

Study Protocol Cover Page Official Study Title: Efficacy of Eco-guided Percutaneous Transperineal Ablation with Neodymium Laser in Patients with Benign Prostatic Hypertrophy

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## 1.0 Introduction

Benign prostatic hyperplasia (BPH) was treated with open surgery until the early 1980s. Over the last two decades, the therapeutic approach has undergone a marked change. Until the second half of the 1980s, the treatment of choice in most cases was trans-urethral treatment (TURP). During the 1990s the appearance of alpha-blocker drugs led many urologists to treat benign hyperplasia with a medical and non-surgical approach. Gradually the number of patients treated with TURP has been reduced in favor of medical therapy. At the same time there has been a growing interest in minimally invasive interventional therapies with the aim of finding a more effective therapy than the medical one and at the same time less aggressive than the trans-urethral treatment. The regional local diffusion of microwaves and other hyperthermic therapies have been used until the advent of the GreenLight PVP technique (green light laser) which has completely supplanted all other minimally invasive techniques. This type of method has many advantages over the traditional TURP technique, especially in patients on anticoagulant therapy. The green light laser technique also reduces the operating times and is very useful for the treatment of large glands that require the administration of considerable amounts of energy. The only study in which the efficacy of the percutaneous ablative treatment with transperineal neodymium laser of benign prostatic hypertrophy was evaluated was conducted by Patelli et. to (1) in 2017, which confirmed a significant volume reduction of the gland through exclusively imaging and clinical follow-up. Using thin needles (21G) a trans-perineal percutaneous approach is possible, with less invasiveness. Placing from two to four sources in the context of the gland based on its volume, it is possible, with applications of short duration, to obtain significant volume reductions of the glandular lobes themselves. Although the surgical approach is currently the most widely used option, mini-invasive surgery is rapidly spreading, representing in many cases the only possibility to intervene on patients for whom the psycho-physical conditions do not allow the surgical approach conventional or for which the extent of the lesion to be treated does not justify the risk of surgery (for example in geriatric patients or patients with BPH at the same time as a neoplastic disease of another site). With the availability of a minimally invasive technology, which guarantees the effectiveness of classical methods, a clear reduction in intervention and hospitalization costs and a reduction in social cost can also be achieved.

## 2.0 Objective of the study

With this we intend to evaluate the efficacy of the percutaneous ablative treatment with neodymium laser, that is the complete profile of safety and tolerability in acute and in the follow up, in patients suffering from Benign Prostatic Hypertrophy using, for the first time, as the main diagnostic tool in the follow-up multiparametric prostate MRI that allows us to evaluate with objective data the volume reduction of the glandular volume in the follow-up, any morphostructural gland changes and the correlation of the aforementioned advanced imaging data with the clinical data.

## 3.0 Design of the study

Non-pharmacological interventional study in which each patient constitutes self-control. The clinical evaluation will be carried out at three different times:

Time 1: eligibility assessment, signing of informed consent

Time 2: admission, laser ablation and control with multiparametric MRI of the post-procedural prostate (T0).

Time 3 Follow up at 3 (T1) -6 (T2) -12 (T3) months from the procedure.

## 4.0 Materials and Methods

### 4.1 Selection of patients

Patients will be recruited by the Departments of Urology and Diagnostic Imaging of the University Hospital "Tor Vergata".

#### 4.1.1 Inclusion criteria

- Age over 65 years
- Benign prostatic hypertrophy (confirmed by multiparametric prostate MRI to be performed pre-treatment)
- PSA value  $\leq 4$  ng / ml
- Indicative flow meter test for obstructive pathology
- Medium-high surgical risk.
- Presence of obstructive symptoms (voiding hesitation, intermittent mitto, reduction of urinary flow, incomplete emptying of the bladder, post-voiding incontinence and irritative symptoms such as urinary frequency, dysuria, nocturia - quantified with IPSS)
- Signature of the information sheet and of the informed consent to the treatment, to the execution of the multiparametric MRI and to the administration of the paramagnetic contrast medium.

#### 4.1.2 Exclusion criteria

- MR signs of malignancy confirmed by biopsy investigation
- Urethral stenosis
- Serious coagulation disorders
- Inadequate compliance
- Ischemic pathology in the previous six months
- Presence of pacemakers
- Active phase inflammatory pathology
- Presence of III dominant prostate lobe
- Contraindications to the execution of MRI (claustrophobia, auricular implants, metal prostheses and other contraindications included in the specific informed consent)
- Paramagnetic contrast medium allergy.
- Acute and / or chronic renal failure (GFR  $< 50$  mL / min and serum creatinine  $> 1.5$  mg / d)
- Not adequate understanding of the information sheet

## 4.2 Pre-procedural evaluation

### 4.2.1 Pre-treatment instrumental clinical examinations

- Specialized clinical evaluation
- Urinary apparatus ultrasonography with evaluation of post-voiding residue
- Multiparametric prostate RM (Using conventional morphological sequences associated with DWI sequence and evaluation after administration of paramagnetic contrast agent administered intravenously)
- Urodynamic studies
- EKG

#### 4.2.2 Pre-treatment blood chemistry tests

- Total and fractionated PSA
- CBC with platelet count and leukocyte formula -PT, PTT, INR
- Urine analysis and Urine culture
- Azotemia
- Creatinine

#### 4.3 Technique of performing a percutaneous laser ablation treatment

The treatments will be performed by the radiology team, on an outpatient basis using the supplied Echolaser XVG combined system. The procedure will be performed with the patient in gynecological position, and in safe conditions according to the current legislation for laser treatments (such as protective glasses). Treatment includes local anesthesia of the perineal region, under ultrasound guidance. At the discretion of the medical team, sedation can be carried out with anesthetic assistance. 2 or 4 needles of 21G, 1 or 2 will be inserted in the right bumper, 1 or 2 in the left bumper. In each needle a 300 micron optical fiber will be inserted - Ditta Elesta s.r.l. - 50041, Calenzano (FI) - Italy, at a distance of 8-10 mm from the urethra. For each lighting, for about 6 minutes, an energy of 1800 J per fiber will be delivered, at the power of 2-3 Watts. At the end the needle and the fiber will be retracted for about 1 cm ("pull-back"). Further lighting will follow, with delivery and duration and power equal to the previous one. Depending on the size of the middle lobe one or more pull-backs can be made. In total the treatment will consist in the delivery up to 3600 J, to the power of 2-3 W for a total duration of 30 minutes. The laser causes hyperthermia, denaturation and coagulative necrosis of proteins. The maximum volume treated in a session and the extent of the ablation vary according to the prostatic volume, anatomy and receptivity of the tissue. At the end of the treatment 20 mg of Urbason ev (if not specifically contraindicated by the patient) will be administered, for anti-edema and anti-inflammatory purposes. An antibiotic, pain relief and gastroprotective therapy will also be established for 1 week. After an adequate observation period, the patient will be discharged.

#### 5.0 Follow-up

The clinical evaluation will be carried out at different times:

##### 5.1 Post procedural follow up

Immediately after the procedure, a multiparametric prostate MRI will be performed, followed by discharge with steroid therapy (prednisone), if not contraindicated, to be scaled and with commitments for programming the subsequent follow-up phases.

##### 5.2 Post-discharge follow-up

Specialist examination, suprapubic ultrasound of the urinary tract (with evaluation of the post-residual residue) and multiparametric prostate MRI at 3 months, 6 months and 12 months and subsequent checks according to clinical judgment.

A chemical-physical urine test and any urine culture should be attached to each clinical-ultrasound evaluation. At each reevaluation the IPSS form and the data collection form will be filled out.

## 6.0 Results and evaluation methods

### 6.1 Primary end point

Absence of obstructive complications and / or improvement of obstructive symptoms related to pre-existing benign prostatic hypertrophy to percutaneous ablative treatment with neodymium laser. The evaluation will be carried out with clinical evaluation, multiparametric prostate MRI, ultrasound of the pubic urinary tract with measurement of the post-residual residue, physical chemical examination of the urine and possibly with urine culture.

### 6.2 Secondary end points

Evaluation of the efficacy of multiparametric prostate MRI in evaluating the response to percutaneous ablative laser diode treatment of benign prostatic hypertrophy immediately after treatment and in short-term follow-up.

Quality of life assessment following percutaneous laser ablation treatment (compilation of the IPSS data sheet and data collection form).

Evaluation of the feasibility of treatment by a team of interventional radiologists.

### 6.3 Assessment methods

The evaluation will be performed according to the procedures defined in the paragraph dedicated to the follow up.

### 6.4 Statistical analysis

The descriptive analysis will be performed by calculating the central tendency, variability, symmetry and kurtosis. For categorical variables we will proceed with the construction of 2x2 contingency tables. For the inferential analysis we will proceed to the calculation of the ANOVA for repeated measures (with statistical analysis between and within), the Odds-Ratio. The result will be considered statistically significant if  $p < 0.05$ .

### 6.5 Sample

Since this is a pilot study, a statistical calculation of the sample size cannot be performed due to the lack of statistics for the purpose. 40 patients are expected to be enrolled in the study.

## 7.0 Duration of the study

12 months

## 8.0 Ethical Aspects

### 8.1 Approval by the Regulatory Authority

All the necessary authorizations issued by the competent authorities will be acquired based on the applicable regulations before the study is started.

### 8.2 Ethical Conduct of the Study and Ethical Approval

The study will be conducted in compliance with good clinical practice (GCP) and all applicable regulations, including the Helsinki declaration.

Research researchers have the responsibility to ensure that this protocol, the informed consent form for the patient and any other information (such as advertisements or information to support and supplement informed consent) are controlled and approved by the competent ethics committee.

#### 8.2.1 Informed patient consent

Patients who agree to participate in the study will sign the informed consent. The information and methods for collecting and drafting informed consent must comply with the applicable regulatory guidelines.

Patients will be adequately informed in the event of substantial amendments presented during the study.

#### 8.2.2 Requirements for the preparation of documents by the researcher

In accordance with the regulatory requirements, the Investigation Physicians will be required to approve periodic safety updates on the conduct of the study and to notify the closure of the study to the competent Ethics Committee (CE).

### 8.3 Storage of data

Once the study is completed and in compliance with the applicable regulatory requirements, a copy of all the study documents will be kept in a safe place.

### 8.4 Confidentiality

The Responsible Physician and other study personnel will maintain the confidentiality of all relevant information and all data and documents produced during the course of the study, and will not use such information, data or records except for the purpose of carrying out the study. These restrictions are not applicable to:

- 1) information made available to the public not by the Responsible Doctor or by the personnel involved in the study;
- 2) information for which disclosure is necessary, even if in confidential form, to the EC for the sole purpose of evaluating the study;
- 3) information for which disclosure is necessary in order to provide adequate medical assistance to the patient of the study;



4) results of the study that can be published.

## 9. Data management and documentation retention

Data Management will be performed in compliance with all applicable standards and procedures. The essential documents relating to the clinical trial will be kept for at least 5 years from the completion of the same (Art. 17 EC Directive 2005/28).

### 9.1 Patient traceability

The registration of all patients participating in this study will be used and maintained by the study staff.

### 9.2 Data collection and retrieval

Patient data will be collected in the data collection form during the clinical evaluation and in the follow up.

### 9.3 Publication of data

The data obtained from the study will be presented at conferences and published in the main national and international journals of scientific relevance.

## 10.0 Estimated costs

There are no additional costs as the supply of optical fibers for interstitial laser therapy will be carried out free of charge by the company Elesta s.r.l. - 50041, Calenzano (FI) - and the pre and post procedural examinations fall within the current clinical activity.

## 11.0 Bibliography

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