

# UROLOGY

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## TRANSRECTAL HIGH-INTENSITY FOCUSED ULTRASOUND FOR TREATMENT OF PATIENTS WITH STAGE T1b-2N0M0 LOCALIZED PROSTATE CANCER: A PRELIMINARY REPORT

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### ABSTRACT

**Objectives.** To present our preliminary clinical results of transrectal high-intensity focused ultrasound (HIFU) in Stage T1b-2N0M0 prostate cancer. Efforts are being made to provide minimally invasive alternative treatment options with equal efficacy and fewer side effects. HIFU delivers ultrasound energy with rapid thermal necrosis of tissue in the focal region without damaging the surrounding tissue.

**Methods.** We performed 28 HIFU treatments in 20 patients with biopsy-proven localized prostate cancer using a modified Sonablate-200 HIFU device. All patient characteristics and the clinical outcome of 20 patients followed up more than 6 months (mean 13.5) were analyzed.

**Results.** A complete response was obtained in 100% (20 of 20) of patients, as evidenced by a negative postoperative prostate biopsy and no elevation on three successive prostate-specific antigen (PSA) determinations. Of the 20 patients, 13 (65%), 5 (25%), and 2 (10%) had PSA nadirs of less than 0.50 ng/mL, 0.50 to 1.00 ng/mL, and 1.01 to 2.00 ng/mL, respectively. Rectourethral fistula and urethral stricture were noted in 1 and 2 patients, respectively, and 1 patient underwent transurethral resection of the prostate because of prolonged urinary retention.

**Conclusions.** Our results show that HIFU can be performed without an incision, with a less severe side effect profile, and, unlike most other prostate treatments, is repeatable. Transrectal HIFU may be a useful option for patients with localized prostate cancer. Its long-term efficacy will be determined by additional follow-up and a Phase II trial. UROLOGY 59: 394-399, 2002. © 2002, Elsevier Science Inc.

Prostate cancer is the leading malignancy in men and the second leading cause of death due to cancer in the United States.<sup>1</sup> In recent years, the rate of prostate cancer in Japanese men has also been increasing. The death rate of prostate cancer per 100,000 men in 1985 increased from 4.5 to 11.4 in 1999 in Japan.<sup>2</sup> With this, the success of early prostate cancer detection has resulted in an increased number of candidates for radical prostatectomy.<sup>3</sup> Despite excellent 5 to 10-year survival rates after radical prostatectomy for organ-con-

finied disease, surgery is associated with significant morbidity.<sup>3-5</sup> 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 radiotherapy, impotence, incontinence, radiation proctitis, and cystitis are recognized late sequelae. Moreover, it has been shown that more than 50% of patients have elevated serum levels of prostate-specific antigen (PSA) after external beam radiotherapy, indicating treatment failure.<sup>6,7</sup>

Recently, a number of alternative minimally invasive treatments have been developed to treat localized prostate cancer. Brachytherapy, cryosurgical ablation of the prostate, three-dimensional conformal radiotherapy, and laparoscopic radical prostatectomy have been used, but a definitive cure cannot always be achieved, and generally the treatment cannot be repeated in cases of local recurrence.<sup>8-13</sup> High-intensity focused ultrasound (HIFU) delivers intense ultra-

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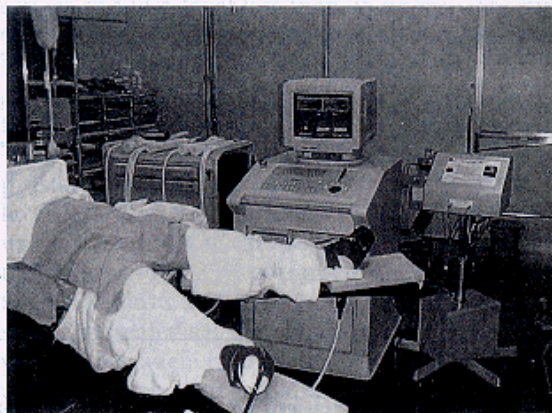


FIGURE 1. Sonablate-200 acoustic ablation device consisting of an operator's console, imaging monitor, transrectal probe, and continuous cooling system.

sound 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.<sup>14</sup> We report our preliminary clinical experience of 28 HIFU treatments in 20 patients with Stage T1b-2N0M0 localized prostate cancer.

## MATERIAL AND METHODS

### HIFU EQUIPMENT

For this study, we used a modified HIFU device called the Sonablate-200 (Focus Surgery, Indianapolis, Ind; Fig. 1). Each discrete high-energy focused ultrasound pulse ablates a volume of  $2 \times 2 \times 10 \text{ mm}^3$  in a single beam for 2.5 and 4.5-cm focal length probes and  $3 \times 3 \times 10 \text{ mm}^3$  of tissue in a split beam for 3.0, 3.5, and 4.0-cm focal length probes.<sup>14-16</sup> The individual focal lesion produces almost instantaneous coagulative necrosis of tissue due to a temperature rise up to 80° to 95°C in the focal zone.<sup>14-16</sup> An automatic cooling device is used during treatment to maintain a constant baseline temperature of less than 22°C in the fluid surrounding the probe at the rectal wall.

### HIFU PROCEDURE

The procedure of HIFU therapy has been previously described.<sup>14</sup> 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, with larger glands requiring longer focal lengths. The treatment continued layer by layer (10 mm thick) from the anterior portion of the gland to the posterior gland. Usually, three successive target areas (anterior, mid-part, and posterior) were defined to treat the whole prostate, including the whole prostatic capsule and seminal vesicles near the peripheral prostate. The urethra was not protected during the HIFU procedure. After treatment, a transurethral balloon catheter or percutaneous cystostomy was inserted into the bladder.

### PATIENT RECRUITMENT AND FOLLOW-UP

The inclusion criteria for treatment were patients with Stage T1b-2N0M0 localized prostate cancer, prostate volumes less than 50 mL, and a serum PSA level less than 20 ng/mL. All patients showed evidence of adenocarcinoma by prostate bi-

opsy. The TNM staging system was used for clinical staging.<sup>17</sup> 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, Ill). Transrectal ultrasonography (TRUS), computed tomography, magnetic resonance imaging, and bone scans were performed in all patients.

Twenty patients (mean age  $72.2 \pm 7.4$  years, range 57 to 86) were included in the trial: 1 patient with clinical Stage T1b, 7 patients with clinical Stage T1c, 9 patients with clinical Stage T2a, and 3 patients with clinical Stage T2b. The mean PSA concentration and prostate volume was  $9.65 \pm 4.43 \text{ ng/mL}$  (range 3.75 to 19.80) and  $25.2 \pm 10.5 \text{ mL}$  (range 13.2 to 50.6), respectively. The histologic grade was Gleason sum 2 to 4 in 4 patients and Gleason sum 5 to 7 in 16 patients. The mean number of biopsy cores and positive cores per patients was 7.1 (range 4 to 10) and 2.6 (range 1 to 4), respectively. Neoadjuvant hormonal therapy using antiandrogen and luteinizing hormone-releasing hormone agonist in 4 patients was introduced for 4.0 months before the visit to our hospital. None of the patients received postprocedure irradiation, androgen deprivation, or other anticancer therapy. Patient status and treatment-related complications were followed up by all available means, including periodic patient visits and self-administered questionnaires dealing with quality of life and potency.<sup>18</sup> The serum PSA level was usually assayed at day 1, 14, 30, 90 and then every 1 to 3 months during follow-up. A sextant prostatic biopsy was performed at 3 months or at the time of any evidence of biochemical failure. The mean follow-up period in the 20 patients was  $13.5 \pm 6.8$  months (range 6 to 31), and 11 patients (55%) were followed up for 12 months or longer.

## RESULTS

The prostate was treated in one ( $n = 12$  patients) or two ( $n = 8$  patients) sessions for a total of 28 procedures in 20 patients (1.4 sessions per patient). The reasons for repeat HIFU treatments were as follows: 1 patient was selectively treated on the right lobe of the prostate because the preoperative prostate biopsy had shown unilateral disease only and 4 patients were retreated because of remaining tumor foci by postoperative prostate biopsy and/or PSA elevation. In addition, 2 patients required a repeat treatment because of larger prostate size (37.9 and 50.6 mL), and 1 patient was retreated because of technical difficulty with the device. Of the 28 HIFU treatments, 4, 3, 2, and 1 different focal length probes were used in 2, 8, 17, and 1 cases, respectively, and a probe change was needed 2.4 times per patient. The mean operating time was 2 hours, 49 minutes (range 55 minutes to 5 hours, 56 minutes). The mean hospitalization stay and postoperative urinary catheterization time was  $6.9 \pm 3.9$  days (range 4 to 20) and  $10.1 \pm 12.6$  days (range 1 to 55), respectively. The mean number of PSA measurements after HIFU treatment per patient was 10.9 (range 3 to 21). A gradual reduction in prostate volume occurred in all patients. The gland size decreased from an initial mean volume of  $24.7 \pm 9.7 \text{ mL}$  (range 13.2 to 50.6) to a final

TABLE I. HIFU therapy for localized prostate cancer

Report	Patients (n)	CR (%)		PR (%)		Failure (%)
		Biopsy Negative PSA <4.0 ng/mL	Biopsy Negative PSA >4.0 ng/mL	Biopsy Positive PSA <4 ng/mL	Biopsy Positive PSA >4 ng/mL	
Beerlage <i>et al.</i> <sup>23</sup>	49*	25	3	37	35	
	62	60	8	26	6	
Gelet <i>et al.</i> <sup>20</sup>	50	56	6	18	20	
Chaussy and Thüroff <sup>24</sup>	—	73	10	2	15	
Current study	20	100	0	0	0	

Key: CR = complete response; PR = partial response; PSA = prostate-specific antigen.  
\* Prostates were selectively treated.

TABLE II. HIFU therapy with different criterion for failure\*

Report	Patients (n)	CR (%)	Failure (%)	Mean Follow-up (mo)
Gelet <i>et al.</i> <sup>21</sup>	82	62	38	17.6 (3-68)
Current study	20	100	0	13.5 (6-31)

Abbreviations as in Table I.

Numbers in parentheses are the range.

\* Criterion for determining failure was a positive biopsy regardless of the PSA concentration or three successive elevations of PSA in patients with negative biopsies.

mean volume of 15.4 ± 6.9 mL (range 5.5 to 29.5) in an average of 7.40 months (range 3 to 23).

All 20 patients (100%) exhibited no evidence of viable tumor cells by postoperative prostate biopsy regardless of the PSA concentration nor did any patient have three successive PSA elevations after a post-treatment nadir.<sup>19,20</sup> Of the 20 patients, 13 (65%), 5 (25%), and 2 (10%) patients had a PSA nadir of less than 0.50 ng/mL, 0.50 to 1.00 ng/mL, and 1.01 to 2.00 ng/mL, respectively. The main pathologic findings at prostate biopsy 3 and 12 months after the procedure showed coagulation necrosis and fibrosis.

Acute urinary symptoms such as frequency, urgency, and difficulty urinating were common during the first 2 months after HIFU treatment. The symptoms proved transitory and were easily managed by medical treatment such as alpha-blockers and/or painkillers such as Voltaren suppository. The urethral catheter in all patients was removed 1 to 2 days postoperatively, but the catheter was reinserted in patients who could not urinate spontaneously and removal of the catheter was attempted every 1 to 2 weeks thereafter. Rectourethral fistula was noted in 1 patient with a cystic lesion in the peripheral part of the prostate 2 months after the second HIFU procedure. He was successfully treated by colonoscopic surgery with paste and direct suture of the fistula under transient cystostomy. Urethral stricture occurred in 2 patients who were both treated by internal urethrotomy with a

cold knife as an outpatient procedure at 6 months postoperatively. One patient opted for transurethral resection of the prostate because of persistent urinary retention at 22 days postoperatively. The pathologic finding of the resected tissue showed coagulative necrosis. No incontinence was observed in follow-up. Postoperative impotence was noted in 3 (30%) of 10 patients who were potent preoperatively as assessed by the self-administered questionnaire.

#### COMMENT

In January 1999, we began HIFU treatment for localized prostate cancer using a modified Sonablate-200 device. Major improvements in our device included a reduction in the HIFU exposure cycle from 16 seconds (4 on/12 off) to 9 seconds (3 on/6 off), which reduced the treatment time by 40%, and 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 × 2 × 10 mm (volume 40 mm<sup>3</sup>) and the split beam focal region is 3 × 3 × 10 mm (volume 90 mm<sup>3</sup>), which reduced the treatment time further by about 50%.<sup>15</sup> These improvements allowed us to treat a 25-mL prostate in less than 3 hours.

In 1996, Gelet *et al.*<sup>21</sup> reported a preliminary experience of HIFU using the Ablatherm prototype 1.0 (EDAP-Technomed, Lyon, France) for treating localized prostate cancer. 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 of 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.<sup>20,22</sup> In 1999, Beerlage *et al.*<sup>23</sup> reported their 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 level less than 25 ng/mL. The first 65 treatments in 49 patients were performed selectively (ie, 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 treated the whole prostate. A complete response (defined as a PSA level less than 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 (Tables I and II).<sup>23</sup> In our study, 1 patient, who was treated selectively in the 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. Recently, many means of imaging analyses have been performed to detect prostate cancer, including TRUS, computed tomography, endorectal coil magnetic resonance imaging, and multiple biopsies of the prostate under TRUS. However, prostate cancer is a multifocal 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.

Several recent studies of HIFU therapy using Ablatherm devices have demonstrated 56% to 73% complete responses with a negative biopsy and a PSA level of less than 4.0 ng/mL (Tables I and II).<sup>22-24</sup> More recently, Gelet *et al.*<sup>20</sup> reported the clinical results of HIFU treatment for Stage T1-2N0M0 localized prostate cancer with PSA levels less than 20 ng/mL using more strict response criteria. Their criteria for determining failure included any positive biopsy regardless of the PSA concentration or three successive elevations of PSA with a velocity of 0.75 ng/yr or greater in patients with negative biopsies. They reported that 62% of their patients showed a complete response (Table II).<sup>20</sup> In this study, 100% of patients showed a complete response as evidenced by a negative biopsy and a PSA level less than 4.0 ng/mL (Table I). When we summarized our clinical outcome by the strict response criteria, 100% of patients also showed a complete response in the present study (Table II). However, about 20% of patients with Stage T1b to T2b and Gleason sum 4 to 7 have a chance of seminal vesicle and lymph node involvement.<sup>25</sup> In addition, Beerlage *et al.*<sup>26</sup> and Van Leenders *et al.*<sup>27</sup> reported that the ventral, lateral, and dorsal side of the prostate, which were removed by radical prostatectomy 7 to 14 days after HIFU treatment using the Ablatherm device, were incompletely destroyed. Examination of the whole prostate after radical prostatectomy 7 to 14 days after HIFU treatment is needed to confirm a true thermal effect by the Sonablate-200. Longer fol-

low-up is also needed to resolve these important questions.

A disadvantage of HIFU treatment for localized prostate cancer is the limit of prostate volume. A prostate of 50 mL size is the limit for the present HIFU device, even using a 4.5-cm focal length probe in our series. It is necessary to develop a longer focal length probe for treating prostates greater than 50 mL in volume. Neoadjuvant androgen deprivation therapy may be useful in larger prostates, especially because reduction of the target volume may increase the efficacy of the HIFU treatment. In addition, patients with intraprostatic large calcifications are not suitable for HIFU. These limitations will be resolved by further development of HIFU.

This is the first report of the HIFU using the Sonablate-200 for localized prostate cancer. Our results showed a more superior effect than the results using the Ablatherm device.<sup>20-24</sup> One advantage of the Sonablate device is that the treatable length of focus in the Sonablate is longer than with the Ablatherm, so that one can treat a larger volume of prostate using the Sonablate (less than 50 mL) than using the Ablatherm (less than 30 mL). In addition, the whole prostate, including the prostatic capsule, was treated using our methods. However, a controlled prospective study is needed to evaluate the true clinical effect.

The mean hospitalization stay in our series was 6.9 days. The main reason for this prolonged stay can be attributed to differences in the insurance system (and payment structure) between Japan and other western countries. Because of the Japanese insurance system, many of the Japanese patients prefer a longer hospitalization. In our experience, HIFU treatments using the Sonablate-200 for patients with localized prostate cancer can be performed as an outpatient procedure or with a 1-night stay, because severe trauma, loss of fluid, and morbidity were not associated with the treatment. One of the most favorable advantages is that HIFU therapy can be repeated in those patients without a complete response after the initial treatment or those who may develop local recurrence.

## CONCLUSIONS

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 suggest that HIFU may be a potentially 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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#### EDITORIAL COMMENT

The authors described their experience using HIFU in Stage T1b-2N0M0 prostate cancer, that is, localized prostate cancer, which is traditionally treated by either radical prostatectomy or radiotherapy, with curative intent. Before discussing this treatment of prostate cancer, the reader should remember that HIFU has been used to treat benign prostatic hyperplasia, but is no longer used because reliable efficacy was not proved. Therefore, the authors must show that a condition that can potentially be cured by other means may be treated with comparable efficacy and safety by this newer HIFU technology. They describe their technique with some clarity and show that they are able to focus on virtually the entire gland and the seminal vesicles.

But are their results convincing? The first anxiety lies in the criteria for selection of patients: it appears that a wide spread of clinical stages was treated, and the range of PSA levels was 3.75 to 19.8 ng/mL, suggesting local spread in some. It would have perhaps been better if the inclusion and exclusion criteria had been tighter. For instance, why did 4 patients receive neoadjuvant hormonal therapy? Also, technically the procedure took a mean of 2 hours, 49 minutes, but the maximal time was 5 hours, 56 minutes. The mean hospital stay and catheterization time were both longer than with radical prostatectomy.

The results of the pathologic examination of the biopsies after treatment and the PSA nadirs are interesting, but the authors did not state when the PSA nadirs occurred. From the reader's point of view, it would have been helpful to have the anxiety allayed that the tumor might recur at a later stage, but, in a condition that requires a genuinely long-term follow-up, this was not addressed. However, the authors have shown that

in the short term at least, there was an absence of viable tumor cells in every patient treated.

The incidence of side effects was relatively high. The long post-treatment catheterization times, that 1 (5%) of 20 patients had a rectourethral fistula, and that 30% were impotent after treatment suggest that further development will be required before this treatment can be proposed as a safe alternative to traditional therapies. It was also suggested that the side-effect profile is acceptable, but the reader may choose to disagree.

The authors are to be congratulated on an honest appraisal of their work. They suggest that this may be an option for treating patients with localized prostate cancer, but I think that before this can be definitely accepted, the exact type of patient who might benefit from it should be defined more strictly, the follow-up should be longer, and the side effects caused by the treatment should be lowered to more acceptable levels.

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#### REPLY BY THE AUTHORS

For prostate cancer, patients who have lymph node metastasis are not suitable at present for HIFU therapy, because HIFU energy cannot treat metastatic lymph nodes even though placed in the intrapelvic lesion. The possibility of lymph node metastasis is higher depending on the clinical stage, grade, and/or serum PSA level. A serum PSA level less than 10 ng/mL is thought to achieve a high success rate using HIFU for localized prostate cancer.

Regarding the question of the treatment of 4 patients with neoadjuvant hormonal therapy, it should be noted that these patients had already received the therapy at another hospital before HIFU treatment.

The total HIFU treatment time was reduced by two major technical developments: (a) the use of a larger focal spot lesion volume from a single beam ( $2 \times 2 \times 10 \text{ mm} = 40 \text{ mm}^3$ ) to a split beam focus ( $3 \times 3 \times 10 \text{ mm} = 90 \text{ mm}^3$ ), and (b) the reduction of the HIFU irradiation interval from 4 seconds on/12 seconds off (16 s/exposure) to 3 seconds on/6 seconds off (9 s/exposure). 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 prostatic tissue in 1 minute and finally perform the HIFU treatment in an outpatient clinic. 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 invasive treatment for prostate cancer.

The length of hospitalization time is discussed in our report. This issue is related to local socioeconomics rather than clinical or technical factors. 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 treatment, and only 10% to 30% of the charges for younger patients are required. Usually, about 30 to 40 days of hospitalization is recommended after radical prostatectomy in Japan, so the reduction to 6 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 to 4 days, and believe that, ultimately, an overnight or outpatient stay may be sufficient.

Catheterization of the patients is required after HIFU treatment and cannot be reduced because of transient edema of the prostate gland. Intermittent self-catheterization or transient placement of prostatic stents might solve this problem.

The serum PSA nadirs occurred within 1 month postoperatively, but longer follow-up is needed to determine clinical outcomes.

Although one rectourethral fistula occurred, no other severe side effects have been seen to date (58 HIFU treatments in 45 patients). We believe that these side effects could be avoided by further refining treatment techniques and using an active continuous flow cooling device to keep the rectal mucosa at a temperature below 20°C during the procedure.

Generally, completeness of cure and preservation of sexual function in the treatment of localized prostate cancer are always controversial, because postoperative impotence depends on preservation of neurovascular bundles that sometimes include tumor invasion. Approximately 30% of the patients exhibited post-HIFU impotence after the HIFU therapy. We believe that this rate is lower compared with radical prostatectomy. In addition, we have been trying to avoid HIFU irradiation on one side of the neurovascular bundle to decrease the rate of postoperative impotence in those patients in whom prostate cancer cells are detected in one lobe only by preoperative sextant prostate biopsy. We believe that an advanced ultrasound guidance system with Doppler may help to avoid treatment of neurovascular bundles more accurately. Obviously, additional experience is required to confirm this important point.

At present, we are convinced that the HIFU therapy could replace the reference standard of radical prostatectomy for localized prostate cancer in the future.

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