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Original Article: Clinical Investigation

Transrectal high-intensity focused ultrasound for treatment of localized prostate cancer

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Objectives: To assess the long-term outcomes of transrectal high-intensity focused ultrasound (HIFU) for patients with localized prostate cancer.

Methods: From May 2003 to present, 137 consecutive patients with T1-2 prostate cancer were treated using the Sonablate 500 and then followed for more than 12 months after their last HIFU treatment. A prostate biopsy was routinely carried out at 6 months and serum prostate-specific antigen (PSA) was measured every 3 months after HIFU. Oncological outcomes as well as treatment-related complications were assessed. Disease-free survival (DFS) was judged using the Phoenix definition (PSA nadir + 2 ng/mL), negative histological findings and no local or distant metastasis.

Results: The median follow up after HIFU was 36 months (range 12–84 months). No patients received adjuvant therapy during this period. The PSA nadir occurred at 2 months after HIFU and the median level was 0.07 ng/mL (0.01–2.01 ng/mL). Of the 133 patients who underwent prostate biopsy or transurethral resection of the prostate at 6 months or later after HIFU, six were positive for cancer cells (4.5%). There were no major postoperative complications, but urge incontinence (16 cases) and dysuria (33 cases) occurred after removal of the urethral catheter. The 5-year DFS rate was 78% based on these criteria, and 91%, 81% and 62% in the low-, intermediate- and high-risk group, respectively.

Conclusions: HIFU represents an effective, repeatable and minimally invasive treatment. It is particularly effective for low- and intermediate-risk patients, and it should be considered as an option for localized prostate cancer.

Key words: biochemical failure, high-intensity focused ultrasound, localized prostate cancer, prostate-specific antigen.

Introduction

Serum prostate-specific antigen (PSA) testing and higher male life expectancy has led to increased diagnosis of localized prostate cancer. There are several treatment options for this disease, including radical prostatectomy through open or laparoscopic surgery. Many such procedures have been carried out over the past 15 years, but significant morbidity has been associated with this surgery, and biochemical (PSA) failure has been observed in 20–40% of cases.[1–4] Several alternative and less invasive treatments have also been developed for localized prostate cancer. In 1995, Madersbacher *et al*.[5] reported the effect of high-intensity focused ultrasound (HIFU) in an experimental study of 10 patients with prostate cancer. HIFU is a non-invasive technique for thermal ablation of tissue that can induce complete coagulative necrosis of a target tumor without requiring surgical exposure or insertion of invasive instruments. Since May 2003, we have treated localized prostate cancer with transrectal HIFU, and we have reported the efficacy and safety of HIFU ablation for patients with stage T1-T2 prostate cancer.[6] Here, we describe our 7-year experience with HIFU for treatment of stage T1 or T2 prostate cancer.

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Methods

Since May 2003, we have administered HIFU therapy to patients with stage T1 or T2 N0M0 prostate cancer using the Sonablate 500 and Sonablate 500 version 4 (Focus Surgery, Indianapolis, IN, USA) machines. All patients had a histological diagnosis of prostate cancer (transrectal biopsy in 131 cases and transurethral resection [TUR] specimens in 7) classified by the D'Amico risk group.[7] The disease was staged with a digital rectal examination, computed tomography, magnetic resonance imaging (MRI) and a bone scintigram when deemed beneficial. All patients gave informed consent to the HIFU treatment and the study was approved by the institutional review board for the protection of human subjects at Takanobashi Central Hospital.

Serum PSA was assayed at 1 month and every 3 months after treatment. A postoperative prostate biopsy was carried out at 6 months. None of the patients received adjuvant therapy during the follow-up period. Disease-free outcomes of the HIFU treatment were determined based on negative histological findings on follow-up biopsy and a negative biochemical test (PSA nadir < +2 ng/mL) using the definition of the American Society for Therapeutic Radiology and

Oncology-Radiation Therapy Oncology Group (Phoenix criterion).[8] Disease-free survival (DFS) was calculated using Kaplan–Meier curves, and a log–rank test was used to evaluate differences between these curves. A multivariate Cox proportional hazards regression model was used to estimate the prognostic relevance of age, clinical stage, Gleason score, prostate volume, pretreatment hormonal therapy, PSA level at diagnosis and nadir of serum PSA, with $P < 0.05$ used to indicate statistical significance.

Patient status and treatment-related complications in the Japanese version of the National Cancer Institute-Common Toxicity Criteria version 2.0.[9] were evaluated in periodic patient visits and by self-administered questionnaires (before, and 3, 6, 12 and 24 months after HIFU). Erectile function was simultaneously measured using the International Index of Erectile Function (IIEF)-5 scale,[10] on which erectile dysfunction is defined as a score ≤7 for subjects who had a pretreatment IIEF-5 score >7.[11]

Results

This series included 137 patients who were followed-up for more than 12 months after their last HIFU therapy. As shown in Table 1, the patients had a median age of 70 years (range 50–82), a median prostate volume of 20 mL (range 8–52) and a median PSA level at diagnosis of 7.2 ng/mL (range 2.8–100). The histological grades corresponded to Gleason scores of ≤6 in 41 patients, 7 in 64 patients and ≥8 in 32 patients. The TNM stages were T1b in eight patients, T1c in 58 patients, T2a in 52 patients, T2b in 14 patients and T2c in five patients. The low-, intermediate- and high-risk groups included 29, 68 and 40 patients, respectively. A total of 31 patients received hormonal therapy for >6 months before HIFU and were followed-up for >24 months after HIFU to exclude effects of neoadjuvant hormonal therapy. A total of 18 patients underwent transurethral resection of the prostate before HIFU therapy for treatment of benign prostate hypertrophy (16 cases) and for reducing the prostate volume (2 cases).

The prostate was treated in one (126 patients) or two (11 patients) HIFU sessions. In total, 148 HIFU procedures were carried out (an average of 1.1 sessions per patient). The reasons for repeating the HIFU treatment were PSA failure in 11 cases and positive biopsies in four cases. All 148 treatments were carried out under spinal anesthesia. The median operation and HIFU exposure times were 148 min (range 80–249) and 88 min (range 47–220). The median hospital stay and urethral catheterization period were 4 (range 3–6) and 13 (range 5–28) postoperative days, respectively. There were no intraoperative adverse effects (Table 2).

The median follow-up period after the last HIFU treatment was 36 months (range 12–84). The median PSA nadir was 0.07 ng/mL (range 0.01–2.01) and this was reached in a median of 2.0 months (range1–6; Table 3). A PSA nadir

Table 1 Characteristics of 137 patients with localized prostate cancer who were followed up for more than 12 months after last high-intensity focused ultrasound

	Median (range) or no. patients (%)
Age (years):	70 (50–82)
Prostate volume (mL):	20 (8–52)
PSA level	
At diagnosis (ng/mL):	7.2 (2.8–100)
<10	90 (66)
10–19	40 (29)
≥20	7 (5)
At pre-ablation:	4.6 (<0.2–18)
Gleason score:	
≤6	41 (30)
7	64 (47)
≥8	32 (23)
Clinical cancer stage:	
T1b	8 (6)
T1c	58 (42)
T2a	52 (38)
T2b	14 (10)
T2c	5 (4)
Risk group:	
Low	29 (21)
Intermediate	68 (50)
High	40 (29)
Treatment before HIFU:	
Endocrine therapy over 6 months	31 (23)
TUR-P	18 (13)
HIFU	11 (8)

HIFU, high-intensity focused ultrasound; PSA, prostate-specific antigen; TUR-P, transurethral resection.

Table 2 Intraoperative and perioperative results with high-intensity focused ultrasound therapy

No. patients:	137
No. sessions:	148 times (average 1.1 sessions per patients)
Anesthesia used:	Spinal anesthesia 148 times
Operation time:	80–255 min. (median, 148 min.)
HIFU exposure time:	47–220 min. (median, 88 min.)
Hospital stay:	3–6 days (median, 4.0 days)
Catheterization period:	5–28 days (median, 13 days)
Adverse effects	None

HIFU, high-intensity focused ultrasound.

Table 3 Results of high-intensity focused ultrasound therapy in 137 patients with localized prostate cancer (median follow up of 36 months, range 12–84 months)

Changes of PSA (ng/mL):			Patients (%)
Nadir; median 0.07 (range, 0.01–2.01)			
<0.2			90 (66)
0.2–1			40 (29)
≥1			7 (5)
Latest; median 0.90 (range, 0.01–7.9)			
<0.2			27 (20)
0.2–<1			51 (37)
1–<4			43 (31)
≥4			16 (12)
Positive histological finding:	**Postoperative 6 months**	**During follow up**	**(Positive rate)**
After first HIFU;			
Prostate biopsy	4 patients	5 patients	Total 12/133 patients (9.0%)
TUR specimen	1	2	
After last HIFU:			
Prostate biopsy:	1	3	Total 6/133 (4.5%)
TUR specimen:	1	1	
Disease free survival rate†:		**3-year**	**5-year**
Overall		83.6%	77.8%
Risk group;			
Low		96.7	91.3
Intermediate		83.9	80.7
High		73.5	61.7

†Phoenix definition and positive histological finding. HIFU, high-intensity focused ultrasound; PSA, prostate-specific antigen; TUR, transurethral resection.

<1.0 ng/mL was noted in 95% of cases. Of the 133 patients who underwent a histological examination at 6 months after the last HIFU, two had positive specimens (1 in prostate biopsy and 1 in TUR of the bladder neck, which was carried out for those with difficulty in voiding). A further four patients (3 in prostate biopsies and 1 in TUR of the bladder neck) had a positive specimen during follow up after 12 months. The 5-year DFS rates were 78% in all 137 patients (Fig. 1), and 91%, 81% and 62% in the low-, intermediate- and high-risk groups, respectively (Fig. 2), with a statistically significant difference between the low- and high-risk groups ($P < 0.05$).

Urethral strictures, urinary difficulty and urgency in voiding were observed in 10%, 22% and 11% of the 137 cases after removal of the urethral catheter. No severe post-operative complications (such as urethro-rectal fistula) were seen in follow up (Table 4). Postoperative erectile dysfunction occurred in 22 of 59 patients (37%) who did not undergo hormonal therapy before HIFU therapy and were preoperatively potent.

In Cox regression analysis, age ($P = 0.013$, 95% CI 1.02–1.18); clinical stage T2c versus T1 ($P < 0.003$, 95% CI 0.03–0.48) and T2c versus T2a ($P = 0.036$, 95% CI 0.06–0.91); PSA level at diagnosis ≥10 versus <10 ($P = 0.002$, 95%CI 1.6–8.69); and PSA nadir levels ($P = 0.032$, 95%CI 1.04–2.82) showed a significant association with prognosis, but

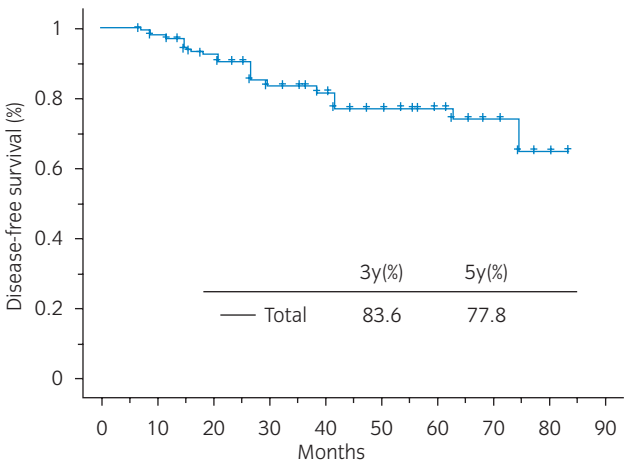

Fig. 1 Kaplan–Meier curve for disease-free survival in all patients.

prostate volume, Gleason score and pretreatment hormonal therapy were not significant. No patients died of prostate cancer, but five died of colon cancer, liver cancer and cardiovascular disease (Table 5).

Discussion

Since the first clinical application of HIFU for treatment of localized prostate cancer by Madersbacher *et al*.[5] (using the Sonablate 200), several investigations of HIFU therapy using Ablatherm or Sonablate systems have been reported for patients with this disease.[12–14] Since May 2003, we have used transrectal HIFU treatment for localized prostate cancer using the Sonablate 500 machine. Our 7-year experience of 137 patients with clinical stage T1 or T2 prostate cancer shows that HIFU is easy to carry out, safe, non-invasive and repeatable; and has no major complications, although difficulty in voiding and grade 1 incontinence were observed in some patients after removal of the urethral catheter, and postoperative erectile dysfunction occurred in 37% of patients. The voiding difficulties and urinary retention were a result of edema of the prostate just after HIFU and to urethral strictures (proximal portion of the external sphinc-

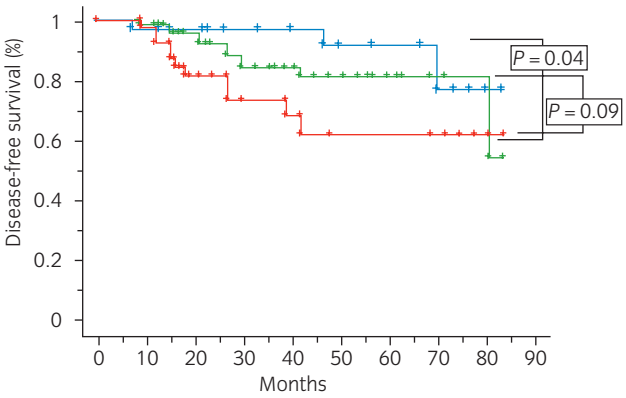

Fig. 2 Kaplan–Meier curve for disease-free survival according to risk group. (—) Low risk; (—) intermediate risk; (—) high risk.

Table 5 Multivariate analysis of factors affecting disease-free survival in 137 patients

Factors	*P*-value	OR	95% CI
Age	0.013	1.10	1.02–1.18
Clinical stage:			
T2c *vs* T1	0.003	0.12	0.03–0.48
T2c *vs* T2a	0.036	0.23	0.06–0.91
T2c *vs* T2b	0.456	0.56	0.13–2.55
Gleason score:			
≥8 *vs* 6	0.123	0.41	0.14–1.27
≥8 *vs* 7	0.367	0.66	0.26–1.63
≥8 *vs* ≤7	0.176	0.56	0.24–1.30
Prostate volume	0.165	0.96	0.92–1.02
Pretreatment hormonal therapy	0.744	1.18	0.44–3.17
PSA level at diagnosis (ng/mL):			
≥20 *vs* <10	0.358	0.48	0.10–2.32
≥20 *vs* 10–20	0.366	2.00	0.45–8.95
≥10 *vs* <10	0.002	3.73	1.60–8.69
PSA nadir level	0.032	1.72	1.04–2.82

PSA, prostate-specific antigen.

Table 4 Morbidity and erectile function after high-intensity focused ultrasound therapy

Complications (137 pts. 148 sessions)	No. patients (%)	
	HIFU ~3 months	After 6 months
Difficult voiding		
Grade 1	10 (6.8)	10 (6.8)
Grade 2	20 (13.5)	4 (2.7)
Grade 3	3 (2.0)	0
Incontinence		
Grade 1	16 (10.8)	1 (0.7)
Urethral stricture	10 (6.8)	2 (1.4)
Urinary infection	6 (4.1)	0
Acute epididymitis	4 (2.7)	1 (0.7)
Prostatic urethral stone	1 (0.7)	2 (1.4)
Vesical stone	0	1 (0.7)

Erectile function	Before HIFU	12–24 months after last HIFU	
IIEF-5 score	>7	≤7	>7
	59	22 (37)	37 (63)

HIFU, high-intensity focused ultrasound; IIEF-5, International Index of Erectile Function-5 scale.

ter and bladder neck) during follow up. We treated these patients with prolonged indwelling urethral catheters, urethral dilatation by a rigid urethroscope and TUR at the bladder neck.

We were able to achieve a satisfactory outcome for disease-free survival in low- and intermediate-risk patients, but not in high-risk patients. These results concur with other recent reports.[15,16] We used the Phoenix definition plus histological results as a basis for judgment of disease-free survival, since we were not satisfied with other definitions currently used to measure the efficacy of HIFU treatment. Recently, specific criteria for assessment of HIFU have been proposed (the Stuttgart criteria),[17] and we intend to compare the results based on the Phoenix-ASTRO and Stuttgart criteria in a future study.

Of the 11 patients in the low- (1 patient), intermediate- (6 patients) and high-risk (4 patients) groups who underwent a second HIFU treatment, two each in the intermediate- and high-risk groups subsequently failed a PSA test. These results suggest that HIFU is an effective treatment in patients with low- and intermediate-risk localized prostate cancer. Currently, we are experimenting with extension of HIFU in sonication of a region of 2–3 mm around the prostate and of the seminal vesicle in high-risk patients. Our multicenter study using the Sonablate 500 machine in a large population of Japanese men with localized prostate cancer suggests that combining neoadjuvant androgen deprivation therapy with HIFU improved the 3-year DFS, with a significant clinical benefit in intermediate- and high-risk patients.[18] We are also trying neoadjuvant endocrine therapy for high-risk patients from 6 to 12 months before HIFU.

Multivariate analysis of factors with a potential effect on disease-free survival showed that age, clinical stage T2c versus T1 and T2a, PSA level at diagnosis $\geq$10 versus <10 ng/mL, and PSA nadir level were significantly associated with prognosis. Therefore, our results suggest that HIFU therapy should be selected for low- and intermediate-risk patients with PSA < 10 ng/mL and clinical stage < T2a. We expected that the Gleason score would have a significant influence on prognosis, as found in other reports,[15,19] but this score did not significantly affect the outcome in our patient population.

There were no serious complications associated with the HIFU procedure. The advantages of HIFU therapy include no bleeding, limited infection, simplicity of the procedure, shorter treatment periods and the potential for repeat treatment. The follow-up period was relatively short and the number of patients in the respective risk groups might not have been enough to examine in the study. However, our results suggest that HIFU is an effective option for low- and intermediate-risk patients with localized prostate cancer. A more effective method of HIFU therapy for high-risk patients is required, and further studies are needed to investigate the efficacy and morbidity of HIFU therapy.

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Editorial Comment

Editorial Comment to Transrectal high-intensity focused ultrasound for treatment of localized prostate cancer

Transrectal high-intensity focused ultrasound (HIFU) is a promising treatment option for localized prostate cancer. However, HIFU is still considered experimental or investigational in the 2010 version of the European Association of Urology guidelines on prostate cancer (http://www.uroweb.org/guidelines/online-guidelines/).

Although encouraging survival data keep emerging in the treatment of localized prostate cancer with HIFU,[1] we still await long-term results before any conclusion can be drawn about survival after HIFU compared with conventional treatment options.

Inoue *et al*.,[2] using the Sonablate 500 machine on 137 patients, presents a promising 5-year DFS rate of 78% overall, with a mean follow up of 36 months. In their paper, Gleason score was not associated with treatment outcome, although 23% of patients had a Gleason score ≥8 at diagnosis. This is in contrast to other studies and it will be interesting to see if this changes with longer follow up.

Somewhat controversially, 11 patients (8%) who needed retreatment with HIFU are not considered as failures by the authors. Conventionally, the need for additional treatment is considered as a failure when assessing treatment efficacy.

One weakness with primary HIFU has been problems treating the anterior part of the prostate as a result of limited length of the HIFU lesions. In the present paper, two patients had transurethral resection of the prostate (TUR-P) in order to diminish the size of the gland and 16 patients for treatment of benign prostate hyperplasia (BPH). This is somewhat confusing, because many patients with BPH have an anterior–posterior diameter exceeding the range of the HIFU device.

In this study, in contrast to other studies,[1] TUR-P was not carried out regularly before HIFU, which might explain the rather long indwelling catheter time (median 13 days) in the present study.

In the present study, the Phoenix criteria specifically validated for the external beam radiation treatment assessment, is applied for assessing treatment failure. It is also widely used in brachytherapy and cryotherapy studies, and should not be considered a great objection against this study. Recently, specific criteria for assessment of HIFU have been proposed,[3] but they are still not validated and it will of interest to see the results when these criteria are being applied.

What about the side-effects? Inoue *et al*.[2] should be honored for using self-administered questionnaires when assessing treatment-related complications and erectile function. Their findings add to previous knowledge that full-gland HIFU treatment has a side-effect profile not substantially better than other treatment options for localized prostate cancer and patients should be informed about this.

One emerging arena for HIFU technology might be focal therapy of prostate cancer. Results from several ongoing studies are awaited. If it can be shown that focal treatment gives acceptable cancer control with considerably fewer side-effects, then the advantage of precise ablative effect with non-invasive technique offered by HIFU technology can be better utilized. A prerequisite for focal therapy is better image techniques of the prostate cancer. Magnetic resonance imaging technology is constantly improving and new ultrasound devices[4] are launched, making it possible to more precisely stage the cancer and also follow up the patients more safely.

As stated by the authors, primary HIFU is currently an option for low- and intermediate-risk patients. Furthermore, the treatment should be offered in a study setting.

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