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Title: MR Image Guided Focal Therapy in Prostate Cancer

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Investigator Roles:

A. Obtain information by intervening or interacting with living individuals for research purposes
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C. Obtaining the voluntary informed consent of individuals to be subjects
D. Makes decisions about subject eligibility
E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
G. Some/all research activities performed outside NIH

Commercial Device: Visualase Thermal Therapy System (Medtronic)

Identifying words: toxicity, thermal ablation, localized prostate cancer, thermal damage, Visualase, PSA levels

PRÉCIS

Background:

- Pilot study is designed to evaluate the safety and feasibility of thermal laser ablation of focal prostate tumors.
- Prostate cancer is relatively slow growing, with doubling times for local tumors estimated at 2 to 4 years.
- Some prostate cancers prove to be small, low grade, and noninvasive and they appear to pose little risk to the life or health of the host. Recent patient series suggest that 20% to 30% of men undergoing radical prostatectomy have pathologic features in the radical prostatectomy specimen consistent with an insignificant or "indolent" cancer which poses little threat to life or health.
- We propose that patients with low volume and low grade disease can be best served with focal ablation of the visible prostate cancer without the side effects of urinary incontinence and erectile dysfunction associated with radiation therapy or radical surgery.

Primary Objective:

- To determine feasibility and safety of magnetic resonance image-guided focal laser ablation of biopsy confirmed and MR visible prostate cancer.

Eligibility:

- Greater than 18 years of age
- Organ confined prostate cancer, observed on MR, and confirmed by Transrectal biopsy
- Preoperative workup as dictated by the NCCN.org prostate cancer guidelines
- PSA < 15 ng or PSA density < 0.15 ng/ml in patients with a PSA > 15 ng

***Design*:**

- Pilot study, testing feasibility, safety and tolerability of thermal ablation of focal prostate cancer
- It is anticipated that 15 patients will be accrued for this study

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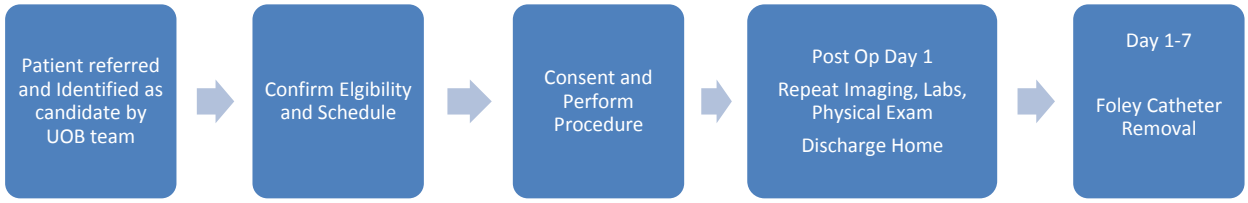
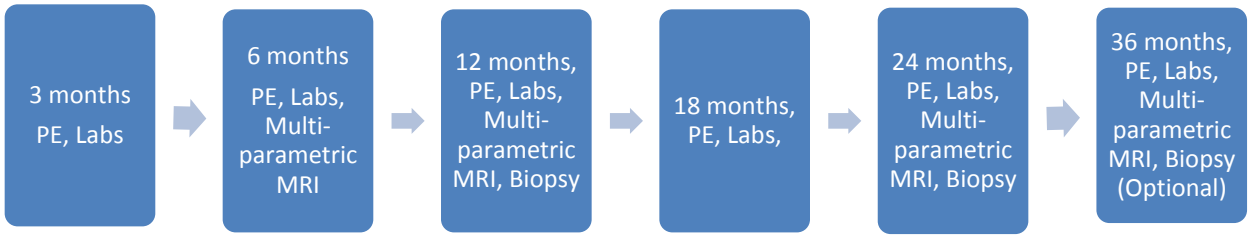


Follow up Schema



1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective(s)

- To determine feasibility and safety of magnetic resonance image-guided laser induced thermal therapy of biopsy confirmed and MR visible, prostate tumor(s) using the Visualase Thermal Therapy System.

1.1.2 Secondary Objective(s):

- To evaluate tolerability of treatment
- To determine changes in imaging and biopsy characteristics after thermal ablation of localized prostate cancer
- To obtain preliminary data, as a follow-up to this study, regarding the effect of thermal ablation using Visualase on short and long term complication rates
- To compare Visualase estimates of thermal damage post contrast MRI images.
- Determine outcome of laser ablation for treatment of prostate cancer using serial PSA, PSA density, changes in imaging, IPSS, and SHIM.

1.2 BACKGROUND AND RATIONALE:

Prostate cancer is currently the most commonly diagnosed non-cutaneous cancer of men in the United States. The American Cancer Society currently estimates that 218,000 new cases were diagnosed last year and that approximately 27,000 deaths were a result of this disease.[1] The advent of more sensitive PSA (prostate specific antigen) testing and advancements in ultrasound and MRI imaging, the ability to detect early prostate cancer has increased dramatically over past decade, however, our ability to treat earlier disease is still limited.

Screening with prostate specific antigen has been associated with a significant risk of over diagnosis in detection of prostate cancer that will not become clinically significant in a given patient's lifetime. A study by Andriole et al in 2009 found that death from prostate cancer did not significantly differ in patients who received routine PSA screening versus patients who did not receive routine PSA screening. This study has led researchers to question the relevance of PSA screening. Conversely, in other studies conducted in Europe by Schroder et al it was found that PSA based screening reduced the rate of death from prostate cancer by 20%. They also reported that they believed that there is a high rate of over diagnosis.[2,3]

Patients may choose between expectant management with active surveillance or aggressive whole gland treatment which may have significant morbidities. Many patients have indolent prostate cancer that may never foreshorten their lifespan and therefore whole gland treatment may "over-treat" these patients. Unfortunately, currently there is no reliable method to identify clinically insignificant prostate cancer so many patients are forced to choose whole gland therapy. Therefore, there is a need to investigate focally directed minimally invasive treatment for prostate cancer.

Active surveillance of prostate cancer with selective, curative, intervention has developed as an option for the treatment of clinically localized, low volume prostate cancer to help separate

those patients who are diagnosed with indolent disease versus those with clinically significant disease. Active surveillance patients are usually diagnosed secondary to PSA screening at earlier stages with low levels of disease. Population epidemiology demonstrates that the majority of these patients will not develop clinically significant disease within their lifetimes.[4] These individuals are then followed with routine PSA screening, DRE, and biopsy to monitor for progression of disease which may warrant delayed selective curative therapy such as surgery and/or irradiation in the event of progression. Patients with less aggressive disease remain on a monitoring protocol until their disease clinically progresses. Surveillance tools are essential for the identification of disease progression. We have used the criteria set forth by authors to select these patients for our trial.[5,6] Klotz and colleagues selected patients with PSA < 15 and Gleason Score 3+4 or less, these patients were followed and intervention was determined if PSA doubling time was less than three years or an increase in Gleason score on biopsy , while being followed. Core length was not employed in our algorithm due to the fact that MR image guided biopsies have statistically significantly longer core length than traditional standard 12 core biopsies. Long term biopsy follow up protocol was a repeat at 1 year then biopsies at 3-4 year intervals.

Recent advancements in computer guidance and electromagnetic field generators have led to the development of next generation MR Image guide biopsy systems. These systems have been shown to have improved outcomes in targeting isolated prostate cancers for biopsy.[7] As a result, several minimally invasive thermal ablation methods, most prominently cryotherapy[8,9] and high-intensity focused ultrasound (HIFU) 9, [10] have been developed and are currently being evaluated. Laser-induced interstitial thermal therapy (LITT) is a novel form of controlled, targeted thermal ablation that offers imaging and targeting of prostate tissue superior to that of either cryotherapy or HIFU. Improvements in the design of medical laser systems used for thermal coagulation of tissue, which include the development of water-cooled applicators to facilitate higher powers capable of rapidly creating larger ablation zones without tissue charring and the development of high-power diode laser sources, have made modern systems smaller, more portable, more powerful, and less expensive than previous generations of medical laser systems.

Because LITT is magnetic resonance (MR) compatible, it confers an imaging advantage over other surgical or ablation techniques that utilize trans-rectal ultrasound to target and monitor treatment.[11] MR imaging provides excellent soft-tissue contrast and three-dimensional (3D) anatomical imaging in any arbitrary plane, which can help to improve treatment planning and targeting.[12, 13] Additionally, MR-based temperature monitoring allows real-time feedback during MRI-guided thermal therapy[14] and, in the case of thermal therapy, and post-treatment imaging can be used to verify treatment delivery.[15] Because MR images clearly depict the prostate anatomy and the surrounding critical structures, MR imaging has been incorporated into planning for external-beam radiotherapy and brachytherapy of the prostate.[14] In addition to these basic features, recently developed/emerging MR technologies, such as MR spectroscopy, MR diffusion imaging, and dynamic contrast-enhanced MR imaging, are promising technologies that may be used to identify regions of disease in the prostate and better target therapy, particularly as high-field scanners (3.0T) become available.[12,13] Clearly, there is a potential role for MR-guided ablation technology in the prostate.

Our in house unpublished data with Choyke and colleagues reported on the correlation of multi-parametric MR with whole mount pathology. Positive predictive value of T2W MRI, ADC maps of DW MRI, MRS, DCE MRI were 0.7, 0.73, 0.93, 0.86, respectively in the overall

prostate gland. The sensitivities of MRI sequences were significantly higher for tumors that were >5mm in diameter as compared with those ≤5mm, as well as for tumors with higher Gleason scores (>7) ($p<0.05$ for all pair wise comparisons). Multi-parametric analysis reveals that multiple MRI sequences provided significantly higher predictive value (all four modalities positive PPV~98% and NPV of 98%) than each single MRI sequence and some doublet MRI sequences ($p<0.01$).

In this study, we propose to evaluate a novel, thermal therapy and feedback system (Visualase® Thermal Therapy System) for the treatment of biopsy confirmed and MR image-able prostate cancer lesions. This system includes the FDA-cleared Visualase Cooled Laser Applicator System (VCLAS), which allows delivery of laser energy while the patient is being imaged by an MRI unit. The Visualase® System works via real-time MR thermal imaging (MRTI) to provide information on the thermal dose delivered to the target, resulting in a more precise and controlled delivery which has heretofore not been possible with previous non-image guided laser technology. We hypothesize that the Visualase system can be integrated into a practical and feasible treatment paradigm for focal prostate cancer therapy.

1.2.1 Devices Used for MRI-guided LITT

Visualase, Inc. currently markets all of the FDA 510(k) cleared medical devices which will be used in these studies. These devices are currently manufactured by the original developer of the technology, BioTex, Inc., Visualase, Inc. The Center for Interventional Oncology / National Institutes of Health owns the device. Each device is listed below:

- Visualase Cooled Laser Application System
- PhoTex 15 Diode Laser Series 980,810,940
- Visualase ENVISION Workstation
- Visualase Thermal Therapy System (combination of three FDA-cleared devices)

Each of the 510(k) cleared devices will be used according to its intended use and indicated statement. The devices will be used for magnetic resonance thermal imaging-guided laser induced thermal therapy in soft tissue prostate lesions.

Visualase Cooled Laser Applicator System (VCLAS) (Cleared for marketing under FDA 510(k): K053087)

The Visualase Cooled Laser Application System (VCLAS) family consists of three (3) components, the Laser Diffusing Fiber (LDF), Cooling Catheter System (CCS) (Figure 1), and Bare Tip Fiber (BTF). The LDF and BTF transmit laser energy to the tissue situated at their distal regions. The LDF comprises a standard silica fiber optic cable affixed with a diffusing tip assembly. The diffusing tip assembly comprises a plastic tube that is filled with a transparent matrix in which light dispersing particles are embedded. The distal end of the tube is sealed with a higher concentration of scattering particles in a conical structure to prevent significant forward transmission of energy. The LDF may be used with a cooling catheter, in particular the compatible CCS but such a catheter is not required. The CCS can be employed with or with or without coolant flow. The use of coolant flow provides cooling for the surfaces of the CCS in contact with both the tissue and the LDF. The BTF is comprised of a standard silica fiber optic

cable identical to fiber optic used in the LDF. The distal end of the BTF is terminated in a flat, polished face and is designed for use in both contact and non-contact applications. The LDF and CCS are indicated for use to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy in medicine and surgery in cardiovascular thoracic surgery (excluding the heart and the vessels of the pericardial sac), dermatology, ear-nose-throat surgery, gastroenterology, general surgery, gynecology, head and neck surgery, neurosurgery, plastic surgery, pulmonology, radiology, and urology. The BTF is intended for use in vaporization, cutting, ablation and coagulation of soft tissues with or without scopes or hand pieces, for contact or non-contact surgery in cardiovascular thoracic surgery, dermatology, ear-nose-throat surgery, gastroenterology, general surgery, gynecology, head and neck surgery, neurosurgery, plastic surgery, pulmonology, radiology, and urology.

1.2.2 PhoTex 15 Diode Laser Series (Cleared for marketing under FDA 510(k): K060304)

The PhoTex$_{15}$ Diode Laser Series (Figure 2) are diode lasers emitting radiation in either a continuous-wave or pulsed-mode in the infrared range at one of the following wavelengths: 980nm, 810nm, and 940nm. The PhoTex$_{15}$ Diode Laser Series provides a means for cutting, coagulation, and vaporization of tissue using a compatible fiber optic delivery accessory. The laser is compatible with any fiber optic delivery accessory terminated with a standard SMA905 connector whose core fiber diameter is 400 micron or larger with a numerical aperture of at least .37. The PhoTex$_{15}$ Diode Laser Series is indicated for use in surgical applications requiring the ablation, vaporization, excision, incision, and coagulation of soft tissue in areas of surgery including: gastroenterology, general surgery, plastic surgery, genitourinary, gynecology, neurosurgery, otolaryngology, head and neck, orthopedics, ophthalmology, pulmonology, and thoracic surgery.

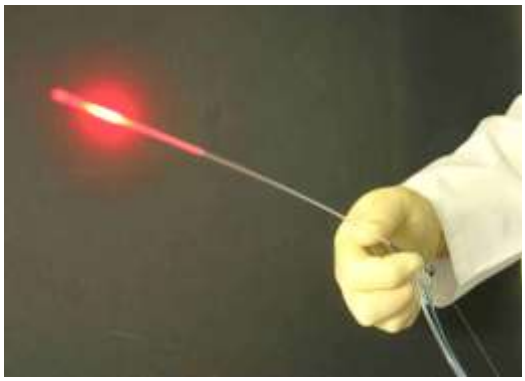


Figure 1: (Above Left) Visualase Cooled Laser Applicator System. Includes 1.65mm Cooling Catheter and Diffusing Tip Laser Fiber.
Figure 2: (Above Right) PhoTex15 Laser. 15W, 980nm Fiber Coupled Diode Laser.

1.2.3 The Visualase® ENVISION Software (Cleared for marketing under FDA 510(k): K063505)

The Visualase® ENVISION platform (Figure 3) consists of a PC-based Linux workstation running the ENVISION software tools in an X-windows environment. The device uses a standard Ethernet connection to retrieve image data files from a compatible MRI scanner host. The images may be retrieved as soon as they have been stored on the MRI host, facilitating near real-time analysis of dynamic MRI data. The Visualase ENVISION software tools perform the following three (3) functions:

- Image Transport
- Image Processing
- Data Display

Figure 3*:* Visualase® ENVISION Software User Interface. Real-time thermal (left) and damage (middle) images are displayed with a high-resolution pre-therapy planning image (right). Targets and limit temperatures are set by "clicking" on any image. Users can see temperature at any point, make measurements, and control most other system functionality through this interface.

The image transport tools negotiate communication with the MRI scanner host, determine the availability of images, facilitate retrieval of image files, facilitate local storage of image files, and notify Image processing tools of new data. The Image processing tools extract relevant data from available MR images and update data analysis information. The Data display tools on the Envision user interface (Figure 4) provide visualization and facilitate manipulation of the data extracted by the Image processing tools. Data may be processed to display dynamic changes in voxel intensity as a function of image acquisition. Such analysis is useful in analyzing the uptake and washout of MR contrast agents and can be useful for discrimination of tissue type or state. When data from compatible sequences is available, images may also be processed to extract the complex phase angle of voxels as a function of image acquisition. Using proton resonance frequency (PRF) shift analysis and image subtraction, changes in complex phase angle may be related back to relative changes in temperature during the study. The Visualase ENVISION workstation is intended to retrieve, store, process, and display temporally dynamic magnetic resonance (MR) data from compatible scanners. The software is capable of analyzing either temporal changes in image intensity as is useful in, for example, dynamic contrast enhancement studies, or temporal changes in complex phase image data as is useful in, for example, phase contrast angiography or in determinations of dynamic phase changes related to temperature changes in soft tissues. The image data may be manipulated and viewed in a number of different ways and the value of data at certain selected points may be monitored and or displayed over time. When interpreted by a trained physician, this device provides information that may be useful in the determination or assessment of a diagnosis, intervention, or course of treatment.

1.2.4 The Visualase® Thermal Therapy System (Cleared for marketing under FDA 510(k): K071328 and K081656)

The Visualase Thermal Therapy System (Figure 4) is indicated for use to necrotize or coagulate soft tissue through interstitial irradiation or thermal therapy under magnetic resonance imaging (MRI) guidance in medicine and surgery in cardiovascular thoracic surgery (excluding the heart and the vessels in the pericardial sac), dermatology, ear-nose-throat surgery, gastroenterology, general surgery, gynecology, head and neck surgery, neurosurgery, plastic surgery, orthopedics, pulmonology, radiology, and urology, for wavelengths 800nm through 1064nm.

When therapy is performed under MRI guidance, and when data from compatible MRI sequences is available, the Visualase system can process images to determine relative changes in tissue temperature during therapy. The image data may be manipulated and viewed in a number of different ways, and the values of data at certain selected points may be monitored and/or displayed over time. When interpreted by a trained physician, this device provides information that may be useful in the determination or assessment of thermal therapy. Patient management decisions should not be made solely on the basis of Visualase analysis.

The Visualase Thermal Therapy System is in effect a combination of the first three devices described and is used for performing Laser Induced Thermal Therapy to destroy malignant or unwanted tissue by delivering laser energy sufficient to cause coagulation and necrosis of the tissue. The Visualase Thermal Therapy System will be used in this study according to indications previously cleared for marketing by the FDA. An MRI technique called Magnetic Resonance Temperature Imaging is used to collect temperature-sensitive parameters throughout the imaged volume. During tumor ablation, MRTI data will be collected and analyzed to display real-time tissue temperatures and an estimate of thermal ablation zone size. Immediately after completion of therapy, MRI (including dynamic contrast T1, T2, and diffusion-weighted imaging) will be used to confirm the achieved thermal ablation zone size.

Figure 4: Visualase® Thermal Therapy System. The Visualase Thermal Therapy system is a combination of the VCLAS applicator, the PhoTex15 Laser, the Envision Workstation and a FDA cleared perfusion pump. The Visualase Thermal Therapy system has been cleared for marketing by the U.S. FDA.

1.2.5 IDE Exempt Study

We have identified this investigation as IDE exempt under 21 CFR Part 812.2(c). All devices used on the study are FDA approved/cleared, are being used as indicated and were not regulated as devices before the enactment of the Medical Device Amendments.

1.2.5.1 Preliminary Human Studies of Visualase Therapy in the Prostate

Four patients underwent MRI guided laser ablation of the prostate using the Visualase system under a treat and resect protocol at the University of Toronto. No patients experienced complications from the ablation or post ablation prostatectomy. A personal communication with the lead investigator: to ask the question regarding difficulty of post ablation prostatectomy, he reports that the ablation did not increase the difficulty or complication associated with performing a post focal ablation prostatectomy. Comparing the MRI predicted ablation zone with whole mount histopathology showed a direct correlation.[16]

1.2.5.2 Preliminary Animal Studies of Visualase Therapy in the Prostate

In seven adult canines, a total of 11 ablations, 9 in normal tissue sites and 2 in tumor sites (immuno suppressed tumor model), were performed under MR guidance. Imaging was performed on a clinical 1.5-T MR scanner (Excite HD, GE Healthcare, Waukesha, WI). Applicators were surgically inserted into the prostate of the 2 tumor-inoculated dogs via a laparotomy procedure. In the remaining 5 dogs, an MR-compatible perineal template grid with MR-visible markers was used to facilitate a transperineal approach (Figure 5).

For treatment planning, the Visualase software was used to read the images from the MRI scanner and to select critical temperature control points. A high temperature control point (90ºC-95 ºC threshold) was placed near the applicator-tissue interface to minimize the possibility of deleterious high-temperature effects (char formation, vaporization, and cavitation), which would limit the size of the ablation zone created and could possibly damage the applicator. If the temperature exceeded this preset limit temperature of 90ºC during treatment, the laser was shut off, the tissue allowed to cool, and then treatment resumed until the full lesion was generated. Low temperature control points (45ºC-50ºC threshold) were set near critical structures, such as the urethra, in order to avoid damage to these tissues. Laser exposure times and power levels were controlled using the workstation interface during treatment delivery.

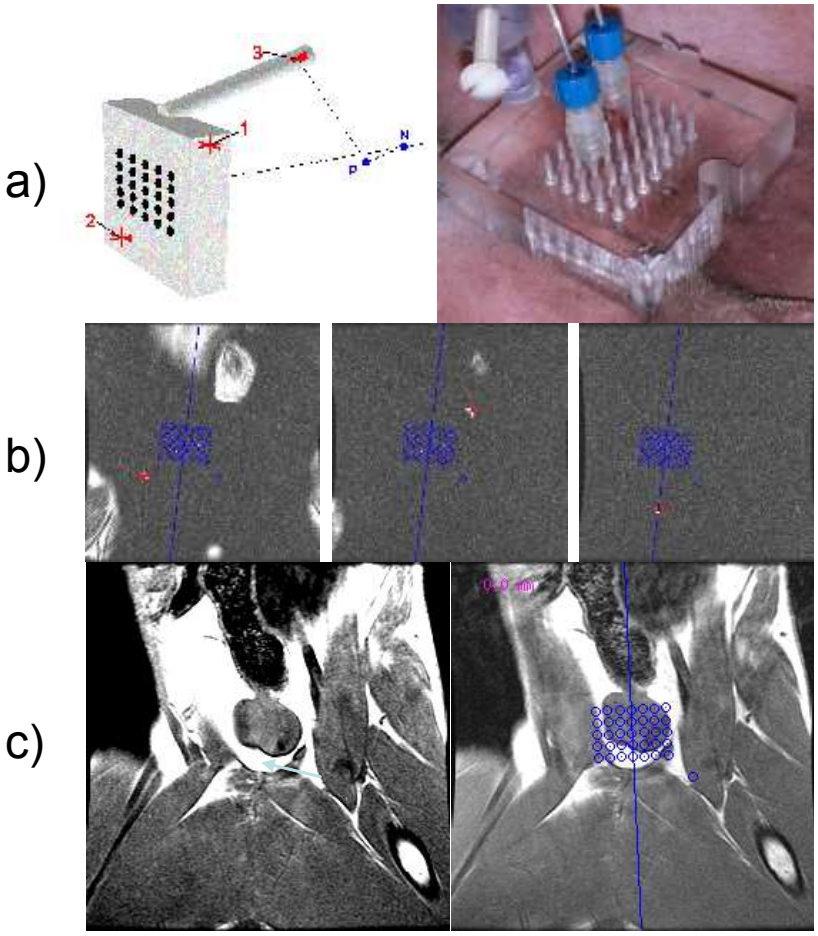


Figure 5. Planning of applicator placement with template guidance. *a)* Diagram of the perineal template demonstrating the location of the 3 MR-visible markers for registration (left) and the actual template on the perineum with 2 laser applicators placed in the prostate (right). *b)* Appearance of the 3 MR-visible markers on 3D T1-weighted images. *c)* An image of the prostate with (right) and without (left) the template grid overlay.

During treatment, temperature changes were monitored in real time using the temperature-dependent proton resonance frequency shift technique and acquired phase-sensitive images every 5 seconds using a gradient recalled echo pulse sequence. Tissue damage estimates from the Visualase software are superimposed on the magnitude MR anatomical images and displayed in real time to aid in treatment decision-making.

Fixed prostate specimens were sliced along planes that were nearly congruent with the treatment plan for histopathologic analysis where a trained veterinary pathologist independently identified the borders of thermal necrosis for all ablation zones.

The mean width was 13.7 mm ± 1.3 mm (range 11.4–15.5 mm) and the mean length was 19.0 mm ± 4.2 mm (range 12.4–26.7 mm) using single and compound exposures with power levels ranging from 4W to 14 W and maximum single exposures of up to 240 seconds (Table 1). The average exposure time per site was 158 seconds, and the average energy delivered was 995 J.

Using the workstation software for monitoring, maximum tissue temperatures were maintained below 90ºC. Temperatures at the margins of the ablated zone ranged between 54ºC and 60ºC. Temperature maps were converted to thermal dose via the Arrhenius relation and displayed in real time (Figure 6). Measurements of the area of Arrhenius-estimated tissue damage were correlated with the outer rim of enhancement on 3D T1-weighted post-contrast images in the same plane to determine the degree of agreement. An excellent correlation between these measurements was observed (Pearson's R2 = 0.94, Figure 7). As desired, the slope of the regression line was close to unity (m = 0.96) and the intercept (b = 8.44 mm2) was small relative to the smallest ablation zone measured (115 mm2). The mean percentage error in the Arrhenius measurement versus the T1 measurement was -0.28% ± 7.6%, with an absolute error of 5.5% ± 4.9%.

Table 1. Summary of MR-guided LITT exposure times and size of ablation zones generated in a cTVT canine prostate model

Subject	Lobe	Site†	Length (mm)	Width (mm)	Power (W)	Time (sec)	Tot. time (sec)	Energy (J)
1	R	A	12.4	13.8	(4, 4)‡	(114, 121)	235	940
1	L*	A B	21.2	13.4	(4, 4) 6	(182, 121) 59	362	1562
2	R*	A B C	26.7	12.9	(4, 6) (6, 6) (4, 4)	(121, 72) (39, 66) (106, 120)	524	2450
3	R	A	23.2	14.6	14.3	40	40	572
4	R	A	17.7	12.5	12	63	63	756
4	L	A	17.5	11.4	(12, 11.3, 6, 6)	(37, 37, 243, 190)	507	3460
5	R	A B	22.8	15.4	12.8 6.4	29 202	231	1664
5	L	A	19.1	14.9	6.4	71	71	462
6	R	A	16.5	15.5	(6, 12)	(32, 104)	136	1440
6	L	A	13.2	12.2	(6, 12)	(33, 74)	107	1086
7	R	A	19.2	14.0	6	90	90	540

*Exposures made in cTVT tissue.
†Different sites treated by pulling fiber back in applicator.
‡In cases where multiple exposures were performed to generate a larger/longer ablation zone, the power and exposure time are expressed as (Exposure 1, Exposure 2, …).

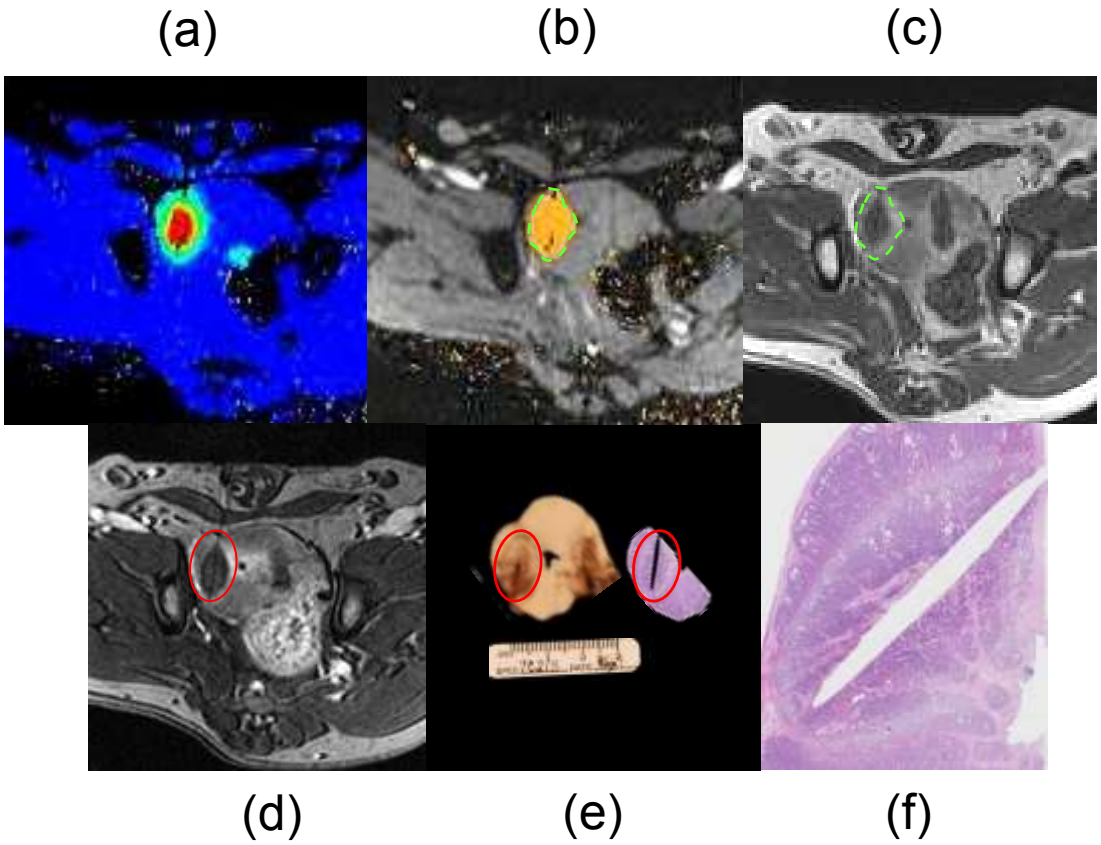


Figure 6. MR-guided LITT in a canine prostate model. MR temperature imaging from the Visualase workstation displays the temperature changes in the prostate in real time (a), are used to estimate and display the TNZ (b), which correlated well with the outer edge of the ring of edema seen surrounding a non-perfused region of tissue on post-treatment (less than 20 minutes) 3D T1-weighted contrast-enhanced images (c). Dotted green lines show the edges of estimated tissue damage projected onto both images (b and c) for visual correlation. The images from (c) were reformatted (d) to better match the actual slices taken from photographic pathology and H&E histology, where the ablation zone is contained inside the red reference line (e). The histological damage demonstrated the classic presentation of thermal necrosis as described in the text, with a very narrow region of transition between normal and necrotic cells (f). Despite slight through-plane refraction and approximated slice orientations, excellent agreement was generally seen.

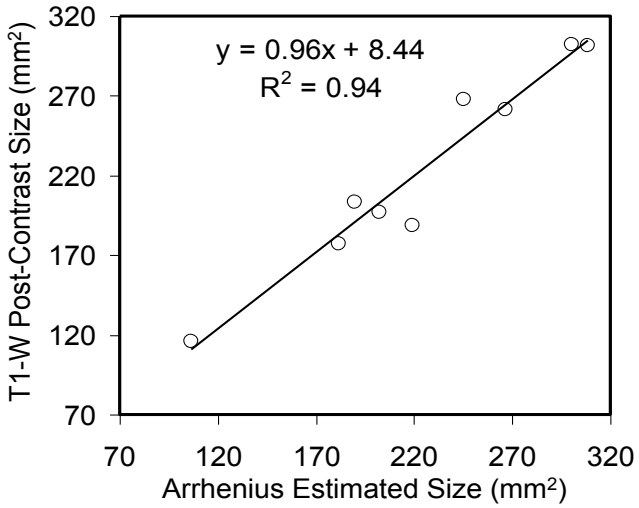


Figure 7. Three-dimensional T1-weighted post-contrast measurements of LITT-induced ablation size (measured from the outer edge of edema) versus the Arrhenius-estimated tissue damage based on MR demonstrated excellent correlation. Linear least-squares regression indicates a slope near unity and a bias much smaller than the area of the smallest ablation zone measured.

1.3 LASER SAFETY:

The NIH approved laser safety protocol will be used in reference to the Visualase laser. Persons using the laser will be trained on safety, as well as use. There are no exposed beams, the door will be placarded, and goggles will be available. Please see accompanying documents for Laser Safety at the NIH.

Point of Contact of Laser Safety:
Arvin George, M.D., NCI/UOB

1.4 PREVIOUS CLINICAL EXPERIENCE: MR-GUIDED LITT USING VISUALASE®

The majority of the clinical experience with Visualase has been in brain tumor applications. To date over 40 treatments have been performed clinically without any procedural complications or notable adverse events. Additionally the system has been used clinically for treatments in bone (n=5), liver (n=8), thyroid (n=2) and prostatic bed for local recurrence (n=1). Figure 8 below shows images from a patient that was treated for a local recurrence in the prostatic bed after prostatectomy. A urethral cooling catheter was placed and chilled water was circulated during therapy. Two applicators were placed into the tumor using the MR-compatible trans-perineal guide template and planning software. The procedure was completed without complication and the patient's Foley catheter was removed after 1 day.

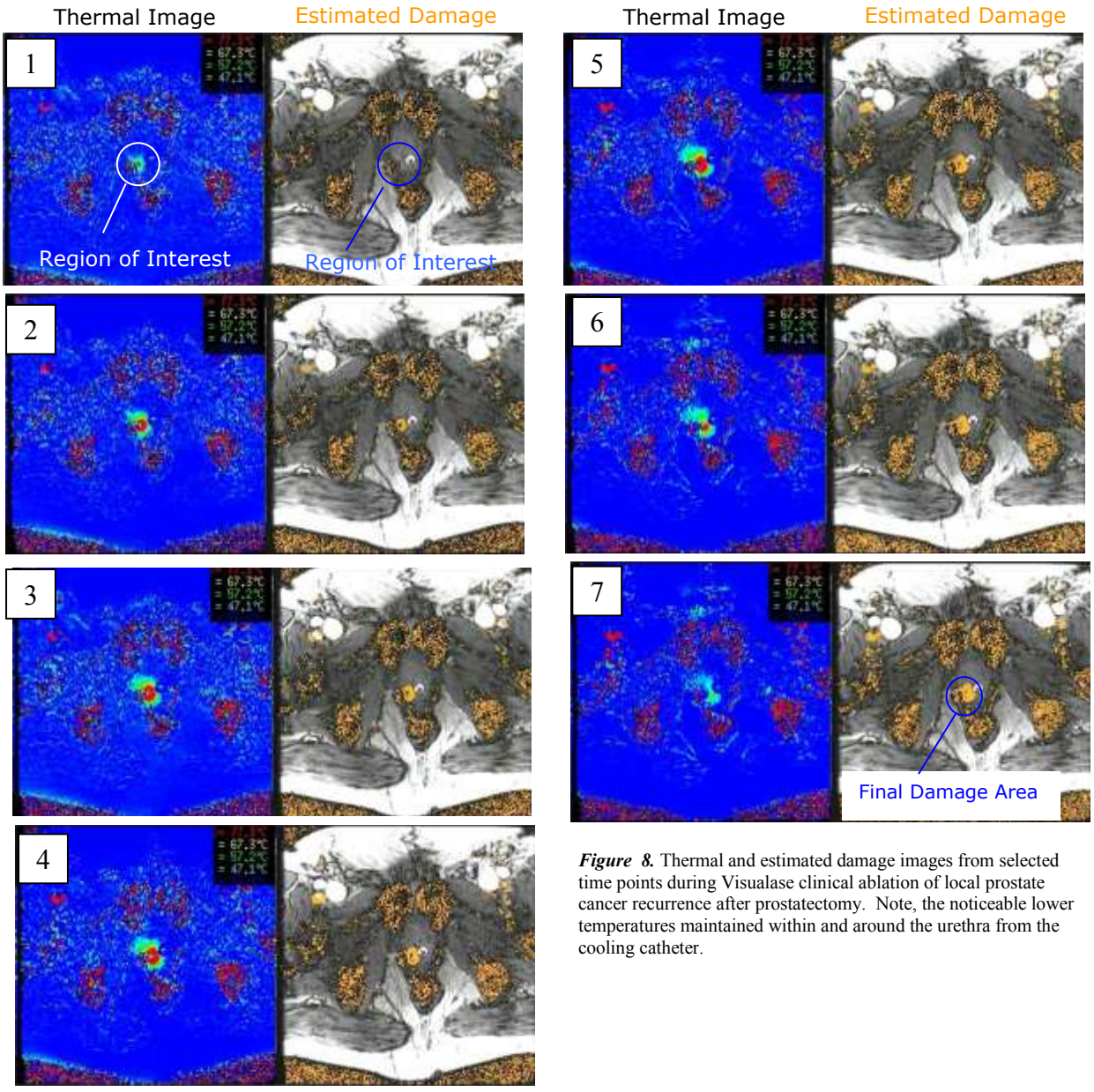


Figure 8. Thermal and estimated damage images from selected time points during Visualase clinical ablation of local prostate cancer recurrence after prostatectomy. Note, the noticeable lower temperatures maintained within and around the urethra from the cooling catheter.

1.5 POST THERAPY FOLLOW-UP AND CONCLUSIONS:

Clinical results thus far from using the Visualase Thermal Therapy System have been positive in all regards. Based on the clinical results to date using the system we can summarize the results as follows:

- In all procedures patients have recovered after therapy without complication
- There were no complaints of pain during therapy or post operatively.

- All patients have been discharged from the hospital within 24 hrs after the procedure, with the exception of one patient who was kept for 48 hours due to additional unrelated care.
- In all cases, the Visualase predicted lesion size agreed with post-treatment MRI-based assessment.
- Visualase guidance has allowed effective treatment of brain, bone, liver, and prostate tumors and avoidance of critical neural structures during therapy.
- Follow-up imaging of up to 18 months has demonstrated destruction of tumor masses and no signs of active tumor present in ablated areas based on contrast MRI studies.
- No significant edema or mass effect has resulted from thermal treatments when patients were maintained on steroids prior to and for short periods after therapy.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Men greater than 18 years of age

2.1.1.2 Organ confined clinical T1C or clinical T2a prostate cancer that is visualized on MR imaging

2.1.1.3 Prostate cancer is diagnosed by transrectal ultrasound guided standard 12 core biopsy or MR image guided biopsies (See Appendix C)

2.1.1.3.1 Gleason Score $\leq$ 7 (3+4), $\leq$ 3 cores positive in a standard 12 core biopsy or $\leq$4 cores positive on MR image guided biopsy where in 2 cores are taken from each of the two MRI target lesions

2.1.1.3.2 If the standard biopsy cores are positive, they must be from the same location in the prostate as MR Lesion was biopsied and proven to be cancer. (Left / Right, Base, Mid Gland, Apex).

2.1.1.4 MRI obtained within 6 months of ablation

2.1.1.5 Metastatic Disease work up as per NCCN guidelines (www.nccn.org) – Bone scan indicated to r/o metastatic disease if [clinical T1 and PSA > 20 or T2 and PSA > 10]

2.1.1.6 PSA $\leq$ 15 ng/ml or PSA density $\leq$ 0.15 ng/ml^2 in patients with a PSA > 15 ng/ml

2.1.1.7 The patient has given written informed consent after the nature of the study and alternative treatment options have been explained.

2.1.1.8 Patients who present with local recurrence or residual tumor after prostate cancer treatment which is visible on MRI.

2.1.2 Exclusion Criteria

2.1.2.1 The presence of 3 or more MR Visible lesions positive on biopsy
2.1.2.2 The presence of extra capsular, seminal vesical invasion or metastatic disease.
2.1.2.3 Patient is unable to tolerate MRI (foreign body, i.e. pacemaker or other implanted device; claustrophobia; inability to tolerate rectal coil; etc…)
2.1.2.4 Patient with inability to follow up
2.1.2.5 Acute urinary tract infection
2.1.2.6 Lower urinary tract symptoms defined by a International Prostate symptom score (IPSS) > 20
2.1.2.7 Patients with renal insufficiency with an estimated glomerular filtration (EGF) <= 30 are excluded, due to they will not be able to undergo gadolinium enhance MRI.
2.1.2.8 Patients with Uncontrolled Coagulopathies who are at increased risk of bleeding.
2.1.2.9 Altered mental status preventing consent or answering questions during conduct of the trial will be excluded for safety purposes.
2.1.2.10 Other serious illnesses according to the PI: involving the cardiac, respiratory, CNS, renal or hepatic organ systems, which would preclude study completion or impede the determination of causality of any complications experienced during the conduct of this study.
2.1.2.11 A Standard 12 core biopsy positive for cancer with no corresponding MR targeted lesion positive for cancer in the same general region of the prostate (Right Apex, Right Mid Gland, Right Base, Left Base, Left Mid Gland, Left Apex)

2.2 SCREENING EVALUATION

The following studies will be completed within 30 days of study entry, unless otherwise specified.

- Complete History and Physical exam, including a digital rectal exam, including vital signs
- Laboratory Testing: CBC, Chem 7, PT/PTT/INR and urine laboratory (urinalysis, culture) determinations; PSA blood level, Comprehensive Metabolic Panel (SMA-20)
- Metastatic disease work up as indicated by NCCN guidelines (http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf).
- A standard prostate biopsy 10 – 12 cores
- MR Image guided prostate biopsy
- Potency and incontinence measurement tools – International Prostate Symptom Scoring (IPSS), and Sexual Health Inventory for Men (SHIM)
- If any other tests have been performed in the evaluation of the subject's prostate cancer, the results will be placed in the subject's study file. These may include CXRs, CT scans, other imaging modalities, and/or biopsies. If any of these tests show there is metastatic disease, the subject will be excluded from the study.

2.3 SCREENING AND REGISTRATION PROCEDURES

2.3.1 Screening Procedures

Individual subjects will be enrolled and evaluated in the outpatient clinic at the Clinical Center of the National Institutes of Health. It is possible that the initial evaluation may occur while a subject is a Clinical Center in-patient. An introductory telephone conversation with the subject may occur with one of the UOB research nurses or associate investigators. At that time, a brief description of the research study will be provided. The subject's medical records including a clinical history, laboratory and x-ray findings, pathologic tissue and physical assessment may be obtained from the referring medical provider or the patient's primary health care provider. These records will be reviewed by one or more Associate Investigators for acceptance of the subject into the study protocol. Tissue received from off-site facilities may be analyzed by the NCI Laboratory of Pathology. If accepted and the subject agrees to participate, arrangements for the initial clinic visit will be made by a research nurse.

It is estimated that each subject traveling to Bethesda from a distance will spend approximately 1-4 days undergoing outpatient clinical evaluations in the Clinical Center. NIH subjects will stay at a local hotel or the Guest House. Affected patients may require hospitalization for treatment of tumors and procurement of tissue. These procedures will be standard of care surgical treatment under an IRB approved tissue procurement protocol. Any experimental forms of therapy will only be conducted on a separate protocol.

For patients living within 115 miles of Bethesda, outpatient studies will be scheduled at the patient's convenience with anticipated Clinical Center outpatient tests occurring over an elapsed period of several weeks.

Due to the nature of this study attempts at randomization will not be possible.

2.3.2 Registration Procedure

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4 BASELINE EVALUATION

The following baseline measurements will be performed upon enrollment on the protocol:

1) Physical Examination
2) Laboratory Evaluation: CBC, Chem 7, PT/PTT/INR, and PSA
3) Urinalysis and culture

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is an open, single-center, non-randomized, pilot study. Fifteen (15) subjects with biopsy proven and MRI-imageable localized prostate cancer meeting all other entry criteria will be admitted to the study. Eligible subjects will undergo MR-thermal image guided laser ablation of all biopsy proven areas of prostate cancer using one or multiple laser probes during a single procedure lasting approximately two hours in duration. Following completion of the thermal treatment, subjects will be evaluated with a physical examination and PSA test. Subjects will be asked to return for PSA determinations and physical exam, biopsies and imaging following treatment. It is anticipated that patient accrual into this study will be completed in approximately 6 months. Each subject will participate in the study for approximately 3 years following the thermal treatment.

3.2 LASER FOCAL ABLATION PROCEDURE

3.2.1 Pre-Procedure Workup

The MRI obtained on the pre-procedure workup will be evaluated by an NIH urologic radiologist (P Choyke MD or his designee) and suspicious areas for cancer will be marked for biopsy. The patient will undergo a standard transrectal ultrasound (TRUS) 12-core prostate needle biopsy and biopsy of any MR suspicious lesions. The biopsies will be fixed and read. The target area of laser ablation will be chosen from our biopsy data. All biopsies obtained in this study will be read by the same NCI urologic pathologist (M Merino MD or her designee) for consistency and report percent core length for each biopsy and percent of primary and secondary Gleason score features. If diffuse disease is detected the patient will be excluded from the protocol as defined in section 2.1.2.

3.2.2 Procedure

3.2.2.1 Step 1: Study Treatment Procedures (Setup)

After the subject has completed all baseline evaluations he will be scheduled for Visualase Therapy. The subject will be placed on a MRI gantry table and routine general anesthesia will be delivered by a registered anesthesiologist. Once induction is achieved and permission to proceed is given by the anesthesiologist the subject will be prepared and draped in the supine position. A urethral cooling catheter will be inserted and an MR-compatible perineal guide template will be placed on the perineum between the patients legs. Axial MRI scans (1.5 T Philips MR) containing both the prostate anatomy and the perineal guide template will be acquired and software on the Visualase System used to register the template to the anatomy.

Targets (previously assessed by NCI radiologist) in the prostate will be selected using the Visualase Plan software which provides the appropriate guide hole and distance to insert laser applicators. A 14ga titanium introducer system will be used to place Teflon catheters into the target area. One 17Ga laser applicator will be placed though each Teflon catheter and into the area targeted for treatment. The course and location of the laser applicators can be assessed by acquiring MR-images prior to therapy.

3.2.2.2 Step 2: Thermal Therapy – DAY 0

The patient will remain positioned within the MRI unit for the duration of therapy. An imaging plane containing the applicator will be chosen, and a T1 planning image will be acquired. After loading the planning image into the Visualase System, temperature sensitive fast RF-spoiled gradient recalled echo (FSPGRE) images will be acquired repeatedly on the MRI and transferred in real-time to the Visualase® workstation for analysis. After establishment of baseline, the laser will be activated at a reduced power level insufficient to cause thermal injury. This intermediary step is performed to verify proper placement of the applicator and proper operation of thermal imaging. Subsequent to this test pulse, laser treatment will be initiated. A single lesion will require between 30-240 seconds of laser-radiation at a power level of 6-15 watts. Typically, imaging will continue for approximately 30-60 seconds after cessation of laser irradiation in order to fully visualize cooling and return to baseline. During each laser treatment, temperatures of the rectal wall and urethral structures closest to the area of prostate being treated will be monitored using the Visualase software. If the temperatures at either point reach 45°C or higher, the system will automatically terminate laser delivery. Thermal therapy treatment may resume after the temperature of the rectum and urethra has dropped to 40°C. If additional treatments are required, the laser applicator will be repositioned or a separate laser applicator will be connected to the system and the above imaging/application procedures will be repeated. At the end of all laser treatments, post treatment MR images (including dynamic contrast-enhanced T1 as well as T2 weighted images) will be acquired for determination of the effective treatment region. Following thermal treatment and after removal of urethral cooling catheter, a Foley-type urethral catheter will be placed and remain in place for 1 to 7 days following the thermal treatment. An anti-spasmodic medication to prevent bladder spasm should be administered following the thermal therapy treatment. Antibiotic prophylaxis will be administered 30 minutes prior to the procedure and given according to AUA antimicrobial Guidelines.[17] This should consist of antibiotics preoperatively and peri-urethral catheter removal.

3.2.2.3 Step 3: RECOVERY:

Subjects will recover in the PACU under anesthesia surveillance. Subjects are to be discharged home the following day.

3.2.2.4 Step 4: Post-Treatment Evaluation Procedures

24 hours following the thermal therapy treatment, the following study procedures will be performed:

- A complete physical examination, including a DRE, when indicated.
- Multi-parametric MR of the prostate

3.2.2.5 Step 5: Removal of Foley Catheter

One to seven days following the thermal therapy treatment, the subject should return to have the foley removed. Antibiotics will be administered orally the day before, the day of and the day after the Foley is removed.

Foley catheter removed and ability to urinate evaluated according to standard procedures. If the investigator determines that the subject is experiencing urinary retention so that the catheter cannot be removed at this visit, this information will be recorded on the case

report form. The investigator will determine when the subject should return for further evaluation. A record will be kept of each subsequent attempt to remove the catheter and the outcome of that attempt. The date the catheter is finally removed as well as any complications and/or medications administered will be recorded on the case report form.

3.3 QUESTIONNAIRES

3.3.1 International Prostate Symptom (Appendix A: IPSS), and the Sexual Health Inventory for Men (Appendix B: SHIM)

Patients with prostate cancer may be asked to complete the International Prostate Symptom (Appendix A: IPSS), and the Sexual Health Inventory for Men (Appendix B: SHIM) questionnaires. These validated tools assess issues in prostate cancer patients. Questionnaires to be administered at all office follow up visits as described in Appendix D: Study Calendar.

3.4 POST PROCEDURE FOLLOW UP SCHEDULE:

3.4.1 Study Calendar

See Appendix D

3.4.2 Follow Up Schedule

3.4.2.1 Repeat Imaging using Multiparametric MRI (Scans can be obtained within +/- 1 month of the target time table)

3.4.2.1.1 Day 0 –MR immediately prior to ablation (localize targets areas) and post ablation with gadolinium (to assess ablated zone)

3.4.2.1.2 Day 1 post operatively

3.4.2.1.3 6 months

3.4.2.1.4 12 months, and

3.4.2.1.5 24 months, and 36 months after the treatment.

3.4.2.1.6 Then yearly thereafter for evaluation under the care of the local medical physician, but data will not be collected on this study (this utilizes the Cleveland clinic post operative imaging protocol used in kidney cancer).[18]

3.4.2.2 Clinic Visits will occur at 3, 6, and 12, 18, 24 months post procedure, then yearly thereafter for a total of 3 years, and include:

3.4.2.2.1 History and physical exam with DRE

3.4.2.2.2 Laboratory evaluations including CBC, Chem 7, PT/PTT/INR and urine laboratory (urinalysis, culture) determinations, PSA blood tests

3.4.2.2.3 Completion of IPSS, and SHIM evaluations

3.4.2.3 Prostate biopsy follow up: (Standard and MR Image guided biopsy of treated targets and any new targets) at 12, 24 months. Further biopsies at 36 months are optional and

additional biopsies as clinically indicated. (Biopsies can be obtained within +/- 1 month of the target time table)

3.4.2.4 Clinically Indicated Radiologic Studies

3.4.2.4.1 MRI of Prostate – if there is concern that there may be a change in size or possible extra-capsular extension of the prostate cancer in question or a concern for hemorrhage or other physiologic change in the nature of the gland.

3.4.2.4.2 MRI of Brain – if there is concern for spread of cancer to the brain.

3.4.2.4.3 Bone Scan – if there is a concern for metastatic spread of the prostate cancer to the skeleton

3.4.2.4.4 CT of Chest/Abdomen/Pelvis – if there is a concern for metastatic spread of the prostate cancer to organs or other viscera.

3.4.2.4.5 Transrectal Ultrasound Guided Biopsy– for evaluation of area of laser ablation as well as to evaluate the possible reoccurrence of prostate cancer.

3.4.2.4.6 Urodynamic Studies – these studies may be warranted in instances where patient experienced dysfunctional voiding.

3.4.2.5 Unscheduled Visits

Unscheduled visits may be necessary during the conduct of the study. At each visit, the subject will be instructed to contact the investigator if he experiences new or worsened urologic conditions or complications. The investigator may request that the subject be seen for a non-scheduled visit. The specific findings from this visit will be recorded in the subject's medical record and appropriate data (i.e., complications) will be recorded on the subject's case report form.

3.5 SURGICAL GUIDELINES:

If patients wish to seek whole gland therapy, subjects may undergo standard of care surgical treatment if clinically indicated.

3.6 RADIATION THERAPY GUIDELINES:

If patients wish to seek whole gland therapy, subjects may undergo standard of care radiation therapy if clinically indicated.

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL INTERVENTIONS AND OFF STUDY CRITERIA

3.7.1 Criteria for Stopping Laser Procedure

During the laser procedure, outcome measures of importance that may interrupt or stop the procedure include the following:

3.7.1.1 Refusal to continue the treatment due to pain in spite of the opportunity to receive pain medication.
3.7.1.2 Observing thermal damage on post contrast MRI which extends beyond the estimated damage maps from the Visualase software or which extends into areas of the Rectum or Urethra will be considered side effects for stopping purposes.
3.7.1.3 Grade 3 or 4 toxicity attributable to the treatment.
3.7.1.4 Patient choice for reasons other than those given above.
3.7.1.5 The investigator feels it is in the best interest of the patient.

3.7.2 Off-Study Criteria

Once the laser focal ablation has been performed, the patient will continue participation in this study until one of the following:

3.7.2.1 Patients decides to withdraw from the study
3.7.2.2 Death
3.7.2.3 Protocol specified follow up (3 years) is completed
3.7.2.4 The investigator determines it is in the patient's best interest, due to an increase in Gleason score on follow-up biopsy or evidence of disease beyond the prostate

The reason for withdrawal must be recorded on the appropriate part of the case report form.

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken offstudy. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES:

All immediate issues and complications relating to laser ablation procedure will be dealt with at the time of surgery. Supportive care will be provided in accordance with the Standard Clinical practice core of good medical practice.

5 BIOSPECIMEN COLLECTION

5.1 TISSUE COLLECTION, SAMPLE STORAGE, TRACKING AND DISPOSITION

All specimens collected during this trial will be analyzed according to the specifications described in this protocol. Excess samples obtained during participation in this trial may be used for research purposes if the subject has consented and enrolled on NIH NCI protocol 97-C-0147. No research tissue analysis is specified in this protocol.
Samples will be destroyed at the completion of this study unless subjects have consented to participate in protocol 97-C-0147, in which case, specimens will be handled according to the specifications of that protocol.

The IRB will be notified in the event samples are inadvertently lost or destroyed. At the completion of this study samples will either be destroyed or IRB approval will be sought if an alternate disposition is determined.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

All patients must have signed an informed consent; and, an on study confirmation of eligibility form must be filled out before enrollment.

Complete records must be maintained on each patient. These will consist of the hospital chart with any supplementary information obtained from outside laboratories, radiology reports, or physician's records. These records will serve as the primary source material that forms the basis for the research record. All relevant data will also be entered on a computer data base from which formal analyses are done.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (Labmatrix) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

The investigator, however, must maintain a list of subject names and identifying information. Subjects will be evaluated in their initial visit to the Clinical Center of the National Cancer Institute. At this time the subject will meet with the principal investigator or his designee as well as a protocol research nurse to answer any questions that they may have. During this evaluation the subject will also undergo a physical exam which includes a digital rectal exam as well as basic blood work (PSA, CBC, CMP, and PT/PTT) and evaluation scans as listed in section 2.2. The subject's records will be screened to determine if he is a candidate for the study. If the subject does not meet all of the inclusion or exclusion criteria, he will be excluded from the study. Any biopsies, blood work, scans, or other clinical information obtained prior to presenting to the Clinical Center will also be requested at this time. At this initial meeting the subject will also be asked to fill out the IPSS, and SHIM evaluations. If any other tests have been performed in the evaluation of the subject's prostate cancer, the results will be placed in the subject's study file. These may include CXRs, CT scans, other imaging modalities, and/or biopsies. If any of these tests show there is metastatic disease, the subject will be excluded from the study.

6.2 RESPONSE CRITERIA

Follow up MRI of the pelvis at day 0, 1 and at 0.5, 1, 2, and 3 years. The targeted lesions on MRI should demonstrate changes consistent with successful treatment (a decrease of enhancement on MP MRI). (Scans can be obtained within +/- 1 month of the target time table)

Follow up systematic core biopsy of the prostate at 1, 2, and 3 (optional) years showing no evidence of invasive prostate cancer in the region of laser ablation. (Biopsies can be obtained within +/- 1 month of the target time table)

Standard and MR image guided biopsy of previous laser ablation sites should show no evidence of cancer.

Follow up DRE and physical exam at 3, 6, 12, 18, 24 months and 3 years. This should show no palpable disease, if disease is detected then further workup with one of the above mentioned tests will be preformed.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

There currently is no large series of data regarding laser ablation of the prostate. Large series of focal laser ablation of solid tumors reports an overall complication rate of 1.5% and a 30 day mortality rate of 0.1%.[19] Trachtenberg et al[20] reported a series of 12 patients. There were no mortalities and the complication rates reported were as follows: Postoperative morbidity was minimal, self-limited and required no intervention. Perineal discomfort was the most common side effect (25% of patients). Two patients had mild hematuria that did not require any intervention and cleared spontaneously, 2 patients had hematospermia and 1 had fatigue. Due to the limited paucity of information we will also in cooperate and follow data points from the focal cryoablation data (table below).[21]

Table 2 – Complications (%) after primary cryosurgery

Ref.	No. patients	Technique	Fistula	Slough	Retention	Incontinence	Impotence	UTI	Perineal pain
Long et al. [16]	975	LN/Ar	0.4	NA	10	7.5	93	NA	NA
Donnelly et al. [17]	76	LN	NA	3.9	NA	1.3	100 (53: >3 yr)	NA	NA
Bahn et al. [15]	590	LN/Ar	0.004	NA	5.5	4.3	95	NA	NA
Ellis et al. [65]	75	Ar	0	6.7	6.7	5.4	82	NA	NA
Han et al. [12]	122	Ar	0	4.9	NA	3	87	NA	6
Prepelica et al. [18]	65	Ar	0	NA	3.1	3.1	NA	NA	3.1
Jones et al. [19]	1198	LN/Ar	0.4	NA	NA	2.9	91	NA	NA
Hubosky et al. [68]	89	Ar	1	2	4	2	NA	1	6

UTI, urinary tract infection; NA, not available; LN, liquid nitrogen; Ar, argon gas.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Unanticipated Adverse Device Effect

Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

All adverse device effects will be followed until return to baseline or stabilization of event. Unanticipated adverse device effects that occur more than 30 days after the last administration of investigational agent/intervention should be recorded and reported as per section 7.2.

7.1.2 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.3 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.4 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.5 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

    NOTE: Grade 1 events are not required to be reported.

7.2.3 Non Reportable Occurrences secondary to the MRI or prostate biopsy.

Patients may have events which we would not consider to be secondary to the laser treatment and therefore not reportable to the IRB. First, the MRI with gadolinium, there is a very low possibility they may develop an acute allergic reaction to the gadolinium, because the patients underwent the MR for the entry process to be screened for the study.
Second, the prostate biopsies performed on the NIH protocol 05-CC-0091 with tissue and specimens acquired on the 97-C-0147 protocol. The patients may develop symptoms post biopsy: Urinary Frequency, Urinary Retention, Dysuria, Hematuria, Erectile Dysfunction, Urinary Tract Infection or Urosepsis post biopsy, which we believe would not be reportable or included in the stopping criteria for the study since these symptoms are not attributed to the laser ablation, especially at the one year and two year biopsy timepoints.

7.2.4 NCI-IRB Reporting of Safety Reports

Only Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.3 EXPEDITED ADVERSE EVENT REPORTING TO THE MANUFACTURER

If an unanticipated adverse device effect occurs, the investigator will immediately contact the manufacturer to report the event. The manufacturer contact for reporting unanticipated adverse device effects will be:

Ashok Gowda, Ph.D
Chief Operating Officer
Visualase, Inc.
8058 El Rio St.
Houston, TX 77054

Phone: (713) 741-0111
FAX: (713) 741-0122
Co

7.4 DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient in detail.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator in a timely manner. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS*)* and to the manufacturer.

In addition, the PI and associate investigators will monitor adverse events on an ongoing basis and modify the protocol and/or consent accordingly. After the first 5 patients are treated, and again after the first 10 are treated, interim assessments will be performed by the PI and associate investigators. This study will be stopped, and the IRB will be notified if adverse events develop which endanger patient safety, although the likelihood of this is so low that it is hard to create or imagine possible examples of such events.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff. If there is mortality the study will be paused and a determination of cause will be pursued. If the cause was due to the laser therapy the pilot study will be concluded. Also, regarding other complications rates if the 30-day complication rate of serious events exceeds 2 patients a further analysis of the technique will be performed, as well as pausing and possible concluding the study if changes cannot be made for improvement.

8 STATISTICAL SECTION

The primary goal of this study is to assess the toxicity, performance and feasibility of the Visualase thermal therapy procedure for focal prostate cancer treatment and then to monitor any complications for the 3 years following treatment. The outcome measures of importance during the thermal treatment are pain, frequency of thermal damage outside of intended treatment areas as measured by post contrast MRI, frequency of not completing the entire procedure, or the frequency of other adverse events and complications. These outcome measures are further defined as follows:

* Observing thermal damage on post contrast MRI which extends into areas of the Rectum or Urethra will be considered side effects for stopping purposes.
* Frequency of not completing the procedure. Not completing the procedure for reasons other than those given above will be considered a side effect for stopping purposes.
* Other adverse events or complications that occur that are classified as Grade 3 or 4 by the National Cancer Institute's Common Toxicity Criteria 4, will be considered a side effect for stopping purposes.

Sample size

The purpose of the study is to assess the safety, performance and feasibility of the Visualase thermal therapy procedure for focal prostate cancer treatment. The sample size is targeted at 15 evaluable patients which is adequate to assess the toxicity rate and can be reasonably recruited in a 6-month period of time. With the accrual of 15 patients, the width of the 80% expected confidence interval of 0.1 and 0.2 toxicity rate is 0.19 and 0.26, respectively.

Stopping rule

For the purpose of protecting patient safety, we implement the following stopping rule for safety monitoring. If one patient experiences a grade 5 event, thought to be possibly or probably due to the laser therapy, the study will be stopped. For grade 3 or 4 event, the study will be stopped according to the following stopping rule.

Number of patients	No. of grade 3 or 4 serious adverse events
3-5	3
6-10	4
11-15	5

The operating characteristic of the stopping rule was assessed by simulations. Based on 10,000 simulations, the probability of stopping early for an excess of serious adverse event over the course of trial is 0.023 when the serious adverse event rate is 0.1 and 0.81 when the serious adverse event rate is 0.40. This is deemed reasonable for protecting patient safety.

Frequency of the outcome measures, response and toxicity will be reported. Paired Student t test will be used to compare the difference between continuous variables (PSA, MRI imaging parameters) measured at baseline and at each follow-up visit. Prior to performing the paired t-test, the distribution of the underlying data will be assessed, and adequate transformation will be undertaken to ensure that the distribution of the transformed data is approximately normal. Descriptive statistics such as frequencies and percentages of categorical variables will be reported. In addition, McNemar's test, though may not have adequate power for this pilot study, will be explored to evaluate the difference in proportion between baseline and at each follow-up.

Longitudinal profiles of parameters recorded in the questionnaires over the course of follow-up for each patient will be plotted and the associated summary statistics such as mean, standard deviation, and mean change between successive follow-up visits will be reported. In addition, linear and non-linear mixed effects models will be explored to model the longitudinal profiles of the parameters of interest. In these models, random intercept will be used to incorporate the within-patient correlation of the repeated observations. If deemed appropriate, random slope will be added to the model to allow for the slope of profile to vary between patients.

9 HUMAN SUBJECTS PROTECTIONS

Confidentiality, individual choice and volunteerism are standard values of the UOB staff relative to their studies and practice. The earliest patient education and counseling begins at the initial contact with one of the protocol nurse coordinators or investigators. After arriving at the clinic,

subjects will have a dialog about: the disorder in question and the protocol study; questions are answered; information material is provided.

As information is gathered from this trial, clinical results will be shared with patients while insuring total patient confidentiality. Clinical data will be frequently gathered and any new significant findings(s) found during the course of the research, which may affect a patient's willingness to participate further will be explained. Moreover, in all publications and presentations resulting from this trial, patients' anonymity will be protected to the maximum extent possible; although, authorized personnel from the National Cancer Institute (NCI) and Food and Drug Administration (FDA) may have access to research files in order to verify that patient rights have been safeguarded.

9.1 RATIONALE FOR SUBJECT SELECTION

Males of all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. Efforts will be made to extend accrual to a representative population.

9.2 STRATEGIES/PROCEDURES FOR RECRUITMENT

Referrals from within the NIH will be welcomed. This protocol also will be available through the NIH clinical trials data base at website address: http://clinicaltrials.gov/

9.3 JUSTIFICATION FOR EXCLUSIONS

Patients with altered mental status that prevents consent or answering questions will be excluded. Patients with uncorrectable coagulopathies may be at increased risk for bleeding, and will be excluded. Patients with multiple co morbid illnesses, sepsis, or multiple high-risk medical problems may be at increased risk for morbidities or mortalities, and will be excluded at the judgment of the PI (Dr. Peter Pinto or his designee). This does not change standard biopsy exclusions. If a patient is unable to hold his or her breath for more than 5 seconds, the study data acquired may be potentially confounding and inaccurate.

9.4 PARTICIPATION OF CHILDREN

Only patients 18 years or older will be enrolled in this study. Prostate cancer is extremely rare in children.

9.5 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **9.6**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can

make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.6 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

This study may be of benefit to subjects by allowing for an early, minimally invasive treatment for low grade confined prostate cancer, as compared to the current treatment standard. It also offers an alternative to those patients who would qualify for watchful-waiting but are uncomfortable with this approach. Those patients who are involved in active surveillance must undergo yearly prostate biopsies that themselves are painful and carry with them a risk of infection and prostatitis. The risks of this study are no greater than those of taking a watchful-waiting approach to treating minimally invasive prostate cancer.

However, for those patients who opt for this protocol there is a risk that their cancer may progress, either through the multifocal nature of prostate cancer or through the inaccuracy of the focally directed process. For these patients, this risk is minimized through thorough follow up with imaging, biopsy, and close monitoring of PSA. Finally, the discomfort that subjects may experience will be minimized as much as possible, however, prostate biopsies and post ablation pain may exist and this will be treated in accordance to the standard of care.

9.7 RISKS/BENEFITS ANALYSIS – MONITORING OF TRIAL

Thus, we believe that this trial may eventually lead to improvements in the safety and delivery of ablation procedures. Although no guarantee of any benefit whatsoever will be made to the patient, experience from pre-clinical trials makes us confident that there is no increased risk to the patient from using the tracked devices that differ very little from conventional needles.

Focal thermal therapy for prostate cancer offers a treatment option intermediate between active surveillance and radical therapy for small volume, low grade prostate cancer. It prevents the side effects of radical therapy and may help decrease the chances of disease progression in active surveillance.

Potential risks associated with use of the Visualase laser thermal therapy system include bleeding, infection, pain, urinary tract symptoms, and damage to the rectal wall, bladder problems, and erectile dysfunction. Visualase applicator placement will be performed under sterile conditions with appropriate anesthesia (local, spinal, or general). If a course of prophylactic antibiotics or analgesics is administered according to standard clinical practice for this type of procedure, this information should be documented as a concomitant medication.

Potential risks associated with the thermal ablation treatment include pain, thermal injury to the adjacent organs, erectile dysfunction, the inability to urinate, and blood in the urine. MR-thermometry and feedback control using the Visualase system minimize the risk of overheating critical structures or areas outside of the intended target tissue.

No serious side effects or complications have been observed in any patients treated to-date with thermal ablation using Visualase.

Minimal risks are inherent within this protocol and include the physical risks of phlebotomy, and imaging contrast.

- Risk Level: Likely but not serious:
    - Risks from a skin puncture (perineum) include some discomfort associated with percutaneous analgesia and a risk of bruising, small scar formation, and a small chance of infection.
    - Voiding irritation frequency and urgency after the procedure secondary to urinary catheter which should be self resolving within a few days if removal.
    - Urinary retention after catheter removal.
    - The safety and efficacy of gadolinium contrast has been well documented and a reaction is less likely while on protocol, due to all patients required an MRI with gadolinium to be evaluated as a possible candidate
    - Minimal risks are associated with the medical procedure of obtaining blood and include some discomfort and bruising.
- Risk Level: Unknown incidence but not serious
    - Erectile Dysfunction
    - Hematuria
- Risk Level: No known risk:
    - There are no known health hazards of ultrasound or MRI at power levels employed for diagnostic purposes
- Risk Level: Very unlikely, but serious:
    - Urinary fistula from ablation of the prostate with rectum.

The PI will continue to monitor the study along with reporting adverse events to the IRB. If there is mortality the study will be paused and a determination of cause will be pursued. If the cause was due to the laser therapy the pilot study will be concluded. Also, regarding other complications rates if the 30 day complication rate of serious events exceeds 2 patients a further analysis of the technique will be performed as well as pausing and possible concluding the study if changes cannot be made for improvement.

9.8 CONSENT PROCESS AND DOCUMENTATION

The investigator will inform patients and their family members (if appropriate) of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The investigator will then provide a copy of the IRB-approved informed consent document for this study. The patient will be allowed to take as much time as he/she wishes, in deciding whether or not to participate. The original signed consent goes to Medical Records; copy placed in research record.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on the study.

For the optional research biopsy in the in the protocol, the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

9.8.1 Telephone consent

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

10 APPENDICES

10.1 APPENDIX A - INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)

Name: Date:

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	**Your score**
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	

	None	1 time	2 times	3 times	4 times	5 times or more	**Your score**
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	

Total IPSS score	

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible

If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Total score: 0-7 Mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

10.2 APPENDIX B - SEXUAL HEALTH INVENTORY FOR MEN

PATIENT INSTRUCTIONS

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that **best describes** your own situation. Please be sure that you select one and only one response for **each question**.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?

Very low	Low	Moderate	High	Very high
1	2	3	4	5

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?

No sexual activity	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than, half the time)	Almost always or always
0	1	2	3	4	5

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than, half the time)	Almost always or always
0	1	2	3	4	5

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Did not attempt intercourse	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
0	1	2	3	4	5

5. When you attempted sexual intercourse, how often was it satisfactory for you?

Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than, half the time)	Almost always or always
0	1	2	3	4	5

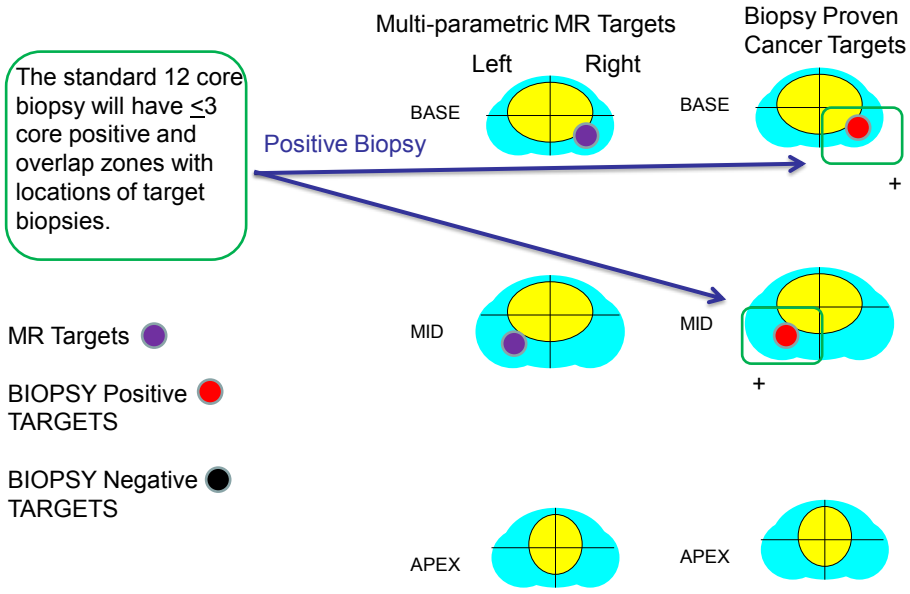
SCORE_____

Add the numbers corresponding to questions 1-5. If your score is 21 or less, you may want to speak with your

10.3 APPENDIX C – BIOPSY CRITERIA ILLUSTRATIONS

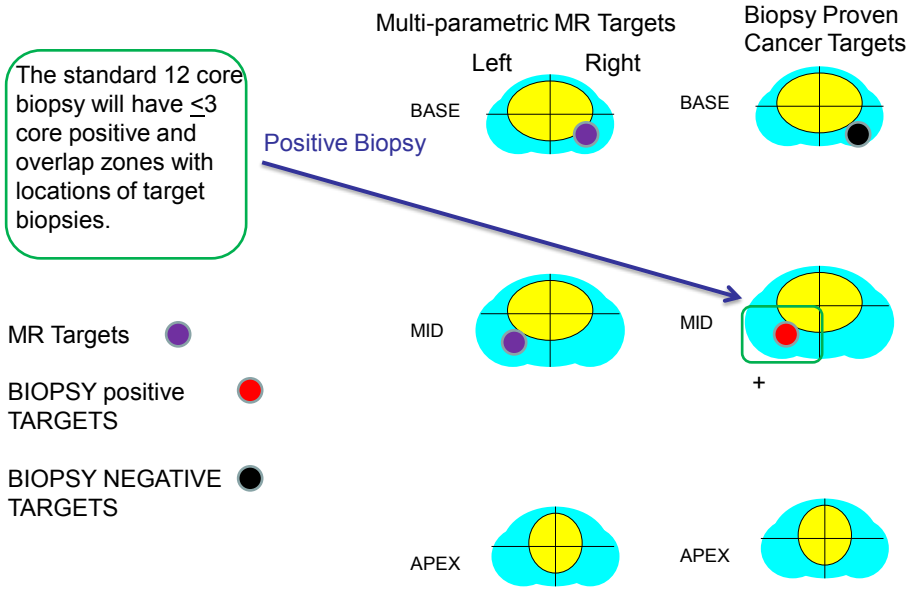
The patient is a candidate:

If both targets are positive (MR Targeted Biopsy ≤4 cores) for two targets and it overlaps with the standard biopsy



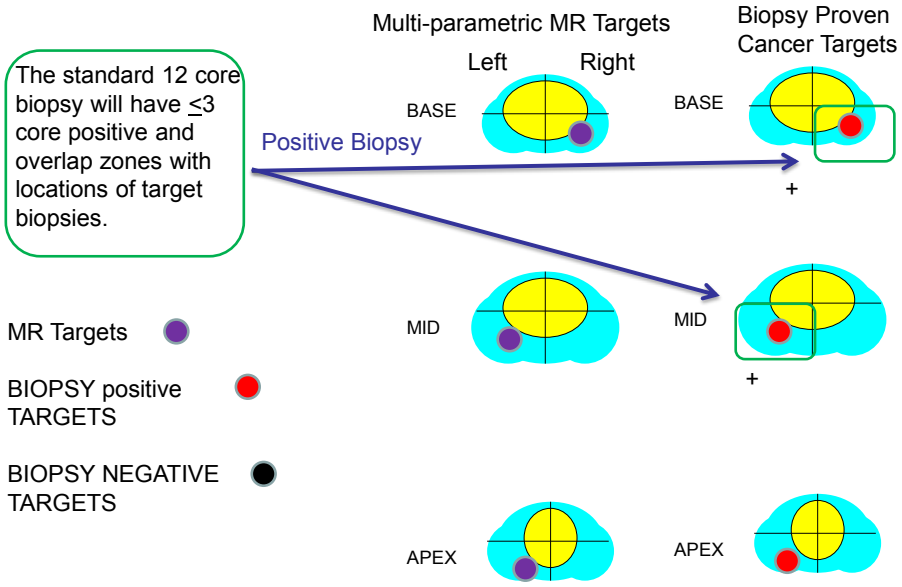
The patient is a candidate:

If one of the two targets are positive (MR Targeted Biopsy ≤4 cores) for one of the two targets and it overlaps with the standard biopsy.



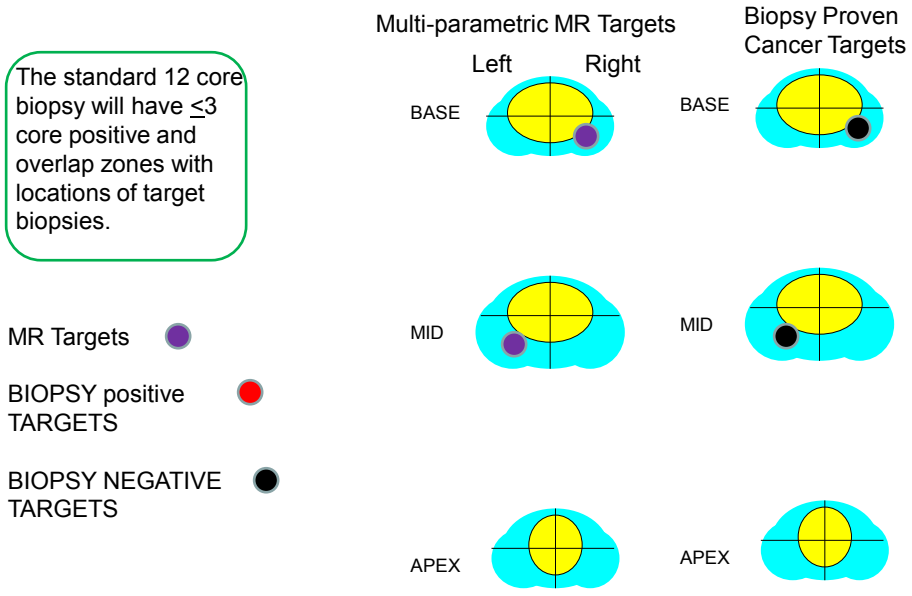
The patient is **NOT** a candidate:

If all Three targets are positive (MR Targeted Biopsy >4 cores) for three targets



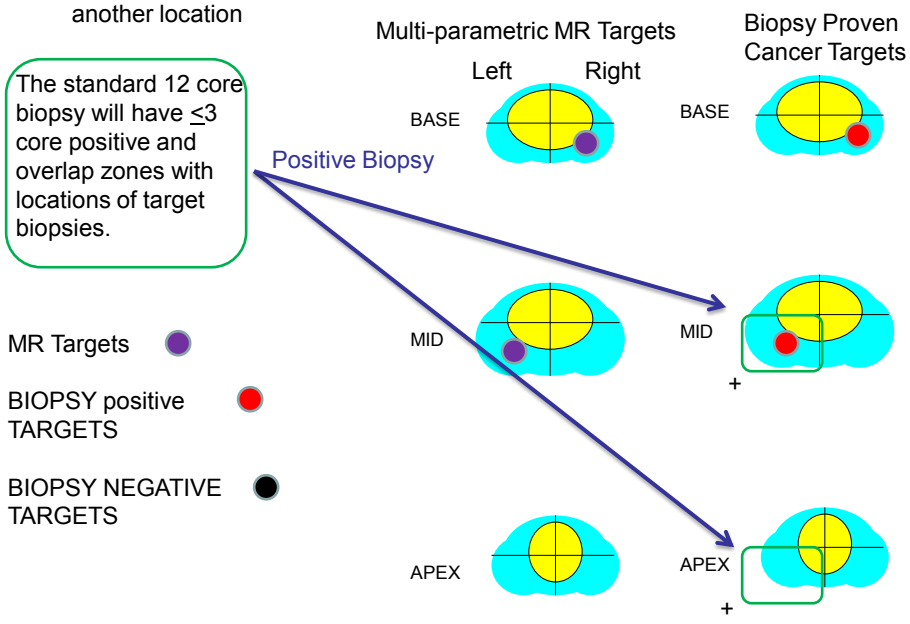
The patient is **NOT** a candidate:

If all targets are negative (MR Targeted Biopsy >4 cores) for two targets



The patient is **NOT** a candidate:

If both targets are positive (MR Targeted Biopsy ≤4 cores) for two targets however there is no overlap with standard biopsy. Cancer was found in another location



10.4 APPENDIX D: STUDY CALENDAR

Procedure	*Screening/ Baseline*	*Treatment Day 0*	*Day 1*	*3 Mos*	*6 Mos*	*12 Mos*	*18 Mos*	*24 Mos*	*36 Mos*
History and PE	X	X	X	X	X	X	X	X	X
Digital rectal exam	X		X	X	X	X	X	X	X
Vital signs	X	X		X	X	X	X	X	X
NIH Advanced Directives Form[1]	X								
Labs									
CBC	X			X	X	X	X	X	X
PT/PTT/INR	X			X	X	X	X	X	X
Chem 7	X			X	X	X	X	X	X
PSA blood level	X			X	X	X	X	X	X
CMP	X								
Urinalysis and culture	X			X	X	X	X	X	X
Prostate Biopsies (10-12 cores)	X								
Prostate biopsy F/U						X		X	X[b]
Thermal Therapy		X							
Metastatic disease work up: may include CT or MRI or Bone scan[c]	X								
MR Imaging	X	X	X		X	X		X	X
Trans rectal ultrasound	X								
Questionnaires (IPSS, SHIM)	X			X	X	X	X	X	X
Response Evaluation	X	X	X		X	X		X	X
Adverse Events		X	→	→	→	→	→	X	X
Concomitant Medications		X	→	→	→	→	→	X	X

[1] As indicated in section **9.5** all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

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