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MISSION

Through worldwide collaboration, CROES seeks to assess, using evidence based scientific methodology, the various aspects of clinical endourology.

VISION

By applying rigorous scientific evaluation to the field of clinical endourology, CROES will enable all urologic surgeons to bring to their patients the most effective and efficient care possible.

PROJECTS

- Global PCNL study
- Global URS study
- Global GreenLight Laser study
- Global Renal Mass study
- Global NBI study

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A RANDOMIZED CONTROLLED TRIAL ON FOCAL THERAPY FOR LOCALIZED PROSTATE CARCINOMA: HEMIABLATION VERSUS COMPLETE ABLATION WITH IRREVERSIBLE ELECTROPORATION

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Focal therapy in prostate cancer

Focal therapy is gaining interest as a treatment modality for prostate cancer.¹ It is defined as a treatment that aims to eradicate known cancer within the prostate and preserve uninvolved prostatic tissue and consequently genitourinary function. Patients with low- and intermediate-risk prostate cancer are the best candidates for focal treatment, especially when it is unilateral disease and clinical stage $\leq cT_{2a}$.² Because of intensified prostate-specific antigen (PSA) testing and improved radiological technologies,³ increased detection of early-stage local prostate cancer has occurred. With this, there will be an increasing demand for focal treatments. Awaiting the ultimate approach of focal therapy as described above, a variety of ablation techniques have been introduced. These techniques include high-intensity focused ultrasound (HIFU), cryotherapy, brachytherapy, photodynamic therapy (PDT), and irreversible electroporation (IRE).

Overview of focal therapies

HIFU is the oldest focal experimental therapy. In 1995, Madersbacher and associates⁴ started with true focal therapy in 10 patients with a result of three complete destruction of the tumor and seven partial destructions. This outcome caused future research only with hemiablation, with a small number of patients. The highest described biochemical disease-free survival is 90% at 5 years.⁵ More multicenter clinical trials of HIFU are forthcoming.⁶

In cryotherapy, several studies on hemiablation have been performed. Truesdale and colleagues⁷ recently performed a study in 77 patients. This showed a biochemical disease-free survival of 73% after 24 months and 13% biopsy-proven recurrence (seven in untreated areas and three in treated areas). This outcome is in conflict with the study by Bahn and coworkers⁸ with a biochemical disease-free survival of 93% after 70 months.⁸ Focal cryoablation is also described by Onik and colleagues,⁹ showing outcomes of 94% and 95% of biochemical disease-free survival after 3.6 and 4.5 years respectively.

Presently in brachytherapy, two studies have been conducted on hemigland and the focal approach of brachytherapy.^{10,11} Protocols are considered for delivering 145 Gy at the index lesion plus a lower dose applied to the contralateral side. The rectal and urethral dose should follow the regular whole-gland brachytherapy guidelines.¹²

In PDT, the focal approach has also been investigated. With this technique, several hemiablations are performed. Moore and coworkers¹³ showed reduction of PSA in 8 of the 10 procedures, accomplished in six patients. Azzouz¹⁴ presented in 2011 his results of 85 patients who underwent a hemiablation with PDT. MRI findings showed 87% necrosis in the treated lobe. In 6 of the 85 patients, temporary side effects were reported.

IRE

IRE is a new ablative therapy in prostate cancer. It is based on a pulsating current that alters the transmembrane potential of biologic cells. If the duration of the applied electrical pulses is below the charging time of the outer cell membrane, a nonthermal interaction of the electric field with subcellular structures occurs.¹⁵ This results in permanent permeabilization of the cell membrane, which disrupts cell homeostasis and leads to cell death. These irreversibly permeabilized cells are left *in situ* and are removed by the immune system.¹⁶ IRE has been shown to effectively ablate tumor cells *in vitro*, in small and large animal experiments,^{17–19} and in a recent safety study on IRE of focal liver, kidney, and lung tumors.^{20,21}

There are two main factors driving research into IRE as a treatment modality. First, tumor ablation experiments in animals and humans have shown that connective tissue structure is preserved, and there is no damage to associated blood vessels, neural tissue, or other vital structures.^{17,18,22} Second, IRE is a nonthermal focal therapy and subsequently there is no “heat sink” effect.²³ It is anticipated that the preservation of surrounding tissue will reduce treatment-induced side effects inherent in current prostate cancer therapies.

Objectives

The Clinical Research Office of the Endourological Society (CROES) is going to conduct a study titled “Multicenter Randomized Two-Arm Intervention Study Evaluating Irreversible Electroporation for the Ablation of Localized Unilateral Prostate Cancer.” With this phase II clinical trial, we want to compare hemiablation with total ablation with IRE in patients with unilateral low- to intermediate-risk prostate cancer. Primary objectives are to determine if hemiablation has fewer side effects than whole-gland ablations measured by International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF), time of catheter a demeure (CAD), Visual Analog Scale pain scores, and length of hospital stay. The secondary objective is to determine the oncologic outcome of IRE hemiablation in comparison with whole-gland ablation. This will be measured by standardized transrectal biopsies and multiparametric MRI findings in follow-up. Furthermore, the objective is to determine if there is a difference in the quality of life between patients who are treated with a hemiablation and whole-gland ablation measured by Functional Assessment of Cancer Therapy-Prostate (FACT-P).

Study design

Patients with confirmed unilateral prostate cancer will be invited to participate in this randomized controlled trial (RCT). Six European centers will randomize 200 patients into hemiablation or complete ablation. To prevent randomly occurring differences in important prognostic factors across the two randomized groups, the randomization is based on risk stratification.²⁴ The first group will receive an ablation of the hemiprostate in which positive biopsy results are present. The patients randomized in the complete ablation group will undergo a whole-gland ablation (see Figure). Follow-up includes quality-of-life questionnaires, laboratory parameters, imaging including MRI and transrectal ultrasonography, and prostate biopsies at regular intervals. The primary objectives will be evaluated at 1 year, whereas the oncologic outcome will be studied at short (1 year), midterm (3 years), and long term (5 years).

The CROES is proud that this study will be conducted in partnership with AngioDynamics. The urologic community is increasingly demanding high-quality research whereas our patients are asking for the least invasive and most effective treatments. The present RCT will help to position the IRE

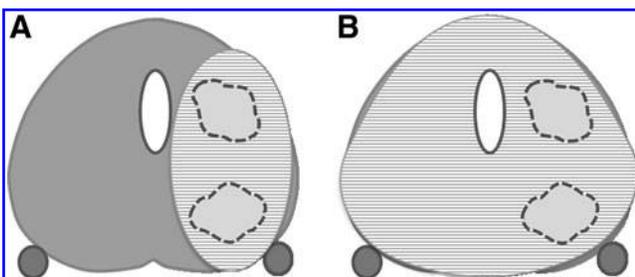


FIG. 1. Different electroporation zones of the prostate. The white oval shape in the middle represents the urethra. The circles at the bottom represent the neurovascular bundles. Striped grey shows the ablation zone. In group A, unilateral disease will be treated with a unilateral ablation. In group B, unilateral disease will be treated with a whole-gland ablation.

treatment within the treatment armamentarium for low-intermediate localized prostate cancer. We are most happy that the initiation of this project leads to CROES launching its second RCT. With this state of the art research, we will be able to reach the ultimate goal of our professional career: To base our best clinical practice on the highest level of evidence.

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- The global PCNL observational study was closed in December 2009.
- The Global Ureteroscopy study and the Global Renal Mass Study were closed in January 2012. Data collection is still ongoing in a selected number of centers.
- The Global Greenlight Laser study was closed in April 2012.
- Ongoing project: The randomized study on Narrow Band Imaging *vs* White Light Imaging.
- For further information, please visit: www.croesoffice.org or contact the Executive Director of CROES, Mrs. Sonja van Rees Vellinga (info@croesoffice.org).