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MRI Guided Prostate Cancer Focal Laser Ablation

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Title:

Magnetic Resonance Imaging (MRI) Guided Focal Laser interstitial thermal Ablation of Localized Prostate Cancer: A Phase II Clinical trial

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Introduction:

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males in 2008 (1). Recently, there has been a significant rise in diagnosis of prostate cancers with even tendency to diagnosis in younger patients and earlier stage.

Prostate cancer should be viewed as a spectrum of diseases ranging from a very indolent low-risk process to an aggressive high-risk potentially fatal disease. The likelihood that a "true" low-risk prostate cancer progresses to metastatic disease is very slim. Much more likely, a high-risk cancer has been present and undetected from the beginning (2).

The introduction of prostate-specific antigen (PSA) in screening strategy for prostate cancer has led to more tumors to be diagnosed at earlier stages with more indolent course that doesn't pose significant risk if left untreated (3). According to the European randomized study of screening of prostate cancer (ERSPC) trial, almost half of those who had surgery were found to have clinical indolent cancers (4). With the significant complication rates of radical therapies (erectile dysfunction seen in 24-90%, urinary incontinence in 2-72% and rectal toxicity in 2-15% (5-8) This raised concerns about overdiagnosis and subsequently overtreatment affecting patient's quality of life.

Active surveillance has been introduced as an alternative treatment to patients with low- risk prostate cancers. However, the inconsistency in active surveillance strategies across centers, lack of a reliable tool to monitor disease progression and ultimately the associated anxiety of patients regarding their disease raise the demand for a treatment option that is as effective as radical therapy while having a substantially low (if any) adverse effect, preserving patient's quality of life.

Focal therapy techniques have been introduced to fill the gap in prostate cancer treatment paradigm. It aims to destroy the tumor itself with adequate safety margin with the advantage of preserving the surrounding non-cancerous tissue. Thus maintaining disease control at acceptable levels, while minimizing complications (4).

The notion of focal therapy applied to treat a neoplastic process that is notoriously known for its multifocal organ involvement warrants a close understanding of the pathological landscape of prostate cancer. Several studies have highlighted the concept of "index tumor" in prostate cancer where many patients with

"*pathologically multifocal*" disease can be considered to have a "*biologically unifocal*" disease. Those patients are found to have a dominant focal tumor along with a smaller burden of non-dominant tumors that rarely contain higher grade disease than the main tumor and are therefore not considered the denominators for disease progression and are unlikely to affect the treatment outcome. Eliminating that dominant tumor focus with targeted therapy that spares the rest of the gland is therefore hypothesized to markedly reduce tumor burden and eradicate the likely source of extra-capsular tumor extension while potentially reducing morbidity and preserving the sexual, urinary, and bowel function (9-13).

With the advent of multiparameteric MRI (Mp-MRI), it is now possible to identify suspicious prostate gland focal lesions, determining their extent and targeting them for biopsy and focal ablation.

Laser interstitial thermal therapy (LITT) is well suited for MRI environment. Laser fibers are flexible so they can fit into the MRI gantry, with no distortion of the electromagnetic field. (14) It has been shown to produce homogenous tissue necrosis that can be monitored by real time temperature maps, a feature that facilitates effective and safe ablation.(15-17)

Previous preliminary studies and phase I trials with short term follow ups, small patient populations showed the potential efficacy and safety of this technique.(18-23) Oto et al (19) trial using transperineal MRI guidance on 9 patients showed no significant change in quality of life parameters during follow up with short term treatment efficacy about 78 % . A more recent Phase I trial by Natarajan et al (23) using transrectal MRI guidance on 8 patients with intermediate risk disease showed absence of major complications and no changes of quality of life parameters and short term treatment efficacy about 62%. A recent phase II trial by Eggener et al (24) showed similar results on intermediate term follow up (at 1 year) regarding the quality of life parameters, however with recurrent tumors in 37 % of patients either in the ablation zone or outside the ablation zone.

We had 14 cases done at our institution so far as part of our routine clinical practice, Targeted tumors consisted of 11 low risk (Gleason 3+3=6), 6 favorable intermediate risk (Gleason 3+4=7), and 2 unfavorable intermediate risk (Gleason 4+3=7) prostate adenocarcinomas. Treatments required 2-4 ablation cycles/laser fiber positioning and resulted in complete tumor necrosis in a single session in all cases. No immediate or delayed complications were encountered. Follow-up durations ranged between 5.3 and 46.0 months (mean ± SD=19.6 ± 10.4 months). Significant drop of pretreatment PSA level occurred in all cases. One patient had a 10 mm focal recurrence at the edge of the ablation zone at his 24-month follow-up time point and was successfully

re-treated with another cycle of laser ablation. Another patient had new suspicious foci remote from the ablation site at his 28-month follow-up time point and is awaiting biopsy. No recurrence was noted in the other cases.

As previous results are promising, we still need to better optimize this technique by studying more diverse and larger patient populations and by assessing the long-term efficacy and safety profiles.

The goals of this Phase II trial are to evaluate 1) the functional outcomes (safety); and 2) the intermediate and long-term oncologic control (efficacy) following MRI guided focal laser ablation of prostate cancer, in an effort to further optimize the patient selection criteria for this interventional treatment.

Study question:

- What is the safety and efficacy of MRI-guided focal laser ablation of localized prostate cancer?

Study objectives:

- To determine the safety and efficacy of MRI guided focal laser ablation of localized low and intermediate risk prostate cancer.

Material and Methods:

Study type:

- A prospective, single-arm, non-randomized, un-blinded trial.

Site of the study:

- Radiology department, Emory University, Atlanta, Georgia, USA

Study population:

Patients referred to the interventional MRI program at Emory University, Atlanta, Georgia, USA.

Eligibility criteria:

- Inclusion criteria:
  - Age ≥18 years
  - Patients with primary organ confined prostate cancer (≤T2c) and Gleason score ≤4+3=7
    - Lesions visible on multiparameteric MRI and subsequently diagnosed by targeted MRI guided biopsy.
- Exclusion criteria:
  - Multifocal intra-prostatic disease, defined as the presence the presence of ≥ 3 non-contiguous pathologically proven foci of cancer.
  - Gleason score >4+3=7
  - Extracapsular spread.
  - Nodal or distant metastasis
  - Contraindications to MRI or general anesthesia.
  - Uncorrectable Coagulopathy.
  - Refusal of participation.
  - Lesions not visualized on the multiparametric MRI

Recruitment Goal:

A total of 20 subjects will be targeted for recruitment to this study.

Intervention:

- **Equipment used in the study:**
    - For transrectal approach:
        - Siemens MRI scanner, 3 Tesla, 32 channel surface coil is used. No endorectal coil.
        - DynaTRIM needle holder/targeting system for transrectal guidance
    - For Transgluteal approach:
        - Siemens MRI scanner, 1.5 Tesla.
    - A 980 nm diode laser system (Visualase Inc.)

- **Pre-intervention investigations:**

  All patients will be subjected to the following:

  - *Lab tests:*
    - Baseline Serum prostatic specific antigen (PSA).
    - Baseline urine analysis.
    - INR and platelet count.
  - *Imaging:*
    - Multiparametric MRI (mpMRI), including high resolution T2WI, diffusion weighted imaging (DWI), dynamic contrast enhanced (DCE) MRI.
  - *Targeted In-bore MRI guided biopsy for suspicious lesions in mpMRI as well as to apparently normal areas to exclude possibly of occult clinically significant tumors (in subjects with limited visible disease).*
  - *Baseline QOL questionnaires.*

- **Procedure:**

  Patient preparation:

  ✓ *Before coming to the hospital:*

- Oral Antibiotics (Fluoroquinolone) for 7 days, starting one day before procedure.
- Oral Urinary tract analgesic (Phenazopyridine) for 5 days.
- Stop anticoagulants for 5 days before the procedure.
- Fasting for at least 8 hours the night before the procedure.
- Bowel preparation: Fleet enema on the morning of the ablation.

✓ *At the hospital*

- A Foley catheter will be placed to protect the urethra during and following the ablation procedure. This will be removed by the interventional MRI program's nurse after 3 days.

Ablation procedure:

- Patient position: Prone
- Anesthesia: general.
- Laser fiber placement will be performed by one of two approaches based on the target location within the prostate gland:
  - Transgluteal:
    - A 14-gauge MR compatible co-axial puncture needle will be introduced into the target lesion via a transgluteal approach under real-time MR fluoroscopy guidance.
  - Transrectal:
    - The rectal piece of the Dyna-TRIM system will be inserted following lubrication with lidocaine gel.
    - The transrectal piece will then be connected to the rest of the system. Preliminary imaging will be obtained to identify the transrectal fiducial line, the target lesion, and to calculate the trajectory angles in 3 planes.
    - Subsequently, a 14-gauge MR compatible co-axial puncture needle will be introduced into the target lesion via the transrectal approach along the calculated trajectory.

  - When the needle position is deemed satisfactory, a 1.5-cm-active tip diode laser fiber will be introduced within an internally cooled catheter through the introducing sheath.
  - The catheter tip location will be confirmed on TSE T2-weighted images in the axial and sagittal oblique planes.
  - The introducer sheath will be withdrawn to allow contact of the active laser tip with the lesion.

- A laser test dose will be done at 9 Watts for about 30 seconds to confirm the site of fiber placement with the subsequent delivery of full dose ablation at 12-27 Watts.
- Ablation duration is determined based on real time feedback of response using real time temperature and damage estimate maps.

Post procedure:

✓ *At the end of ablation:*

- Post procedure scans will be performed, consisting of axial, sagittal, coronal VIBE scans, before and after IV administration of gadolinium-based MR contrast agent.
- Additionally, axial, sagittal, and coronal high-resolution TSE T2-weighted images will be performed.

✓ *Starting at recovery:*

- Ibuprofen 400 mg oral tablet by mouth, every 6 hours.
- Tamsulosin 0.4 mg oral capsule by mouth, q24 hours.

✓ *After leaving the hospital:*

- Foley's catheter will remain for 3 days- will be removed in the radiology department. Subjects will be evaluated for urine obstruction or leak at that time.

- **Follow ups:**
  - Immediately after the procedure, at 3 weeks, 3 months, 6 months, one year (primary end point) and two years (2ry end point) after procedure.
  - All follow up visits will include mp-MRI, serum PSA, QOL questionnaires.
  - In bore MRI guided biopsy will be done after one and two years for the ablation site and any other suspicious areas discovered in follow up scans. Biopsies outside these time points will be obtained if new MRI suspicious sites are noted on follow up MRIs or if PSA level is trending up.

- **Possible complications:**
  - Urinary tract infection, sepsis

- Hematuria
- Urinary retention
- Erectile dysfunction
- Urinary incontinence
- Fecal incontinence
- Bleeding per rectum
- Recto-ureteral fistula
- Urinary tract obstruction.

- **Outcome:**

Primary endpoint:

- Treatment Efficacy: measured by recurrence rate at 1-year post-ablation (i.e. number of recurrences/number of subjects).

Secondary endpoint:

- Recurrence rate at two-year post ablation time point.

**recurrences are defined as any newly developed mpMRI abnormality contiguous with the ablation zone and proved by subsequent targeted biopsy.

  - Methods of assessment (each follow up visit):
    - Mp-MRI scans with each follow up visit:
      - Ablation zone: assessed for residual tumor.
      - Non-ablated areas: for new tumor(s).
      - MRI guided biopsy for the ablation site after one and two years or if a suspicious lesion developed during follow-ups.
    - Serum PSA.

- Safety and functional outcomes:

- Complications: Grade 3 complications or higher as defined as National cancer institute's common toxicity criteria version 4: *incontinence or urinary retention necessitating surgical intervention or new-onset erectile dysfunction not responsive to medication.*
- *Urinary function* →will be assessed by IPSS at baseline pre-ablation visit and with each follow up visit.
- *Erectile function* → will be assessed by SHIM baseline pre-ablation visit and with each follow up visit.

- Other Procedural complications: Infection, bleeding, hematuria, fistula.

Participant timeline:

**Each follow up time point is calculated from the previous visit, not from procedure date

Recruitment strategy:

- We will rely on either physician referral or self-referral.
- Self-referred subjects will be counseled about standard of care treatment options. For these subjects, the study team will document evaluation by a radiation oncologist for each participant and decline of the recommended modality.
- No financial incentives will be offered.

- Posting basic descriptive information on ClinicalTrials.gov

Informed consent:

- Informed consents will be obtained in person on 1st visit in a private room.
- Subjects will be allowed time to discuss with others before deciding to enroll.
- The study process and details will be discussed verbally with the patients.
- Time will be allowed for questions.
- A hand-out will be provided to the patients with frequently asked questions.

Data collection & management:

- All patients' data will be documented in the electronic medical records (powerchart) through the standard clinical process.
- All treatment-related hard copy documents will be scanned into the electronic medical records (powerchart).
- Measurements on imaging will be done by the PI.
- Data to be collected will include:
    - Preprocedure:
        - Clinical data:
            - Demographic: Age, Ethnicity
            - Past medical history
            - Baseline erectile function (SHIM)
            - Baseline urinary continence (IPSS)
        - Lab: baseline PSA + previous PSA trends
        - Previous prostate pathology reports
        - Imaging/Targeted biopsy:
            - Lesions number, size, shape, location, signal characteristics.
            - Targeted biopsy results (lesions Gleason score, cancer core length%, percentage of different Gleason patterns if applicable, number of cores).
            - Prostate volume
    - Procedure data:
        - Number of lesions ablated
        - Ablation sessions: Number, Duration, energy deposited.
        - Approach used: Transgluteal, Transrectal.
        - MRI equipment used (1.5 vs 3 Tesla)
        - Whole Procedure duration
        - Immediate complications (if any)
        - Immediate post ablation imaging findings: ablation zone size, prostate volume size, ablation zone signal characteristics.
    - Post ablation data:
        - Each follow up:

- Imaging:
    - Ablation zone: Volume, shape, signal characteristics.
- Biopsy (if applicable).
- Serum PSA
- Erectile function (SHIM), urinary symptoms (IPSS). Urinary continence.

Plans for participant retention to study follow ups:

- Contacts:
    - Obtain different ways of contact information to the participants (different phone numbers, email, mailing address) to facilitate future communications with them.
- Sharing:
    - Participants shall feel how important this study for them and for future patients, this can be achieved by actively involving them in the study process by:
        - Discussing the importance and impact of the study.
        - Explaining clearly the need for commitment to the long term follow up plan.
        - Sharing updated study data as they are analyzed.
        - Discussing all of their concerns and if applicable ask them for comments and recommendations.

- Convenience:
    - Flexible appointment scheduling.
    - Availability of different contact information of study staff for the patients.

Statistical analysis plan:

The primary endpoint is the recurrence rate at 1 year, defined as the number of recurrences divided by the number of patients. For this study, Simon's two-stage design will be utilized, using the Minimax design. (25, 26) The null hypothesis that the true recurrence rate is 0.49 will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 6 or more recurrences in these 18 patients, the study will be stopped. Otherwise, 2 additional patients will be accrued for a total of 20. The null hypothesis will be rejected if 6 or fewer recurrences are observed in 20 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true recurrence rate = 0.22.

Recurrence rate at 1 year, as well as at follow-up visits at 3 weeks, 3 months, 6 months, and 2 years will be estimated, and exact 95% confidence intervals will be estimated using the Clopper-Pearson method (27). Number of complications and rate of complications will be summarized using frequencies and percentages. Additionally, all numeric patient characteristics will be summarized using mean, standard deviation, median,

and range, and all remaining categorical patient characteristics will be summarized using frequencies and percentages. No loss to follow-up is expected.

Erectile function and urinary function will be summarized at baseline and at each follow-up visit using Quality of Life (QoL) assessments – SHIM for erectile function and IPSS for urinary function. Scores will be aggregated across questions, and grouped into ordinal categories. For each QoL measurement, frequencies and proportions of each ordinal category will be reported at baseline and at each follow-up visit. To assess the measurements longitudinally, we will consider an ordinal logistic regression model using a generalized estimating equations (GEE) approach for handling correlation within patients in order to evaluate the impact of time on erectile and urinary function.

Stopping rules for safety are detailed in the DSMP section below.

Data and safety monitoring plan (DSMP):

The PI will ensure that the protocol is conducted in a consistent manner and that all PHI from the study obtained is handled in a HIPAA compliant manner.

1. Monitoring the Progress and Safety of the Trial

a. What are the potential risks and benefits for study participants?

Risks:

- Urinary tract infection, sepsis
- Hematuria
- Urinary retention
- Erectile dysfunction
- Urinary incontinence
- Fecal incontinence
- Bleeding per rectum
- Recto-ureteral fistula
- Urinary tract obstruction.
-

The benefit to the patient is receiving a standard treatment protocol with the possibility of extra imaging which may enhance the diagnostic ability of the physician. Subject participation may help future patients having this same procedure.

b. What is the screening process and how it will be used to protect participants?

MRI scans will be conducted only on patients who require a clinically indicated MRI as determined by a urologist and/or a radiologist, who have no additional contraindications to MRI, and who do not meet other exclusion criteria for MRI. When the patient arrives for MRI (or if seen earlier at the interventional MRI clinic as a part of pre-procedure evaluation), he will undergo routine screening to ensure the absence of any incompatible implants or devices, screening and consent for intravenous contrast (if clinically indicated) making sure there are no contraindications to contrast if contrast is indicated.

c. What are the measures to protect participants against risk?

Patients will be initially counseled about the current standard of care treatments available and that the study procedure is experimental. The study team will document evaluation by a radiation oncologist for each self-referred participant and decline of the recommended modality.

Proper identification of cancerous lesion(s) will be performed with pre-treatment multiparametric MRI to assess the technical appropriateness of MRI guided focal laser ablation. Prior to starting the ablation procedure, normal saline may be infused into the recto-prostatic space (hydro-dissection) to protect the rectum from injury during ablation if that process is deemed necessary on pre-procedure imaging. Subjects undergoing the treatment procedures will benefit from real-time monitoring with temperature maps and damage estimate maps performed online as the ablation procedure is being conducted. Additionally, an immediate post-procedure new baseline MRI of the prostate will be performed before the subjects leaves the MRI unit. This will also be used to evaluate for and manage any immediate complications.

Procedures will be performed on an out-patient same-day surgery basis. Subjects will recover in the standard recovery area and discharged on the same day unless a complication occurs.

In addition to the screening processes described above, the patients will be monitored all the time by a trained anesthesiologist as the procedures will be done under general anesthesia. The Unit Emergency Cart is immediately available to the MRI suite for the entirety of the MRI examination. The MRI technologist as well as the anesthesiologist will maintain visual observation of the patient throughout the procedure.

d. Who will monitor the trial, what type of information will be reviewed, what are the parameters for defining abnormal values and what is the periodicity of review?

External monitoring:

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Internal monitoring:

The PI for the study, Dr. Sherif Nour in the Department of Radiology and Imaging Sciences will ultimately be responsible for monitoring the trial. The study coordinator will ensure that all protocol elements are implemented as proposed. This will be in conjunction with other members of the study team and various co-investigators. An internal monitoring committee of the study team will meet every 3 months to review quality and safety data related to the trial. The information that would be reviewed are number of UPs (defined below in #2), the type of UP, a review of the response to the UP and its effect on patient outcome, and an analysis of what could have been done to prevent the UP.

e. What are the stopping rules for the study?

The stopping rule will be: Three or more Grade 1 or Grade 2 UPs, or greater than two Grade 3 UPs in one 3-month period.

In case of testing a new MRI pulse sequence during these procedures, we will observe for any unexpected hazards related to noise effect or skin heating.

f. What procedures are in place for multicenter trials, if applicable?

N/A. This is a single center trial.

g. How will conflict of interest, or the perception of a conflict, be managed?

The study team, including individuals obtaining consent from the patient to participate in the study, have no financial or other interest in whether or not the patient participates. MRI's will be conducted only on patients who require a clinically indicated MRI, who have no additional contraindications to MRI, and who do not meet other exclusion criteria as outlined above.

2. Reporting of Unanticipated Problems (UPs)

a. What constitutes a UP (include a definition, grading scale, and "study relatedness" criteria)?

UP: A problem not expected to be encountered during the course of the typical clinical policy and protocol used for performing MRIs in patients having an interventional procedure.

Grade 1: Auditory disturbances or skin erythema related to testing new pulse sequences.

Grade 2: Skin burn or a significant change in vital signs requiring the interventional procedure to be aborted, when these changes are related to testing new pulse sequences.

Grade 3: Patient death

UPs not specifically related to the study (MRI is performed in these patients for a clinically indicated reason and in accordance with a standard clinical protocol), will not be reported to the IRB but will rather be reported through the regular clinical pathways.

b. What is the process for assuring that UPs are reported appropriately?

All UPs (grade 2 and 3) will be reported directly to the study PI and logged at the MRI console by the MRI technologist. The study PI will be responsible for reporting UPs to the IRB.

c. What are the timelines for UP collection and reporting?

UPs will be collected as they occur, and promptly reported to the IRB, as appropriate.

3. Reporting of Suspensions or Terminations

a. Which actions (FDA, Sponsor, IRB, etc.) will be reported and who insures these actions are reported appropriately?

All Grade 2 and 3 UPs will be reported to the IRB. The study PI will insure these are reported appropriately. There are no sponsors of this study.

4. Assuring Data Accuracy and Protocol Compliance

a. How are data accuracy and protocol compliance assured?

Data on UPs will be cross-referenced with clinical notes in the electronic medical record. Protocol compliance will be assured by use of a standardized clinical protocol for all patients, as summarized in the IRB study protocol.

b. What are the procedures to assure protocol adherence (i.e., protocol compliance checks, external data-audits, regular data verification, etc.)?

Protocol adherence will be assured by use of a standardized clinical protocol for all patients having an interventional procedure in MR, as summarized in the IRB study protocol. The designated study coordinator shall maintain a log book for protocol compliance checks on each study participant. An internal monitoring committee of the study team will meet every 3 months to assure protocol adherence.

c. How are protocol deviations reported?

Protocol deviations will be reported to the PI, who will report them to the IRB.

d. How is noncompliance reported?

Noncompliance with the protocol will be reported to the PI, who will report them to the IRB.

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