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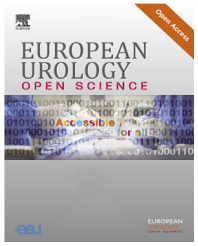

Trial Protocol

Prostate Cancer IRE Study (PRIS): A Randomized Controlled Trial Comparing Focal Therapy to Radical Treatment in Localized Prostate Cancer

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Abstract

The aim of focal treatments (FTs) in prostate cancer (PCa) is to treat lesions while preserving surrounding benign tissue and anatomic structures. Irreversible electroporation (IRE) is a nonthermal technique that uses high-voltage electric pulses to increase membrane permeability and induce membrane disruption in cells, which potentially causes less damage to the surrounding tissue in comparison to other ablative techniques. We summarize the study protocol for the Prostate Cancer IRE Study (PRIS), which involves two parallel randomized controlled trials comparing IRE with (1) robot-assisted radical prostatectomy (RARP) or (2) radiotherapy in men with newly diagnosed intermediate-risk PCa (NCT05513443). To reduce the number of patients for inclusion and the study duration, the primary outcomes are functional outcomes: urinary incontinence in study 1 and irritative urinary symptoms in study 2. Providing evidence of the lower impact of IRE on functional outcomes will lay a foundation for the design of future multicenter studies with an oncological outcome as the primary endpoint. Erectile function, quality of life, treatment failure, adverse events, and cost effectiveness will be evaluated as secondary objectives. Patients diagnosed with Gleason score 3 + 4 or 4 + 3 PCa from a single lesion visible on magnetic resonance imaging (MRI) without any Gleason grade 4 or higher in systematic biopsies outside of the target (unifocal significant disease), aged ≥40 yr, with no established extraprostatic extension on multiparametric MRI, a lesion volume of <1.5 cm^3, prostate-

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specific antigen <20 ng/ml, and stage ≤T2b are eligible for inclusion. The study plan is to recruit 184 men.

1. Introduction

Prostate cancer (PCa) is the leading cause of cancer death among men in the western world. It has been shown that early detection of PCa decreases mortality but has limitations, with low specificity leading to unnecessary biopsies, overdiagnosis, and overtreatment of indolent cancers. Radical treatments for localized PCa are associated with a significant risk of morbidity in terms of incontinence and impotence, while providing only small survival benefits in comparison to active surveillance (AS) [1–3]. Over the two past decades, advances in the field of prostate magnetic resonance imaging (MRI) together with an effort to reduce treatment morbidity have led to the development of methods for FT of PCa. Early evidence suggests a lower risk of side effects and a preserved chance of cure in comparison to current radical treatments [4]. For a selected group of patients with PCa, FT therefore potentially offers both cure and preserved quality of life after treatment. However, since long-term follow-up and randomized trials are lacking, these treatments are still considered experimental in guidelines, emphasizing the need for more randomized studies evaluating FTs [5–7].

Among the different ablative techniques for FT in PCa, irreversible electroporation (IRE) uses high-voltage electric pulses to increase membrane permeability and induce membrane disruption in cells [8,9]. In comparison to other ablative treatments, IRE is a nonthermal technique that potentially causes less damage to the surrounding tissue, and has shown promising functional and oncological outcomes [10,11]. Two recent reviews reported pad-free continence rates of 91–100% and preserved erectile function in 79–100% of men treated with IRE. The in-field recurrence rate ranged from 0% to 33% [12,13]. Valerio et al [14] reported promising safety data, with 100% (n = 24) preservation of continence and 95% (19/20) preservation of erectile function when applying IRE to a median ablation volume of 12 ml.

Since randomized controlled trials comparing traditional curative treatments with FT using IRE are lacking, we designed the Prostate Cancer IRE Study (PRIS) to compare functional outcomes after FT with IRE to either radical prostatectomy (RP) or radiation treatment (RT) in patients with intermediate-risk localized PCa.

2. Objectives

The aim of the proposed research is to evaluate the genitourinary, rectal, and overall health-related quality-of-life outcomes and cancer control of FT for unifocal localized PCa using IRE.

2.1. Primary aim

The primary aim is to evaluate functional outcomes in men treated for unifocal localized PCa with IRE in comparison to conventional treatment with either RP or RT.

2.2. Secondary aims

The secondary aims are:

- To evaluate adverse events in men treated for unifocal localized PCa with IRE in comparison to conventional treatment with either RP or RT;
- To evaluate progression-free and treatment-free survival in men treated for unifocal localized PCa with IRE in comparison to conventional treatment with either RP or RT; and
- To conduct an economic evaluation of each technique.

3. Study design

PRIS includes a pilot study and a main study comprising two parallel randomized controlled trials comparing IRE with robot-assisted RP (RARP) in study 1 or RT in study 2 in men with newly diagnosed intermediate-risk PCa (NCT05513443). The complete study protocol is presented in the Supplementary material and the design is summarized in Figure 1.

This study is a collaboration between hospitals in the Stockholm Region, Sweden that are treating men with PCa. Study inclusion and treatment occur at the local hospital. If the local hospital is unable to perform the allocated treatment, a referral to any of the participating hospitals is made. Follow-up of participants is performed at the local hospital in collaboration with the study Administration and Clinical Trials Office at Karolinska University Hospital.

3.1. Inclusion criteria

The study aims to recruit 184 men. Patients aged ≥40 yr diagnosed with Gleason score 3 + 4 or 4 + 3 PCa in a single MRI-visible lesion without any Gleason grade 4 or higher on systematic biopsies outside of the target (unifocal significant disease, Gleason score 3 + 3 allowed outside the target), no established extraprostatic extension (EPE) on multiparametric MRI (mpMRI; EPE ≤3), a lesion volume <1.5 cm^3, prostate-specific antigen (PSA) <20 ng/ml, and stage ≤T2b are eligible for inclusion.

Patients with an intraductal tumor, previous treatment for PCa, a severe illness such as concomitant cancers, severe cardiovascular disease, or dementia, or contraindications to MRI will be excluded.

Preoperative diagnostic assessment with mpMRI followed by software-guided targeted and systematic biopsies

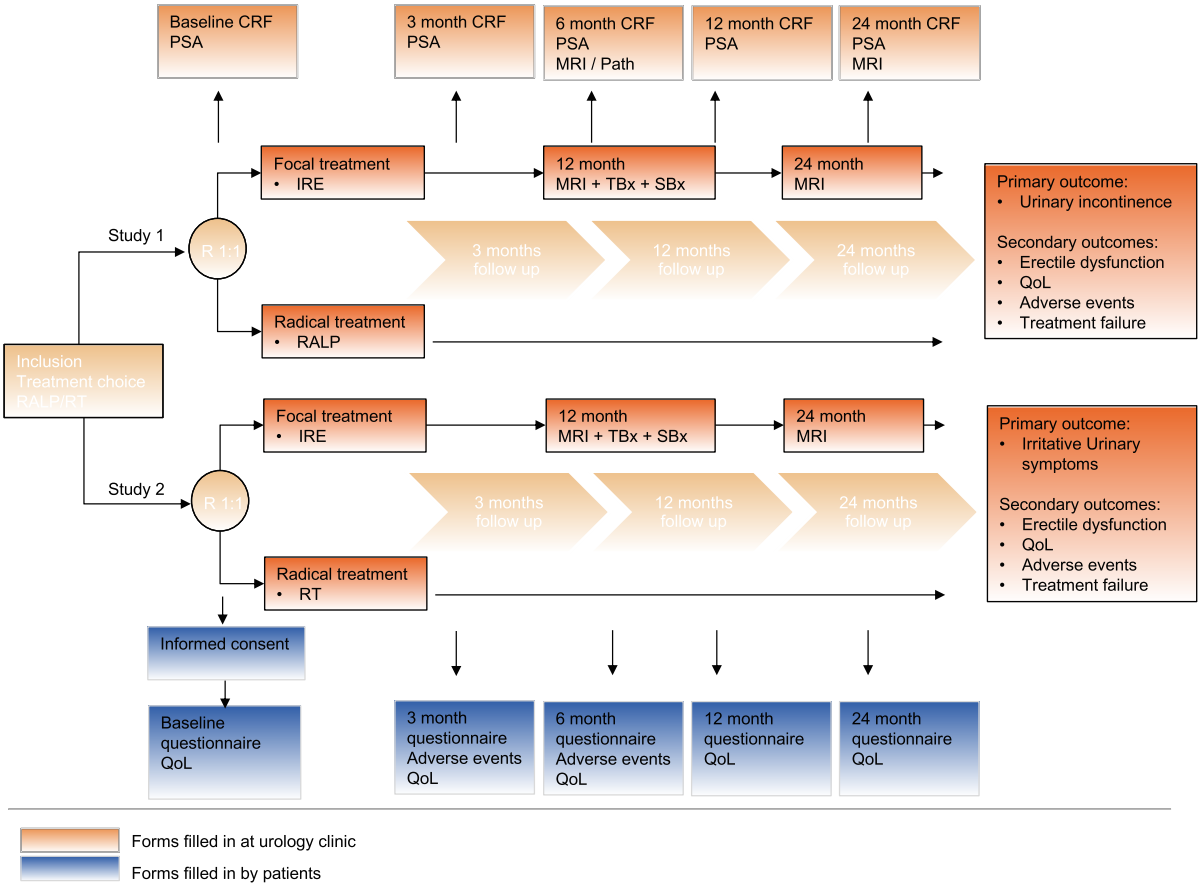

Fig. 1 – Overview of the design of the Prostate Cancer IRE Study (PRIS), which includes two parallel randomized controlled trials comparing IRE with RALP or RT in men with newly diagnosed intermediate-risk prostate cancer. The primary outcome in study 1 versus study 2 is incontinence and irritative urinary symptoms as assessed via the Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire, measured 12 mo postoperatively. Patients in the experimental arms will undergo per-protocol multiparametric MRI and fusion-guided TBx as well as SB at 12 mo postoperatively. At 24 mo, multiparametric MRI will be performed in the experimental arms, and all patients with rising PSA or signs of residual disease on MRI will undergo TBx. SBx will be performed at 2 and 4 yr if residual International Society of Urological Pathology grade group 1 cancer is detected. IRE = irreversible electroporation; RALP = robot-assisted radical laparoscopic prostatectomy; RT = radiotherapy; MRI = magnetic resonance imaging; QoL = quality of life; TBx = targeted biopsy; SBx = systematic biopsy; PSA = prostate-specific antigen; CRF = case report form.

is mandatory to ensure that there is no significant disease outside of the lesion. Radiology readings will be performed by expert uroradiologists at the local study site and centralized MRI review will be performed by the study expert radiologist (F.J.) for all men in the experimental arms. Areas suggestive of PCa will be graded according to Prostate Imaging-Reporting and Data System (PI-RADS) v2.1. Fusion biopsies will be performed by sampling three or four cores from each suspicious lesion using MRI-ultrasound fusion equipment via a transrectal or transperineal technique. Systematic prostate biopsies using a template of 12 biopsy cores will be taken from the peripheral zone of the prostate (apical, mid gland, and base) according to national Swedish guidelines.

3.2. Recruitment

Patients will be included from four different hospitals within Stockholm County: Karolinska University Hospital, Danderyd Hospital, S:t Göran Hospital, and Södersjukhuset. Patients who fulfill the criteria for inclusion, after having given their oral and written consent, are registered and randomized 1:1 to either their chosen traditional curative treatment in line with existing national guidelines (robot-assisted radical prostatectomy or radiation) or FT with IRE.

3.2.1. *Pilot study*

The pilot study will be conducted at Karolinska University Hospital in Stockholm before the main study and will involve 40 patients (20 FT, 20 radical treatment). The objective of this pilot study is assessment of the treatment zone using MRI and evaluation of adverse events directly after the FT. Inclusion and exclusion criteria are identical for the main study and the pilot study.

3.2.2. *Main study*

The plan is to start the main study 6 wk after the pilot study. In total, 112 men will be included in study 1 comparing IRE to RARP, and 62 men will be included in study 2 comparing IRE to RT (men from the pilot phase are included).

Patients in study 1 and study 2 are randomized separately 1:1 to standard treatment or FT. The randomization is stratified by study site. Allocation is open for participants and the treating physician. Men randomized to the control

arms are not allowed to cross over to the experimental arms. Men randomized to the experimental arms with FT are allowed to choose the treatments offered in the control arm.

4. Interventions

4.1. Experimental arm: FT using IRE

Men randomized to the experimental arms will be offered FT of PCa with IRE technology. The IRE treatment will be performed under general anesthesia with neuromuscular blockade, with the patient placed in the gynecological position and the tumor lesion located using a BK Medical transrectal fusion ultrasound probe. The IRE needles are then placed transperineally with a safety margin of 5–7 mm around the outer perimeter of the tumor according to largest volume measured on MRI, using a 17GA Civco brachytherapy grid guided by the ultrasound/MRI fusion images. Electrical pulses are then sent through the needles to treat the tumor in the center using the Nanoknife technique (Angiodynamics).

Postoperative assessment will involve follow-up with PSA measured at 3, 6, 12, and 24 mo, and mpMRI at 12 and 24 mo. The first 20 patients in the experimental arms will also undergo mpMRI after 1 wk to evaluate the treatment zone. All patients in the experimental arms will undergo per-protocol mpMRI and fusion-guided and systematic biopsies at 12 mo postoperatively to evaluate oncological outcomes. At 24 mo, mpMRI will be performed in the experimental arms and all patients with rising PSA or signs of residual disease on MRI will undergo targeted biopsy. Centralized MRI review for all post-treatment MRI scans will be performed by the study expert radiologist for all men in the experimental arms. Systematic biopsies will be performed at 2 and 4 yr if residual International Society of Urological Pathology grade group (GG) 1 cancer is present, according to national guidelines on AS. In the event of a significant tumor burden remaining, patients will be offered radical treatment. Residual disease will be treated in accordance with current guidelines, whereby men with more than a few mm of Gleason score 3 + 4 PCa are recommended to consider radical treatment with surgery or radiation at the discretion of the treating physician.

4.2. Control arm (traditional curative treatment)

4.2.1. PRIS study 1: IRE versus RARP

Patients eligible for prostatectomy will be randomized to RARP or FT with IRE. RARP without lymph node dissection will be performed according to national guidelines.

4.2.2. PRIS study 2: IRE versus RT

Patients eligible for RT will be randomized to either RT of the prostate without irradiation to lymph nodes according to national guidelines or to FT with IRE performed as previously described.

5. Outcome definitions and data collection

The primary objective of PRIS is to compare the impact of PCa treatment using IRE, RP, or RT on urinary function. Erectile function, quality of life, treatment failure, adverse events, and cost effectiveness will be evaluated as secondary objectives.

Primary and secondary endpoints are listed in Table 1. Given that the two radical treatments have very different side effects after treatment, different primary endpoints will be used for the two studies. The primary outcome in study 1 (IRE vs RP) is continence, defined as use of zero pads as assessed by the Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire at 12 mo. The primary outcome in study 2 is irritative urinary symptoms at 12 mo, measured using the EPIC-26 questionnaire.

All data will be collected using an electronic system. Patient-reported data will be collected using paper forms on five different occations: before treatment and 3, 6, 12, and 24 mo after completion of treatment. Participants will fill in Swedish translations of internationally validated questionnaires on functional outcomes and quality of life. In addition to EPIC-26, the International Index of Erectile Function (IIEF), EuroQoL-5 Dimensions (EQ5D), and International Prostate Symptom Score (IPSS) questionnaires will be administered. Clinical data including tumor characteristics, treatment technique and execution, laboratory values, MRI data, pathology data, adverse events, and adjuvant treatments will be collected before treatment and at 3, 6, 12, and 24 mo after completion of treatment by the investigator and research nurses. Patients in the control arms will be followed according to the clinical protocol, with consecutive

Table 1 – Primary and secondary endpoints, definitions, and outcome measurements

Endpoint	Definition	Metric used	Time points
Primary endpoint			
Study 1: urinary incontinence at 12 mo	EPIC-26, Q3	≥1 pad/d (yes) vs none (no)	BL and 3, 6, 12, and 24 mo
Study 2: irritative urinary symptoms at 12 mo	EPIC-26, Q4e	Moderate/large problem (yes) vs no/small problem (no)	BL and 3, 6, 12, and 24 mo
Secondary endpoints			
Erectile function at 12 mo	IIEF score	Decrease in IIEF score	BL and 3, 6, 12, and 24 mo
Urinary incontinence at 12 mo	EPIC-26, Q3	Change in score	BL and 3, 6, 12, and 24 mo
Voiding function at 12 mo	IPSS	Change in IPSS	BL and 3, 6, 12, and 24 mo
Bowel function at 12 mo	EPIC-26, Q6	Change in score	BL and 3, 6, 12, and 24 mo
Adverse events at 3 mo	Clavien-Dindo [25]	Proportion of patients by Clavien-Dindo grade	3, 12, and 24 mo
Quality of fife	EQ5D		

BL = baseline; EPIC-26 = Expanded Prostate Cancer Index Composite; EQ5D = EuroQoL-5 Dimensions; IIEF = International Index of Erectile Function; IPSS =International Prostate Symptom Score.

Table 2 – Treatment failure definition by study arm and treatment received

Setting	Definition	Metric used	Time points measured
Experimental arms	Need for additional FT or WGT or ADT Need for WGT or ADT Need for WGT or ADT or GG 2 at 12-mo Bx	Any treatment (yes/no)	Time from randomization to treatment failure
Control arm: RARP	Postoperative PSA ≥0.2 ng/ml or adjuvant treatments including ADT	PSA	Time from randomization to treatment failure
Control arm: RT	PSA >2 ng/ml above the nadir (Phoenix) or adjuvant treatments including ADT	PSA	Time from randomization to treatment failure

ADT = androgen deprivation therapy; Bx = biopsy; FT = focal treatment; GG = International Society of Urological pathology grade group; PSA = prostate-specific antigen; RARP = robot-assisted radical prostatectomy; RT = radiation treatment; WGT = whole-gland treatment.

PSA tests. The first 20 patients in the experimental arms will be followed up with mpMRI after 1 wk and thereafter for all patients with PSA measurement at 3, 6, 12, and 24 mo, and mpMRI at 12 and 24 mo with targeted biopsies for cases with a rise in PSA or signs of residual disease on MRI. Systematic biopsies will be performed at 2 and 4 yr for cases with residual GG 1 cancer.

The definition of treatment failure will vary according to the treatment received (Table 2). Specifically, treatment failure will be defined as (1) a need for any additional focal or whole-gland treatment or androgen deprivation therapy (ADT), or diagnosis of GG ≥2 PCa at 12 mo biopsy after IRE; (2) biochemical recurrence with PSA ≥0.2 ng/ml or adjuvant treatments including ADT after RP; and (3) PSA >2 ng/ml above the nadir (Phoenix definition of biochemical recurrence) or adjuvant treatments including ADT after RT.

To the best of our knowledge, cost analyses of IRE in comparison to radical treatment are lacking. Therefore, an economic evaluation to estimate the lifetime costs, quality-adjusted life years (QALYs), and cost effectiveness for the trial arms from a societal perspective will be performed. QALYs will be modeled using the reported study outcomes combined with health state values reported in the literature and background health state values for the Swedish population.

6. Statistical and ethical considerations

The study protocol has been reviewed and approved by the regional ethical review board (2021-01598). To reduce the number of patients for inclusion and the study duration, we set functional outcomes as the primary study outcome. Providing evidence of the lower impact of IRE on functional outcomes will lay a foundation for the design of future multicenter studies with an oncological outcome as the primary endpoint. We used data available from published prospective studies to estimate the probability of incontinence and irritative urinary symptoms at 12 mo after FT, RARP, and RT [15–18].

For study 1 we estimated incontinence incidence of 20% in the RARP arm and 2% in the IRE arm. A sample size of 112 men (56 in each arm) was determined for a two-tailed test with a significance level (α) of 0.05 and power of 0.80. In the power calculation we took into account expected noncompliance and dropout at a rate of 15%. For study 2 we estimated irritative symptom incidence of 30% in the RT arm and 2% in the IRE arm. A sample size of 62 men (31 in each arm) was determined for a two-tailed test with a significance level (α) of 0.05 and power of 0.80, and assuming a dropout/noncompliance rate of 15%. In total, 184 men are planned for inclusion in the trial, of whom 97 (10 + 56 + 31) will undergo FT. For a study period of 24 mo and with approximately 800 diagnosed with intermediate-risk PCa in Stockholm County annually, we estimate that 1000 men would be eligible for inclusion during the study period. An acceptable accrual rate of 25% would result in 250 recruited men over a period of 24 mo. Given the plan of two study sites for FT, each site would have to plan for 25 treatment-days per year (3 FTs per day).

A data safety and monitoring board consisting of three individuals with expertise in clinical trials and statistical analysis will review complications and survival data and make recommendations on changes to the protocol and/or termination of the trial if needed. An interim analysis will performed after 30% of the study population (80 men) has completed the control or experimental arms.

7. Summary

Localized PCa is treated with surgery or RT, both of which affect surrounding tissues, with negative effects on functional outcomes, including urinary and erectile dysfunction. Technological advances in prostate imaging have led to improvements in localization of cancerous lesions within the prostate gland, resulting in better ability to restrict treatment to cancer-affected areas [19–21]. In addition, mpMRI has shown promising results in follow-up after FT in delineating any in-field or out-of-field recurrence or progression [22]. PRIS aims to compare functional outcomes after FT with IRE to either RARP or RT and thus to provide level 1 evidence supporting FT for selected patients with localized PCa. We strongly believe that patient selection is the key factor for the design of such trials in PCa.

FTs have been used during the past decade as an alternative to both AS and radical treatment. In the early era of FT, low-risk tumors were mostly selected for treatment, with the rationale that minimally invasive interventions could reduce the anxiety and psychological burden in selected men on AS living with an untreated cancer, which could inappropriately cause men to choose radical treatment [23,24]. However, since evidence has shown that men with confirmed low-risk disease have an extremely low risk of dying from PCa, all current guidelines recommend AS for this group of patients, and thus FT for this group must be considered as overtreatment [6]. Conversely, patients with intermediate-risk PCa may benefit from FTs in attempts to reduce the treatment-related side-effects in this group otherwise treated with radical therapy. Notably, long-term outcome data for

patients with intermediate-risk PCa undergoing radical therapies have shown a net benefit in terms of cancer control and biochemical recurrence; however, prevention of death is seen in few patients within 10 yr and is rare among men older than 65 yr [2]. For the subset of patients with clinically significant PCa in a solitary lesion, FTs represent a promising combination of cancer control and preservation of periprostatic tissue integrity. Among the different FT techniques, IRE seems to offer a lower risk of harm.

Author contributions: Anna Lantz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lantz, Jäderling, Clements, Discacciati, Grönberg, Eklund, Stricker, Emberton, Aly, Nordström.
Acquisition of data: Lantz, Nordlund, Falagario, Jäderling, Özbek, Clements, Discacciati, Grönberg, Eklund, Stricker, Emberton, Aly, Nordström.
Analysis and interpretation of data: Nordlund, Falagario, Jäderling, Özbek, Clements, Discacciati, Grönberg, Eklund, Stricker, Emberton, Aly, Nordström.
Drafting of the manuscript: Lantz, Nordlund, Falagario.
Critical revision of the manuscript for important intellectual content: Nordlund, Falagario, Jäderling, Özbek, Clements, Discacciati, Grönberg, Eklund, Stricker, Emberton, Aly, Nordström.
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Appendix A. Supplementary data

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