CROES
CLINICAL RESEARCH OFFICE OF THE ENDOUROLOGICAL SOCIETY

REGISTRY OF IRREVERSIBLE ELECTROPORATION FOR THE ABLATION OF PROSTATE CANCER WITH USE OF NANOKNIFE DEVICE

A Multi-Center, International Registry to evaluate the treatment of Prostate Cancer in terms of Recurrence, Functional outcomes and Safety.

Protocol ID: Registry IRE Nanoknife®

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Coordinating investigator	Prof Jean de la Rosette – Chairman CROES
Steering Committee **Principal investigators**	Amsterdam: Prof. Jean de la Rosette Chicago: Dr. Scott Eggener Heidelberg: Prof. Markus Hohenfellner Los Angeles: Prof. Inderbir Gill London: Prof. Mark Emberton Modena: Prof. Maurizio Brausi New York: Dr. Jonathan Coleman Paris: Dr. Eric Barret Valencia: Dr. Jose Dominguez Escrig Rick Stark (ex officio AngioDynamics) Frank Facchini (ex officio AngioDynamics)
Sponsor	Clinical Research Office of the Endourological Society Office manager: Mrs. S. van Rees Vellinga info@croesoffice.org
Subsidising party **Representative**	**AngioDynamics** 14 Plaza Drive Latham, NY 12110 United States of America

PROTOCOL SIGNATURE PAGE

Confidentiality Statement

I agree to perform this registry, to maintain the procedures required to carry it out and to abide by the terms of this protocol.

This registry protocol is designed by CROES and may not be used or published without their consent. Each Principal Investigator will sign a separate Data Transfer Agreement.

SPONSOR REPRESENTATIVE

Name:

Date:

Signature:

INVESTIGATOR (S)

Name:

Date:

Signature:

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

BMI	**Body Mass Index**
CROES	**Clinical Research Office of the Endourological Society**
DMS	**Data Management System**
eCRF	**Electronic Case Report Form**
IIEF	**International Index of Erectile Function**
IPSS	**International Prostate Symptom Score**
IRE	**Irreversible Electroporation**
PI	**Principal Investigator**

SUMMARY

Rationale: The treatment of prostate cancer with Irreversible Electroporation (IRE) may offer advantages in terms of patient outcomes and side effects over current ablative and surgical techniques. Indications and outcomes for this treatment have not yet been studied in an *in vivo* setting. The aim of this study is to complement the outcomes from the randomized controlled trial that is being conducted, and to provide data to compare quality between participating centers in order to improve treatment with IRE in terms of recurrence and safety.

Objectives: To assess the recurrence of prostate cancer in patients who were treated with IRE after 1 and 5 years, determine the baseline characteristics of the patients, and to collect information on possible differences between centers in treatment with IRE.

Study design: This is an international prospective observational study in which data is recorded from consecutive patients for 5 years who are treated with irreversible electroporation using Nanoknife® with 5 years of follow up.

Study population: The study population comprises those patients who undergo treatment with IRE Nanoknife® for ablating prostate cancer.

Main study parameters/endpoints: Primary endpoint of the study is recurrence of prostate cancer at 1 year post-treatment. The last follow up will be at 5 years after treatment.

1. INTRODUCTION

Current surgical and ablative treatment options for prostate cancer have a high incidence of side effects, such as incontinence, erectile dysfunction or bowel damage. These side effects impair the quality of life of the patients and have an impact on patients' decision to undergo early curative interventional treatments, and are due to procedure related damage of the blood vessels, bowel, urethra or neurovascular bundle. New treatments that limit damage to these structures have the potential to improve patient outcomes.[1] Ablation with Irreversible Electroporation (IRE) has shown to be effective and safe in destroying tumour cells and to have the advantage of sparing surrounding tissue and vital structures.[2-4] However, indications for and outcome of treatment with IRE Nanoknife® have not been studied before. To study the characteristics of patients and their outcomes, the Clinical Research Office of the Endourological Society (CROES) has initiated this registry.

2. OBJECTIVES

Primary Objective:

The aim of this registry is to assess the recurrence of prostate cancer at 1 and 5 years, as well as the change in functional outcomes (e.g. incontinence or erectile function) from baseline. Secondary objectives are to establish which indications lead to treatment with IRE Nanoknife® setting and safety assessment measured by number of complications and adverse events.

2.1 Study design

This is an international prospective observational multi-center study in which data on consecutive patients for 5 years with prostate cancer who undergo IRE are collected. Data from each patient will be collected at participating centers over a 5-year period. Patients' data at baseline visit (pre-IRE), peri-operative data and follow up for 5 years will be recorded. Follow up data will be collected according to the following schedule:

1 – 2 weeks after surgery

1st year: every 3 months

2nd year: every three months

3rd year: every 6 months

4th and 5th year: once a year.

Data from participating centers will be collected through electronic Case Report Forms (eCRFs), with use of an online Data Management System (DMS), which is located and

maintained at the CROES Office. All analyses will be performed by members of the CROES Office.

The data collection or patient participation in this study does not interfere with the choice of treatment, sample collection, procedures and the treatment itself, which should entirely follow standard hospital practices, including the follow up.

2.2 Population

The study population comprises those patients diagnosed with histologically confirmed prostate cancer and are scheduled for treatment with IRE Nanoknife®.

2.3 Inclusion criteria

Observational data from patients who meet the inclusion criteria below will be recorded:

- Is diagnosed with histologically confirmed prostate cancer
- Is scheduled for IRE Nanoknife®
- Has signed informed consent form

2.4 Exclusion criteria

No specific exclusion criteria are defined.

3. METHODS

3.1 Study parameters/endpoints

3.1.1 Main study parameters

- Recurrence rate of prostate cancer at 1 and 5 year
- Change in functional outcomes in terms of uroflow (maximum flow, voided volume, post void residual) from baseline, including patient experience (quality of life), measured by the International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF-5) questionnaires

3.1.2 Other study parameters

- Safety, assessed by proportion of complications or intra-, peri-, and post-operative adverse events
- Functional outcomes, such as incontinence or erectile function

- Efficacy, in terms of oncological outcomes (e.g. presence and number of positive biopsies within treated area or metastasis)

3.2 Data collection

This registry will follow all consecutive patients during 5 years who are diagnosed with prostate cancer and are scheduled for IRE. All participating centers will include patients who meet the inclusion criteria. Patients will be followed and their data will be collected for up to 5 years. Principal Investigators (PIs) or research nurses at local sites will fill out the eCRFs in the DMS at the appropriate time points. The CROES Office will send regular updates on the completeness of their data and is responsible for reminding PIs for supplying the follow up data.

3.3 Study Duration

This registry will include consecutive patients for 5 years. Since patients will be followed for 5 years, the total study duration is 10 years.

3.4 Description of data to be collected

Baseline characteristics: age, Body Mass Index (BMI), comorbidity, medication use, medical history (including history of prostate cancer and treatment), assessment of cancer and uroflow parameters.

Intra-, peri-, and post-operative details: duration, imaging guidance, device specifications, complications, medication use, catheter use.

Follow up: recurrence, biopsies, uroflow, complications.

4. STATISTICAL ANALYSIS

4.1 Primary study parameters

Primary study parameters are proportion of recurrence at 1 and 5 years after treatment and change in functional outcomes from baseline.

4.2 Other study parameters

Other study parameters will be descriptives of baseline characteristics of the patients, complications or adverse events (intra-, peri-, and post-operative), use of medication and hospital stay, functional outcomes and efficacy in terms of oncological outcomes.

4.3 Handling missing and spurious data

All analyses will be carried out on available data, with reporting of proportions of missing data. All analyses will be performed using SPSS 20 or R 3.0 or higher. Results will be presented in tables reporting at least the number of subjects, mean, standard deviation, minimum and maximum for continuous data; and number of subjects and percentages for categorical data. For testing, a significance level of 5% will be maintained.

5. ETHICAL CONSIDERATIONS

5.1 Regulation statement

This study will be registered at clinicaltrials.gov. This study may additionally be registered at and approved by the competent authorities, when required by local law.

6. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

6.1 The Steering Committee

The Steering Committee consists of selected and renowned members of the Endourological Society and has the overall responsibility of the study.

Tasks and responsibilities include:

- To create and approve the final protocol
- To co-author protocol amendments whenever necessary
- To select the network of investigators
- To monitor progress of study enrolment of centers
- To ensure a scientifically sound and safe conduct of the study
- To review and approve the statistical analysis plan
- To guarantee the integrity of data collection and analyses
- To address and resolve study management problems
- To assist in the analyses and presentation of the results

Representatives of the CROES council may join the meetings of the Steering Committee.

6.2 Handling and storage of data and documents

The investigator or his/her designee will document all data obtained during the study on the individual eCRFs provided by CROES. Investigators will have access to the DMS, and will receive their own username and password. Only data from their own center is accessible to investigators. Data managers from the CROES will have full access to all

data collected during this study, for purposes of monitoring data collection and analyzing the data. The electronic database will be maintained at the central data collection site selected by the CROES council and shall be updated on a regular basis as determined by the CROES council. A manager, selected by the CROES council, at the central data collection site will maintain and coordinate the data collection. As determined by the CROES council, all PIs will receive feedback on the data collection regularly. Patient data will be entered anonymous, the key to coded information is held at each study center for its own patients and is the responsibility of the local PI. Handling of personal data is in compliance with the Dutch Personal Data Protection Act.

The number of centers participating in this study is not limited, although all sites must receive approval of the CROES council before commencing the data collection in this registry. Prior to receiving approval of the CROES council, an IRB approval shall be provided to the central data collection center when mandatory according to local law. Subject to the approval of the CROES council, the PI at study sites should preferably be a member of the Endourological Society. Study sites may be proposed by the members from the Steering Committee or on recommendation from a third party.

Primarily, data belongs to the CROES in its function as an organ of the Endourological Society. After a request to the Steering Committee and receiving authorization from the CROES council, study participant members can present data at relevant occasions.

6.3 Monitoring and Quality Assurance

Monitoring this registry will be done by data managers at the CROES office. All data entered into the web-based DMS will be secured and checked for irregularities. In addition, the DMS provides detailed overview reports of inclusion and runs queries to check for inconsistencies in collected data, to ensure a reliable dataset. To minimize missing data, regular messages will be sent to investigators to encourage and remind them of entering data collected at follow up time points.

During the registry or after the registry has been completed, the Steering Committee and/or CROES representatives may carry out an audit. The audit will focus on data source verification and critical values in the database. Regulatory bodies may also inspect the study. If an investigator is contacted by a regulatory authority with a request for an inspection, the investigator must inform CROES immediately.

6.4 Amendments

Amendments are changes made to the research after a favourable opinion by the Steering Committee has been given.

6.5 Public disclosure and publication policy

The Steering Committee will revise and give final approval to any paper derived from the data collected in the course of the study. Based on contribution and level of input, the Steering Committee will determine the author names and order of those authors on any paper derived from this dataset.

REFERENCES

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3. *Altunc, S. Subnanosecond pulsed-power generated electric fields for cancer treatment. IEEE Nucl Plasma Sci Soc News **34**, (2009).*

4. *Schoenbach, K. H. et al. Bioelectric Effects of Intense Nanosecond Pulses. IEEE Transactions on Dielectrics and Electrical Insulation 1088–1109 (2007).*