PROTOCOL OF A THESIS FOR PARTIAL FULFILLMENT OF M.D. DEGREE IN UROLOGY

Title of the Protocol: Transperineal Targeted Focal Laser Ablation of Localized Intermediate Risk Prostatic Adenocarcinoma (Pilot Study)

Postgraduate Student: Khaled Adel Ahmed Ahmed
Degree: M.B.B.Ch., MSc, Faculty of Medicine – Ain Shams University– Egypt.

DIRECTOR: **Prof. Dr. Hassan Sayed Shaker**
Academic Position: Professor
Department: Urology
Faculty of Medicine, Ain Shams University

DIRECTOR: **Assoc. Prof. Dr. Haytham Mohamed Nasser**
Academic Position: Associate Professor
Department: Diagnostic & Interventional Radiology and Molecular Imaging
Faculty of Medicine, Ain Shams University

DIRECTOR: **Assoc. Prof. Dr. Aliaa Sayed Sheha**
Academic Position: Associate Professor
Department: Diagnostic & Interventional Radiology and Molecular Imaging
Faculty of Medicine, Ain Shams University

DIRECTOR: **Assoc. Prof. Dr. Waleed Elsayed Mohamed Mousa**
Academic Position: Associate Professor
Department: Urology
Faculty of Medicine, Ain Shams University

DIRECTOR: **Dr. Haitham Mohamed Ali Mohameden**
Academic Position: Lecturer
Department: Urology
Faculty of Medicine, Ain Shams University

Faculty of medicine
Ain Shams University
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1.INTRODUCTION/ REVIEW

Prostate cancer (PCa) is the second most common neoplasm diagnosed in men with an estimated 1.4 million diagnoses and 375,000 deaths worldwide in 2020 [1].

For localized prostate cancer (PCa), active surveillance (AS) or whole gland treatment (ie, radical prostatectomy [RP] and radiotherapy) are considered standard treatment options. Unfortunately, treatment-related morbidity is high. [2]

The ProtecT trial showed urinary incontinence rates of 3% and 20% and erectile dysfunction rates of 66% and 79% for radiotherapy and radical prostatectomy, respectively [2]. Radiotherapy can also cause rectal problems with a small increased risk of radiotherapy-induced secondary malignancy. [3]

Consequently, over the past few years, there has been a notable escalation in scholarly attention towards the implementation of focal therapeutic interventions for patients diagnosed with low- and intermediate-risk prostate cancer (PCa).

This tissue-preserving strategy has at its core the reduction of treatment-related toxicity by minimizing damage caused to the prostate and adjacent structures while attempting to retain the benefits of treating cancer. [4]

The rationale of focal therapy (FT) is based on the theory that the largest lesion with the highest grade, the so-called "index lesion," determines the risk of metastases and thus the patient's prognosis [5, 6].

FT involves ablating only the index lesion, thereby minimizing damage to collateral tissue such as neurovascular bundles, external urinary sphincter, bladder neck and rectum. [4]

Over the past few years, different types of energy sources in FT have been studied. These consist of high-intensity focused ultrasound (HIFU), irreversible electroporation (IRE), cryotherapy, photodynamic therapy (PDT), focal laser ablation (FLA) or laser interstitial thermotherapy, radiofrequency ablation (RFA), and focal brachytherapy. [7]

According to the European Association of Urology (EAU), low-risk and intermediate-risk patients may undergo local procedures using HIFU or cryotherapy within clinical trials or registries, with the aim of achieving long-term cancer control and reducing morbidity associated with surgery and radiation therapy [8].

Many groups have published limited data on outcomes following **in-bore** MRI-guided focal therapy, and many others are actively engaged or considering prospective comparative effectiveness research in this area.

Our primary objectives encompasses a thorough evaluation of the short-term oncological & functional outcomes of MRI-US or PSMA PET/CT-U/S **fusion-guided** focal laser ablation (FLA) for the treatment of a small, localized, intermediate-risk prostate cancer.

Concurrently, our secondary aim involves an assessment of the utility of multiparametric magnetic resonance imaging (mpMRI) as a diagnostic pre-treatment tool and during the post-treatment follow-up to examine the morphostructural alterations in the prostate gland resulting from FLA. Additionally, we aim to assess its reproducibility in determining the response to FLA therapy, correlating these findings with biopsy results, with the ultimate objective of establishing its predictive diagnostic value in identifying residual or recurring tumors.

2.AIM/ OBJECTIVES

To assess the effectiveness of MRI-US or PSMA PET/CT-U/S fusion-guided focal laser ablation (FLA) for the treatment of a localized, intermediate-risk prostate cancer in terms of short-term oncological & functional outcomes.

3.METHODOLOGY:

Patients and Methods/ Subjects and Methods/ Material and Methods

- **Type of Study**: Retrospective Observational Pilot study
- **Study Setting**: El-Demerdash University Hospital & Shaker Hospital.
- **Study Period**: 12 months.
- **Sample Size**: based on the rarity of cases in this study and the expensive cost of treatment, also this study is a pilot study. This protocol is exempted from sample size calculation. (No. of the patients will be 30)
- **Study Population**: Males with localized, intermediate risk prostatic adenocarcinoma

  Self-funded study (the researcher himself will pay for the data collection).

  The patients will not pay any fees.
- **Inclusion Criteria:**
  - Male
  - Over 45 years old
  - Prostate cancer visible on mpMRI or PSMA PET/CT and positive in the targeted biopsy.

- Gleason score 7 (ISUP grade 2/3)
- PSA 10-20 ng/mL
- Clinical stage T2b
- Refusing radical prostatectomy.

- **Exclusion Criteria:**
  - Prostate cancer invisible on mpMRI or PSMA PET/CT but positive in the systematic biopsies.
  - Presence of >2 MRI-visible lesions and positive in the biopsies.
  - Extracapsular extension
  - Seminal vesicle invasion
  - Presence of metastases detected by imaging
  - Gleason Score > 7
  - Clinical stage > T2b
  - PSA > 20 ng/mL
  - Acute urinary tract infection (UTI)
  - Severe lower urinary tract symptoms defined as an IPSS >20
  - Severe coagulation disorders
  - Inadequate compliance
  - Contraindications to MRI
  - Paramagnetic contrast agent allergy
  - Acute and/or chronic renal failure
- **Ethical Considerations:** Approval will be obtained from the ethical committee at Ain Shams University before starting the research and all patients will consent to be included in this study after explanation of the study procedures and the follow up course.
- **Study Procedures:**

The pre-procedural evaluation consisted of complete blood count, coagulation profile, urine examination and urine culture, and evaluation of post-voiding residue and uroflowmetry.

As the procedure of FLA is guided by MRI-US or PSMA PET/CT-U/S fusion images, a 3T mp MRI scan or PSMA PET/CT scan is recommended for each patient at Time 0.

On Siemens 3T MAGNETOM Skyra scanner, multiple MRI sequences will be

taken including T1, T2WI, DWI, ADC and STIR axial, coronal and sagittal images.

Injection of 2-4 ml/s of gadolinium and then post contrast dynamic imaging will be taken.

Malignant lesions will appear low signal at T2WI in comparison to the high signal intensity of the peripheral zone with restricted DWI and post gadolinium contrast enhancement.

The FLA is performed by a joint team of an expert interventional radiologist and an expert urologist on prostate MRI-US or PSMA PET/CT-U/S procedures, in a Day-Hospital setting, in a radiological interventional room or an OR.

The patient is placed in the lithotomy position, and Ciprofloxacin 500 mg is administered as antibiotic prophylaxis. The biolitec® LEONARDO® DUAL 45 Diode Laser System operating at 860 nm provides energy for the ablation.

The mpMRI data are loaded to the US system (Canon Aplio a550) via the DICOM network or a DVD and the live US image is linked with the MR image by Smart Fusion.

Under general or spinal anesthesia, thin needles (14 Gauge) are inserted transperineally under real-time US guidance fused with MRI or PSMA PET/CT. One to five needles are used depending on the lesion size and configuration because the multi-fiber approach can extend the coagulation area.

The laser light is conveyed from the source to the target through flexible, small-caliber (360 μm), flat-tipped quartz optical fibers. Multiple overlapping ablations are performed in order to assure complete coverage of the target.

The laser fiber protrudes 5 mm from the needle tip. The pull-back technique consists of pulling back the introducer by 1 cm and performing a second illumination to increase the length of the ablation area.

The laser energy is released in pulsed mode (intermittently in a series of pulses rather than continuously – 0.8 seconds on & 0.4 seconds off), with a power of 15 Watts and is activated for for an average of 2 minutes (100 pulses) per ablation zone.

The laser therapy is performed entirely under US guidance fused with MRI or PSMA PET/CT for the real-time monitoring of the correct positioning of applicators and the extension of the area of damage.

At the end of the procedure, all patients are observed for a minimum period of 2 h.

An oral NSAID as anti-edema therapy is prescribed.

Patients are discharged with antibiotic therapy for 14 days, given pain-relief

drugs if needed.

A copy of the patients' files will be anonymously given to the researcher.

Follow-up with clinical evaluation performed by monthly PSA measurement until it reaches its nadir (fixed value for 2 months) and every 3 months thereafter. Repeat mpMRI is done for assessment of tissue changes as well as residual or recurrent disease after 10 days, then after 3 months, after 6 months then every 6 months thereafter. The IPSS and IIEF-5 questionnaires are submitted at 3, 6, 12 months.

Systematic and target MRI/US fusion-guided prostate biopsies are performed after 12 months or if PSA increases > 2 ng/mL, nadir PSA doubled or new suspicious lesions in mpMRI.

Failed cases are offered a further session of focal therapy if the lesion is still suitable for FLA. Radical therapy is also offered according to patient preference, or in cases of increasing volume or stage of disease or progression to high grade disease.

Treatment success is operationally defined as the absence of contrast-enhancement in MRI examinations conducted during the follow-up period, in conjunction with a negative target biopsy at the conclusion of the 12-month period and evaluation of serum PSA.

4.REFERENCES

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