Study Protocol Cover Page Official Study Title: : Efficacy of Eco-guided Percutaneous Transperineal Ablation with Neodymium Laser in Patients with Low-Intermediate Risk Prostate Cancer: Non-Pharmacological Interventional Study
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Protocol Extension on long-term efficacy of Focal Laser Ablation for Prostate Cancer among a multicenter registry

A multi-center international registry to evaluate the TPLA-TRLA treatment, new Focal Laser Ablation modality, of focal prostate cancer with regards to long-term efficacy, functional outcomes and safety.

PROTOCOL TITLE 'Protocol Extension on long-term efficacy of TPLA for Prostate Cancer among a multicenter registry'

Short Title	**Registry FLA for Pca**
Version	**1.2**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

DMS	**Data Management System**
eCRFs	**Electronic Case Report Forms**
FLA	**Focal Laser Ablation**
IPSS	**International Prostate Symptom Score**
IQOL	**Incontinence Quality of Life**
METC	**Medical research ethics committee (MREC);**
mpMRI	**Multi-parametric MRI**
Participant	**Centre that is participating in this registry**
PROMs	**Patient reported outcome measures**
SHIM	**Sexual Health Inventory for Men**
TPLA	**Transperineal laser ablation**
TRLA	**Transrectal laser ablation**
VAS	**Visual Analogue Scale**
Wbp	**Personal Data Protection Act**
WMO	**Medical Research Involving Human Subjects Act**

SUMMARY

Rationale: The treatment of low-intermediate risk prostate cancer with focal laser ablation (FLA), a new Focal Laser Ablation (FLA) modality, may offer advantages in life quality and functional outcomes over current standard therapies. As the technique is relatively new, indications and outcomes for this treatment are subject of investigation. Clinical information from these treatments can be useful as part of the validation process of this technique. The aim of this registry is to collect data on patients treated with transperineal/transrectal laser ablation of the prostate outside clinical trials and to provide data on safety and functional outcomes in these patients in order to standardize the treatment.

Objective: To assess long-term safety and efficacy of focal laser ablation for low-intermediate risk prostate cancer, to assess functional outcomes, to assess safety, to determine baseline patient characteristics, to collect information on possible differences between centers applying treatment of focal laser ablation and to explore the optimal treatment indications and possible limitations.

Study design: This is an international prospective observational registry in which data will be recorded of patients who are treated with focal laser ablation low-intermediate risk prostate cancer.

Study population: Male patients treated with focal laser ablation for low-intermediate risk prostate cancer.

Main study parameters/endpoints: The primary endpoint of this registry is safety and long-term efficacy (avoidance or postponing of surgery for prostatectomy; benefits of FLA vs surgery will be monitored and put into the registry of focal laser ablation for low-intermediate risk prostate cancer followed with multi-parametric MRI, measured by the lack of histopathological evidence of tumor recurrence during 6-month and 12-month follow-up; annual follow-up with mpMRI and biopsies for 5 years.

1. INTRODUCTION AND RATIONALE

Current treatment options for focal low-intermediate risk prostate cancer is surgery or radiotherapy. Treatment side effects and quality of life impairment might hamper patients to allow surgical treatment. On the other hand, side effects of radiotherapy eventually include damage to the rectum and bladder. A minimal invasive technique with reduced postoperative morbidity and equal functional outcomes as standard treatment is desired to solve these problems.

The SoracteLite EchoLaser system can be applied for FLA, a new FLA modality, of the prostate. The aim of this prospective registry is to collect data on patients treated with FLA and to provide data on indications, functional and safety outcomes in these patients in order to get more insight in the treatment.

2. OBJECTIVES

- To assess long-term efficacy in patients treated with focal laser ablation for low-intermediate risk prostate cancer.
- To verify if FLA may represent a valid and safe way to postpone or even avoid radical prostatectomy
- To assess functional outcomes in patients treated with focal laser ablation for prostate cancer.
- To assess safety outcomes measured by the number intra- and postoperative adverse events in patients treated with focal laser ablation.
- To determine characteristics of patients treated with focal laser ablation.
- To identify possible differences between centers and possible relations between treatment application and outcomes.
- To explore the optimal indications and possible limitations of FLA for low-intermediate prostate cancer.

3. STUDY DESIGN

This is an international prospective observational registry in which data on consecutive patients with low-intermediate prostate cancer treated with TPLA/TRLA is collected. Centers from any country may apply for participation in this registry. Data from each individual patient will be collected at the participating centers in a maximum of five years. Patients' data at baseline and follow-up visits will be recorded, as well as data of intra- and postoperative complications. Data will be collected through electronic Case Report Forms (eCRFs), with use of an online

Data Management System (DMS). Investigators or research nurses at local sites will complete the eCRFs in the DMS.

The data collection or patient participation in this registry does not interfere with the choice of treatment, sample collection, procedures or the treatment itself, which should entirely follow standard hospital practice.

4. STUDY POPULATION

4.1 Population (base)

The study population comprises those patients presenting low-intermediate risk prostate cancer who are planned to undergo focal laser ablation in the participating centers, after completing the primary follow-up.

4.2 Inclusion criteria

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

- Male (>18 years old)
- Presenting with focal low-intermediate prostate cancer (pTNM T2bN0M0)
- Focal lesion of 2cm or less; Gleason 6-7 (GG1-GG2)
- Signed informed consent form approved by the ethical committee of the University of Rome “Tor Vergata”, Italy.

4.3 Exclusion criteria

- Age < 18 years, urethral stenosis, multi-focal cancer, neurological disturbances
- Previous prostatic surgery or radiotherapy

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

Long-term treatment efficacy measured by the time until possible histopathological tumoral recurrence.

5.1.2 Secondary/endpoints

Experienced functional effectiveness measures by change in Sexual Health Inventory for men (SHIM) and (Incontinence Quality of Life) IQoL at 6 and 12 months initially and annually for 5 years. Decreasing the need for surgical prostatectomy and/or radiotherapy.

Treatment safety measured by the complications at 30 days, according to the Clavein-Dindo classification.

5.2 Study duration

This registry will be open for inclusion for five years. Since individual patients will have a follow-up of five years, the total study duration will be 10 years.
Interim analysis will be made and published during the course of the study carried out by the principal investigators, depending on the number of patients enrolled.
Earlier termination of the enrollment may also be decided by principal investigators, depending on number of patients enrolled.

5.3 Description of data to be collected

Baseline characteristics: age, height, weight, comorbidities, medication use, medical history, biopsies, mpMRI: location of tumor, dimension of the tumor, dimension of necrosis according to mpMRI, eventual residual dimension.

Intra- and perioperative information: procedure duration, device treatment specifications (e.g. number of fibers used, power per fiber, energy per fiber, total delivered energy, distance between fibers, pull back of the fibers and distance), complications, postoperative catheter placement and duration.
Follow-up: symptoms, complications (e.g. retention, fever, hematuria, erectile dysfunction, stricture), re-treatment (surgery, radiotherapy or FLA).

6. STATISTICAL ANALYSIS

6.1 Primary study parameter(s)

The mean time until histopathological tumor recurrence. The mean time for the need for retreatment including standard deviations. In addition, the percentage of retreatment and types of retreatment will be calculated at the end of the registry.

6.2 Secondary study parameter(s)

Experienced functional effectiveness is calculated by the change in Sexual Health Inventory for men (SHIM) and (Incontinence Quality of Life) IQoL score at different time points of the study.

Other study parameters will be descriptive of baseline characteristics of the patients, complications and/or adverse events intra-operative and at 30 and 90 days, medication use, hospital stay and functional outcomes.

6.3 Handling missing and spurious data

All analyses will be carried out on available data, with reporting of proportions of missing data. The University of Rome "Tor Vergata" will perform all analyses using SPSS 24 or more recent. Results will be presented in tables reporting the number of subjects, mean, standard deviation, minimum and maximum for continuous data; and number of subjects and percentages for categorical data.

7. ETHICAL CONSIDERATIONS

7.1 Regulation statement

This registry will be registered at cinicaltrials.gov. This registry may additionally be registered at and approved by the competent authorities, when required by local law. The local investigator is responsible to perform FLA according to local regulations.

7.2 Recruitment and consent

When there is an indication for treatment of low-intermediate risk prostate cancer by FLA, the doctor will inform the patient about this registry. The doctor will explain the observational character of this registry and that data will only be recorded. There will be no change in the treatment or follow-up. Furthermore, data is saved in an encoded way. At any time, the patient can refuse or ask to stop the data registration. Data registered until then will remain available for research.

The patient will be encouraged to take time to consider participation in the registry. Additional questions will be answered. The patient should sign the consent at the consultation or at the next appointment.

The participant is responsible for correct informed consent of all subjects before entering data into the DMS.

8. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

8.1 The Steering Committee

The Steering Committee tasks and responsibilities include:

- To review and approve the final protocol and amendments
- To select the network of investigators
- To monitor progress of registry enrolment of centers

- To monitor the data collection process
- To ensure a scientifically sound and safe conduct of the registry, eventually by executing an audit
- To review the statistical analysis plan
- To guarantee the integrity of data collection and analyses
- To address and resolve registry management problems
- To assist in the analyses and presentation of the registry results

8.2 Handling and storage of data and documents

The investigator or his/her designee will document all data obtained during the registry on the individual eCRFs provided by the University of Rome “Tor Vergata” location PTV. Investigators will have access to the DMS, and will receive their own username and password. Only data from their own center is accessible for investigators. Data managers from the University of Rome “Tor Vergata” location PTV will have full access to all data collected during this registry, for purposes of monitoring data collection and analyzing the data. The University of Rome “Tor Vergata”, will maintain the electronic database. The DMS is compliant with GCP, GDPR, and 21 CRF 11. It is located in a secure and fully certified datacenter. The DMS is certified to store medical data (NEN7510, ISO 9001, 14001 and 27001:2013). Patient data will be entered encoded; the key to coded information is held at each study center for its own patients and is the responsibility of the local Investigator. Handling of personal data by the DMS is in total compliance with the General Data Protection Regulation (GDPR) – Regulation (EU) 2016/679.

The number of centers participating in this registry is not limited, although all sites must receive approval of the University of Rome “Tor Vergata” location PTV and Steering Committee before commencing the data collection in this registry. Prior to receiving approval of University of Rome “Tor Vergata” location PTV, an IRB approval / waiver shall be provided when mandatory according to local regulations. Sites may be proposed by the members of the Steering Committee or on recommendation from third parties.

Data handling and safety is arranged in the regulatory document to which all participants to the registry have committed by signing an accession form. The regulatory document is in line with the GDPR. All participating centers will need to apply to the GDPR.

Primarily, the participant that includes its data in the registry shall remain the owner of its data and the results arising from the registry shall belong to University of Rome “Tor Vergata” location PTV.

After a request to the Steering Committee and receiving authorization from the University of Rome “Tor Vergata” location PTV, study participant members can present data at relevant occasions.

8.3 Monitoring and Quality Assurance

University of Rome “Tor Vergata” location PTV, will perform monitoring of this registry. 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, messages will be sent to investigators to encourage and remind them of entering data collected at follow-up time points.

During the registry or once the registry has been completed, the Steering Committee and/or University of Rome “Tor Vergata” location PTV 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 registry. If a regulatory authority contacts an investigator with a request for an inspection, the investigator must inform the University of Rome “Tor Vergata” location PTV immediately.

8.4 Amendments

Substantial amendments will be reviewed by Steering Committee for their opinion prior to implementation.

8.5 Public disclosure and publication policy

It is the intention of the registry to jointly publish the results. Based on contribution of participants, their scientific representatives will be involved in publications and according to their contribution included in the authors list. Each of the participants may send a request to the Steering Committee for a specific research topic to be investigated by the Coordinator. The Coordinator shall have a co-authorship position in all publications resulting from such requests. All acknowledgments shall be in accordance with the ICMJE guidelines for publication.

9. REFERENCES

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