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Original Article

Five years experience of transrectal high-intensity focused ultrasound using the Sonablate device in the treatment of localized prostate cancer

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Background: High-intensity focused ultrasound (HIFU) is a minimally invasive technique used in achieve coagulation necrosis. We evaluated biochemical disease-free survival rates, predictors of clinical outcome and morbidity in patients with localized prostate cancer treated with HIFU.

Methods: A total of 181 consecutive patients underwent HIFU with the use of Sonablate (Focus Surgery, Indianapolis, IN, USA). Biochemical recurrence was defined according to the criteria recommended by the American Society for Therapeutic Radiology and Oncology Consensus Panel. The median age and pretreatment prostate-specific antigen (PSA) level were 70 years (range 44–88) and 9.76 ng/mL (range 3.39–89.60). A total of 95 patients (52%) were treated with neoadjuvant hormones. The median follow-up period for all patients was 18.0 months (range 4–68).

Results: The biochemical disease-free survival rates at 1, 3 and 5 years in all patients were 84%, 80% and 78%, respectively. The biochemical disease-free survival rates at 3 years for patients with pretreatment PSA less than 10 ng/mL, 10.01–20.0 ng/mL and more than 20.0 ng/mL were 94%, 75% and 35%, respectively ($P < 0.0001$). Multivariate analysis identified pretreatment PSA ($P < 0.0001$) as a independent predictor of relapse.

Conclusion: High-intensity focused ultrasound therapy appears to be a safe and efficacious minimally invasive therapy for patients with localized prostate cancer, especially those with a pretreatment PSA level less than 20 ng/mL.

Key words high-intensity focused ultrasound, minimally invasive therapy, prostate-specific antigen, prostate cancer.

Introduction

Prostate cancer is the most common malignancy in men and the second leading cause of death due to cancer in the United States.[1] In Japan, although the incidence of prostate cancer has been much less than in American and European countries, it has been sharply increasing during the last two decades.[2,3]

Recently, a number of alternative less invasive treatments has been developed for patients with localized prostate cancer, who are not appropriate for surgery, or who do not want to experience the potential side-effects of surgery. Three-dimensional conformal radiotherapy (3D-CRT), brachytherapy, intensity-modulated external beam radiotherapy (IMRT), cryosurgical ablation of the prostate and laparoscopic radical prostatectomy have been applied to treat this group of patients.[4–8]

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High-intensity focused ultrasound (HIFU) induces 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.[9,10] HIFU could non-invasively induce complete coagulative necrosis of a target tumor without requiring surgical exposure or insertion of instruments into the lesion. Recently, benign prostatic hyperplasia, prostate cancer, renal cell carcinoma and testicular tumor have been treated with HIFU.[11–19] We report herein our 5-year experience with 181 consecutive patients treated with HIFU for clinical stage T1c-2N0M0 localized prostate cancer.

Methods

High-intensity focused ultrasound equipment

For this study, we used the Sonablate (Focus Surgery, Indianapolis, IN, USA) HIFU device. A treatment module includes the ultrasound power generator, transrectal probes, the probe positioning system, and a continuous cooling system (Fig. 1). The transrectal HIFU probes use proprietary transducer technology with low-energy ultrasound (4 MHz) for imaging of the prostate and for the

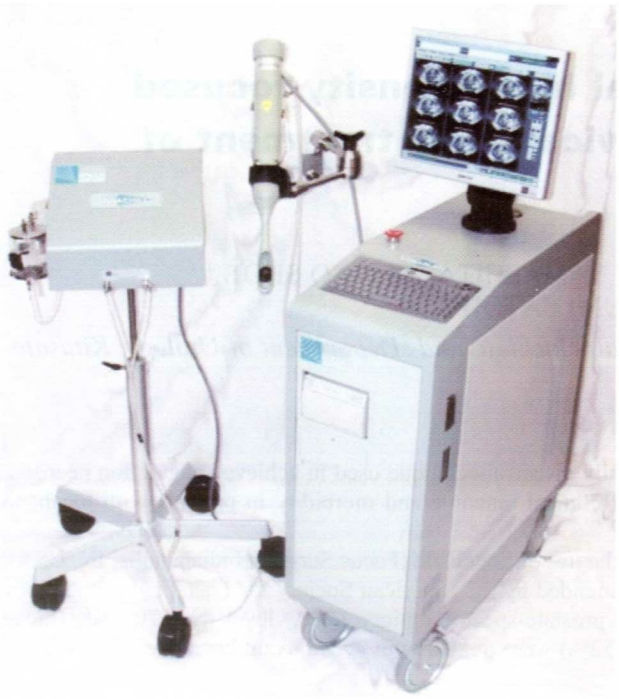

Fig. 1 The Sonablate-500 device consists of an operator's console, imaging monitor, transrectal probe and an automatic continuous cooling system.

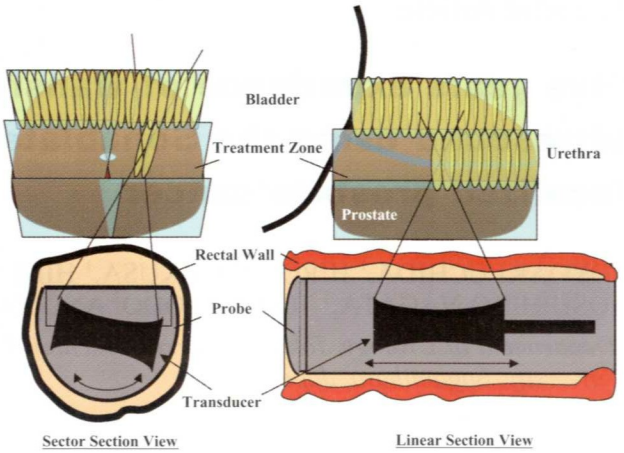

Fig. 2 The computer-controlled transducer ablates the entire prostate tissue. Focal lesions are overlapped in linear rows (left) at each of the lateral sector positions (right) to create a volume lesion.

delivery of high-energy ablative pulses (site intensity, 1300–2200 W/cm^2). The single piezoelectric crystal alternates between high-energy power for ablative (3 s) and low-energy for ultrasound imaging (6 s).[15,20]

The probe houses a computer-controlled positioning system which directs each ablative pulse to the targeted region of the prostate. Each discrete high-energy focused ultrasonic pulse ablates a volume of 3 mm × 3 mm × 12 mm of tissue.[15] The total acoustic power is initially set at 24 and 37 W for 3.0 and 4.0-cm focal length probes, respectively. The individual focal lesion produces almost instantaneous coagulative necrosis of the tissue due to a temperature rise of 80°C to 98°C in the focal zone.[15,20,21] Under computer control, the ultrasound beam is steered mechanically to produce consecutive lesions in a manner such that all focal lesions overlap laterally and longitudinally to ensure necrosis of the entire targeted prostate volume (Fig. 2). An automatic cooling device is used during treatment to maintain a constant baseline temperature of less than 18°C in the transrectal probe which helps to prevent thermal injury of the rectal mucosa.

High-intensity focused ultrasound procedure

The method for using HIFU to treat prostate cancer has been described elsewhere.[15,22] Briefly, all patients were anaesthetized by epidural or spinal anaesthesia, and were placed in a supine and open leg position. The probe was inserted manually into the rectum and was fixed in position by an articulating arm attached to the operating table. Before the start of the treatment, the operator uses longitudinal and transverse sonograms to obtain an image of the prostate and selects the prostate tissue volume to be ablated by a set of cursors on these images. After selection of the treatment region of the prostate from the verumontanum to the bladder neck, the treatment was started. Transrectal probes with focal lengths of 3.0 and 4.0 cm were used according to the size of the prostate as determined by transrectal ultrasound (TRUS), with larger glands requiring longer focal lengths. The treatment continued layer by layer (10 mm thickness) from the apex to the base. Usually, three successive target areas (anterior, mid-part and base) were defined to treat the whole prostate (Fig. 2). After treatment had been completed, a transurethral balloon catheter or percutaneous cystostomy was inserted into the bladder.

Patient recruitment

As a rule, the inclusion criteria for treatment were patients with stage T1c-2bN0M0 localized prostate cancer. Due to the limited focal length of HIFU, gland volume can not be 40 mL or larger. Patients with anal stricture or large calcifications more than 1.0 cm in the prostate were excluded from the study. None of the patients was received adjuvant hormonal and/or chemotherapy. All patients were fully informed of the details of this treatment and provided written consent preoperatively.

The median pretreatment prostate-specific antigen (PSA) level was 9.76 ng/mL (range 3.39–89.60). Pretreatment PSA in patients treated with neoadjuvant hormones was examined before hormonal therapy. The TNM stage was T1c in 92 patients (51%), T2a in 63 patients (35%) and T2b in 26 patients (14%).[23] All patients had a histological diagnosis of prostatic adenocarcinoma according to the Gleason grading system. The histologic grade was Gleason score 2–4 in 23 patients (13%), 5–7 in 134 patient (74%), and 8–9 in 24 patients (13%).[23] Neoadjuvant hormonal

Table 1 Characteristics in 181 patients with localized prostate cancer

Median age (range)	70 (45–88)
Median PSA (range)	9.76 ng/mL (3.39–89.6)
Prostate volume (range)	21.6 (7.1–68.8)
Number neoadjuvant hormonal therapy (%)	
No	86 (48)
Yes	95 (52)
Pretreatment PSA (%):	
10 or less	92 (51)
10.1–20	59 (33)
20.1–	30 (16)
Clinical stage (%):	
T1c	92 (51)
T2a	63 (35)
T2b	26 (14)
Gleason score (%):	
2–4	23 (13)
5–7	134 (74)
8–10	24 (13)
Risk group (%)	
Low	52 (29)
Intermediate	81 (45)
High	48 (26)
Median months follow up (range)	18.0 (4–68)

PSA, prostate-specific antigen.

therapy was delivered in 95 patients (52%) before the visit to our hospital. The patients was classified into three groups depending on serum PSA levels greater than 10 ng/mL, Gleason score 7 or more and stage T2b disease. Low risk involved none of these factors. Intermediate risk involved one, and high risk involved two or more.[24] The patients were classified into low (52 patients), intermediate (81 patients) and high (48 patients) risk groups. The mean and median follow-up period for all patients was 21.1 and 18.0 months (range 4–68), respectively (Table 1).

Clinical follow up and definition of outcome

Patient status and treatment-related complications were followed up by all available means, including periodic patient visits and self-administrated questionnaires dealing with urinary continence and erectile function.[25] Serum PSA was usually assayed every 1–6 months during follow-up. All patients had a minimum of 1 years of follow up and at least three follow up PSA values. A postoperative prostate biopsy was performed on all patients at 6 months. The American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition for biochemical failure, that is, three consecutive increases in post-treatment PSA after a nadir has been achieved, was used to define biochemical failure.[26] The time to biochemical failure was defined as midway between the post-treatment PSA nadir and the first of three consecutive PSA increases. None of the patients received androgen deprivation after HIFU or other anticancer therapy before documentation of a biochemical recurrence.

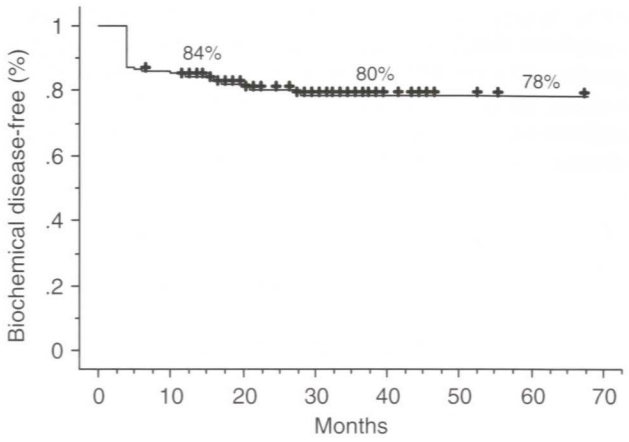

Fig. 3 Kaplan–Meier biochemical disease-free survival curves according in all patients.

Statistical analysis

All statistical analyses were performed using commercially available software (StatView 5.0; Abacus Concepts, Berkeley, CA, USA). The χ^2-test was used to assess the correlation between preoperative and postoperative parameters. The distributions of biochemical disease-free survival rates were calculated according to the Kaplan–Meier curves, and the log–rank test was used to compare curves for groups. For statistical analyses, variables were classified including clinical stage as T1c, T2a or T2b and with or without neoadjuvant hormonal therapy, while age, prostatic volume, pretreatment PSA and Gleason score were evaluated in continuous fashion. A multivariate Cox proportional hazards regression model was used to estimate the prognostic relevance of age, volume of the prostate, pretreatment serum PSA level, clinical stage, Gleason score and with or without neoadjuvant hormonal therapy on survival. All *P*-values less than 0.05 reflected statistically significant differences.

Results

The prostate was treated in one (156), two (22) or three (1) HIFU sessions for a total of 209 procedures in 181 patients (1.2 sessions/patient). A total of 95 patients (52%) were treated with neoadjuvant hormones for 6 months on average (range 1–50). The median time of operation and hospitalization was 152 min (range 51–390 min) and 4.0 days (range 2–20). The gland size decreased from an initial volume of 24.3 mL to a final median volume of 12.8 mL ($P < 0.0001$) in an average of 6.5 months (range, 3–23) interval. Biochemical disease-free survival rate in all patients at 1, 3, and 5 years was 84%, 80% and 78%, respectively (Fig. 3). The biochemical disease-free survival rates at in patients whose serum PSA was less than 10 ng/mL, 10–20 ng/mL and more than 20 ng/mL were 94%, 75% and 35%, respectively ($P < 0.0001$; Fig. 4). Biochemical disease-free survival rate in patients with low, intermediate and high risk groups were 92%, 75% and

64%, respectively ($P = 0.0012$; Fig. 5). No statistically significant difference was noted in patients with Gleason grading ($P = 0.6407$), staging ($P = 0.1339$) and with or without neoadjuvant hormonal therapy ($P = 0.3476$). In multivariate analyses, only pretreatment PSA levels (hazard ratio 1.051; $P < 0.0001$; 95% CI 1.034–1.068) demonstrated a statistically significant variable in these patients but no statistically difference was noted in patients with age, prostate volume, neoadjuvant hormonal therapy, stage and Gleason score (Table 2).

Thirty-nine (22%) patients developed a urethral stricture and 11 (6%) patients developed epididymitis (Table 3). Two (1%) patients developed a rectourethral fistula. Transient grade I incontinence was observed in one patient. One patient underwent transurethral resection of the prostate for prolonged urinary retention for 2 months. Twenty percent (9/45) of potent patients without neoadjuvant hormonal therapy complained of postoperative erectile dysfunction. Three patients were recovered with sildenafil citrate but the remaining six patients did not want further treatment. Nine percent (9/97) of potent patients with or without neoadjuvant hormones complained of retrograde ejaculation.

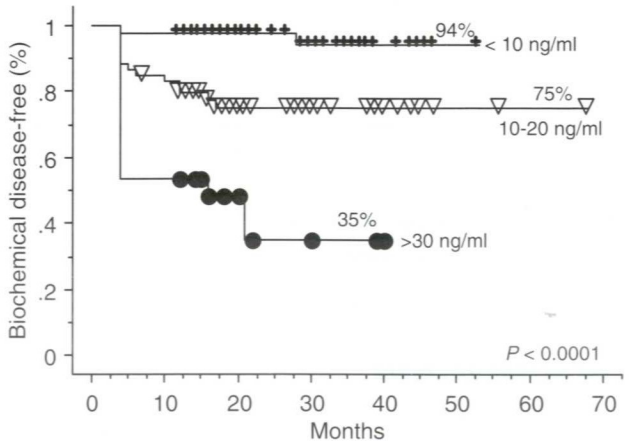

Fig. 4 Kaplan–Meier biochemical disease-free survival curves according in patients with serum prostate-specific antigen.

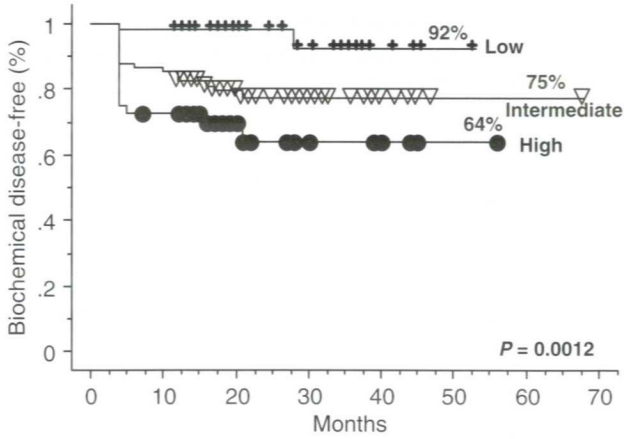

Fig. 5 Kaplan–Meier biochemical disease-free survival curves according in patients with risk group.

Discussion

In 1995, Madersbacher *et al.* reported the effects of HIFU in 10 cases of localized prostate cancer.[21] Histologically, HIFU-treated lesions of the prostate demonstrated a coagulation necrosis with a sharp boundary. In 1996, Gelet *et al.* reported a preliminary experience with HIFU using

Table 2 Multivariate analyses of factors affecting biochemical disease-free survival in 181 patients with localized prostate cancer

Parameters	Hazard ratio	95% CI	*P*-value
Age	1.008	0.961–1.057	0.7486
Prostate volume	0.992	0.957–1.028	0.6607
Pretreatment PSA	1.051	1.034–1.068	<0.0001
Stage	–	–	0.3335
T1cN0M0	1.000	0.401–2.491	0.9995
T2aN0M0	0.544	0.197–1.499	0.2389
Gleason score	1.152	0.900–1.475	0.2612
Neoadjuvant therapy			
(–)	1.053	0.482–2.299	0.8972
(+)	1.000	–	–

PSA, prostate-specific antigen.

Table 3 Complications and treatments

Complication	Patients (%)	Treatments (Number of patients)
Urethral stricture	39 (22)	Periodical urethral dilation (39) Internal urethrotomy (3), TURP (3)
Epididymitis	11 (6)	Antibiotics
Rectourethral fistula	2 (1)	Transient colostomy (1), cystostomy (1)
Stress incontinence (grade 1)	1 (0.6)	Spontaneous recovered in 1 month
Prolonged urinary retention	1 (0.6)	TURP
Erectile dysfunction (45 potent patients)	9 (20)	3 pts recovered with sildenafil citrate
Retrograde ejaculation (97 potent patients)	9 (9)	No treatment

TURP, transurethral resection of the prostate.

the Ablatherm device (EDAP-Technomed, Lyon, France) for treating localized prostate cancer.[13] Beerlage *et al.* reported the results of HIFU treatments in 111 patients with clinical stage T1–3N0M0 prostate cancer and a PSA level less than 25 ng/mL. The first 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 whole prostate was treated in the second 62 patients. A complete response (defined as a PSA level less than 4.0 ng/mL and a negative biopsy) was achieved in 60% of the patients with whole prostate treated and in 25% of selectively treated patients.[14]

Recently, Chaussy and Thuroff summarized clinical outcome by the ASTRO definition as 84.2% stability rate in the HIFU group and 80% rate in the combination with TURP and HIFU group in 1 years.[27] When summarizing our clinical outcome by the ASTRO definition, 78% of the patients were biochemically disease-free at 5-year follow up. In particular, patients with a preoperative PSA less than 10.0 ng/mL showed 94% and 77% biochemical disease-free survival at 4- and 5-year follow up. The clinical outcome in our series of patients with a pretreatment PSA less than 20 ng/mL were comparable to the outcome of patients treated with radical prostatectomy.[28,29] In addition, our result is a similar to the series of brachytherapy (Table 4).[30] As a useful preoperative parameter, pretreatment PSA level ($P < 0.0001$) was a significant independent predictor of time to biochemical recurrence by multivariate analyses.

The development of obstruction and possibly sloughing is the most common side-effect of HIFU because the gland will swell, and there will be necrosis of some or all of the urethra. As previously noted, gland size must be less than 40 mL. If the gland is larger, downsizing is required with total androgen ablation using a gonadotropin-releasing hormone agonist and a non-steroidal antiandrogen. Also, extensive or large calcifications will interrupt, block and reflect the HIFU beam, so these glands cannot currently be treated. If there is rectal stricture, this does not allow the probe to be placed. Many European centers are performing prostate incisions or TURP prior to HIFU in an attempt to alleviate this problem.[27,31] Generally, radicalism of prostate cancer and preservation of sexual function are always controversial because postoperative impotence depends on preservation of neurovascular bundles that sometimes include tumor invasion. In our study, 20% of the patients exhibited erectile dysfunction after HIFU therapy. Interestingly, three out of nine erectile dysfunction patients who desired the treatment for postoperative erectile dysfunction were recovered with sildenafil citrate. We considered that this rate is lower when compared to radical prostatectomy and radiation therapy.[28,29] In our series, grade I transient incontinence was noted in only one (0.6%) patient. This is very low rate in compared with other leading treatments.[4–8,28,29] Obviously, further experience is required to confirm this important consideration.

Table 4 Comparison with clinical outcome between brachytherapy

	Low risk	Intermediate risk	High risk
Blasko *et al.*	94%	82%	65%
Beyer	88%	79%	65%
D'Amico *et al.*	85%	33%	5%
Zelfsky *et al.*	88%	77%	38%
Stock *et al.*	88%	60%	–
Potters *et al.*	92%	74%	55%
Ours	92%	75%	64%

For many reasons, transrectal HIFU appears to be highly attractive as a minimally invasive treatment for localized prostate cancer. HIFU treatment requires no incision or puncture, with no bleeding, can be performed on an outpatient basis and is repeatable, although patients with local recurrence have already been treated with radiation therapy.[32] In addition, radiation therapy including brachytherapy and even surgery can be performed after HIFU.

Conclusion

Although, HIFU is a relatively new procedure of prostate cancer treatment, it represents what may become the next generation of minimally invasive therapy for localized prostate cancer.

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