

Study Code: PRIS
Version No: 1.5
Date: 2025-01-13

Prostate Cancer IRE study - PRIS

Study Protocol

This study protocol adheres to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines

Title:	Prostate Cancer IRE Study (PRIS) – A randomized controlled trial comparing focal to radical treatment in localized prostate cancer
Study code:	PRIS
Version number:	1.5
Date:	2025-01-13
Sponsor:	Karolinska University Hospital, Stockholm
Principal Investigator	Anna Lantz

Signature Page

Sponsor

I am responsible for ensuring that this protocol includes all essential information to be able to conduct this study. I will submit the protocol and all other important study-related information to the responsible investigator(s) so that they can conduct the study correctly. I am aware that it is my responsibility to hold the staff members who work with this study informed and trained.

Sponsor Signature	Date
Printed Name Anna Lantz	

Principal Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the study. By signing my name below, I agree to conduct the study in compliance with this protocol, the Declaration of Helsinki, ICH GCP (Good Clinical Practice) guidelines and the national and international regulations governing the conduct of this clinical study.

I will submit this protocol and all other important study-related information to the staff members and responsible investigators who participate in this study, so that they can conduct the study correctly. I am aware of my responsibility to continuously keep the staff members and responsible investigators who work with this study informed and trained.

I am aware that quality control of this study will be performed in the form of monitoring, possibly audit, and possibly inspection.

Principal Investigator Signature	Date
Anna Lantz	

Protocol version

Version 1.1: 2021-03-12

Date and version identifier

Revision Version, date, author	Reason	Main Change
1.2, 2022-02-11, Anna Lantz	- Given that the two radical treatments have very different side effects after treatment, different endpoints will be used in two parallel studies, study 1 comparing focal therapy to radical prostatectomy and study 2 comparing focal therapy to radiation therapy - Not to include the primary learning curve for the primary outcome.	- Revision of study design - The first 10 men treated with focal therapy will not undergo randomization or be a part of the primary analysis - The changes in the protocol have been approved in an amendment to the ethical committee Dnr 2021-06102-02
1.3, 2022-06-08, Anna Lantz	- Studies show low accuracy of detecting clinically significant disease after IRE with MRI. - During study trip we got knowledge of the importance of using mpMRI also for treatment planning - To use mpMRI with contrast patients with renal insufficiency have to be excluded - Inclusion of clinical stage $\leq$ T2b is consistent with a unifocal lesion	- We add systematic biopsies to the 12 month fusion-rebiopsy in IRE-arms. - mpMRI also before treatment (Table 1) - Adding exclusion criteria: renal insufficiency; GFR<30 - Inclusion criteria of clinical stage is revised to $\leq$ T2b

1.4, 2023-12-01, Anna Lantz	1. International expertise state that it is safe to treat tumors up to 4.0 cm³ 2. To reduce unnecessary registrations 3. To reduce unnecessary registrations given the low risk for adverse events after 3 months post surgery	1. Change the volume criterion for tumor size from <1.5 cm³ to <4.0 cm³ 2. Remove heart/lung status from the 3, 12, and 24-month follow-ups 3. Modify the registration of adverse events (AE) and serious adverse events (SAE) from 24 months to 3 months
1.5, 2025-01-10, Anna Lantz	1. Slow inclusion 2. Slow inclusion 3. Monitor possible differences between groups concerning urinary tract infections and urinary retention 4. Waiting time for surgery is often longer than 6 weeks without affecting outcomes 5. Reduce unnecessary visits. No medical need for physical visit at 12 and 24 months, can be replaced with phone call. 6. Ensure treatment zone that covers the whole tumour. 7. Clarify that the research participant information only includes the treatment they have been randomized to.	1. Extend the inclusion period by 2 years. 2. Allow for referral from all Swedish regions. Add satellite sites, specifying its tasks, and assigned co-investigators. Change FPI accordingly. 3. Add urinary tract infection and urinary retention as possible adverse events 4. Extend the time to surgery in both arms to up to 6 months (currently 6 weeks). 5. Remove the mandatory physical visit at 12 and 24 months. 6. All patients undergoing focal treatment should have an MRI 2–4 weeks post-treatment.

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		7. Divided the research participant information into two versions: one for PRIS 1 (focal treatment/RALP) and another for PRIS 2 (focal treatment/radiation therapy)
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List of used acronyms and abbreviations

Abbreviation	Term/Explanation
AE	Adverse Event = any untoward medical occurrence
AS	Active Surveillance
CRF	Case Report Form
EPIC	Expanded Prostate Cancer Index Composite
EPM	Etikprövningsmyndigheten (English: Swedish Ethical Review Authority)
EQ5D	EuroQoL-5 Dimensions
GCP	Good Clinical Practice
FT	Focal treatment
HIFU	High Intensity Focal Ultrasound
ICH	International Council for Harmonization
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
IRE	Irreversible Electroporation
ISUP	International Society of Urological Pathology grading of prostate cancer
ITT	Intention-to-treat = including all data from all subjects who have participated in the study
LVFS	Läkemedelsverkets författningssamling (English: Swedish Medical Products Agency's statutes)
mpMRI	multi-parametric magnetic resonance imaging
bpMRI	bi-parametric magnetic resonance imaging
PCa	Prostate cancer
PIRADS	Prostate Imaging Reporting and Data System
PP	Per Protocol analysis = including only data from subjects who have completed the study completely in accordance with the protocol, with no deviations from the protocol
PSA	Prostate specific antigen
RFA	Radiofrequency Ablation
RT	Radical treatment
SAE	Serious Adverse Event = serious untoward medical occurrence
TBx	Targeted biopsy
SBx	Systematic biopsy

Synopsis

Title: Prostate Cancer IRE Study – A randomized controlled trial comparing focal to radical treatment in localized prostate cancer (PRIS)

Study code: PRIS

Short background/Rationale/Purpose:

Prostate cancer is the most common cancer and the leading cause of cancer death among men in Sweden. In year 2018 over 10 000 men were diagnosed with prostate cancer and more than 2,500 died due to the disease, approximately 20% of these in the Stockholm region. The same year 877 men got diagnosed with intermediate risk prostate cancer in Stockholm Region, the group that is potentially eligible for the suggested research. Prostate cancer incidence rates in Sweden are now comparable to rates in countries that had an early introduction of PSA testing, while prostate cancer mortality rates in Sweden are higher than in most other countries. (1)

Tissue sparing treatments for tumours in solid organs are used in several different areas; breast, renal and lung cancers are examples of tumours that are commonly treated with tissue sparing approaches to preserve organ function and minimize damage to adjacent structures. (2-4) A common feature of these tumours is the precise cancer localization. Within prostate cancer diagnostics the rapid evolution and improvement of MRI and targeted biopsies has just recently made it possible to localize the significant tumour areas in the prostate which lays the foundation for focal therapy. The aim of focal therapy is to treat the tumour while preserving benign prostate tissue and the surrounding structures; urethral sphincter, the neurovascular bundles, bladder neck and rectum in order to decrease the risk for postoperative side-effects.

Study objectives:

Primary objective:

To evaluate functional outcomes in men treated for unifocal ISUP 2-3 localized prostate cancer with focal treatment in comparison to conventional treatment with either radical prostatectomy or radiation therapy

Secondary objectives:

- To evaluate adverse events in men treated for unifocal ISUP 2-3 localized prostate cancer with focal treatment in comparison to conventional treatment with either radical prostatectomy or radiation therapy
- To evaluate progression free and treatment free survival in men treated for unifocal ISUP 2-3 localized prostate cancer with focal treatment in comparison to conventional treatment with either radical prostatectomy or radiation therapy
- Economic evaluation of each technique

Study design: Randomized controlled trial with two parallel studies, study 1 comparing focal therapy to radical prostatectomy and study 2 comparing focal therapy to radiation therapy
Study population: Patients diagnosed with localized intermediate risk prostate cancer
Number of subjects: In total 184 men: • 112 men in study 1 comparing focal therapy to radical prostatectomy • 62 men in study 2 comparing focal therapy to radiation therapy • 10 first men undergoing focal therapy will not undergo randomization or be a part of the primary analysis
Inclusion criteria: Men with clinically significant intermediate-risk PCa or dominant unifocal clinically significant intermediate-risk and small contralateral low-risk disease and met all of the following criteria: • Age at inclusion ≥ 40 years • MRI-visible lesion ◦ $\leq$EPE 3 ◦ <4.0 cubic cm³ lesion volume • Gleason score 3 + 4 or 4 + 3 from a single MRI-visible lesion without any Gleason grade 4 in systematic biopsies outside of the target • PSA level ≤ 20 ng/ml • Clinical stage $\leq$ T2b disease • Unifocal significant disease • Life expectancy of ≥ 10 years • Sufficient proficiency in the Swedish language to understand written and verbal information about the trial, its consent process and the study questionnaires
Exclusion criteria: • Intraductal tumour • History of treatment for prostate cancer; surgery, radiation, chemotherapy or hormonal treatment • History of cardiac arrhythmias • Pacemaker • Renal insufficiency; GFR<30 • Severe illnesses such as concomitant cancers, severe cardio-vascular disease or dementia • Contraindications for magnetic resonance imaging (MRI) e.g. magnetic cerebral clips, cochlear implants or severe claustrophobia • History of bladder cancer • History of previous pelvic radiotherapy
Investigational product: Men in the experimental arms will be treated with focal therapy using IRE technique. IRE stands for "irreversible electroporation" and involves the use of high voltage electrical pulses to treat solid

tumours by increasing membrane permeability and inducing membrane disruption, leading to cell death. The technique is CE marked and used in Sweden today in radical ablative therapies in the treatment of tumours in the liver, kidney and pancreas. During the treatment, which takes place under anaesthesia, the patient is placed in gynaecological position and the tumour lesion is located with transrectal MRI fusion ultrasound. Thereafter the needles are placed around the tumour in the prostate using a brachy grid, guided by the ultrasound/MRI fusion images. Through the needles electrical pulses are then sent to treat the tumour in the centre using the Nanoknife technique.

Study outcomes:

Primary outcome study 1:

- Urinary incontinence at 12 months

Primary outcome study 2:

- Irritative urinary symptoms at 12 months

Secondary outcome(s):

- Erectile dysfunction
- Adverse Events
- Progression free and treatment free survival
- Quality of life

Study period: Q4 2021 – Q2 2027

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ADMINISTRATIVE INFORMATION

TITLE

Prostate Cancer IRE Study – A randomized controlled trial comparing focal to radical treatment in localized prostate cancer (PRIS)

TRIAL REGISTRATION

Intended registry: Clinical trials.gov

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INTRODUCTION

ABSTRACT

Prostate cancer is the leading cause of cancer death among men in the western world. Early detection of prostate cancer has been shown to decrease mortality but has limitations with low specificity leading to unnecessary biopsies, over-diagnosis, and over-treatment of indolent cancers. Radical treatments of localized prostate cancer are associated with a significant risk for morbidity in terms of incontinence and impotence, while providing only small survival benefits compared to active surveillance. (5-7)

Advances in the field of prostate cancer MRI together with the effort to reduce treatment morbidity has led to development methods for focal treatment of prostate cancer during the latest decades. These new treatment modalities have been developed as minimally invasive treatments to reduce functional side-effects while providing equally safe oncological results. Early evidence shows that focal therapies has a favorable toxicity profile. However, the majority of existing studies are single-center, non-comparative and with short follow-up. (8) Additionally, current evidence lacks reliable comparative data against standard interventions, such as radical prostatectomy and radiation therapy. Several focal thermal therapies such as High Intensity Focal Ultrasound (HIFU), Cryotherapy, Radiofrequency Ablation (RFA) have emerged as minimally invasive alternatives to conventional radical treatments. Irreversible Electroporation (IRE) is a novel image-guided tissue ablation technology that induces cell death through short pulsed electric fields. In comparison to thermal therapies IRE has the advantage of being non-thermal with elements of tissue selectivity which significantly reduces toxicity on anatomical structures surrounding the tumour. (9)

The aim of this study is to evaluate the feasibility to treat localized prostate cancer diagnosed with MRI and targeted/systematic biopsies, with IRE in comparison with conventional radical treatments with the primary objective to locally control the tumour with a minimum of side effects.

BACKGROUND AND RATIONALE

Prostate cancer is the most common cancer and the leading cause of cancer death among men in Sweden. In year 2018 over 10 000 men were diagnosed with prostate cancer and more than 2,500 died due to the disease, approximately 20% of these in the Stockholm region. The same year 877 men got diagnosed with intermediate risk prostate cancer in Stockholm Region, the group that is potentially eligible for the suggested research. Prostate cancer incidence rates in Sweden are now comparable to rates in countries that had an early introduction of PSA testing, while prostate cancer mortality rates in Sweden are higher than in most other countries. (1)

Tissue sparing treatments for tumours in solid organs are used in several different areas; breast, renal and lung cancers are examples of tumours that are commonly treated with tissue sparing approaches to preserve organ function and minimize damage to adjacent structures. (2-4) A common feature of these tumours is the precise cancer localization. Within prostate cancer diagnostics the rapid evolution and improvement of MRI and targeted biopsies has just recently made it possible to localize the significant tumour areas in the prostate which lays the foundation for focal therapy. The aim of focal therapy is to treat the tumour while preserving benign prostate tissue and the surrounding structures; urethral sphincter, the neurovascular bundles, bladder neck and rectum in order to decrease the risk for postoperative side-effects.

MRI IN PROSTATE CANCER DIAGNOSTICS AND FOLLOW-UP AFTER IRE

Level one evidence has shown that MRI has a high negative predictive value in ruling out significant prostate cancer and is when combined with targeted biopsies superior to systematic biopsies in detecting significant prostate cancer. (10) (11) (12) Multi-parametric MRI has shown promise in follow up after IRE to delineate the treated volume. (13)

TRADITIONAL CURATIVE TREATMENT OF PROSTATE CANCER

Level one evidence has shown that curative treatment of prostate cancer decreases prostate cancer mortality in men with intermediate and high-risk prostate cancer but is associated with a substantial risk for side effects. (14-16)

The risk for erectile dysfunction and incontinence after radical prostatectomy has been reported as high as 70-90% and 17-20%, respectively. (15, 17) The risk for functional impairment after radiation therapy has shown lower rates but is still strongly affecting patient's quality of life. (15)

FOCAL ABLATION OF PROSTATE CANCER

The last two decades minimally invasive interventions have been developed as an alternative to whole gland therapies in prostate cancer in an attempt to reduce the side-effects associated with radical treatment and thereby improve quality of life. The aim of minimally invasive interventions (partial ablation or focal therapy) is to reduce morbidity by lowering the risk of damage to the surrounding tissue such as neurovascular bundles and the urethral sphincter, responsible for the erectile function and urinary continence. The incidence of localized prostate cancer is continuing to

increase, highlighting the demand for less aggressive organ-sparing treatments to overcome the current overtreatment of localized prostate cancer.

Focal therapy has during the last decade in selected countries been an alternative to both active surveillance and radical treatment. In the early era of focal treatment mostly low risk tumours were selected to treatment with the rationale that minimally invasive interventions could reduce the anxiety and psychological burden in selected men on active surveillance, living with an untreated cancer, which inappropriately could cause men to choose radical treatments. (18) (19) However, since evidence has shown that men with a confirmed low risk disease have extremely low risk of dying from PCa, all current guidelines recommend AS for this group of patients, thus focal treatment for this group must be considered as over-treatment. (20) The latest years intermediate-risk patients have been selected for focal therapies in an attempt to reduce the treatment related side-effects since this group otherwise would undergo radical therapy. Evidence has shown a benefit of radical therapies in the intermediate-risk group with respect to cancer control however prevention of death seen in few patients within 10 years and rare in men over 65 years of age. (6)

There are several different treatment modalities for focal therapy where most therapies have been achieved with ablative technologies; cryotherapy, HIFU, photodynamic therapy, electroporation, and focal RT by brachytherapy or cyberknife, with the purpose to ablate tumours selectively whilst limiting toxicity by avoiding damage to surrounding tissue. (21)

Early evidence in focal treatment of PCa has shown promising functional and oncological results for well selected patients. A systematic review comprising 37 articles reporting on 3230 patients undergoing focal therapy reported continence and potency in 83.3–100% and 81.5–100%, respectively. Concerning oncological outcomes, the rate of significant disease at control biopsy varied between 5 and 46%. (8) However, prospective evidence of oncological outcomes after focal therapy with HIFU has shown failure-free survival of 88% and metastasis-free survival of 98% and cancer-specific survival of 100% at 5 years. (22)

IRREVERSABLE ELECTROPORATION (IRE)

The IRE technique uses high-voltage electric pulses to treat solid tumours by increasing the membrane permeability and inducing membrane disruption, leading to cell death. The technique is used in radical ablative therapies in the treatment of tumours in the liver, kidney, pancreas and prostate. (23, 24)

ADVERSE EVENTS AND FUNCTIONAL OUTCOMES

Focal treatment within prostate cancer has been developed in an attempt to decrease long term side effects after treatment. In comparison to alternative ablative treatments, IRE causes less damage to the surrounding tissue because of the nonthermal technique that does not affect the structural integrity of the surrounding tissue. In the treatment of prostate cancer two recent reviews report pad-free continence rates of 91-100% and preserved erectile function in 79-100% in men treated with IRE. In-field recurrences range from 0-33%. (25, 26) Furthermore, in a report from Valerio et al. IRE has shown

promising safety data with 100% (n=24) preservation of continence and 95% (19/20) preservation of erectile function when applying median 12ml of ablation volume. (27) Compared to radical therapies there are no head to head comparisons but in a propensity-score-matched analysis, functional outcomes after IRE was superior to RALP (pad-free incontinence and erectile function). In this analysis 70% of IRE-treated men had no cancer in follow up biopsies. (28)

Concerning complication rates after IRE, two studies report 1/25 and 0/63 treated patients had Clavien-Dindo ≥ 3 and “high-grade AE”, respectively. (29, 30) In a retrospective analysis by Valerio et al. IRE showed no complications noted initially. (27) In a retrospective analysis of 471 men treated with IRE, showed 1.4% with severe AE. Urinary continence was preserved in 100% cases and IRE-induced ED in 3% of cases. Recurrence 10% of cases (biopsies if MRI showed PIRADS ≥ 4). (31)

ONCOLOGICAL OUTCOMES

Concerning oncological outcomes after IRE the same large retrospective study of 471 men treated with IRE, including 66% high-risk PCa, showed recurrence in 10% of cases, determined by a rise in PSA value with corresponding findings on mpMRI and/or PSMA-PET/CT and biopsies if MRI showed PIRADS ≥ 4 . (31) The risk for recurrence was increasing with higher Gleason grade. Though in a prospective analysis of 30 men with low to intermediate risk PCa, the rate of in-field treatment failure was higher; 18% (5/28) using MRI and targeted biopsies at 6 months. (32) However, in the most recent report on 123 prospective cases (91% intermediate risk), infield recurrence was 2.7-9.8% on transperineal mapping biopsies at 12 months post treatment. In total 14% were retreated (18/123). (33) Furthermore, the same research group reported on treatment of 50 apical tumors and only one patient had in-field recurrence, no Clavien-Dindo ≥ 3 was reported and 2% (1/50) required one pad per day for continence. (34)

FOLLOW-UP

In 30 men undergoing repeat MRI after IRE, MRI was able to visualize IRE ablation effects (9/30= 30% showed recurrence at 1 yr). (35) However, sensitivity of MRI to detect residual cancer (GS $\geq 4+3$ or >6mm) was limited in an analysis of 76 men using transperineal mapping biopsies as reference (sens 43% infield; 33% outfield). Thus, biopsies should be performed as part of a follow up protocol. (36)

CARDIAC SYNCHRONIZATION

For treatment of hepatic and pancreatic tumors, cardiac arrhythmias were noted in 22% of cases without treatment synchronized with the cardiac cycle 1.2% with cardiac synchronization. It is not clear if synchronization should be performed when treating prostate. (37)

OBJECTIVES

The aim of the proposed research is to evaluate the cancer control, genitourinary, rectal and overall health-related quality of life outcomes of focal therapy for unifocal localized prostate cancer using irreversible electroporation (IRE).

PRIMARY AIM

- To evaluate functional outcomes in men treated for unifocal ISUP 2-3 localized prostate cancer with focal treatment in comparison to conventional treatment with either radical prostatectomy or radiation therapy

SECONDARY AIMS

- To evaluate adverse events in men treated for unifocal ISUP 2-3 localized prostate cancer with focal treatment in comparison to conventional treatment with either radical prostatectomy or radiation therapy
- To evaluate progression free and treatment free survival in men treated for unifocal ISUP 2-3 localized prostate cancer with focal treatment in comparison to conventional treatment with either radical prostatectomy or radiation therapy
- Economic evaluation of each technique

TRIAL DESIGN

This study is a randomized controlled exploratory trial comparing focal therapy to conventional radical treatment of prostate cancer with the primary aim to evaluate functional outcomes 12 months after treatment.

Patients will be included from 4 different hospitals within the Stockholm County; Karolinska University Hospital, Danderyd Hospital, St Görans Hospital, Södersjukhuset. Initial inclusion in the study was slow and due to this reason referrals from all Swedish regions were allowed in 2024. Eligible patients, after MRI and targeted/systematic biopsies, will be men with clinically significant intermediate-risk PCa or dominant unifocal clinically significant intermediate-risk and small contralateral low-risk disease without previous history of prostate cancer treatment.

All potential patients are reviewed at a conference with the assessment of MRI images. If the case is deemed suitable, the patient is invited to Karolinska for a screening visit. For patients randomized to the experimental arm (focal treatment), the treatment will be performed at Karolinska. For those randomized to the conventional arm (surgery), the procedure can be carried out either locally or at Karolinska. The change of allowing for referrals from other regions in 2024 aims to accelerate the inclusion rate to complete the study within a reasonable timeframe and to increase the opportunity for all regions of the country to access the new focal treatment method within the framework of the study.

Potential study participants will have a visit scheduled together with an urologist and oncologist, where a treatment decision of radical prostatectomy or radiation therapy will be done together with the patient. At this visit the patient will receive oral and written information about the study. If the patient is interested in participating, a baseline visit is scheduled during which informed consent is obtained and the patient randomized to one of two standard treatments or focal treatment.

Patients eligible for radical prostatectomy will be randomized in study 1 to focal treatment or radical prostatectomy. Patients eligible for radiation therapy will be randomized in study 2 to focal treatment or radiation therapy. Time between randomization and treatment will be ≤ 6 months.

Patients will be asked to fill out study specific questionnaires with questions on functional outcomes and quality of life.

Main outcome measurement in study 1 will be urinary incontinence at 12 months post treatment and in study 2 irritative urinary symptoms 12 months post treatment. Further outcomes will be erectile dysfunction, adverse events, progression-free and treatment-free survival.

DESIGN OVERVIEW

Figure 1: Design overview

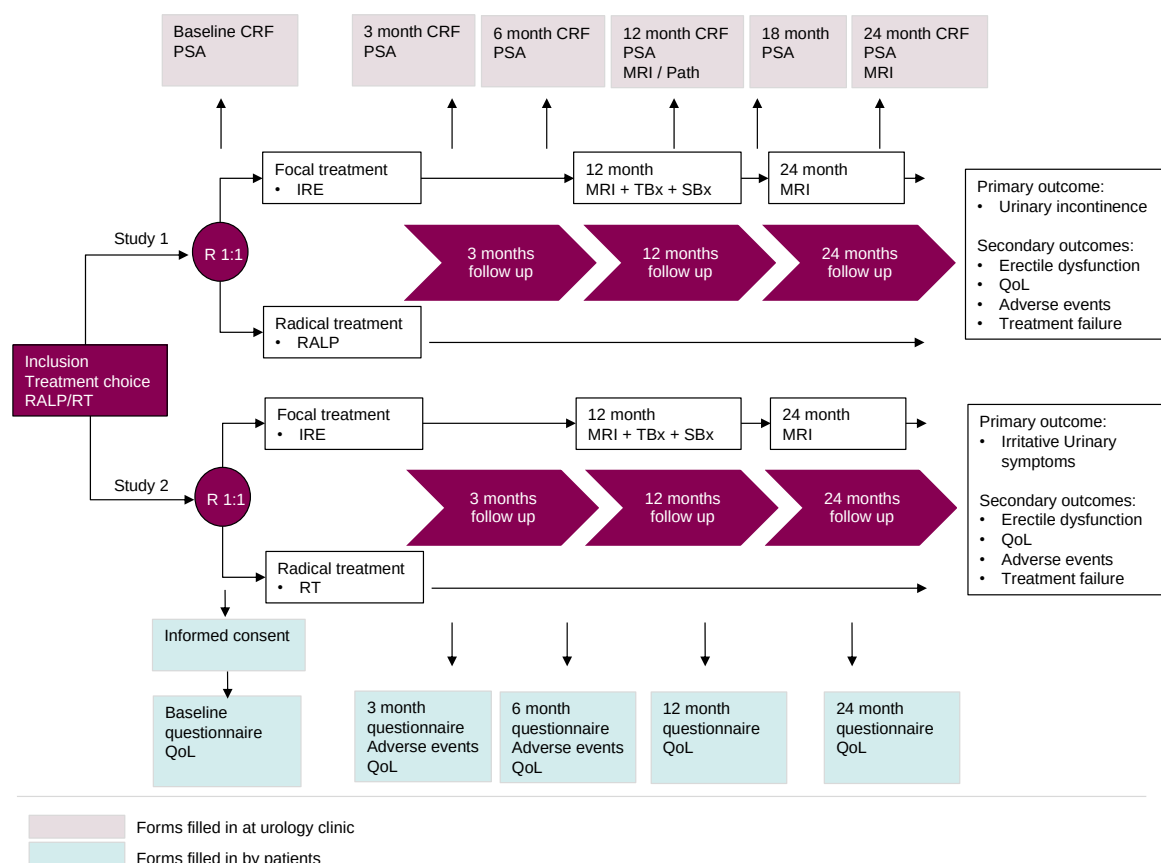


Table 1. Schedule of assessments during and after treatment

	Before treatment (Screening ≤6 W)	Baseline/ Inclusion	Treatment period:	Follow up after completed treatment									End of Study
				2-4 W	3 m	6 m	12 m	18 m	24 m	Y 3	Y 4	Y 5	
Inclusion and exclusion criteria		X											
Informed Consent		x											
Randomization		x											
Physical Exam (ausk heart and lungs)	x												
Medical history	x												
Lab values (PSA)	x				x	x	x	x	x	x	x	x	
MRI*****	x			x***			x***		x***	x***	x***	x** *	
Tbx	x						x***		x*	x*	x*	x*	
Sbx	x						x***		x**		x**		
Pathology	x				x***** *		x***		x* x** x***	x*	x*	x*	
Study treatment: focal therapy, RP or RT			x										
Treatment failure					x*****		x*****		x*****				
Adjuvant treatment(s)					x*****		x*****		x*****				
QoL (IIIEF, EQSD, EPIC-26, IPSS)		x			x	x	x		x				
Adverse events					x								
End of Study													x

Table 1: Schedule of assessments. Abbreviations: Weeks (W), months (m), Year (y), magnetic resonance imaging (MRI), Radical prostatectomy (RP), Radiation therapy (RT), Targeted biopsy only (Tbx), Systematic biopsy (Sbx), Quality Of Life (QoL), International Index of Erectile Function (IIIEF), EuroQoL- 5 Dimensions (EQSD), Expanded Prostate Cancer Index Composite (EPIC-26), International Prostate Symptom Score (IPSS).

- * For cause biopsy only if PSA rise/suspecting at MRI, only in the focal treatment arm
- ** If known residual ISUP1 Sbx every 2-3 years
- *** In the focal treatment arm
- ***** Treatment failure and adjuvant treatment will be registered at 3, 12 and 24 months, but the registration will include the actual dates for time to event analyses
- ***** In radical prostatectomy arm
- ***** bpMRI at inclusion, complemented with a mpMRI in the focal treatment arms before treatment for treatment planning. Follow-up MRI in focal treatment arms will be multiparametric.

METHODS: PARTICIPANTS, INTERVENTIONS, OUTCOMES

STUDY SETTING

This study is performed as a collaboration between the hospitals in the Stockholm Region for treatment of men with prostate cancer. From 2024 referrals with prostate cancer patients from all other Swedish regions were included. Study inclusion and treatment within the experimental arm; focal therapy, is performed at Karolinska. Konventional treatment with radical prostatectomy is performed at Karolinska or the local hospital. If the local hospital is un-able to perform the allocated treatment, referral to any of the participating hospitals is performed. Follow-up of participants are performed at the local hospital in collaboration with the study administration and Clinical Trials Office, Karolinska University Hospital.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

Men with clinically significant intermediate-risk PCa or dominant unifocal clinically significant intermediate-risk and small contralateral low-risk disease and met all of the following criteria:

- Age at inclusion ≥ 40 years
- MRI-visible lesion
 - $\leq$ EPE 3*
 - <4.0 cubic cm³ lesion volume - (calculated $W \times D \times H \times \pi/6$ where $W \times D \times H$ measured on T2w images)
 -
- Gleason score 3 + 4 or 4 + 3 from a single MRI-visible lesion without any Gleason grade 4 in systematic biopsies outside of the target
- PSA level ≤ 20 ng/ml
- Clinical stage $\leq$ T2b disease
- Unifocal significant disease
- Life expectancy of ≥ 10 years
- Sufficient proficiency in the Swedish language to understand written and verbal information about the trial, its consent process and the study questionnaires

*Extraprostatic extension; 5-grade Likert scale 1=

EXCLUSION CRITERIA

- Intraductal tumour
- History of treatment for prostate cancer; surgery, radiation, chemotherapy or hormonal treatment
- History of cardiac arrhythmias
- Pacemaker
- Renal insufficiency; GFR <30
- Severe illnesses such as concomitant cancers, severe cardio-vascular disease or dementia
- Contraindications for magnetic resonance imaging (MRI) e.g. magnetic cerebral clips, cochlear implants or severe claustrophobia
- History of bladder cancer
- History of previous pelvic radiotherapy

INTERVENTIONS

CONTROL ARM (TRADITIONAL CURATIVE TREATMENT)

RADICAL PROSTATECTOMY AND RADIATION TREATMENT

Men eligible for radical prostatectomy and randomized to the control arm will undergo radical prostatectomy in line with national guidelines. Lymphadenectomy might be

performed at the discretion of the treating physician. Men eligible for radiation therapy and randomized to the control arm will undergo radiation therapy in line with national guidelines.

<https://kunksapsbanken.cancercentrum.se/diagnoser/prostatacancer/vardprogram/>

EXPERIMENTAL ARM

FOCAL TREATMENT USING IRE TECHNIQUE

Men randomized to the experimental arms will be offered focal treatment of prostate cancer with IRE technology. IRE stands for "irreversible electroporation" and involves the use of high voltage electrical pulses to treat solid tumors by increasing membrane permeability and inducing membrane disruption, leading to cell death. The technique is used in Sweden today in radical ablative therapies in the treatment of tumors in the liver, kidney and pancreas. Prior to treatment a Foley catheter is placed. During the treatment, which takes place under anesthesia, the patient is placed in gynecological position and the tumour lesion is located with BK transrectal fusion ultrasound. Thereafter the needles are placed transperineal around the tumor in the prostate using a brachytherapy grid (17Ga Civco brachytherapy grid), guided by the ultrasound/MRI fusion images. Through the needles electrical pulses are then sent to treat the tumor in the center using the Nanoknife technique. After treatment patients are treated with diuretics to flush the kidneys post treatment.

Before the start of the study, the treating urologists in the experimental arms will go on a study trip to University College London (UCL) to receive clinical training in the IRE technology. As described above the technique is performed with needles that are placed transperineally via brachy grids. The intended treating urologists already have extensive clinical experience and knowledge of transperineal fusion biopsies, which lays a good foundation for learning the new IRE technology. In the pilot phase (n = 40), proctors for IRE technology will initially be present to ensure that the treatments are performed in an optimal way. All men in the experimental arms will undergo mpMRI and targeted plus systematic follow-up biopsies 12 months after treatment to follow up the treatment effect. In the event of a significant tumor burden remaining, patients will be offered curative treatment.

FOLLOW-UP

Patients in the control arms will be followed according to clinical protocol with consecutive PSA tests. Patients in the experimental arms will be followed-up with mpMRI after 2-4 weeks and thereafter with PSA/STHLM3 at 3, 6, 12, 24 months and mpMRI at 12 and 24 months with targeted biopsies if rise in PSA or signs of residual disease at MRI. Systematic biopsies will be performed at 2 and 4 yrs if known residual ISUP 1 cancer.

TREATMENT FOR PARTICIPANTS NOT WISHING TO COMPLETE ASSIGNED TREATMENT

Men randomized to the control arms are not allowed to cross over to the experimental arms.

Men randomized to the experimental arms with focal therapy are allowed to choose the treatments offered in the control arm.

OUTCOMES

PRIMARY ENDPOINT

Study 1	Definition	Metric used	Time points measured
Urinary continence at 12 mo	Q3, EPIC-26	≥1 pad/day (“Yes”) versus none (“No”)	Baseline, 3mo, 6mo, 12 mo, 24 mo

Study 2	Definition	Metric used	Time points measured
Irritative urinary symptoms at 12 mo	Q4e, EPIC-26	Moderate/big problem (“Yes”) versus no/small problem (“No”)	Baseline, 3mo, 6mo, 12 mo, 24 mo

SECONDARY ENDPOINTS

	Definition	Metric used	Time points measured
Erectile function at 12 mo	IIEF score	Decrease in IIEF score	Baseline, 3mo, 6mo, 12 mo, 24 mo
Urinary continence at 12 mo	Q3, EPIC-26	Change in score	Baseline, 3mo, 6mo, 12 mo, 24 mo
Voiding function at 12 mo	IPSS	Change in IPSS score	Baseline, 3mo, 6mo, 12 mo, 24 mo
Bowel function at 12 mo	Q6, EPIC-26	Change in score	Baseline, 3mo, 6mo, 12 mo, 24 mo

Adverse Events at 3 mo	Clavien-Dindo (38)	Proportion of each Clavien-Dindo score	3, 12 and 24 months
Quality of Life	EQ5D		
Treatment failure, defined as follows, according to study arm and treatment received:			
Treatment Failure, experimental arms	1. Need for additional focal or whole gland treatment or ADT 2. Need for whole gland treatment or ADT 3. Need for whole gland treatment or ADT or ISUP 2 at 12 mo biopsy	Any treatment (y/n)	Time between randomisation and Treatment Failure
Treatment Failure, control arm (surgery)	Post-operative PSA ≥ 0.2 ng/ml or adjuvant treatments including ADT	PSA	Time between randomisation and Treatment Failure
Treatment Failure, control arm (radiation)	PSA > 2 over nadir (Phoenix) or adjuvant treatments including ADT	PSA	Time between randomisation and Treatment Failure

RECRUITMENT

STRATEGIES FOR ACHIEVING ADEQUATE STUDY OBJECTIVES

Clinical anchorage was achieved from all hospitals in Stockholm, enabling adequate inclusion speed to the study. The clinical feasibility is ascertained from the first pilot phase of the study.

METHODS: ASSIGNMENT OF INTERVENTIONS

ALLOCATION

A pilot study is planned to be implemented at the Karolinska University Hospital in Stockholm before the main study with 40 patients (20 focal therapy/20 radical

treatment). The objective of this study is assessment of the treatment zone using MRI and evaluation of adverse events directly after the focal treatment. Inclusion- and exclusion criteria would be the same as in the main study. The main study is planned to start in 6 weeks after the pilot study.

In total 112 men will be included in study 1 comparing focal therapy to radical prostatectomy and 62 men will be included in study 2 comparing focal therapy to radiation therapy (men from pilot phase included).

Since the experimental arms using the IRE technique is implemented through this trial the first 10 patients undergoing IRE will not undergo randomization or be a part of the primary analysis, not to include the primary learning curve for the primary outcome. These 10 patients will be performed before the start of the pilot phase.

REGISTRATION AND RANDOMIZATION

Patients who fulfil the criteria for inclusion are, after having given their oral and written consent, registered and randomized in the ALEA system, operated by the CTO, Theme Cancer, Karolinska University Hospital, Solna, Sweden.

Patients in study 1 and 2 are randomized separately 1:1 to standard treatment or focal treatment. The randomization is stratified by study site.

Allocation is open to participant and the treating physician. A confirmation e-mail will be sent out to the entering investigator, research nurse, sponsor and monitor. An enrolment Log/Patient birth date must be filed at the center. The patient will receive the next consecutive code number in the trial and treatment arm according to randomization.

METHODS: DATA COLLECTION, MANAGEMENT, ANALYSIS

DATA COLLECTION AND MANAGEMENT

Data will be collected using an electronic system, PheedIt, which is based on the SAS system provided by Region Stockholm. A data management plan is delivered by CTO, CKC, documenting the database and all procedures for the data management. The investigator must verify that all data entries in the CRFs are accurate and correct. If certain assessments according to the protocol are not performed for any reasons, or if certain information is not available, not applicable or unknown, this must be indicated in the CRF by the investigator. The investigator is required to sign off reported data.

Patient-reported data will be collected using paper forms on four different occasions; before treatment and 3, 12 and 24 months after completed treatment. Participants will fill in Swedish translations of internationally validated questionnaires about functional outcomes and quality of life; International Index of Erectile Function (IIEF), EuroQoL-5

Dimensions (EQ5D), Expanded Prostate Cancer Index Composite (EPIC-26) and International Prostate Symptom Score (IPSS).

Clinical data will be collected on five different occasions during the course of the study; before treatment and 3, 6, 12 and 24 months after completed treatment. Clinical data is entered into the eCRF by the investigator and research nurses and contains details on tumor characteristics, treatment technology and execution, lab values, MRI data, pathology data, adverse events and adjuvant treatments.

CASE REPORT FORM

All enrolled patients will be given a study ID. The ID list which is the key to patient identification will be kept in a secure place at the clinic, only accessible to study personnel. All handling of personal data will be made according to the requirements of the General Data Protection Regulation (GDPR) and the Patient Data Act (SFS 2008:355), for protection of the integrity of the study subjects. Patients will consent to processing of their personal data when consenting to study participation.

An electronic Case Report Form (eCRF) in PheedIT will be completed for each enrolled patient. Investigators will ensure completion and review of the eCRF. The electronic CRF system fulfills all regulatory requirement for collection of clinical study data (21 CFR part 11 and ICH-GCP). Investigators have the personal responsibility for the accuracy and authenticity (and sign off) of all clinical and laboratory data that are entered the eCRF. Appropriate eCRF training of study personnel will be performed prior to enrollment of the first study subject. A copy of the completed eCRF will be archived at the study site. In case of an emergency, or at the request of the competent authorities the eCRF will be made readily available.

STATISTICAL ANALYSIS

Binary endpoints will be compared using Chi-square tests. Cumulative proportions of men reaching treatment failure over time will be estimated using the Kaplan-Meier method and compared using the log-rank test. Patients will be followed for treatment failure until 24 months posttreatment.

SAMPLE SIZE

Given that the two radical treatments have very different side effects after treatment, different endpoints will be used for the two studies, using urinary incontinence in the comparison with radical prostatectomy (power calculation 1) and irritative symptoms in the comparison against radiation therapy (power calculation 2). We used available data from published prospective studies to estimate the probability of incontinence and irritative urinary symptoms at 12 months after focal therapy, radical prostatectomy and radiation therapy. (15, 17, 21) (39) The estimated probabilities are reported in the table below.

Table 2. Estimated probabilities of functional outcomes after radical and focal treatment from current evidence.

		Power calc 1: Incontinence	Power calc 2: Irritative symptoms
Radical treatment	Radical prostatectomy	20%	-
	Radiation therapy	-	30%
Focal treatment		2%	2%

For the RP vs FT study (study 1) a total sample size of 112 men (56 in each arm) is determined, setting the significance level (alpha) to 0.05 and the power to 0.80, assuming a 15% drop-out / non-compliance rate.

For the RT vs FT study (study 2) a total sample size of 62 men (31 in each arm) is determined, setting the significance level (alpha) to 0.05 and the power to 0.80, and assuming a 15% drop-out / non-compliance rate.

The first 10 men treated with focal therapy will not undergo randomization or be a part of the primary analysis, not to include the primary learning curve for the primary outcome. These 10 patients will be performed before the start of the pilot phase.

In total 184 men are planned for inclusion in the trial, where 97 (10+56+31) will undergo focal treatment.

Based on a study period of 24 months and approximately 800 diagnosed intermediate risk prostate cancer in Stockholm county per year, an assumption of 1000 men would be eligible for inclusion during the study period. An acceptable accrual of 25% would result in 250 recruited men during 24 months. Given the plan of 2 study sites for FT, each site would have to plan for 25 treatment-days per year (3 FT per day).

HEALTH ECONOMIC EVALUATION

The primary aim of the health economic evaluation is to estimate the life-time costs, quality-adjusted life-years (QALYs) and cost-effectiveness for the trial arms from a societal perspective. QALYs will be modelled using the reported study outcomes combined with health state values reported in the literature and background health state values for the Swedish population. As per Swedish recommendations, the costs and QALYs will be calculated from both healthcare and societal perspectives, and the costs and QALYs will be discounted at 3% per year, with sensitivity analyses using 0% and 5% per year. We will model the costs and QALYs using a Markov model. To evaluate cost-effectiveness, we will calculate incremental cost-effectiveness ratios. In the absence of an established cost-effectiveness threshold in Sweden, we will use 500,000 SEK per QALY gained as a threshold between a moderate and high cost per QALY gained. We will account for uncertainty in key parameters using one-way and probabilistic sensitivity analyses. For the probabilistic analysis, we will report acceptability curves and expected value of perfect information for non-dominated strategies. We will also report costs, QALYs and other outcomes (e.g. progression to metastatic prostate cancer, prostate cancer death) for two-year and ten-year time horizons.

METHODS: MONITORING

The sponsor will appoint an independent monitor for quality control of the study. Monitoring will be performed before, during and after study completion in accordance with the ICH GCP guidelines and applicable ethical and regulatory requirements. The extent of monitoring will be described in a monitoring plan, which will be approved by the sponsor. Study conduct, source data, adherence to study protocol, GCP and regulatory requirements will be monitored.

The study will be monitored by staff authorized by the Center for Clinical Cancer Studies (CKC). The CKC at Theme Cancer, Karolinska University Hospital, Solna serves as the Clinical Trial Office (CTO) for the study, to ensure accurate, complete and reliable data according to GCP rules.

Before study initiation, the study protocol and CRF will be reviewed with the investigator and the study personal. The monitor will visit the site during the ongoing study in order to verify adherence to the clinical study protocol, completeness and accuracy of data entered in the CRF by comparing them with the source documents, and ensure that the subject's rights, safety, and well-being are met. The monitor will review the progress of the clinical study, and review CRF and original source data/documents with the study personal, for accuracy of data recording, and facilities used in the clinical study. Visits will be documented in a monitoring log in the investigator site file and a monitoring report for each visit will be sent to the principal investigator and the sponsor.

The investigators will permit study-related monitoring, audits, IEC review and regulatory inspection(s), providing direct access to source data/hospital records. The Investigator verifies that each subject has consented in writing to direct access to the original source data/hospital records by the use of written patient information and signed Informed Consent. The data recorded in the CRFs will be controlled for consistency with the source data/hospital records during the monitoring (source data verification). Any discrepancies of data will be documented and explained in the monitoring reports.

HARMS AND AUDIT / DATA SAFETY AND MONITORING BOARD (DSMB)

A DSMB is assembled and will consists of three persons with expertise in clinical trials and statistical analysis; Professor Anna-Bill Axelsson, Biostatistician Hans Garmo and Professor Ola Bratt. The committee will review complications and survival data. It will also make recommendations on changes to the protocol and/or terminating the trial. The DSMB audits protocol and process descriptions and one interim data extraction performed by the SDA after 30% (80 men) have completed the control or experimental arms. The co-investigators are blinded to the interim data and analysis results. The work of the DSMB is regulated in the DSMB Charter.

AMENDMENTS TO TRIAL PROTOCOL

Substantial changes to the initially approved study protocol are only possible through approved protocol amendments and by agreement from all responsible persons. Information on non-substantial changes should be clearly noted in the amended protocol.

In the event that substantial changes to the protocol (e.g., changing of the main objective, primary or secondary endpoints, method to measure the primary endpoints, changing of the investigational product or dosage) will be made during the course of the study, approval from the Swedish ethical Review Authority (Etikprövningsmyndigheten, EPM) shall be obtained before any changes are implemented. A change that concerns a new site, new investigator or a new study patient information sheet shall only be approved by EPM.

No changes to the study procedures shall be implemented without the mutual agreement between the Principal Investigator and the sponsor. It is the responsibility of the sponsor to submit amendments to the authorities.

ASSESSMENT OF CLINICAL EFFICACY

QUALITY OF LIFE ASSESSMENT

Background

One of the secondary aims of this study is to compare patients' functional outcomes and health-related quality of life (HRQoL) and their differences, between the treatment arms during the course of treatment and at follow-up. Assessment during follow-up is important in order to evaluate the long-term HRQoL effects of the various treatments. All patients included in the PRIS trial will be requested to fill out the questionnaires. Before inclusion in the study, the patient is informed orally and in writing about the assessment of the HRQoL and functional outcomes. The study nurse gives the patient the first questionnaires, which is completed at the ward or at the clinic during the randomization visit. Completion of the questionnaires takes about 10–20 min.

Points of assessment

The questionnaires will be assessed at 4 points up to 2 years after study entry: The first point of assessment is at the randomization visit, after informed consent has been obtained.

Instruments

- To evaluate urinary function and erectile dysfunction
 - IPSS
 - EPIC-26 for Questionnaire for the evaluation of continence
 - IIEF-5
- To evaluate quality of life
 - EQ5D
- Additional questions

- Sociodemographic questions
- Regret
- Penile shortening
- Retrograde ejaculation
- Ejaculatory volume

HANDLING OF ADVERSE EVENTS

DEFINITIONS

Adverse Event (AE)

Adverse event (AE): Any untoward medical occurrence in a clinical investigation where subjects are administered a medicinal product and, which does not necessarily have a causal relationship with the treatment, can be an unfavorable and unintended sign (including an abnormal laboratory discovery), symptom or disease temporally associated with the use of the medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Event (SAE)

Serious adverse event (SAE): Any untoward medical occurrence that at any dose/treatment:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital anomaly/malformation

Medical and scientific assessment will be made to determine if an event is “serious” and whether it would prompt reporting in other situations, for example important medical events that may not be directly life-threatening or result in death or hospitalization but may compromise the study subject or may require intervention to prevent one of the other results set forth in the definitions above. These should also normally be considered as SAEs.

REPORTING AND REGISTRATION OF ADVERSE EVENTS

At each study visit, adverse events (AE) are registered, starting after undergone treatment up to the final follow-up visit at 3 months. All AEs that occur during the study and which are observed by the investigator/study nurse or reported by the subject will be recorded in the medical record and in the CRF regardless of whether they are related to the investigational product or not. Assessment of causal relationship, severity, and whether the AE is considered an SAE or not will be made by the investigator. At minimum, for each AE/SAE, a description of the event is recorded (diagnosis/symptom

if diagnosis is missing), start and stop dates, causal relationship, severity, if the AE is considered an SAE or not, measures and outcome.

Reporting of Adverse Events (AE)

AEs will be recorded on a separate AE form in the CRF, with complete information regarding seriousness, intensity and causality and all AE assessments will be made by an investigator.

Expected adverse events based on knowledge of the disease in question and expected clinical course are hematuria, hematospermia, rectal bleeding, urinary incontinence and erectile dysfunction are therefore not to be reported as AE in this clinical study.

Reporting of serious Adverse Events (SAE)

In addition, SAEs will also be reported by the investigator to the sponsor on a separate SAE form within 24 hours after the SAE has been communicated to the investigator. Follow-up information describing the outcome of the SAE and actions taken will be reported as soon as available. Assessment of the SAE being expected for the investigational product or not will be made by the sponsor in agreement with the principal investigator. The original SAE form must be filed with the CRF or in the investigator site file.

An SAE has to be reported within 24 hours after notification by the study personnel and be sent to the CTO, CKC, Theme Cancer, Karolinska University Hospital Solna, mail address : ctosafety.karolinska@regionstockholm.se. Serious Events which possibly may be related to the study treatment will be followed and reported during the entire follow-up period until resolution. SAEs will be reported up to 28 days after treatment.

Follow-up of Adverse Events

If an AE has been reported for a patient, the nature of the event and its clinical course must be fully documented. The investigator must follow-up the subject until the AE is resolved, becomes clinically insignificant, or is stabilized, unless the subject is lost to follow-up. If a subject is lost to follow-up the investigator must make every effort to contact the subject.

ETHICS AND DISSEMINATION

Compliance to the protocol, GCP and regulations

This study is designed and shall be implemented, executed and reported in accordance with the study protocol, principles of the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP E6 (R2)), applicable local regulations (i.e. European Directive 2001/20/EC) and the ethical principles of the Guidelines of the World Medical Association (WMA) Declaration of Helsinki (as amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013). This is to ensure the safety and integrity of the study subjects as well as the quality of the data

collected. A favorable ethical opinion will also be obtained from the Swedish Ethical Review Authority prior to the commencement of this study.

Ethical review of the study

It is the responsibility of the Principal Investigator to obtain approval of the study protocol, the patient information and the Informed Consent form from the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM) before enrollment of subjects into the study:

PROCEDURE FOR OBTAINING INFORMED CONSENT

Men with intermediate risk prostate cancer who meet the criteria for inclusion will be invited to the study at the time of their visit to the urologist and oncologist who makes the treatment decision. At the visit, each potential participant will receive oral and written information. Informed consent will be obtained at the baseline/randomization visit, scheduled at least two days later, to ensure that the patients have time to consider the information. .

Patients who fulfil inclusion and exclusion criteria must be provided with full and adequate verbal and written information about the objectives, the study outline and possible risks and benefits of participating in the study. They have the right to ask questions about the study and should be given adequate time to make the decision to participate in the study or not. The patients must be clearly informed that the data collected in the study will not identify individuals taking part in the study, following the Law in Personal Data and the EU Data Protection Directive. The patients must be informed that participation is voluntary, and that they can decline further participation in the study at any time without stating any particular reason. The subjects should further be informed that a decision not to participate in the study or to withdraw will not be questioned or affect their future medical care or treatment at the clinic. Written Informed Consent must be obtained from all participating subjects before enrolment in the study. The Informed Consent form has to be filed in the Investigators File and one copy has to be given to the patient. No trial-related procedures can take place before a written Informed Consent is obtained. The subjects will consent:

- a) To participate in the study,
- b) To allow monitors and regulatory authorities to gain full access to hospital records in order to control data collected in the study,
- c) To record, collect and process data and to store data in a database

DATA PROTECTION

All data will be collected electronically and collected in a database. Patients will receive a study ID. Researchers who work with the material and perform the statistical analyzes will not have access to social security numbers. Responsible researchers are responsible for data processing and are guaranteed access to data.

If any part of the data is handled by any other organization, inside or outside the EU, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (GDPR) and other relevant legislation, before any data transfer takes place.

The content of the informed consent form complies with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their study data will take place. The subject information and the informed consent form will explain how study data are stored to maintain confidentiality in accordance with national data legislation. All information processed by the sponsor will be pseudonymized (coded) and study subjects will be identified by a study ID. The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the study, including the subject's medical history.

All study subjects will be informed that any data collected until consent withdrawal/discontinuation may be used in the study data analysis. Patient data will be stored in a database where study data is coded, and the code key will be stored where only the researchers who are directly involved in the project will have access to the information. All data will be stored and processed in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR). All participants can request in writing to find out what information about themselves from what information has been collected and to whom the information has been disclosed. The study will be conducted according to "Good Clinical Practice" (GCP), (ICH-GCP E6(R1)), as well as applicable national laws and regulations (LVFS 2011:19), and in full conformance with principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice and Hong-Kong).

DECLARATION OF INTEREST

No person in the scientific steering group has declaration of interest to show related to focal treatment of prostate cancer.

ACCESS TO DATA

Responsible researchers will have access to the collected data. The research group has a scientific steering group with responsibility for monitoring that the project runs as it should and also deciding on how the data should be used. All withdrawals of data will be logged with information about who and for what purpose the withdrawal was made.

DISSEMINATION POLICY

Analyses results on the posed aims will be submitted for peer-reviewed publication and submitted for presentation at scientific congress. Communication of the results will be made to patient organizations (Prostatacancerförbundet) and non-scientific channels. No use of professional writers is planned. The study protocol is made publicly available through (clinicaltrials.gov).

INTERNATIONAL COLLABORATIONS

Oncological outcomes would optimally be primary outcomes when evaluating a new technique for treating prostate cancer. However, given the overall low risk for oncological failure in this patient population with intermediate risk prostate cancers, it is difficult to power that kind of analysis. To handle this problem, we have initiated an international collaboration with Professor Stricker; Chairman of the Department of Urology at St Vincent's Campus, the Director of St Vincent's Prostate Cancer Centre and the Clinical Director of the Australian Prostate Cancer Research Centre, Sydney, Australia. We plan to do two separate parallel trials, using the same trial protocols, collecting the same data, to enable pooled data analysis after finalization of each respective trial. No personal information will be shared between the four clinical sites.

QUESTIONNAIRES

All men will fill out a questionnaire for measuring functional outcomes and quality of life.

- To evaluate urinary function and erectile dysfunction
 - IPSS
 - EPIC-26 for Questionnaire for the evaluation of continence
 - IIEF-5
- To evaluate quality of life
 - EQ5D
- Additional questions
 - Sociodemographic questions
 - Regret
 - Penile shortening
 - Retrograde ejaculation

STUDY PROCESS

STEP 1: SELECTION AND INCLUSION

Men with localized prostate cancer, eligible for inclusion according to stated inclusion and exclusion criteria, will be enrolled in the study at the different study sites after treatment decision between radical prostatectomy and radiation therapy has been done. Potential participants will be invited by their treating urologist. The patient will receive oral and written information about the study. The research participant and investigator sign the informed consent after taking part of all given information.

STEP 2: DISEASE STAGING

All eligible men should have undergone an mpMRI with lesion delineation using the mim Software. MRI are performed in line with local protocols from participating hospitals.

Participants are staged using 12 core systematic biopsies and 3-4 targeted biopsies to any PIRADS ≥ 3 MRI lesions.

STEP 3: TREATMENT

Men eligible for radical prostatectomy and randomized to the control arm will undergo radical prostatectomy in line with national guidelines. Lymphadenectomy might be performed at the discretion of the treating physician. Men eligible for radiation therapy and randomized to the control arm will undergo radiation therapy in line with national guidelines.

Men randomized to the experimental arms will be offered focal treatment of prostate cancer with IRE technology. Prior to treatment a Foley catheter is placed. During the treatment, which takes place under anesthesia, the patient is placed in gynecological position and the tumour lesion is located with BK transrectal fusion ultrasound. Thereafter the needles are placed transperineal around the tumor in the prostate using a brachytherapy grid guided by the ultrasound/MRI fusion images. Through the needles electrical pulses are then sent to treat the tumor in the center using the Nanoknife technique. After treatment patients are treated with diuretics to flush the kidneys post treatment.

STEP 4: FOLLOW UP

2-4 week

- MRI of ablation zone in pilot phase for the focal treatment arm

3 months (clinical visit physician)

- PSA test
- Patient questionnaire
- Follow up of adverse events

6 months (phone call physician)

- PSA test

12 months (clinical visit physician or phone call physician for men in RALP arm)

- PSA test
- Patient questionnaire
- Follow up of adverse events
- mpMRI in the focal treatment arm followed by TBx and SBx

18 months (phone call physician)

- PSA test

24 months (clinical visit physician or phone call physician)

- PSA test
- Patient questionnaire
- Follow up of adverse events
- MRI in the focal treatment arm. For cause TBx only if PSA rise/suspecting at MRI
- If known residual ISUP1 SBx

Year 3-5 (phone call physician)

- PSA test
- For cause biopsy only if PSA rise/suspecting at MRI, only in the focal treatment arm
- If known residual ISUP1 SBx every 2-3 years

STEP 5: DATA ANALYSIS:

Primary data sources are:

1. Complete treatment (1/0)
2. Short-term side effects (complications: bleeding, pain, GI complications, infection etc.)
3. Long-term side effects (incontinence, erectile function, QoL)
4. Time to salvage treatments

ETHICAL CONSIDERATIONS

The study has received Ethical approval.

Main application: Dnr 2021-01598

Amendment 1: Dnr 2021-06102-02

Amendment 2: Dnr 2022-03008-02.

Amendment 3: Dnr 2022-06840-02.

Amendment 4: Dnr 2023-07608-02.

IS THERE AN INCREASED RISK OF MISSING AGGRESSIVE CANCERS DURING FOCAL TREATMENT?

The rapid development of multiparametric MRI in PCa, which allows for tumour localization and biopsy guidance is one of the key factors for the evolution, development and improved performance of focal therapies. (10) Once a lesion could be visualized reproducibly on imaging, targeting of lesions for destruction has become increasingly feasible. However, limitations in MRI, with underestimation of lesion sizes and low sensitivity for lower grade PCa affects oncological results after focal therapies, due to cancers missed by imaging or biopsies and to incomplete ablation of identified lesions. Another possible limitation of focal therapies is the known multifocality of a majority of localized PCa. Evidence has shown that most men have 2 to 3 cancer foci and that there usually exists a dominant lesion accounting for approximately 80% of the total tumour volume. However, evidence has shown that prostate cancer index lesions with the highest tumour grade predominantly influences the progression of disease, (40, 41) indicating that treatment of the index lesion alone affects progression free survival. (42, 43) Due to this knowledge of multifocal disease in localized PCa we intend to include only patients with clinically significant unifocal tumours. However, indolent multifocal non-dominant lesions (Gleason Score 3+3=6, <3mm) will be permitted.

HOW DO WE PROTECT THE PERSONAL INTEGRITY?

Information obtained in the study will be collected in one database. The purpose of the database is to collect study data in a proper and safe way for a long time. All information about the participants will be treated with utmost confidentiality and with strong safeguards to preserve their anonymity. Information that can be used to identify the participant (such as name, address and social security numbers) is always kept separate from other data (such as survey responses and blood tests). All questionnaire data and test results will be treated to prevent unauthorized access to them. The samples will get a unique code so that outsiders cannot identify them. The participants' samples are treated in accordance with the Swedish Biobank Act.

Everyone who works with the PRIS-study are under confidentiality agreements. Results from the study are presented only as statistics in which individual answers cannot be traced.

Treatment of the personal data is in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR). All participants may request in writing to find out what information about them self from which information has been collected and to whom the data has been disclosed.

TIMELINE

Year 1 (2022)

2021-06-14 Approval from the ethics review board
2022-05-20 Study trip UCL London, clinical teaching
2022-09-01 Technical installation started and technical pilot phase
2022-09-28 Treatment of first patient
2022-09-28 2023-02-01 Clinical pilot phase (n = 40)

Years 2-5 (2023-2026)

2022-10-01 2023-02-01 Evaluation safety, early experiences
2023-02-01 2026-02-01 Randomized study phase
2026-02-01 2026-06-01 Analysis and decisions routine clinical implementation

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