Phase I/II Trial of High Intensity Focused Ultrasound for the Treatment of Previously Untreated Localized Prostate Cancer

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Purpose: We examined the safety and potential efficacy of transrectally delivered high intensity focused ultrasound for the full gland ablation of previously untreated localized prostate cancer.

Materials and Methods: A total of 20 patients with localized prostate cancer underwent 1 to 3 high intensity focused ultrasound treatments of the prostate. The primary outcome was safety and the secondary outcomes were prostate specific antigen, prostate biopsy and quality of life measures.

Results: A total of 19 patients had complete followup. Serious adverse events related to treatment were limited with the most common adverse event being transient urinary retention more than 30 days in duration in only 10% of patients. Rectal injury occurred in 1 patient. With 1 to 3 treatments 42% of the patients achieved prostate specific antigen less than 0.5 ng/ml and a negative prostate biopsy.

Conclusions: High intensity focused ultrasound in patients with previously untreated prostate cancer is generally well tolerated and it has the potential to completely ablate the prostate gland. With further refinement of the optimal treatment dose and technique this technology has the potential to be an effective form of therapy for localized prostate cancer.

Key Words: prostate; prostatic neoplasms; ultrasound, high-intensity focused, transrectal

High intensity focused ultrasound uses high energy ultrasound waves to destroy the tissue around a focal point 3 to 5 cm from the energy source without injuring the intervening tissue. At the focal point of the transducer ultrasound energy is concentrated and absorbed by the tissue, producing temperatures that exceed 80C, resulting in coagulative necrosis. This technique was initially investigated in the 1940s and 1950s to destroy selective regions in the central nervous system. It is now recognized that HIFU has the capability of transdermally/transmucosally coagulating and destroying tissue in various conditions that have medical applications, including the uterus, spleen, liver, kidney, breast and bone.

In 2000 we received FDA approval to perform a phase I/II feasibility study to test the safety and efficacy of the SB-500 device for previously untreated localized prostate cancer. The investigational device exemption was limited to 20 patients. This report is the result of the study.

MATERIALS AND METHODS

An investigation device exemption for this study was obtained from the United States FDA in November 2000. All patients were treated after obtaining informed consent following approval from the institutional review board. A total of 20 patients were enrolled and treated in this study. They underwent 1 (8 patients), 2 (10) or 3 (2) HIFU treatments to the prostate with the last treatment occurring in August 2004. Inclusion criteria included pathologically confirmed prostate cancer, Gleason score 7 or less, pretreatment PSA 10 ng/ml or less and stage T1–T2 disease. All patients underwent staging bone scan within 6 months before study participation and they did not receive hormone therapy for at least 3 months before treatment.

In all cases treatment was performed using general anesthesia. The SB-500 uses a 4 MHz high frequency transducer probe placed in a condom filled with degassed water and inserted into the rectum. The water in the condom is circulated and actively chilled to less than 20C, serving as an acoustic coupler and cooler between the transducer and rectum. The SB-500 uses split beam technology, which enables the SB-500 to image the prostate throughout HIFU treatment. With the SB-500 device 2 split beam transducers with different focal lengths (3.0 and 4.0 cm, respectively) are mounted back to back in the same probe, which enables the treating surgeon to target tissue located along the anterior as well as at posterior regions of the prostate without changing the probe.

The transducer is mechanically scanned linearly to produce a sagittal image of the prostate and mechanically rotated to obtain a transverse image of the prostate (fig. 1). During initial probe placement in the rectum the focal zone of the 4.0 cm transducer is positioned to include the anterior edge of the prostate. After full ablation of the anterior portion of the prostate the probe is repositioned in the rectum to permit treatment of the mid portion of the prostate. Finally, the probe is repositioned a third time to treat the posterior

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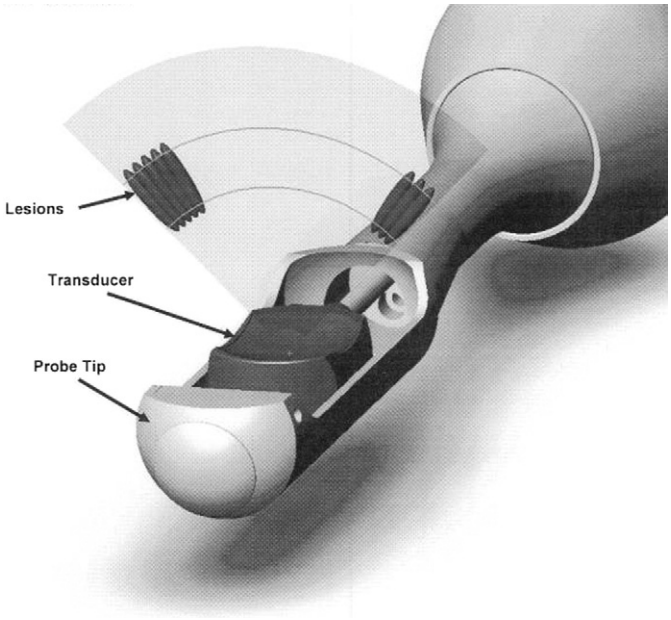

FIG. 1. Computer generated rendering of transducer movement and lesion placement.

portion edge of the prostate with the 3.0 cm transducer. Thus, the entire prostate is treated without the need to remove the probe.

Energy at each site is delivered in a treatment cycle, in which the treatment zone is heated for 3 seconds, followed by a cooling period of 6 seconds, during which the prostate is imaged in the transverse and sagittal planes. Under software guidance the transducer is then positioned at the next treatment site remote from the original site until the entire treatment zone has been ablated. This treatment approach allows the cooling of each treatment site to limit tissue heating outside of the targeted region.

Of the 34 treatments 29 used a percutaneous cystostomy tube, which was placed just before treatment. A Foley catheter was placed after treatment in 5 cases. To determine when urinary retention resolved this tube was capped while the patient emptied the bladder, and then opened to empty the bladder and determine residual urine volume. The catheters were removed when post-void residual urine volume was less than 100 ml. The Appendix shows the patient followup protocol.

This protocol was designed to primarily assess the safety of this device. However, we designed this trial to only include patients with a high probability of having disease confined to the prostate. We collected efficacy data, including serum PSA determinations, at each visit and extended core needle biopsy of the prostate was done at study termination. A minimum 10-core prostate biopsy was performed in all patients at 180 days and patients were re-treated if biopsy showed persistent malignancy. All patients were offered retreatment when a positive biopsy was obtained, up to a maximum of 3 HIFU treatments. All patients were informed of alternative treatments before each re-treatment.

RESULTS

A total of 23 patients enrolled in this study. Three men failed the screening processing, resulting in 20 who were treated with HIFU for prostate cancer. One of the 20 patients who underwent HIFU treatment to the prostate experienced myocardial infarction unrelated to HIFU treatment and died 145 days after treatment, resulting in 19 with full followup data available.

Eight patients underwent a single HIFU treatment, 10 underwent 2 treatments and 2 underwent 3 treatments. Five patients had negative biopsies but PSA greater than 0.5 ng/ml. They were not re-treated using HIFU. Six patients had positive biopsies. They refused further HIFU treatment or elected alternative treatment.

Efficacy

Figure 2 shows PSA results. After each treatment PSA demonstrated a dramatic increase at 48 hours with a PSA nadir achieved by 90 days for 88% of treatments. Four cases achieved the lowest PSA measure at 6 months. A single patient was on luteinizing hormone-releasing hormone agonist therapy 6 months before HIFU treatment. In this patient PSA was less than 0.1 ng/ml before treatment and it remained so after treatment. Biopsy was negative at 180 days.

Table 1 lists prostate biopsy results. At the onset of this study the optimal energy to be delivered to the prostate was unknown. It was based in part on preclinical data in a canine model and a previous trial for the treatment of benign prostatic hyperplasia. Thus, in the spirit of a safety trial the initial total acoustic power values for the transmitted ultrasound were chosen to be low to avoid serious adverse events. Based on the results following initial treatments total acoustic power values were increased and results improved in re-treated cases.

The primary efficacy end point for this study was PSA less than 0.5 ng/ml and negative prostate biopsy at 180 days. Table 2 shows the results using those success criteria.

Adverse Effects

Table 3 lists adverse effects. The most serious adverse effect was the cardiac mortality that occurred approximately 145 days after treatment. That patient experienced no complications of therapy and had PSA less than 0.5 ng/ml at the time of death. This death was determined to be unrelated to

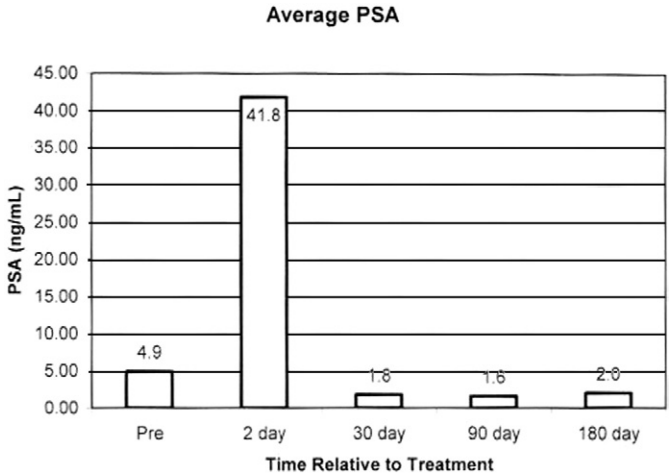

FIG. 2. Average PSA at each interval

TABLE 1. *Biopsy results of each treatment*

	Overall	Treatment No. 1	2	3
No. neg	13	5	7	1
No. pos	6	15	5	1
Total No.	19	19	12	2
% Neg	68	26	58	50

HIFU treatment. The most serious adverse effect related to treatment was a rectourethral fistula, which occurred during re-treatment in 1 patient. This patient was treated with diverting colostomy and the fistula subsequently healed without further intervention. This developed after a second treatment in a patient after we increased the energy delivered. We believe in retrospect that it was due to positioning the focal zone too close to the rectal wall.

Transient urinary retention occurred following every treatment with 2 treatments resulting in urinary retention greater than 30 days in duration. Mean catheterization time was 12 days (range 2 to 44). No patient experienced bladder neck contracture or urinary stricture during the study course.

Urinary dysfunction was assessed using I-PSS. Table 4 shows I-PSS results by symptom grade, including mild—less than 8, moderate—8 to 19 and severe—20 to 35. There was a general decrease in I-PSS symptom score ($p = 0.08$). Of the 19 patients 12 experienced a decreased I-PSS score, in 2 scores were unchanged and 5 reported an increase in symptoms. No patient required transurethral surgery.

Urinary incontinence was assessed by physician interview at each outpatient visit. While 4 patients reported urinary incontinence, none reported the need to wear pads.

ED was assessed using IIEF-5 with certain definitions for the IIEF-5 score, including no ED—22 to 25, mild ED—17 to 21, mild to moderate ED—12 to 16, moderate ED—8 to 11 and severe ED—less than 8. Ten patients who were potent before treatment attempted sexual activity following treatment, including 8 with no ED and 2 with mild ED. Six months after treatment 4 of these patients reported severe ED, none reported moderate ED, 2 reported mild-moderate ED, 1 reported mild ED and 3 reported no ED.

DISCUSSION

HIFU was initially tested in experiments in the canine prostate by Gelet,[1] Bihrle[2] and Kincaide[3] et al. Use of the transrectal probe for treating benign prostatic hyperplasia in humans was first reported in the mid 1980s by Bihrle et al from the department of urology at our institution[4] and by Madersbacher et al from Vienna.[5] In this study HIFU was used to coagulate the periurethral area of the prostate. Two subsequent and larger studies examined the efficacy and safety of HIFU for symptomatic benign prostatic hyperplasia.[6,7]

Madersbacher et al were the first to examine the feasibility of HIFU for localized prostate cancer.[8] They found that, when it was administered before radical prostatectomy, HIFU resulted in a sharply demarcated lesion without injury to the rectal wall or neurovascular bundles. Beerlage et al subsequently confirmed these findings using the Ablatherm® device.[9]

Kiel et al treated 62 patients with localized prostate cancer with the Ablatherm between 1997 and 2000.[10] Overall these investigators used relatively lax criteria for treatment success, defining this as negative biopsies and PSA less than 4 ng/ml. These criteria were met by 87% of the low risk and 55% of the moderate risk group. Of patients at low risk 71% achieved a PSA nadir of less than 1.0 ng/ml and a negative biopsy, while 46% of those at high risk had a negative biopsy and a PSA nadir of less than 0.5 ng/ml.

In 2000 Chaussy and Thuroff reported a 3-year experience with HIFU using the Ablatherm device for localized prostate cancer.[11,12] A total of 232 HIFU sessions were done in 184 patients (1.26 treatments per patient), 48% of the patients received neoadjuvant hormonal therapy and mean followup was 193 days. These investigators noted a decrease in the incidence of rectourethral fistulas from 3% to 0.5% as a result of adding a cooling coupling fluid in the rectum. They also reported that a third of their patients had significant voiding symptoms before treatment and they underwent transurethral prostatic resection postoperatively.

As reported in 2003, recent results of the Ablatherm device described HIFU treatments in 402 patients treated

TABLE 2. *Success rate of each treatment*

	Overall	Treatment No. 1	2	3
No. success	8	2	5	1
No. failure	11	17	7	1
Total No.	19	19	12	2
% Success	42	11	42	50

Success defined as PSA less than 0.5 ng/ml and negative biopsy.

TABLE 3. *Adverse effects of HIFU treatment*

Adverse Effect	No. Pts (%)	No. Treatments (%)	No. Unresolved by 180 Days (%)
Overall	20	34	
Anal discomfort	1 (5)	1 (3)	0
Bladder stone	1 (5)	1 (3)	0
Bladder spasm	1 (5)	1 (3)	0
Dysuria	3 (15)	3 (9)	0
Epididymitis	1 (5)	1 (3)	0
Gross hematuria	3 (15)	3 (9)	0
Perineal discomfort	1 (5)	1 (3)	0
Rectourethral fistula	1 (5)	1 (3)	0
Urinary incontinence	4 (20)	5 (15)	1 (5)
Urinary retention greater than 30 days	2 (10)	2 (6)	0
Urinary tract infection	8 (40)	9 (26)	1 (5)

TABLE 4. *Urinary symptom grade after HIFU treatment*

Symptom Grade	No. Pts: Enrollment	Study End
Mild	10	15
Moderate	8	4
Severe	1	0
Totals	19	19

at 6 sites in Europe.[13] A total of 35 patients (9%) underwent previous radiation therapy and 104 (26%) were being treated with some form of hormonal therapy. The average number of treatments per patient was 1.47 with 28% of patients requiring 2 treatment sessions. A total of 288 patients underwent sextant biopsy after HIFU and 87% had a negative biopsy, including 92%, 86% and 82% in the low, intermediate and high risk groups, respectively. Mean nadir PSA in the low, intermediate and high risk groups was 1.3, 1.4 and 3.1 ng/ml, respectively. Complications were similar to what we noted in our study. The most serious complication was urethrorectal fistula, which developed in 5 patients (1.2%) before the use of the rectal cooling device. Complications have been associated more often with re-treatment,[14] as in our study. Mild to moderate stress incontinence developed in 11% and 3% of the patients, respectively, while severe incontinence requiring intervention developed in 1.5%. Finally, impotence was reported in only 35% of patients.

Uchida et al are the only investigators to report experience with the Sonablate® 200 device for localized prostate cancer.[15] A PSA nadir of less than 0.5, 0.5 to 1.0 and 1.01 to 2.0 ng/ml was achieved in 65%, 25% and 10% of patients, respectively. This group subsequently reported an overall 5-year biochemical disease-free rate of 67%.[16,17] Patients with preoperative PSA less than 10 ng/ml demonstrated a 5-year disease-free survival rate of 88%.

This report describes the results of the first successfully completed United States based clinical study of HIFU treatment for low risk prostate cancer receiving no other therapy. This study was structured as a feasibility study to demonstrate the safety and to a lesser degree the efficacy of SB-500 technology. Using a success definition of a negative extended field biopsy at 6 months and a PSA nadir of less than 0.5 ng/ml success was achieved in 42% of patients overall and in 65% of those who underwent re-treatment, when indicated. Transient urinary retention developed in all patients and a single patient had a rectourethral fistula, which healed with temporary fecal diversion.

The initial treatments in each patient were generally disappointing (tables 1 and 2). To investigate this issue after treating the first 5 patients an amendment was made to the protocol to permit the insertion of needle thermocouples in and adjacent to the prostate. This thermocouple feedback was used to adjust the power levels for re-treatments, resulting in an improved success rate. In addition, an analysis of energy density was performed by determining the acoustic energy transmitted into the prostate, normalized for prostate volume. This study demonstrated that initial treatments that resulted in a negative biopsy had a significantly higher energy density than treatments that resulted in a positive biopsy ($p < 0.02$). A recent publication presents an approach for controlling transmitted power levels that consistently produced a nadir PSA of less than 0.2 ng/ml in 21 of 25 patients.[18]

CONCLUSIONS

The study demonstrates the feasibility of full ablation of the prostate with adequate power levels. Full prostate ablation induces temporary prostatic swelling and voiding dysfunction but long-term serious complications are unusual. This feasibility study was a critical piece in obtaining an FDA investigational device exemption for the pivotal study of the SB-500 for localized prostate cancer. HIFU technology holds promise as an approach to ablate the prostate with acceptable morbidity.

APPENDIX

Followup Schema

48 Hours	30 Days	90 Days	180 Days
Physical examination, anoscopy	Physical examination	Physical examination	Physical examination
PSA	PSA	PSA	PSA
Quality of life assessment	Quality of life assessment	Quality of life assessment	Quality of life assessment
			Needle biopsy of prostate (minimum of 10 cores)

Abbreviations and Acronyms

ED	=	erectile dysfunction
FDA	=	Food and Drug Administration
HIFU	=	high intensity focused ultrasound
I-PSS	=	International Prostate Symptom Score
PSA	=	prostate specific antigen
SB-500	=	Sonablate 500

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EDITORIAL COMMENTS

HIFU is a noninvasive therapy for prostate cancer that has been investigated for more then 10 years. These authors report a feasibility study in a small group of 20 patients with the SB-500 device. The focus of this report is short-term safety and efficacy, which is novel since the literature does not contain many reports of patients treated with this device. This study accurately evaluates adverse events and shows HIFU to be associated with low morbidity except for a rectourethral fistula that occurred early in the series. Objective evaluation of efficacy in this study was limited by the fact that the energy delivered to the prostate was increased during the trial due to poor initial cancer control results. In Europe HIFU is no longer considered an experimental treatment because longer followup has been reported, particularly with the Ablatherm device lately.[1] The value of a study with a 6-month followup is limited at a time when the role of HIFU must be defined by series with long-term followup.[2]

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According to these authors the primary goal of the study was to document the safety of the method and secondarily to show the potential efficacy of transrectally delivered HIFU with the Sonablate. Neither topic shows convincing results. This study in a small group of patients suffers from some limitations that make the comparison of the 2 actually available devices difficult. The series does not define the real potential of HIFU treatment for prostate cancer. During 3½ years a low number of patients (20) were treated with the Sonablate. Since a followup of only 180 days is reported after the last treatment in 2004, the major question that remains is what happened to the patients after the reported 6-month followup?

The authors confirm the use of the device for full gland ablation but they were only able to achieve this in 20% of patients with the first treatment. The overall statistic for the nadir shows a 90-day nadir of 1.6 ng/ml. This excludes full gland treatment. Other studies show a nadir of 0.1 ng/ml, which documents more complete treatment (reference 14 in article).

A 5% incidence of rectourethral fistula and a urinary incontinence rate of 20% do not represent a low complication rate. Obviously no patients in this study needed transurethral intervention. This is in contrast to other investigators who reported a 30% incidence rate of obstruction after HIFU, requiring transurethral prostate resection. The short followup in this study may be responsible for the low number of surgical events after HIFU. These authors provide no data on potency after HIFU.

The 2 serial HIFU devices (Ablatherm and Sonablate) have multiple technological differences in construction, security features, indications and results.[1] Since the article mentions these differences, each device should have been adequately discussed. The only common features of the 2 technologies are the name HIFU and the piezoelectric transducer placed by the transrectal approach. Experimental and clinical research, and data on 1 of these devices should not automatically enable conclusions about the efficacy, side effects and profile of the other device.

As documented by more than 10,000 treatments in Europe and multiple publications, HIFU already provides reliable treatment for organ confined prostate cancer, and delivers promising results as salvage therapy after external beam radiotherapy and even after radical prostatectomy.

HIFU may already justifiably be stated to be a new treatment option in urology.

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Recently the trend in all surgical disciplines has been toward less invasive treatments. The growing interest in HIFU technology stems from its many potential applications as minimally invasive therapy. Recently HIFU has been used in many countries for localized prostate cancer and salvage therapy after radiation.[1,2] This is the first report from the United States in which the second-generation HIFU device was tested in a phase I/II clinical study for localized prostate cancer. I hope that HIFU will be validated in a well designed, multicenter, phase III study in the United States and receive approval from the FDA. This report would provide interesting information on HIFU technology to urologists. In the near future many patients with

localized prostate cancer might be treated with HIFU in a short time on an outpatient basis and return home on the same day with minimum morbidity.

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