

## Feasibility Study for the Treatment of Brachytherapy Failure Prostate Cancer using High-Intensity Focused Ultrasound

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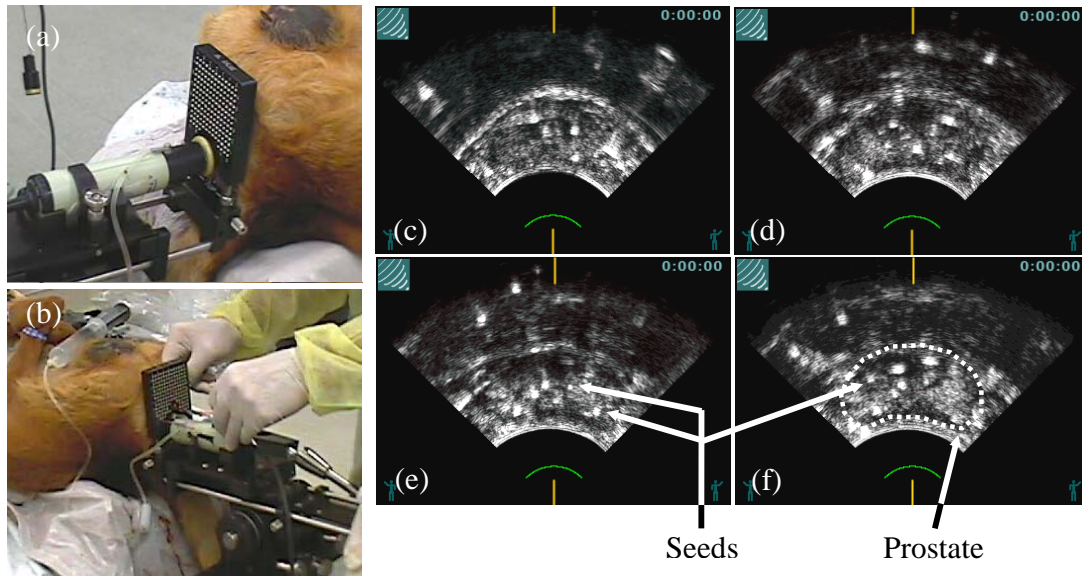
**Abstract.** Prostate cancer patients who were previously treated using Brachytherapy and have recurrence of cancer are currently being excluded from ongoing prostate cancer clinical trials utilizing HIFU. It is thought that the presence of seeds in the prostate may obstruct HIFU energy delivery. Recent *in-vivo* canine (N=4) experiments suggest, however, that such exclusions may not be necessary. Between 27 and 56 spent <sup>125</sup>I seeds and stainless steel dummy seeds were implanted under ultrasound guidance in the canine prostates. The prostates were then fully treated with HIFU using the Sonablate<sup>®</sup>500 system (Focus Surgery, Inc., Indianapolis, IN), with the same treatment protocol and HIFU parameters used for current human prostate cancer treatments (3s ON, 6s OFF, 24-37W TAP). Ultrasound images and X-ray images were used to record seed locations pre- and post HIFU treatment, respectively. Temperature was monitored during the treatment in various locations inside and around the prostate including the rectal wall. The canine prostate, bladder, and rectal tissues were removed 1/2 hour after the HIFU treatment. These tissues were imaged by X-ray prior to seed removal, and examined for thermal damage at the gross-pathological and cellular levels. This initial study suggests that the Brachytherapy seeds did not alter the spatial temperature distribution in the prostate during the HIFU treatment (as compared to treatments performed without seeds), and tissue destruction at the cellular and macro level is similar to that seen in treatments performed without seeds. Treatment specifics, thermometry, and histology data highlighting these results will be presented.

### INTRODUCTION

There are few effective salvage therapies for treating local failures after definite prostate brachytherapy. Brachytherapy failure patients are currently excluded from prostate cancer treatments utilizing HIFU because it is presumed that the presence of seeds in the prostate may affect HIFU energy delivery. However, little is known about the effect of prostate brachytherapy seeds on the safety and efficacy of HIFU to ablate prostate tissue. It is also not known whether the presence of these seeds will result in elevated temperatures at the rectal wall and surrounding tissue. The work presented in this paper tries to answer some of these initial questions using a canine model, and looks at the feasibility and safety of using HIFU to treat prostates with indwelling brachytherapy seeds.

## MATERIALS AND METHODS

A canine model (N=4) was used for the *in vivo* experiments. The study was conducted as per the approved protocol by the local experimental research committee. The animals were anesthetized and intubated during the entire procedure. Decayed prostate brachytherapy  $^{125}\text{I}$  seeds (Imagyn Medical Technologies, Irvine, CA) and stainless steel dummy seeds of the same dimensions (4.4 mm long, 0.7 mm diameter) were transperineally implanted in the prostate under ultrasound guidance while the animal was held in the lithotomy position, as shown in Figure 1. Typically, between 27 and 56 seeds were implanted in each prostate, with an average of 43 seeds implanted per prostate.



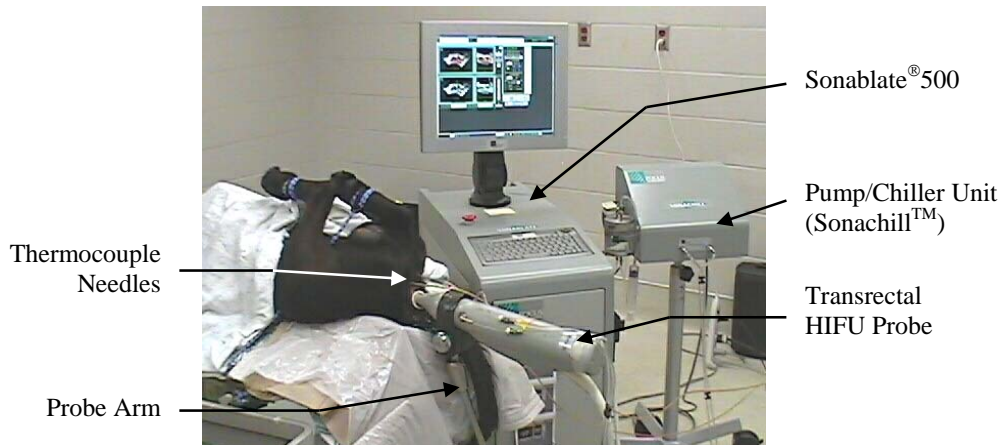
**FIGURE 1.** Seed Implantation under Transrectal Ultrasound Guidance (a,b), and Seed location verification inside the prostate using the Sonablate<sup>®</sup>500 prior to HIFU treatment (c-f), sector images.

The canine prostates were then treated with the Sonablate500<sup>®</sup>HIFU System (Focus Surgery, Inc., Indianapolis, IN), using the same treatment parameters as those used for HIFU prostate cancer treatments in humans [1]. These parameters were:

- 4.0 MHz transrectal HIFU therapy probe with dual focal lengths (40/30 mm),
- 0-37 W total acoustic power (TAP) while using the 40 mm transducer,
- 0-24 W TAP while using the 30 mm transducer,
- 3 seconds HIFU ON time, 6 seconds HIFU OFF time for each shot,
- entire prostate gland was treated, and
- an anterior to posterior treatment sequence was used.

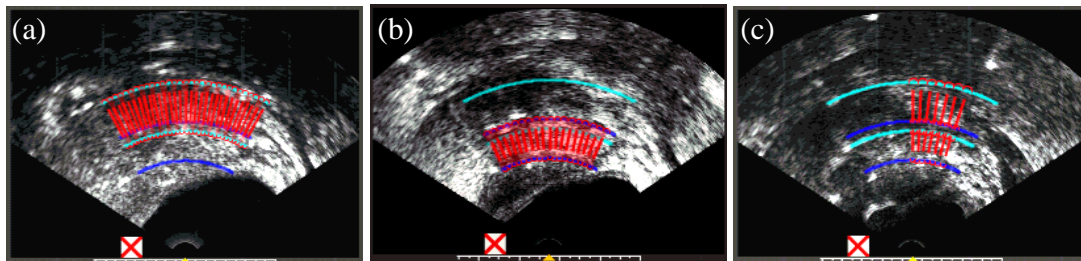
Treatment with these parameters results in coagulative necrosis of prostatic tissue in the focal zone of the transducer due to temperature elevations to 80-95°C within 3 seconds [2,3]. An active pump/chiller unit (Sonachill<sup>TM</sup>) was also used to maintain rectal wall temperatures below 25°C, and to provide coupling for the HIFU energy between the transducer and the prostate. In 3 animals, up to 9 thermocouples were

implanted in various locations inside the prostate and close to the rectal wall to record the temperatures during the treatment. The treatment setup for these experiments is shown in Figure 2.



**FIGURE 2.** Treatment Setup utilizing commercial Sonablate®500 System, Transrectal Probe, and Pump/Chiller cooling unit. Thermometry System not shown.

The HIFU treatment was interactively planned on the Sonablate®500 by defining the treatment zones for each 3 mm thick prostate slice on the transverse images. The HIFU treatment started from the anterior region of the canine prostate (typically utilizing the 40 mm focal length transducer, Figure 3a), and continuing to the posterior region (typically utilizing the 30 mm focal length transducer, Figure 3b), so as to treat the entire prostate gland. Additional treatment zones were defined (example, Figure 3c) to treat regions not covered during previous treatments, or to re-treat zones, as required.

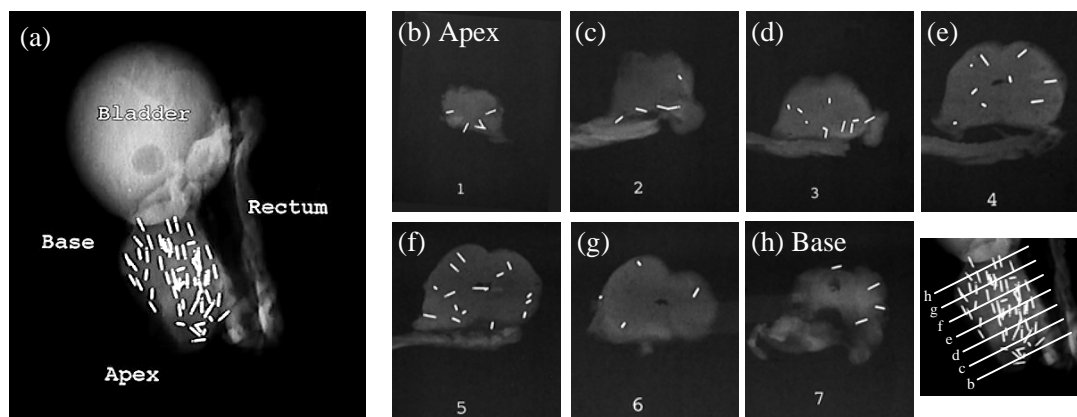


**FIGURE 3.** Anterior (a) to Posterior (b) whole Prostate HIFU Treatment Planning (red zones) based on Sector Ultrasound Image Data (15 sector slices cover the entire prostate from Base to Apex with 3 mm spacing; 1 sector slice shown). Simultaneous planning at edge of gland (c).

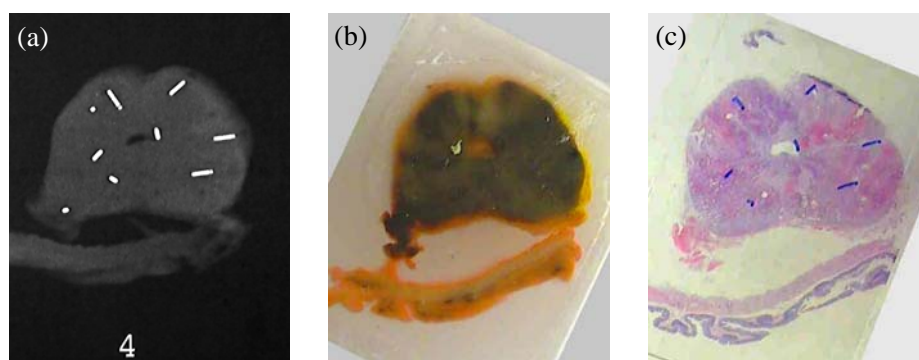
After the HIFU treatment, the animal was sacrificed and the prostate, bladder, and rectum were removed for inspection, X-ray imaging, and histo-pathological evaluation.

## RESULTS

X-Ray images taken after the prostate was removed showed that the implanted seeds were uniformly distributed throughout the gland, as desired (Figure 4). These images also served as a seed location reference for correlation with the histological slides (Figure 5). Prior to fixing the individual prostate sections in paraffin (typically 7 sections, 5 mm wide), the seeds were removed and discarded.



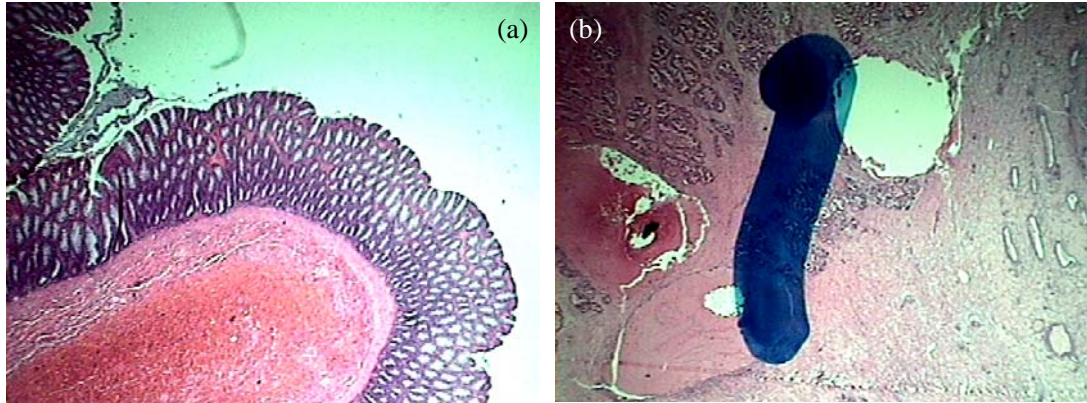
**FIGURE 4.** Prostate X-Ray Images showing the seed distribution prior to sectioning (a), and showing seed location for each 5 mm wide section for later correlation with histology, from apex (b) to base (h).



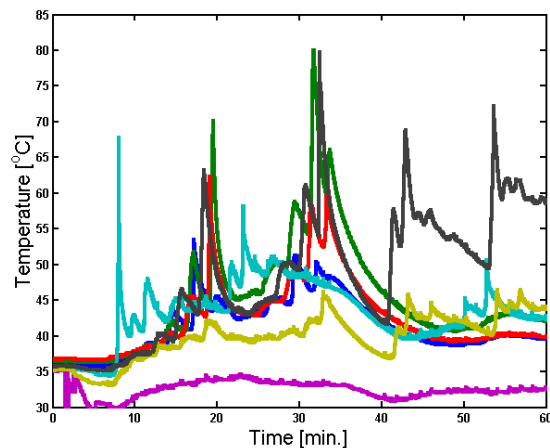
**FIGURE 5.** The X-Ray Images were used to locate the seed position during the histological evaluation of the various prostate sections (images for mid-section 4 (e) in Figure 4 are shown): X-ray image (a), section fixed in paraffin (b) with dark areas indicative of necrotic tissue, and marked seed location on H&E stained slide (blue lines), (c).

Grossly, the presence of brachytherapy seeds did not appear to affect the HIFU lesion production. Typically, cells located around and behind the seeds themselves showed similar behavior to HIFU as those located elsewhere in the prostate (Figure 6). On gross review, the rectal wall showed submucosal hemorrhage in 2 animals, that occurred most likely as a result of needle insertion during seed placement, as histologically this area did not show any evidence of thermal injury. The rectum was grossly and histologically without evidence of thermal damage in all specimens (Figure 6). On histologic review, tissue destruction at the cellular level was similar to

that seen in treatments performed without seeds. Furthermore, the collected thermometry data revealed intraprostatic temperature elevations to be in excess of 80°C when the transducer focal zone coincided with the location of the thermocouple (Figure 7), similar to HIFU treatments performed without seeds. Temperature measurements near the rectal wall remained low (partly due to the active cooling system), and were also similar to those measured during HIFU treatments performed in the absence of seeds.



**FIGURE 6.** Histology Results: example of intact rectal wall lining (a), and fully ablated tissue around brachytherapy seed (b), similar to thermally ablated tissue without the presence of seeds.



**FIGURE 7.** Thermometry Data collected from various locations inside the canine prostate (populated with seeds) and location close to rectal wall (bottom-most trace) during the HIFU treatment.

## CONCLUSIONS

These preliminary results are encouraging: the presence of intraprostatic brachytherapy seeds did not appear to impact the HIFU lesion production in the prostate nor lead to adverse rectal wall toxicity. While histologically some tissue regions did not show signs of full ablation, it was difficult to determine if these were due to the presence of the seeds, incomplete or lower-power treatment planning and execution, or other causes (such as seed migration during and after the HIFU treatment). A more extensive and careful histological study performed on prostates with seeds treated with HIFU removed from the animals several weeks after the treatment is required to examine survival of partially treated tissue, or initially viable

tissue located in pockets between fully ablated tissue. The safety of this procedure was established with these sets of experiments, however, providing hope for a possible alternate salvage therapy for brachytherapy failure patients in the future. The presence of intraprostatic temperatures similar to those temperatures seen during HIFU prostate treatments without seeds are a further indication of the feasibility of such a procedure. Finally, future experiments will have to focus on HIFU treatment efficacy (while keeping the safety aspect demonstrated here) in the presence of seeds, and the effect of seed density and seed location on the treatment. A human feasibility (Phase I) clinical trial is planned.

## ACKNOWLEDGMENTS

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