A Multi-Center Randomized Single-Blind Two Arm Intervention Study Evaluating Irreversible Electroporation for the Ablation of Prostate Cancer

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Primary: - To evaluate differences in side effect profile of patients treated with focal or extended ablation performed with image-guided IRE for the ablation of prostate carcinoma. - To evaluate differences in quality of life of patients treated...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON47783

Source
ToetsingOnline

Brief title
IRE-RCT

Condition

- Reproductive neoplasms male malignant and unspecified
- Male genital tract therapeutic procedures

Synonym
Prostaat Carcinoma, Prostate Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,CROES

Intervention

Keyword: Focal Therapy, Irreversible Electroporation, Prostate Cancer, RCT

Outcome measures

Primary outcome

To evaluate differences in side effect profile of patients who have been treated with focal or extended ablation performed with image-guided IRE for prostate carcinoma:

- To determine post procedural erectile dysfunction measured by the International Index of Erectile Function-5 (IIEF-5).

- To determine the treatment related adverse events measured by CTCAE Version 4.0

- To determine the urinary side effects by the International Prostate Symptom Score (IPSS), IPSS quality of life and use of pads.

- To evaluate differences in quality of life of patients measured by the Expanded Prostate Index Composite (EPIC) and Visual Analogue Scale (VAS) pain score.

The patient groups randomized in focal ablation and extended ablation will be compared.

Secondary outcome

- To determine the oncological efficacy as measured by the proportion of men who are free of any prostate cancer in the two different groups. This will be examined by standardized prostate biopsies and targeted biopsies after multiparametric-MRI at 1 year post-IRE.

- To evaluate the efficacy of MRI in the imaging of ablation success, extend of the ablation zone, 3 months and 6 months, 1,2,3,4 and 5 years post IRE ablation.

Study description

Background summary

Current surgical and ablative treatment options for prostate cancer have a high incidence of (temporary) incontinence, erectile dysfunction and/or bowel damage. These side effects impair the quality of life of prostate cancer patients and impact on patients* decision to undergo early, potentially curative interventional treatments. These side effects are due to procedure related damage of the blood vessels, bowel, urethra and/or neurovascular bundle. New treatments that limit damage to these structures have the potential to improve patient outcomes. Ablation with Irreversible Electroporation (IRE) has shown to be effective and safe in destroying tumour cells and to have the potential advantage of sparing surrounding tissue and vital structures such as blood vessels and nerves.

Study objective

Primary:
- To evaluate differences in side effect profile of patients treated with focal or extended ablation performed with image-guided IRE for the ablation of prostate carcinoma.

- To evaluate differences in quality of life of patients treated with focal or extended ablation performed with image-guided IRE for the ablation of prostate carcinoma.

Secondary:
- To evaluate the oncological efficacy of image guided IRE for the focal and extended ablation of prostate carcinoma.

- To evaluate the efficacy of MRI in the imaging of ablation success, extend of the ablation zone, 3 months, 6 months and 1, 2, 3, 4 and 5 years post IRE ablation.

Study design

Multi-centre Randomized Clinical Trial: 106 patients with confirmed unilateral (T1c-T2a) low risk (Gleason sum score 6) or intermediate risk prostate cancer (Gleason sum score 7) will be offered to have the IRE treatment. These patients will be randomized into one of the two arms of the study.

Arm 1: Focal ablation of the prostate at the location of positive biopsies.

Arm 2: Extended ablation of the prostate at the side of the positive biopsies.

The imaging data (MRI and ultrasound) will be entered into the Planning Software system of the IRE-device. The volume of the prostate is measured and a specified ablation zone will be determined. The patients will be admitted for overnight stay in the hospital on the morning of the scheduled IRE procedure. The IRE will be performed under general anaesthesia following the anesthesiological protocol and the specified zone identified in the planning stage will be ablated. IRE electrode needles will be placed into the prostate under ultrasound image guidance with a transperineal approach using a grid. When the needles are in place, electric pulses of one to two minutes duration are used to ablate the specified zone. The total procedure time will be approximately 1.5 hour.

Data will be collected and patients will be followed up at 1 day post-operatively, 2 weeks, 1 month, 3 months, 6 months, 12 months and thereafter annually until 5 years post-IRE.

Intervention

Arm 1: Focal IRE ablation of the prostate at the location of positive biopsies.

Arm 2: Extended IRE ablation of the prostate at the side of the positive biopsies.

Study burden and risks

A variety of ablation techniques have been used in the treatment of localised prostate cancer. These techniques include cryoablation, high-intensity focused US (HIFU), RFA, microwave coagulation, Vascular Targeted Photodynamic Therapy (VTPT) and Interstitial Laser Thermotherapy (ILT)40 . These focal techniques have been receiving increasing interest, and show significant potential in the management of prostate cancer due to the higher detection rate of localised prostate cancer due to the PSA test, and to the improved technology available 41-43. They are gaining increasing popularity because they are minimally invasive, require only a short hospital stay, and may have a better side effect profile, lower morbidity and less impact on the quality of life 40. Most current techniques however, have been shown to have limitations.

Cryoablation involves freezing undesirable tissue by direct contact with a cryogen-cooled probe. Cryotherapy has a higher morbidity than other minimally invasive techniques, in particular a high rate of erectile dysfunction of 80%.29 Other disadvantages are the thick probes that are difficult to use, tissue damage at the margins of treatment, and injury to adjacent structures.

HIFU has had good short to medium results in low to intermediate risk prostate cancer and larger trials are being conducted. This is a non-invasive technique utilising hyperthermia to cause coagulative necrosis of the targeted area29. It shows potential as a therapy in both whole gland ablation and focal ablation44. Erectile dysfunction is theoretically a likely side effect but has not been adequately documented. Swelling of the prostate post-procedure is a more common side effect, and causes frequently urinary retention. This technique is limited by difficulty in treating the entire prostate gland, in particular the anterior prostate45. In 1999 HIFU was validated in a study in which one side of the prostate was ablated. After two weeks the efficacy of the ablation was compared with the histopathological results after radical prostatectomy46. 9 patients were treated in this study with in all patients complete necrosis of the ablated tissue. However in 2 patients a small residual tumour was seen. There were no fistulae reported in this series.

Advantages of minimally invasive techniques / Focal therapy
The recent downward migration of prostate cancer stage on diagnosis, most likely due to the increased use of PSA tests. This has opened the door to focal strategies tailored to the management of organ-confined, early stage prostate cancer 45+47.

With the obvious advantage of avoiding a major invasive surgical procedure, minimally invasive techniques have the potential for diminished side effects, and thus may provide a more desirable treatment option. While prostate cancer may be slow growing and classified as low risk, it is difficult to distinguish which cancers require treatment from those that do not 29. Focal techniques may

provide a more definitive treatment option than active surveillance, and may be better tolerated by older patients with comorbidities, with the potential for fewer side effects. Recently published long-term survival rates of patients undergoing primary or salvage cryotherapy for prostate cancer are also promising. Results indicated an 87% overall 10-year prostate-cancer-specific survival, despite early cryotherapy technology and the majority of patients being high risk 48.

While solid tumours in other organs such as the breast, skin and kidney, were initially treated with radical surgery, focal, organ-sparing therapies are now common and result in lower morbidity and disfigurement with equivalent rates of cancer control 29.

The major disadvantage with these techniques may be that they may not control the cancer as well as the established techniques 40. Another disadvantage of some conventional ablation techniques is potential damage to surrounding structures, which can cause symptomatic problems, in many cases as the result of thermal damage.

Expected advantages of IRE compared to current treatment options
IRE has a number of advantages compared to thermal ablation and radical surgery, these include:

• Small needle electrodes with radiology guidance
• Very short high voltage pulses create permanent pores in cell membranes
• Fast - around 5-10 minutes per treatment
• Rapid disappearance of targeted cells
• No residual cavity or distortion
• Almost no post-operative pain
• Sparing of supporting and vital structures and consequently offers an alternative when thermal ablation and surgery are precluded.

Risks
Hazard
General anesthesia (procedural)
Muscle Blockade (procedural)
Cardiac Arrhythmia (both procedural and device, unlikely from device due to distance)
Multiple Prostate Biopsies (procedural)
IRE electrode needles placed in or through sensitive structures. (Foreseeable misuse)
Insufficient Muscle Blockade (procedural)
Vascular Dissection (device)
Perforation (device)
Hemorrhage (device)
Lack of Sterile Technique/Breach of Sterile Field (procedural)

ECG (EKG) Disruption after pulsing (2-3 sec)
Tumour Recurrence (device)
Tumour Seeding (procedural)
Nerve Damage (device)
Acute or Sub-acute Vascular Damage (device)

Injury to Prostatic Urethra or External Sphincter (device)
Urethro-rectal Fistula (Both procedural or device)
Rectal Tear/ Perforation (from TRUS guided biopsy or Endorectal MRI coil) (procedural)
Postoperative Hemorrhage (device)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histologically confirmed organ-confined unilateral prostate cancer on transperineal template prostate biopsies or MRI targeted biopsies in combination with systematic biopsies (clinical stage T1c-T2a)
2. Gleason score 6 or Gleason score 7
3. PSA <15 ng/ml or PSA > 15 ng/mL counseled with caution
4. Life expectancy of > 10 years

Exclusion criteria

1. Bleeding disorder as determined by prothrombin time (PT) > 14.5 seconds, partial thromboplastin time (PTT) > 34 seconds, and Platelet Count < 140/uL
2. No ability of subject to stop anticoagulant and anti-platelet therapy for 7 days prior the procedure.
3. Active urinary tract infection (UTI)
4. History of bladder neck contracture
5. Anaesthesia Surgical Assignment category III or greater
6. History of inflammatory bowel disease
7. Concurrent major debilitating illness
8. Prior or concurrent malignancy except for basal cell carcinoma of the skin
9. Cardiac History including arrhythmias, ICD or pacemaker
10. Prostate calcifications greater than 5 mm
11. Biologic or chemotherapy for prostate cancer
12. Hormonal therapy for prostate cancer within 6 months prior to procedure
13. Previous radiation to pelvis
14. Transurethral resection of the prostate / Urethral stent
15. Prior major rectal surgery (except haemorrhoids)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-06-2015
Enrollment:	16
Type:	Actual

Medical products/devices used

Generic name:	Irreversible electroporation system
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	03-02-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	18-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	28-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	10-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL50791.018.14