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Original Article: Clinical Investigation

Transrectal high-intensity focused ultrasound for the treatment of localized prostate cancer: Eight-year experience

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Objective: To report on the long-term results of high-intensity focused ultrasound in the treatment of localized prostate cancer.

Methods: A total of 517 men with stage T1c–T3N0M0 prostate cancer treated with Sonablate devices (Focus Surgery, Indianapolis, IN, USA) between January 1999 and December 2007 were included in the study. Biochemical failure was defined according to the Phoenix definition (prostate-specific antigen nadir + 2 ng/mL).

Results: The median follow-up period for all patients was 24.0 months (range, 2 to 88). The biochemical disease-free rate (BDFR) in all patients at 5 years was 72%. The BDFR in patients with stage T1c, T2a, T2b, T2c and T3 groups at 5 years were 74%, 79%, 72%, 24% and 33%, respectively ($P < 0.0001$). BDFR in patients in the low, intermediate and high-risk groups at 5 years were 84%, 64% and 45%, respectively ($P < 0.0001$). The BDFR in patients treated with or without neoadjuvant hormonal therapy at 7 years were 73% and 53% ($P < 0.0001$), respectively. In multivariate analysis, pretreatment prostate-specific antigen levels (hazard ratio 1.060; $P < 0.0001$; 95% confidence interval 1.040–1.080), neoadjuvant hormonal therapy (hazard ratio 2.252; $P < 0.0001$; 95% confidence interval 1.530–3.315) and stage ($P = 0.0189$) were demonstrated to be statistically significant variables. Postoperative erectile dysfunction was noted in 33 out of 114 (28.9%) patients who were preoperatively potent.

Conclusions: High-intensity focused ultrasound therapy appears to be minimally invasive, efficacious and safe for patients with localized prostate cancer, particularly those with low- and intermediate-risk cancer.

Key words: HIFU, minimally invasive therapy, prostate cancer, ultrasound.

Introduction

Prostate cancer is the most common malignancy in men and the second leading cause of death due to cancer in the USA.[1] Prostate cancer has been treated in various ways, depending on the severity of the condition, age of the patient, staging, Gleason score and serum prostate-specific antigen (PSA) level. A radical prostatectomy has long been regarded as the appropriate therapy for patients with organ-confined prostate cancer. Despite the excellent 5– to 10–year survival rates after a radical prostatectomy for organ-confined disease, surgery is associated with significant morbidity, including blood loss due to transfusion-related complications, erectile dysfunction in 30–70% of cases, and stress incontinence in up to 10% of patients.[2,3] In addition, surgical intervention is not typically considered for patients whose life expectancy is less than 10 years. Recently, a number of alternative, less-invasive treatments have been developed for patients with localized prostate cancer who are either not eligible for surgery or who do not want to risk 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 all been applied for the treatment of this group of patients.[4–7]

High-intensity focused ultrasound (HIFU) is a non-invasive technique that induces coagulative necrosis of a tumor without surgical exposure or insertion of instruments into the lesion.[8] The energy decreases sharply outside the focal zone, thus creating a sharp border between the targeted and non-targeted tissue. Transrectal HIFU is well suited for the anatomic position of the prostate, because the transducer can be introduced into the rectum and brought within 5 cm of the target, no intervening structures are present between the rectum and the prostate and both can be visualized on ultrasonography. In addition, the prostate is located in the pelvic space so that respiratory movement is minimal. These advantages make it one of the most attractive options for the

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localized treatment of tumors. Prostate cancer has been treated with transrectal HIFU since January 1999.[9,10] This report describes the 8-year experience with 517 consecutive patients treated with HIFU for clinical stage T1c–3N0M0 localized prostate cancer.

Methods

As a rule, the inclusion criteria for treatment were patients with biopsy-proven and stage T1c–3N0M0 localized prostate cancer.[10] All patients were treated after obtaining informed consent following approval from the institutional review board for the protection of human subjects at Tokai University School of Medicine.

This study used three generations of HIFU devices: the Sonablate 200 (SB200) from January 1999 to February 2000, the Sonablate 500 (SB500) from March 2000 to October 2006 and the Sonablate 500 version 4 (SB500 V4) from October 2006 and thereafter (Focus Surgery, Indianapolis, IN, USA). This treatment module includes the ultrasound power generator, transrectal probes, the probe positioning system, and a continuous 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/cm^2). The single piezoelectric crystal alternates between high-energy power for ablative and low-energy for ultrasound imaging.[10] Many developments were added in each of the subsequent HIFU devices. Each focus lesion was enlarged from a single beam ($2 \times 2 \times 10$ mm = 0.04 cc) in the SB200 to a split beam ($3 \times 3 \times 12$ mm = 0.108 cc) in the SB500 and SB500 V4. Angle treatment was extended from 75 degrees (SB200) to 90 degrees (SB500 and SB500 V4), which can treat the whole prostate without probe repositioning. The third development was that treating cycles were reduced from 16 s (4 s on and 12 s off interval) for SB200, 9 s (3 s on and 6 s off interval) for the SB500 and 4.5 to 6 s (3 s on and 3 s off or 3 s on 3 s on and 3 s off interval) for the SB500 V4, respectively. Bi-directional color Doppler was added from the SB500 to detect blood vessels surrounding the neurovascular bundle localization and added the capability to exclude the area from the treatment plan. The two-dimensional STACK feature was added in the SB500 V4. This system allows the physician to quickly review and refine a complete prostate treatment plan for more thorough and improved treatment planning during ongoing treatment. Individual treatment sites can be added or removed from the treatment plan with a single mouse click.

All patients were anesthetized by general, epidural or spinal anesthesia, and were placed in a supine and open-leg position. 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, and the probe was then inserted manually into the rectum. The probe was fixed in position by an articulating arm attached to the operating table. After selection of the treatment region of the prostate from the verumontanum to the bladder neck, the treatment was commenced. 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, with larger glands requiring longer focal lengths. The treatment continued layer by layer from the apex to the base. Usually, three successive target areas (anterior, mid-part and base) were defined to treat the whole prostate. After treatment was completed, a transurethral balloon catheter or percutaneous cystostomy was inserted into the bladder.[10]

The serum PSA was assayed every 1 to 6 months during follow up. A postoperative prostate biopsy was performed on all patients at 6 months. Biochemical failure was defined according to the Phoenix definition (PSA nadir + 2 ng/mL).[11] None of the patients received adjuvant therapy during the follow up. Repeat HIFU was carried out in patients whose PSA was elevated more than 4.0 ng/mL and when there were positive biopsy findings. HIFU-related complications were defined using the Japanese version of the National Cancer Institute-Common Toxicity Criteria version 2.0.[12] Erectile function was estimated based on the International Index of Erectile Function (IIEF)-5 scores.[13] Erectile dysfunction is defined as a score ≤ 7 on the IIEF-5 for subjects who had a pre-treatment IIEF-5 >7.[14] Patients were stratified according to the American Joint Committee on Cancer risk factors: low risk, less than or equal to clinical Stage T2a, Gleason score ≤ 6, and PSA level <10 ng/mL; intermediate risk, less than or equal to clinical Stage T2b, and/or Gleason score 7, and/or PSA level of 10.01–20 ng/mL; high risk, more than or equal to Stage T2c, Gleason score ≥ 8 and/or PSA level >20 ng/mL.

Statistical analyses

All statistical analyses were performed using the Stat View 5.0 software program (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 times were calculated according to the Kaplan–Meier curves and the log–rank test was used to compare curves between the groups. A multivariate Cox proportional hazards regression model was used to estimate the prognostic factors. *P*-values of <0.05 were considered to indicate statistically significant differences.

Results

The baseline characteristics of the 517 patients are summarized in Table 1. The median follow-up time was 24 months (range 2–88 months). The first 31 patients were treated with

Table 1 Characteristics in 517 patients with localized prostate cancer

Patients (*n*)	517
Median age (years)	68 (45–88)
Median PSA (ng/mL)	9.2 (2.8–49.6)
Median prostate volume (mL)	21.9 (4.6–68.8)
HIFU machines (*n*)	
Sonablate 200	31 (6)
500	385 (74)
500 ver. 4	101 (20)
Clinical stage (*n*):	
T1c	294 (57)
T2a	22 (4)
T2b	82 (16)
T2c	87 (17)
T3	32 (6)
Gleason score (*n*):	
2–4	37 (7)
5–7	413 (80)
8–10	67 (13)
Neoadjuvant hormonal therapy (*n*)	
No	174 (34)
Yes	343 (66)
Risk group (*n*)	
Low	142 (28)
Intermediate	197 (38)
High	178 (34)

Parentheses are ranges or percentages. HIFU, high-intensity focused ultrasound; PSA, prostate-specific antigen.

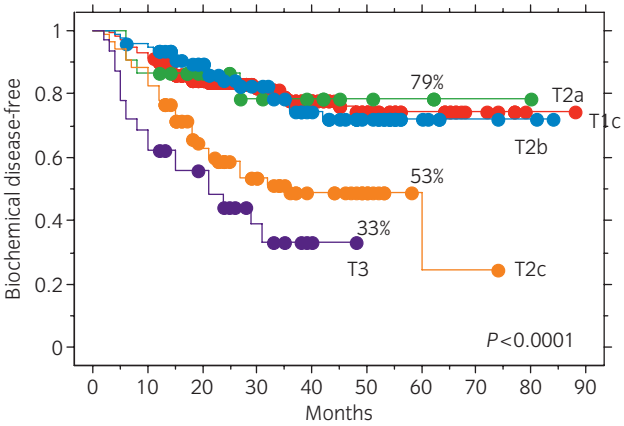

Fig. 1 Biochemical disease-free survival curves according to the clinical stage.

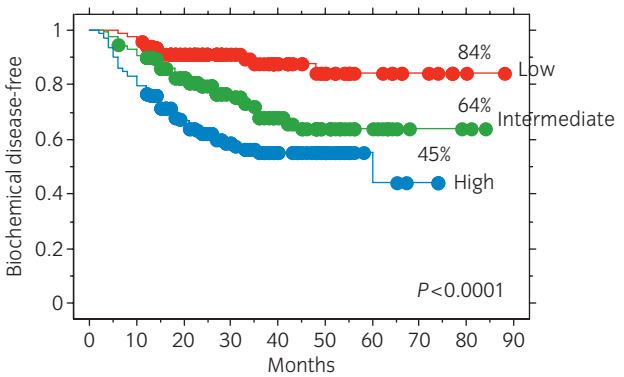

Fig. 2 Biochemical disease-free survival curves according to the risk group. High, high-risk group; Intermediate, intermediate-risk group; Low, low-risk group.

the SB200 from 1999 to 2002; 385 patients were treated with the SB500 from 2002 to 2005; and 101 patients were treated with the SB500 V4 from 2005 and thereafter. The prostate was treated in one ($n = 415$), two ($n = 86$), three ($n = 14$), or four ($n = 2$) sessions. In total, 637 HIFU procedures were performed (average 1.2 sessions/patient). The median age and serum PSA level were 68 years (range 45 to 88) and 9.2 ng/mL (range 2.8 to 49.6). The median operating time and volume of the prostate were 142 min (range 35–390) and 21.9 cc (range 4.6–68.8), respectively. The TNM stage was T1c in 294 patients, T2a in 22 patients, T2b in 82 patients, 2c in 87 patients and T3 in 32 patients. All patients had a histological diagnosis of prostatic adenocarcinoma according to the Gleason grading system. The histological grade was a Gleason score of 2–4 in 37 patients, 5–7 in 413 patients and 8–10 in 67 patients. The number of patients in the low-, intermediate- and high-risk groups was 142, 197 and 178 patients, respectively (Table 1).

None of the patients died due to prostate cancer during the follow up. Of the 483 patients who underwent a follow-up biopsy, 401 (83%) showed no evidence of vital prostate cancer.

The biochemical disease-free rate (BDFR) in all patients at 5 years was 72%. The BDFR in the groups of patients with stage T1c, T2a, T2b, T2c and T3 at 5 years was 74%, 79%, 72%, 53% and 33%, respectively ($P < 0.0001$, Fig. 1). The BDFR in the groups of patients with Gleason scores 2–4, 5–7 and 8–10 at 5 years were 71%, 63% and 68%, respectively ($P = 0.4933$). The BDFR in patients in the low-, intermediate- and high-risk groups at 5 years were 84%, 64% and 45%, respectively ($P < 0.001$, Fig. 2). The BDFR in patients with or without neoadjuvant hormonal therapy were 73% and 52%, respectively ($P = 0.0126$, Fig. 3).The BDFR in patients treated with the SB200 and SB500 at 7 years were 51% and 65%, respectively; for those treated with the SB500 V4 at 2.5 years the BDFR was 92% ($P = 0.0052$). In multivariate analyses, pretreatment PSA levels (hazard ratio 1.060; $P < 0.0001$; 95% confidence interval [CI] 1.040–1.080), neoadjuvant hormonal therapy (hazard ratio 2.252; $P < 0.0001$; 95% CI 1.530–3.315) and stage ($P = 0.0189$) demonstrated statistically significant variables in these patients but no statistical

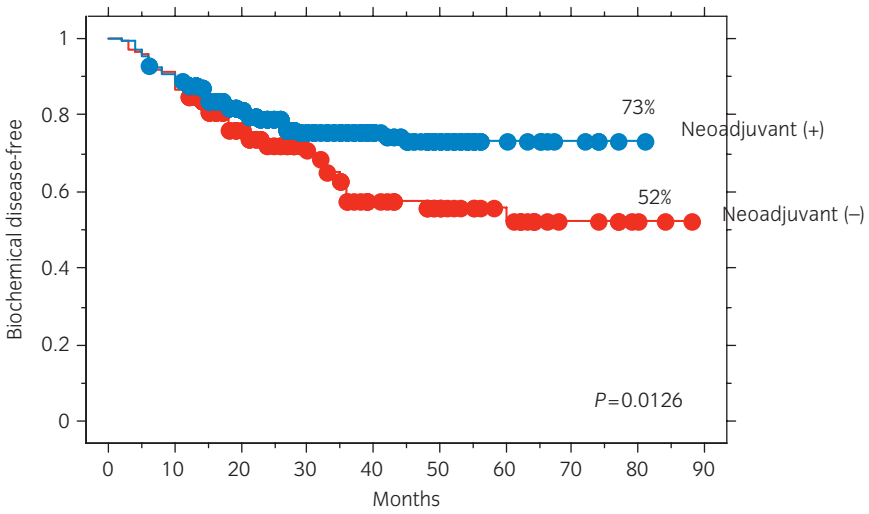

Fig. 3 Biochemical disease-free survival curves according to neoadjuvant hormonal therapy.

Table 2 Multivariate analyses of factors affecting biochemical disease-free survival in 517 patients with localized prostate cancer

Parameters	Hazard ratio	95% CI	*P*-value
Age	0.985	0.962–1.009	0.2138
Prostate volume	0.987	0.967–1.007	0.2076
Pre-treatment PSA	1.060	1.040–1.080	<0.0001
Stage	–	–	0.0189
Gleason score	1.038	0.896–1.203	0.6160
Neoadjuvant therapy	2.252	1.530–3.315	<0.0001
HIFU machine	–	–	0.0695

HIFU, high-intensity focused ultrasound; CI, confidence interval; PSA, prostate-specific antigen.

difference was noted in patients according to age, prostate volume, Gleason score or difference of HIFU machine (Table 2).

Grade 3 or 4 urethral stricture was observed in 105 patients (16.6%). Twenty-one patients (3.3%) were treated with transurethral resection of the prostate and the remaining patients were treated with periodical urethral dilation with metal sounds. Prolonged urinary retention more than 14 days was noted in 84 patients (13.2%). Grade 2 acute epididymitis was noted in 28 patients (4.4%). A rectourethral fistula was noted in six patients (0.9%) who were all treated more than twice. Five of six patients were treated with a transit colostomy and direct closure of the fistula under colonoscopy, and the colostomy was reversed. One patient was spontaneously closed with balloon catheterization for 2 months. Transit grade I incontinence was observed in five patients (0.8%). Postoperative erectile dysfunction was noted in 33 out of 114 (28.9%) patients who were preoperatively potent and retrograde ejaculation was observed in 43 of 211 potency patients (20.3%), with or without neoadjuvant hormonal therapy (Table 3).

Table 3 Complications in 517 patients

Complications	No. of patients (%)
Urethral stricture	105/637 (16.6)
Prolonged urinary retention (*n*)	84/637 (13.2)
Epididymitis	28/637 (4.4)
Recto-urethral fistula	6/637 (0.9)
Urinary incontinence (grade 1)	5/637 (0.8)
Bladder neck contracture	4/637 (0.6)
Hematospermia	2/637 (0.3)
Perineal edema	2/637 (0.3)
Erectile dysfunction†	33/114 (28.9)
Retrograde ejaculation	43/211 (20.3)

†Eleven patients recovered from erectile dysfunction after the administration of Sildenafil. The percentages were calculated according to 637 high-intensity focused ultrasounds taken from 517 patients.

Discussion

Since Madersbacher *et al.* in 1995 and Gelet *et al.* in 1996 first reported treating patients with HIFU for prostate

cancer, a number of studies of this minimally invasive therapy have been published.[8–10,15] Thuroff *et al.* reported that of 402 patients with localized cancer treated with curative intent, 87% of the treated patients had negative biopsy findings on the follow up.[16] Gelet *et al.* assessed the long-term results in patients with low-risk disease (initial PSA level <10 ng/mL, Gleason score ≤6). At 5 years, 78% of the patients were considered to be free of disease and had negative biopsy results.[17] For those with intermediate- and high-risk groups, the disease-free rate was 53% and 36%, respectively. In a recent series, Blana *et al.* treated 163 patients with low- and intermediate-risk disease who were followed up for at least 3 years using the Ablatherm HIFU device. The actuarial biochemical disease-free rate (PSA level <2 ng/mL greater than the nadir) at 5 years in all, low- and intermediate-risk disease was 75%, 77% and 71%, respectively.[18]

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, there is no bleeding, it can be performed on an outpatient basis and it is repeatable even though patients with local recurrence have already been treated with radiation therapy.[19]

The definition of success for HIFU procedures in general has not been standardized. Success has been defined in a number of ways including PSA levels and post-HIFU prostate biopsy findings. In 1996, Gelet *et al.* defined a complete response as a PSA level <4.0 ng/mL and a negative biopsy of the prostate.[15] The American Society for Therapeutic Radiology and Oncology (ASTRO) criteria (three successive increases of PSA) has also been used for analysis.[20] More recently, ASTRO published a new definition of biochemical failure according to the sensitivity to predict clinical outcome after radiation therapy.[11] The 'Phoenix ASTRO' criteria define biochemical failure as an increase in the PSA level of 2.0 ng/mL greater than the nadir or positive biopsy findings. Biopsy findings were not used in the current study as the sole outcome criterion. Generally, prostate biopsy is not routinely performed and is usually applied in a case of PSA elevation after radiation therapy and radical surgery.[20] HIFU is similar to radiation therapy because neither involve the removal of the prostate, such as when performing a radical prostatectomy. However, the HIFU effect is not entirely the same as radiation therapy. The Phoenix definition probably does not enable a valid comparison between radiation therapy and HIFU patients because of the difference in time to PSA nadir (2–3 months for HIFU *vs* 18–36 months for radiation therapy). A specific response criterion is therefore needed to evaluate the clinical outcome after HIFU. The biochemical disease-free rate at 5 years after intensity-modulated radiotherapy has been reported to be 94% for low-risk patients.[4] Zelefsky *et al.* reported a multi-institutional study after brachytherapy with an 8-year relapse-free survival rate using the Phoenix ASTRO criteria of 74% and 61% for the low- and intermediate-risk groups, respectively.[5] Using the Phoenix criteria, the biochemical disease-free rate at 5 years was 84%, 64% and 45% in the low-, intermediate and high-risk groups, respectively, in the current series. In our series, clinical outcome using SB500 version 4 is shown to be better that using SB200 and SB500. The main reason for this improvement may be due to the STACK feature, which can change the treatment region even during treatment. In addition, patients with neoadjuvant androgen deprivation therapy showed a significant clinical outcome. Sumitomo *et al.* reported that combining short-term neoadjuvant androgen deprivation therapy with HIFU treatment showed a significantly better clinical outcome to intermediate-risk and high-risk patients.[21] However, more patients and longer follow up are needed to clarify the improvement.

At present, the main problem arises from swelling of the prostate after treatment, which can require prolonged catheterization or cystostomy drainage. In the current series, 13.2% of the patients were catheterized for more than 14 days after HIFU. Recently, transurethral resection of the prostate or bladder neck incision immediately before HIFU were shown to reduce the treatment-related morbidity, such as postoperative prolonged urinary retention, urinary catheterization time and urinary infection.[22] It is difficult to treat the whole prostate with HIFU if it has a volume of more than 40 mL because of the distance from the transducer to the anterior margin of the prostate. Neoadjuvant hormonal therapy is useful to reduce the volume of the prostate. Chaussy *et al.* performed transurethral resections of the transition zone just before HIFU to reduce the volume of the prostate.[22] Debulking the prostate not only renders the anterior segments more accessible to HIFU, but also reduces the risk of postoperative urinary retention and the need for prolonged catheter drainage or cystostomy. Generally, the radicalism of prostate cancer and preservation of sexual function are always controversial because postoperative impotence depends on the preservation of neurovascular bundles that sometimes exhibit tumor invasion. In the current study, 28.9% of the patients exhibited erectile dysfunction after HIFU therapy. Recently, interest in focal therapy for prostate cancer with HIFU has been renewed.[23] Further experience is therefore required to confirm this important conclusion.

Conclusions

Transrectal ultrasound-guided HIFU is therefore considered to be a promising treatment for prostate cancer, especially in patients with low- and intermediate-risk disease. Refinement of the HIFU technology will improve the clinical outcome and safety. Further studies with randomized controlled trials with other modalities such as a radical

prostatectomy or radiation therapy and a longer follow up will clarify the benefits of this treatment.

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