

Transrectal High Intensity Focused Ultrasound for the Treatment of Localized Prostate Cancer

T. Uchida¹, N. T. Sanghvi², T. Satoh¹, A. Irie¹,
T. Omata¹, S. Baba¹
M. O. Koch³ and T. A. Gardner³

¹*Kitasato University, Sagamihara, Japan,* ²*Focus Surgery, Inc. Indianapolis, IN 4622,* and ³*Indiana University School of Medicine, Indianapolis, IN 46204*

Abstract. High-intensity focused ultrasound (HIFU) delivers ultrasound energy via a transrectal probe to produce rapid thermal necrosis of prostate tissue in the focal region without damaging the surrounding tissue. Since 1992, we have been treating prostate diseases- both benign and malignant with HIFU. In this study our main objectives were to evaluate efficacy and safety of the HIFU for the treatment of T1b-2N0M0 stage prostate cancer (PCa). We performed over 100 HIFU treatments in 84 patients with biopsy-proven localized prostate cancer using the Sonablate™ HIFU device. We present data on 49 (62 HIFU sessions) patients who underwent six months follow-up and post-operative biopsy. Demographics of these patients are (mean ± SD): age 71.9 ± 6.9 years, prostate volume 27.6 ± 11.6 ml, PSA 17.74 ± 17.9 ng/ml. Gleason scores: 2-4, 5-7 and 8-9 in 14, 30 and 9 patients respectively. 34, 11 and 1 patient received one, two and three HIFU treatment sessions respectively. A mean operating time was 2 hrs 47 min (55-356 min). All patients were treated under epidural anesthesia. Patients were followed with sextant biopsies and serum PSA. The clinical outcome of 49 patients followed for at least 6 months (mean 16.7 ± 16.4 months) is as follows. Complete Response (CR -defined as negative biopsy and PSA velocity of < 0.75 ng / ml of three successive readings) was observed in 95 %, 80%, 40 % and 0% for the patients who had pre-operative PSA level (ng/ml) of less than 10, 20, 30 and higher respectively. PSA results were strongly correlated to the completeness of the HIFU treatment. One earlier patient treated with the Sonablate-200 device developed a rectourethral fistula and 10 patients developed a urethral stricture. Our follow-up would suggest that transrectal HIFU therapy can be used safely to ablate localized prostate cancer with minimal adverse events with a relatively high CR rate and the ability to deliver repeated HIFU treatments without added toxicity. This will allow for repeated HIFU therapy for treatment failures. Additional follow-up continues to confirm the long - term durability of treatment.

INTRODUCTION

Prostate cancer is the leading malignancy in men and the second leading cause of death due to cancer in the United States.¹ In recent years, the rate of prostate cancer in Japanese males is also increasing. The death rate of prostate cancer per 100,000 men in 1985 increased from 4.5 to 11.4 in 1999 in Japan.² The Surveillance, Epidemiology and End Results program of the National Cancer Institute (NCI) has shown a 52% decrease in the rate of distant metastatic prostate cancer between 1990 and 1994.³ With this change in stage distribution, treatments have also changed. Radical prostatectomy rates increased from 17.4/100,000 in 1988 to 54.6/100,000 in 1992.³ In Japan also, the success of early prostate cancer detection has resulted in an increased number of candidates for radical

prostatectomy.⁴ Despite excellent 5- to 10-year survival rates after radical prostatectomy for organ-confined disease, surgery is associated with significant morbidity, such as blood loss with transfusion-related complications, impotence in 30% to 70% of cases, and stress incontinence in up to 10% of patients.³⁻⁶ In addition, surgical intervention is not typically considered for patients whose life expectancy is less than 10 years. Although the immediate complication rate is lower with radiation therapy, impotence, incontinence, radiation proctitis, and cystitis are frequent late sequelae.⁷⁻⁹ Moreover, it has been shown that over 50% of patients have elevated serum levels of prostate-specific antigen (PSA).⁷⁻⁹

Recently, a number of alternative minimally invasive treatments have been developed to treat localized prostate cancer. Brachytherapy, cryosurgical ablation, three-dimensional conformal radiotherapy and laparoscopic radical prostatectomy have been applied, but a definitive cure cannot always be achieved, and generally the treatment cannot be repeated in cases of local recurrence.^{10,16} Since 1992, we have examined the effect of high-intensity focused ultrasound (HIFU) for canine prostate and kidney, and have been treating benign prostatic hyperplasia with transrectal HIFU.^{17,19} HIFU delivers intense ultrasound energy, with consequent heat destruction of tissue at a specific focal distance from the probe without damage to tissue in the path of the ultrasound beam. It has been clinically demonstrated that HIFU can be used to destroy tissue and cure cancer without stimulating metastasis.^{20,21} We report herein our clinical experience treating 100 patients with stage T1b-2N0M0 localized prostate cancer by the Sonablate™ HIFU device.

PATIENTS AND METHODS

HIFU EQUIPMENT

For this study, we used both a modified second and third generation HIFU devices the Sonablate™ -200 and the Sonablate™ -500 (**Fig. 1**; Focus Surgery, Inc., Indianapolis, IN, USA). The Sonablate™ are computer-controlled devices intended to provide HIFU treatment for both benign prostatic hyperplasia and localized prostate cancer. A treatment module includes the ultrasound power generator, multiple transrectal probes of different focal depth, the probe holding articulated arm, and an active water cooling system. The transrectal HIFU probes use proprietary transducer technology with low-energy ultrasound (4 MHz) for imaging of the prostate and for the delivery of high-energy ablative pulses (site intensity, 1300-2200 W/cm²). The single piezoelectric crystal alternates between high-energy ablative (1-4 seconds) and low-energy (6-12 seconds) ultrasound for a total cycle of 7 to 16 seconds.

Before the start of the treatment, the operator uses longitudinal and multi-slices of transverse ultrasound images of the prostate and selects the prostate tissue volume to be ablated by a set of cursors on these images. The probe houses a computer-controlled positioning system that directs sequence of ablative pulses to the targeted region of the prostate. Each discrete high-energy focused ultrasonic pulse ablates a volume of 3x3x10 mm³.²² The individual focal lesion produces almost instantaneous coagulative necrosis of tissue due to a temperature rise of 80° to 95° C in the focal zone.^{22,23} Under computer control, the ultrasound beam is steered mechanically to produce consecutive overlapping lesions laterally and longitudinally to ensure necrosis of the entire targeted prostate

volume (**Fig. 2**). An active automatic cooling device is used during treatment to maintain a constant baseline temperature of less than 20°C in the transrectal probe that helps to prevent thermal injury of the rectal mucosa.



Figure 1: The Sonablate™-500 HIFU device with a transrectal probe attached to an articulated arm. The arm is fixed to an operating table and the user adjusts the probe position to optimize both imaging and treatment of the prostate. The active cooling device circulates cold water to keep the rectal temperature at a safe level. The device has both imaging and HIFU capability on the same transducer that ensures absolute coordination of imaging and treatment position to image and monitor tissue changes on each ablative pulse.

HIFU PROCEDURE

Patient preparation included a cleansing enema, and all patients were anesthetized by epidural anesthesia and intravenous sedation. A condom was placed over the probe and degassed water was used to inflate the condom that was covered with ultrasound gel for close coupling of the ultrasound probe to the rectal wall. The patient was placed in the lithotomy position and the probe inserted manually into the rectum. A 16F Foley balloon catheter was inserted into the bladder for identifying the urethra and bladder neck and 100-150 cc saline solution was introduced into the bladder. Probes with focal lengths of 2.5, 3.0, 3.5, 4.0 and 4.5 cm were used according to the size of the prostate as determined by TRUS, with larger glands requiring longer focal lengths. The probe was fixed in position by the articulating arm attached to the operating table and locked in place once imaging of the prostate optimized the position. After selecting the treatment region of the prostate from the verumontanum to the bladder neck, the HIFU treatment was started. The balloon catheter was removed just before the HIFU treatment. The treatment continued layer by layer (10 mm thick) from the apex to the base. Usually, three successive target areas (anterior, mid-part and base) were defined to treat the whole prostate (**Fig.3**). The contralateral lobe was then treated using the same procedure. Hyperechoic zones, which correspond to microbubbles induced in the treated area, occasionally, appeared in the targeted area during the HIFU procedure. When this hyperechoic phenomenon appeared in the targeted area, the power intensity of HIFU was lowered. After disappearance of the hyperechoic phenomenon, power intensity was returned to the normal levels. The thermal effect of transrectal HIFU is extremely precise with a sharp temperature gradient and fall-off characteristics. Therefore, in cases where the cancer is unilateral and preservation of potency is considered mandatory by the patient, the contralateral neurovascular bundle could be excluded from the treatment. After completing treatment, a transurethral balloon catheter, or percutaneous cystostomy using a 16F or 12F Foley balloon catheter was inserted into the bladder.

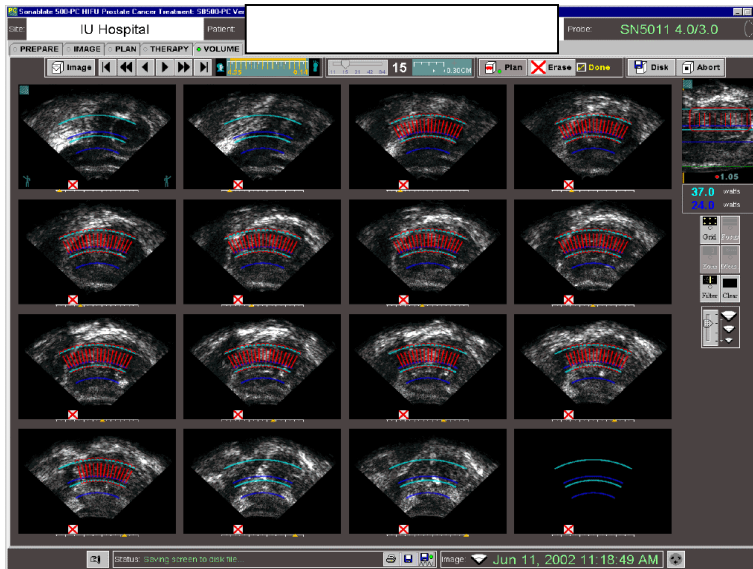


Figure 2: The prostate is scanned from the bladder neck to the apex. Each image slice is marked for the treatment using the cursor. The corresponding longitudinal image on the right upper corner shows the extent of treatment in the long axis.

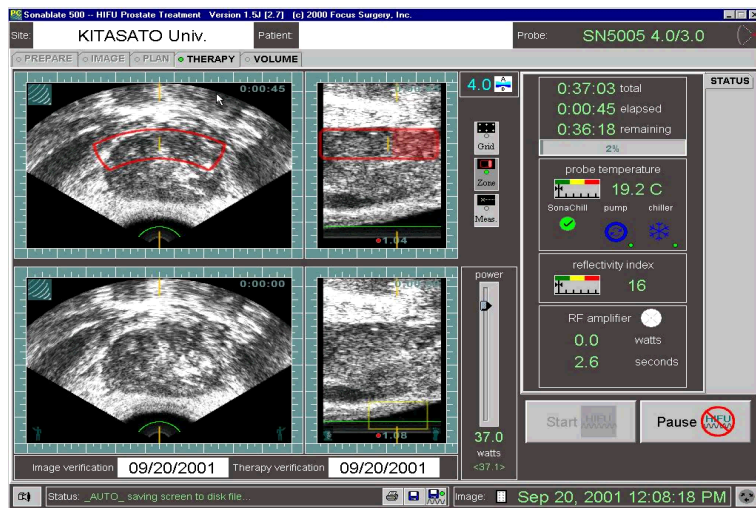


Figure 3: In the treatment mode images of the prostate - both pre-treatment (lower panel) and during the treatment (upper panel) - are displayed to observe tissue changes. In addition temperature, reflectivity index are used for safe operation. The adjustable power level allows the user to decrease and control micro-bubble activity, giving better treatment with increased safety.

PATIENT RECRUITMENT

As per the approved protocol by the local committees, the inclusion criteria for treatment were patients with stage T1b-2N0M0 localized prostate cancer, prostate volumes less than 50 cc. Patients with anal stricture were excluded from the study.

All patients were fully informed of the details of this treatment and provided written consent preoperatively. All patients underwent a digital rectal examination and measurement of serum PSA using an AxSYM PSA assay (Abbott Laboratories, Abbott Park, IL, USA). TRUS, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the pelvic cavity including the prostate were performed to detect evidence of carcinoma and intrapelvic lymph node metastasis. A chest x-ray, abdominal ultrasound or CT of the liver, and bone scans were performed to detect distant metastasis in all patients. All enrolled patients had negative preoperative metastasis in the lung, liver, bone and intrapelvic lymph nodes. All patients showed evidence of adenocarcinoma by prostate biopsy. The TNM staging system was used for clinical staging.²⁴

FOLLOW-UP AND OUTCOME

Total of 49 (62 HIFU treatments) patients with a mean age of 71.9 ± 6.9 years (range, 54-86 years) have been followed over 16.7 months (6-42 months). The mean pre-PSA concentration and prostate volume were 17.74 ± 17.90 ng/mL (range 3.39-89.60 ng/mL) and 27.6 ± 11.6 mL (range 11.4-68.8 mL) respectively. The Gleason sum was 3 to 4 in 14 patients, 5 to 7 in 30 patients, and Gleason sum 8 to 9 in 5 patient.

Patient status and treatment-related complications were followed up by all available means, including periodic patient visits and self-administrated questionnaires dealing with continence and potency. Serum PSA was usually assayed at day 1, 14, 30 and then every 1 to 3 months during follow-up. A randomized sextant control prostatic biopsy was performed at 6 months or when there was any evidence of biochemical failure. Patients with a rising PSA concentration and a negative prostatic biopsy underwent a bone scan and a CT scan to assess for metastatic disease. We defined the complete response (CR) as No evidence of viable tumor cells by postoperative biopsy nor three successive elevation of PSA velocity <0.75 ng/year. Based on this definition further data analysis was performed and reported in our results.

RESULTS

The prostate was treated in 1 (n=34 patients), 2 (n=11 patients) or 3 (n=1 patient) HIFU sessions for a total of 62 procedures in 49 patients (1.4 sessions/patient). Reasons for repeat HIFU treatments were: early experiments with On/Off time and large prostate size or partial treatment. The mean operating time was 2 hours 50 minutes (range, 55 minutes to 356 minutes). The mean hospitalization stay and postoperative urinary catheterization time were 6.5 ± 3.5 days (range, 3-20 days) and 9.7 ± 10.7 days (range, 1-55 days), respectively. A gradual reduction in prostate volume occurred in all patients. The gland size decreased from an initial mean volume of 27.6 ± 11.6 cc (range 11.4-68.8 cc) to a final mean volume of 16.1 ± 9.4 cc (range, 4.4-50.3 cc) in average 7.3 (range, 3-23) months interval. The data were analyzed for complete response as a function of pre-treatment level. The results of this analysis are given below in Table 1.

In addition the data set was subjected to multivariate statistical analysis to define the best correlations to several variables. The best correlation was found between the outcome and pre-treatment PSA. The result of this analysis is given below in Table 2.

Table 1: Complete Response Vs Pre-Treatment PSA range in ng / ml

Pre-treatment PSA level in ng/ml			
0 – 10 ng/ml	10.1-20 ng/ml	20.1-30 ng/ml	30.1-Higher ng/ml
CR / # Pts.	CR / # Pts.	CR / # Pts.	CR / # Pts.
21 / 22	12 / 15	2 / 5	0 / 7
95%	80 %	40 %	0 %

Table 2.0 Multivariate Analysis of data by Cox Regression Test

Factor	Hazard Ratio	95% CI	p value
Age	0.976	0.903 – 1.055	0.5425
Stage	0.623	0.279 – 1.392	0.2485
Gleason score	1.716	1.018 – 2.892	0.0428
Neoadjuvant**	1.774	0.333 – 9.435	0.5015
PSA	1.067	1.030 – 1.106	0.0003*

** LH-RH agonist with or without antiandrogen

* PSA has the highest correlation to outcome.

DISCUSSIONS

In 1995, Madersbacher et al. reported the effect of HIFU (using the old Sonablate™ 200) in an experimental study of 10 cases of histologically demonstrated, hypoechoic and palpable, localized prostate cancer.²³ In this study, only the focal region of the prostate showing a hypoechoic pattern by TRUS was treated by HIFU. The organs were subsequently removed. In 2 cases, the entire carcinoma had been ablated by the procedure, but in the other 8 cases, a mean of 53% of cancer tissue had been destroyed. However, this study was discontinued primarily as it took 8-9 hours to treat 20 ml volume of the prostate tissue. In January 1999, we began HIFU treatment for localized prostate cancer using a modified Sonablate™-200 device. Major improvements of our device included: (1) a reduction in HIFU exposure cycle from 16 seconds (4 On/12 Off) to 9 seconds (3 On/6 Off) which reduced treatment time by 40%, and (2) the introduction of a novel transducer and electronics that splits a single ultrasound beam into multiple beams (termed “split beam”) to cover a larger tissue volume per exposure. The single beam had a focal region of 2 mm x 2 mm x 10 mm (volume = 40 mm³) while the split beam focal region is 3 mm x 3 mm x 10 mm (volume = 90 mm³) that further reduced treatment time about 50%.¹⁵ These developments dramatically shortened the treatment time for a 25 ml prostate gland from 6 hours to 2 hours. Our ideal goal is to be able to treat 1 ml of prostate tissue in 1 minute and finally performed the HIFU treatment in an outpatient clinic under local anesthesia. Like diagnostic ultrasound phased array, HIFU array can provide beam steering controlled by electronics in real-time with energy delivery under computer control to make a true advanced minimally treatment for prostate cancer.

In 1996, Gelet et al. reported a preliminary experience of HIFU using Ablatherm prototype 1.0 (EDAP-Technomed, Lyon, France) for treating localized prostate cancer.²¹ They later summarized their clinical outcome in which a complete response was obtained in 56% of the patients with no residual cancer and a PSA less than 4 ng/ml. Biochemical failure (no residual cancer and a PSA greater than 4 ng/ml), biochemical control (residual cancer and a PSA less than 4 ng/ml), and failure (residual cancer and a PSA greater than 4.0 ng/ml) were noted in 6%, 18% and 20% of patients, respectively.^{20,22} In 1999, Beerlage et al.²³ reported results of 143 HIFU treatments using the Ablatherm prototype 1.0 and 1.1 in 111 patients with clinical stage T1-3N0M0 prostate cancer, and PSA less than 25 ng/mL. The first 65 treatments in 49 patients were performed selectively (i.e., a

unilateral or bilateral treatment in one or two sessions was performed depending on the findings from TRUS and biopsies) and the second 78 treatments in 62 patients that treated the whole prostate. A complete response (defined as a PSA < 4.0 ng/ml and a negative biopsy) was achieved 60% in the group with whole prostate treatment and in 25% of the selectively treated patients.²³ In our study, one patient who was treated selectively in right lobe of the prostate for adenocarcinoma identified by a prostate biopsy, showed a gradual elevation of PSA as well as viable cancer cells by a postoperative prostate biopsy, and then 2nd HIFU treatment was performed on whole prostate and then PSA level has kept low level as well as negative biopsy. Recently, many means of imaging analyses have been performed for detecting prostate cancer including TRUS, CT, endorectal coil MRI and multiple biopsies of the prostate under TRUS. However, prostate cancer is a multi-focal disease and it is not yet possible to determine sites of microscopic focus of cancer cells by imaging analysis alone. Therefore, the whole prostate must be treated, as the results of this HIFU study and other studies corroborate.

The mean hospitalization in our series was 6.5 days. This issue is related to local socio-economics rather than clinical or technical. There is a significant difference in the national insurance systems between Japan and other countries. In Japan, patients older than 70 years of age do not pay for treatments, and only 10-30% of the charges for younger patients are required. Usually, about 30-40 days hospitalization is recommended after a radical prostatectomy in Japan, so the reduction to 6.5 days for the HIFU treatment of localized prostate cancer is a notable improvement. After recently performed HIFU treatments for localized prostate cancer, we were able to release the patient in 3-4 days, and feel that ultimately, an overnight or outpatient stay may be sufficient. One of the most favorable advantages is that HIFU therapy can be repeated in those patients that fail to experience a complete response with the initial treatment or those who may develop a local recurrence. Nine and 1 patients were performed two and three times HIFU treatments in our series. However, reasons of repeat HIFU treatments were short on or long off interval is 6 patients, large prostate volume for 2, partial treatment for 2 and 1 for machine trouble. We have tried a variety on/off interval time to reduce a total operation time. *Patients who were treated with 3 sec On / 6 Sec off time did not require repeated treatments.*

For many reasons, transrectal HIFU appears highly attractive as a minimally invasive treatment for localized / recurrent prostate cancer. One of the most favorable advantages is that HIFU therapy can be repeated or added even though patients with local recurrence have already been treated with a radical prostatectomy, cryoablation of the prostate and radiation therapy including brachytherapy. On the other hand, radical prostatectomy, external beam radiation therapy or brachytherapy cannot be repeated in these patients. A large number of generally younger men who were treated for clinically localized prostate cancer have already had, or are now experiencing, recurrence. If approximately 200,000 patients are diagnosed with prostate cancer per year, of whom two-thirds are treated with surgery or radiation, and up to 40% relapse, up to 50,000 men per year may relapse detected by a PSA increase.²⁵ Options for these patients include observation, external beam radiotherapy to the prostatic bed and/or hormonal therapy. For radiation cases, the choices are similar except that salvage prostatectomy, cryotherapy and perhaps brachytherapy are options for carefully selected cases. HIFU may be able to treat these

patients who diagnosed with local recurrence. The HIFU procedure is very easy and does not require a sterile environment, therefore, it may be possible to perform the HIFU procedure on an outpatient basis.

HIFU treatment is minimally invasive, bloodless (no incision), can be performed on an outpatient basis, has low cost, and avoids systemic side effects. These features combined with the optional curative effect are ideal treatment for patients with localized prostate cancer. The small number of patients and the relatively short follow-up period in our series limit our ability to draw any definitive conclusions. We believe that the data we present here suggests that HIFU may be potentially a useful treatment option for patients with localized prostate cancer and that it has an acceptable side effect profile to warrant further investigation.

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