipro	N.A
12	Immunology treatment	No	Cipro	14
13	Acute prostatis prior to biopsy	No	Cipro	2
14	As a precaution due to major prostate tumour	No	Cipro	N.A
15	Diabetes	Yes	Cipro	17
16	Earlier prostatities	No	Cipro	0
17	Diabetes	Yes	Cipro	22
18	Earlier prostatities	No	Cipro	1
19	Diabetes	Yes	Cipro	10

20	Extra biopsy cores	No	Cipro	N.A
21	Residual urine	No	Cipro	31
22	Diabetes	Yes	Cipro	N.A
23	Ongoing Prostatitis	No	Cipro	1

Discussion

In this study, we determined the rate of infectious complication rate after transrectal ultrasound guided transrectal prostate biopsies in the population-based Göteborg prostate cancer screening 2-trial. We found that 1.7% (14/810) of the screened men undergoing TRUS biopsies developed UTI while 0.5% (4/810) of the screened men undergoing TRUS biopsies needed hospital care due to infections. Other studies have shown an infection rate between 0 and 6.3% regarding hospitalization. (25-27, 35) Infectious complications due to transrectal biopsy is increasing. (36) However the infection rate in this study is remarkably low. The lower infection rates in this study compared to other studies are probably due to several factors. Two main reasons being the study population consisting of men with a lower median age (58.7) and data regarding infection rates were based on a screening population. In other words, men were invited to participate compared to other studies where men were most likely seeking healthcare due to LUTS. A large amount of the men in this study had mild to no symptoms regarding LUTS (IPSS-score). The results in this study is not transferable to the general population but can on the other hand be used in a screening setting.

In recent time transperineal biopsies has increased in use since there has been several researchers reporting a lower risk of sepsis with this approach as compared to transrectal biopsies. But there are also studies showing no significance in infectious complications between transrectal and transperineal biopsies.(12, 37, 38). The amount of infectious complications are on such low levels that it can set a new standard for future screening of prostate cancer, even with the use of transrectal biopsies.

There was no significant difference between targeted versus systematic biopsies regarding the infectious complication rate. Several studies have investigated the difference between complications in targeted versus systematic biopsies. Although there is a difference between complications it is hard to show any significance.(39, 40) The question still prevails if there are any differences between these two techniques and further studies are necessary. There is however no significant difference between targeted biopsy techniques and UTIs. (12) It would have been interesting to continue this study with an investigation regarding wether the number of biopsy needles could have an impact on the infectious rate.

Strengths and Limitations

A weakness regarding data is that the majority of the results are calculated through questionnaires answered by patients. This can lead to confusion regarding questions or questions not being correctly answered, which raises the question of the correctness of the infection rates. Question number 14 (Due to urinary tract infection or rigor/fever as a result of the prostate biopsy, did you need to take antibiotic medication in addition to the one you received in conjunction with the prostate biopsy procedure?) in the questionnaire seemed to lead to misunderstanding which may have resulted in a higher infection rate. One could also argue that there might be patients that had answered “No” on all questions regarding UTI that had had a UTI. On the other hand, questionnaires are an excellent method for gathering a large amount of information from a large study group. Such as this scenario where there was a compact time schedule and a large study population. To evaluate infection rates even more thoroughly a complete assessment of medical charts would be necessary. Furthermore, we could not gain access to general practioners journal system which led to missing data regarding type of antibiotics prescribed and results of blood/urine cultures.

In this study, UTI were defined as UTI if it had been treated with antibiotics. Neither

symptoms of UTI nor results of urine culture were included. The limit of 30 days post biopsy is commonly used by other studies and infections are unlikely to happen after 30 days since infections are an acute side effect. (27, 35) In terms of biopsy complication rates, hospitalization should be a better way to determine more severe infection rates and is easier to compare with other study results since it leads to a bigger usage of healthcare resources such as hospital beds and staff. One could argue that the low infection rate suggests that a screening program could be safe when exclusively looking at the numbers. On the other hand there was one patient that ended up in the ICU due to sepsis. Considerations are still necessary regarding the risk of obtaining an UTI versus the benefit of curing early stages of prostate cancer. Researchers are getting closer to a clinical screening program for prostate cancer, this study shows that it might be possible regarding infectious complications and biopsies.

Conclusions

Infectious complication rates are lower in a screening group compared to the majority of previously reported infection rates after transrectal biopsy. The results can be used to evaluate further screening studies and also be implied as a reference in future screening programs.

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Appendices

Appendix 1, showing crosstable of systematic versus targeted biopsy

Type of biopsy	Targeted biopsy	Systematic and systematic+targeted biopsy	Total
UTI	5	13	18
No UTI	394	398	792
Total	399	411	810
Fishers Exact Test	N.A	N.A	P value =0.093

Populärvetenskaplig sammanfattning

Infektion efter prostatabiopsi i en screeningstudie

Författare:	Karl Eriksson
Examensarbete:	30 hp
Program:	Läkarprogrammet
År:	2021
Handledare:	Kimia Kohestani
Nyckelord:	Prostatacancer, prostatabiopsi

Prostatacancer är den vanligaste cancern i Sverige och leder till flest cancerorsakade dödsfall hos män. Prostata är ett organ som sitter mellan urinblåsan och ändtarmen och producerar sädesvätska som spermierna transporteras i. För att kunna fastställa en cancerdiagnos behöver man utöver patientens sjukdomshistoria och klinisk undersökning av en urolog göra en så kallad prostatabiopsi. En prostatabiopsi tas genom att man för in tunna nålar i prostatan som

tar med sig en bit vävnad. Vävnaden kommer sedan studeras i mikroskop för att bedömas om det skulle röra sig om cancer. På senare år har biopsimetoden utvecklats, förut utgick man endast från ultraljud för att underlätta för urologen att sticka rätt i prostatan med nålarna. Nålarna sticks då in i prostatan utefter en mall, så kallad systematisk biopsi. Idag görs många gånger en magnetkamerabild av prostatan innan biopsin för att kunna rikta nålarna till olika ställen med misstänkta förändringar, så kallad riktad biopsi. Innan biopsin ges lokalbedövning över området för att minska obehag. Lättare komplikationer efter en prostatabiopsi är lätt blodfärgat urin, blodfärgad utlösning och ibland lättare blod i avföringen. Dessa komplikationer är relativt vanliga men är ofarliga och går mestadels över av sig själv. Urinvägsinfektioner är inte lika vanligt och kräver antibiotikabehandling. Allvarligare komplikationer kan vara en kraftigare blödning från ändtarmen eller en infektion som kan kräva sjukhusvård. Dessa komplikationer är mycket ovanliga i Sverige. Urinvägsinfektion efter prostatabiopsi i Sverige ligger idag på runt 6%.

Denna studie undersöker i hur stor utsträckning män i en screeningstudie för prostatacancer drabbas av infektion till följd av prostatabiopsi. Studien baserades på totalt 810 män. Datan baseras på Göteborg-2-studien som undersöker nya tillvägagångssätt för screening hos män i 50-60 års åldern i Göteborg och i närliggande kommuner. Denna studie undersöker även om förekomst av infektion efter prostatabiopsier skiljer sig mellan riktade och systematiska biopsier.

Resultatet i denna studie visar att 14 av 810 män (1,7%) fick en urinvägsinfektion som behandlades med antibiotika och endast 4 av 810 (0,5%) män fick en infektion som krävde sjukhusvård. Det var ingen statistiskt säkerställd skillnad i infektionsfrekvensen mellan riktade och systematiska biopsier. En stor del av studiepopulationen hade inga (7,8%) eller lättare urinvägsbesvär (34,5%). Anledningen till denna låga infektionsfrekvens kan dels bero på en lägre ålder vid biopsi samt att många av patienterna i studien inte hade så påtagliga urinvägsbesvär. Detta resultat kan användas för att vidareutveckla forskning kring prostatacancerscreening och på sikt vara med i grunden till ett kommande screeningprogram.

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