

Eight Years' Experience With High-Intensity Focused Ultrasonography for Treatment of Localized Prostate Cancer

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OBJECTIVES	To report on the long-term results of high-intensity focused ultrasonography (HIFU) in the treatment of localized prostate cancer.
METHODS	Patients with clinical Stage T1-T2N0M0, biopsy-proven, localized prostate cancer, with a serum prostate-specific antigen (PSA) level of ≤ 20 ng/mL, Gleason score of ≤ 7 , and with no previous curative prostate cancer treatment, were included. All patients underwent HIFU using the Ablatherm device and were required to have a minimal follow-up of 3 years after the last HIFU session to be included in this analysis. Follow-up included PSA measurement and biopsy performed 3-6 months after treatment and in conjunction with an increasing PSA level. Biochemical failure was defined according to the Phoenix definition (PSA nadir + 2 ng/mL). In determining the disease-free survival rate, treatment was considered to have failed if any of the following occurred: biochemical failure, positive biopsy findings, or the initiation of salvage treatment.
RESULTS	The study included 163 patients. Within the 4.8 ± 1.2 years of follow-up, no patient died of prostate cancer. Of the 163 patients, 86.4% achieved a PSA nadir of < 1 ng/mL and 92.7% had negative post-treatment biopsy findings. The actuarial biochemical survival rate at 5 years was 75%. The actuarial disease-free survival rate at 5 years was 66%, with salvage treatment initiated for 12% of the patients. On multivariate analysis, the pretreatment PSA level was the only statistically significant predictive factor of recurrence ($P = .005$).
CONCLUSIONS	The results after long-term follow-up have indicated that HIFU is an efficient and safe treatment for patients with localized prostate cancer. UROLOGY 72: 1329-1333, 2008. © 2008 Published by Elsevier Inc.

High-intensity focused ultrasonography (HIFU) is an alternative approach for the treatment of organ-confined prostate cancer. Acoustic energy is delivered from a transducer and is absorbed in the target area, leading to mechanical effects, cavitation, and thermal effects without damaging tissue in the path of the ultrasound beam. This minimally invasive treatment option has been studied for > 10 years and has been described in detail elsewhere.¹

After feasibility studies and short-term evaluations, we present the data from 163 consecutive patients treated with HIFU from October 1997 to August 2003 for localized prostate cancer with a minimal follow-up of 3 years.

MATERIAL AND METHODS

Equipment

All patients were treated with the second Ablatherm prototype developed in 1997 and the Ablatherm-Maxis device (EDAP, Lyon, France).

Procedure

In brief, the treatment was performed under spinal anesthesia with a suprapubic tube in situ. The treatment was started 6 mm distant from the apex to protect the external sphincter. According to the size of the gland, 1-4 overlapping target areas were defined and treated from the apex to the bladder neck. In patients treated after 2000, transurethral resection of the prostate (TURP) was performed immediately before HIFU under the same anesthesia. This treatment strategy was chosen to reduce the risk of prolonged retention, resect calcification within the prostate, and reduce the size of the gland.

Patients

The patients were considered for HIFU if they were not considered suitable for radical prostatectomy (significant comorbidity and/or life expectancy < 10 years) or refused to undergo

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surgery or external beam radiotherapy. The diagnosis was affirmed by transrectal biopsy (minimum of 6 cores) in patients with a prostate-specific antigen (PSA) level >4 ng/mL and/or positive digital rectal examination findings. All patients were treated from December 1997 to August 2003 and had clinical Stage T1-T2N0M0 biopsy-proven localized prostate cancer, a serum PSA level of ≤20 ng/mL, and a Gleason score of ≤7. The patients were excluded if they had undergone any previous prostate cancer treatment. Before HIFU, a short-term (≤3 months) course of neoadjuvant hormonal therapy was applied in some cases to reduce the prostate volume or to offer patients therapy before they underwent HIFU. Hormonal therapy was ceased before HIFU treatment. All patients provided written informed consent before entering the study, which was approved by the local ethics committee. This report included only those patients with a minimal follow-up of 3 years, with the follow-up period defined as the interval between the last HIFU treatment and the most recent PSA measurement. 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.

Follow-up

The follow-up examinations included transrectal ultrasonography, digital rectal examination, and PSA measurement every 3 months during the first year and every 6 months thereafter. Follow-up sextant biopsies were recommended at 3-6 months after treatment and if any evidence was found of an increasing PSA level. Patients with an increasing PSA level but negative control biopsy findings underwent bone and computed tomography scans to exclude metastatic disease. Patient status and treatment-related complications were followed up by periodic patient visits and self-administered questionnaires. Questions regarding stress incontinence included the number of pads the patient used. Grade 1 was defined as the loss of urine during strenuous exercise, using not more than 1 pad daily; grade 2 as the loss of urine during light exercise; and grade 3 as the loss of urine at rest or during sleep. Patients were asked about erectile function, defined as being able to complete intercourse with or without oral pharmaceutical assistance.

Biochemical failure was defined according to the Phoenix definition (PSA nadir + 2 ng/mL).² The disease-free survival rate (DFSR) was calculated using a failure definition in which the treatment was considered to have failed if biochemical failure occurred, if cancer was found on follow-up biopsy, or if salvage therapy was initiated. Repeat HIFU was not considered as salvage treatment.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences software, version 15 (SPSS, Chicago, IL). The parametric *t* test was used for quantitative variables and the Mann-Whitney *U* test for nonparametric variables. Categorical variables (success rates at the last evaluation) were compared using χ^2 test. Actuarial estimates for survival were calculated using life table methods. The log-rank test was used to compare the curves created using Kaplan-Meier models. A multivariate Cox proportional hazards regression model was used to estimate the prognostic relevance of age, prostate volume, PSA level, Gleason score, clinical stage, neoadjuvant hormonal therapy,

Table 1. Patient baseline characteristics

Patient (n)	163
Mean ± SD age (y)	66 ± 7.1
Mean ± SD PSA (ng/mL)	7.9 ± 3.7
PSA ≤10 ng/mL (n)	119 (73)
PSA 10.1-20 ng/mL	44 (27)
Gleason score	
Median	5
Range	2-7
Gleason score 2-6 (n)	138 (84.6)
Gleason score 7 (n)	25 (15.4)
Mean ± SD prostate volume (cm ³)	23 ± 8.2
Clinical stage (n)	
T1a	11 (6.7)
T1b	10 (6.1)
T1c	18 (11)
T2a	91 (55.8)
T2b	33 (20.2)
Risk group (n)	
Low	84 (51.5)
Intermediate	79 (48.5)

Abbreviation: PSA, prostate-specific antigen.
Data in parentheses are percentages.

and TURP on treatment failure. *P* < .05 was considered statistically significant.

RESULTS

The baseline characteristics of the 163 patients meeting the inclusion criteria are summarized in Table 1. The mean follow-up time was 4.8 ± 1.2 years (range 3-8.6). The first 47 patients (treated before 2000) received HIFU only, the subsequent 116 patients were treated with a combination of TURP and HIFU. Of the 116 TURP specimens from the patients who underwent TURP before HIFU, 65 (56%) revealed tumor on pathologic examination without significant differences in the Gleason score of the biopsy cores and TURP specimen (*P* = .595). The prostate was treated in 1 (n = 129), 2 (n = 33), or 3 (n = 1) sessions. In total, 195 HIFU procedures were performed (average 1.2 sessions/patient).

With a mean of 664 ± 169 single lesions per session, the mean volume treated was 36.5 ± 16 cm³. Compared with the mean gland volume, 173% of the volume was treated by overlapping the treatment areas. The median operating time was 168 minutes (range 80-300). Before treatment, 60 patients underwent short-term neoadjuvant hormonal therapy, which was discontinued before HIFU treatment. No statistically significant differences in baseline characteristics were observed between the patients who did or did not receive hormonal therapy. To exclude any effect of hormonal therapy, these patients were excluded from the PSA nadir analysis. The remaining 103 patients achieved a PSA nadir within 6 months of treatment, with 64% reaching a nadir of ≤0.2 ng/mL, 18.5% a nadir of 0.21-1 ng/mL, and 14% a nadir >1 ng/mL.

Five patients died during follow-up but none of prostate cancer. Of the 124 patients who underwent follow-up biopsy, 115 (92.7%) showed no evidence of vital

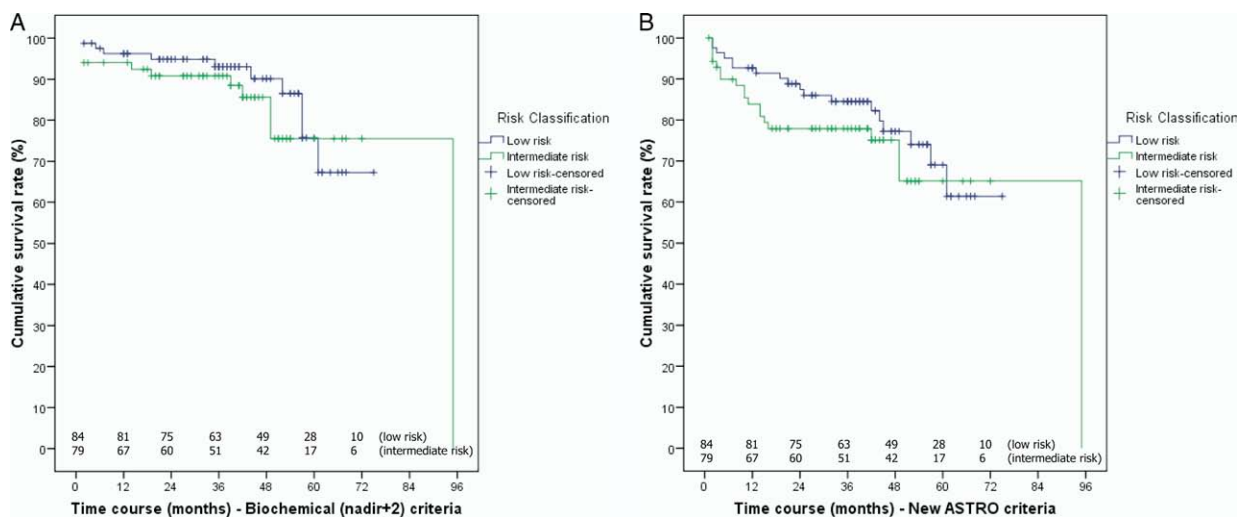


Figure 1. Kaplan-Meier curve according to patients with risk groups. **(A)** Biochemical failures-free survival. **(B)** Disease-free survival.

prostate cancer. No statistically significant difference was found between the low-risk (92.5%) and intermediate-risk (93%) groups ($P = .933$).

Salvage treatment was initiated for 20 (12.2%) patients. Of these 20 patients, 8 (4.9%) received hormonal therapy, 10 (6.1%) received external beam radiotherapy, and 2 (1.2%) underwent salvage radical prostatectomy. Patients chose to undergo salvage treatment after having been informed of all options and according to their medical status. No statistically significant difference was found for administration of salvage therapy between the low-risk (9.5%) and intermediate-risk (15.2%) groups ($P = .253$).

The actuarial biochemical DFSR at 5 years was 75%, with no statistically significant difference between the low-risk (77%) and intermediate-risk (71%) patients ($P = .437$; Fig. 1A). The 5-year actuarial DFSR was 66%, with no statistically significant difference between the low-risk (70%) and intermediate-risk (61%) patients ($P = .322$; Fig. 1B). No statistically significant difference was found between patients who did or did not undergo TURP before HIFU in terms of biochemical failure-free survival ($P = .345$) and disease-free survival ($P = .993$). On multivariate analysis, the pretreatment PSA level (hazard ratio 1.151, 95% confidence interval 1.039-1.274; $P = .007$) was the only statistically significant predictive factor affecting the DFSR.

Grade 1 incontinence was observed in 10 (6.1%) patients, 3 (1.8%) patients had grade 2 incontinence, and no patient reported grade 3 incontinence. Valid data on erectile function were available for 127 (77.9%) patients at the last follow-up visit. Of the 127 patients, 76 were potent before HIFU and were considered in the analysis. Of the 76 patients, 42 (55.3%) reported full erectile function, being able to complete intercourse with or without oral pharmaceutical assistance, and 34 (44.7%) were impotent. Bladder outlet obstruction caused by necrotic tissue or scarring requiring transurethral surgical

intervention developed in 40 (24.5%) patients during follow-up. No statistically significant difference was found in the rate of postoperative obstruction between those who underwent HIFU alone (26.7%) and those who underwent HIFU and TURP (19.1%; $P = .422$). Acute urinary tract infections occurred in 11 (7.8%) patients and transient (<6 months) pelvic pain in 6 (3.7%) patients.

COMMENT

Since the first reports by Madersbacher et al.³ in 1995 and Gelet et al.⁴ in 1996 of patients treated with HIFU for prostate cancer, an increasing number of studies of this minimally invasive therapy have been published. In the present study, only patients with a minimal follow-up of 3 years were included. With a mean follow-up of 4.8 years, a well-founded evaluation was possible regarding the efficacy of HIFU as a prostate cancer treatment.

The early achievement of the nadir PSA level within 6 months provided early evidence of the treatment efficacy of HIFU,^{5,6} with 86.4% of the patients in our study reaching a PSA nadir of <1 ng/mL. However, the definition of treatment failure after any prostate cancer treatment is a matter of contentious debate, and HIFU is no exception. Most HIFU studies used a combination of biopsy results and PSA cutoff values. The initial reports used a high PSA cutoff of 4 ng/mL, which was soon abandoned.^{4,7} In a previous analysis, we investigated the success after HIFU using a low PSA cutoff of 0.4 ng/mL as proposed by Amling et al.⁸ and found a DFSR at 22 months of 71.5%. However, by applying this low PSA cutoff, some patients might have been judged to have treatment failure, despite a stable but slightly elevated PSA level. This motivated the use of the original biochemical failure definition of 3 successive increases put forward by the American Society for Therapeutic Radiology and Oncology (ASTRO). Using this definition,

Uchida et al.⁹ reported a post-HIFU biochemical DFSR of 78%. More recently, ASTRO published a new definition of biochemical failure according to the sensitivity and specificity of the definition to predict clinical failure. The "Phoenix" criteria define biochemical failure as an increase in the PSA level of 2.0 ng/mL greater than the nadir. Although neither the ASTRO nor Phoenix criteria are recommended for use in patients treated with modalities other than radiotherapy, they have come to be applied to patients treated with other therapies such as cryoablation¹⁰ and radical prostatectomy.^{8,11}

Admittedly, the use of the Phoenix definition is a shortcoming of the present analysis. However, we believe similarities exist between radiotherapy and HIFU that make it reasonable to do so. A HIFU-specific definition of biochemical failure is needed, but this cannot be done until large data sets are available. Using the Phoenix failure criteria, the biochemical disease-free rate at 5 years was 75% for low- and intermediate-risk patients. Depending on the dose and technique, the biochemical failure-free survival rate at 5 years after external beam radiotherapy has been 69%-94% for low-risk patients.^{12,13} Few studies on low-dose brachytherapy using the Phoenix ASTRO criteria have been published. Zelefsky et al.¹⁴ reported a multi-institutional study involving patients with a median follow-up of 63 months after brachytherapy with a 8-year relapse-free survival rate of 74% and 61% for the low- and intermediate-risk groups, respectively.

In our series, 92.7% of patients had negative biopsy findings compared with the range (68%-93%) given in published reports.¹⁵ However, biopsies should not be used as the sole outcome criterion because only positive biopsy findings are evidentiary owing to sampling error.

Using the Phoenix definition, we found an actuarial DFSR at 5 years of 66% in our study. An equal 5-year DFSR of 66% was recently reported by Poissonnier et al.⁵ However, it is difficult to fully understand this outcome in relation to other therapies. To our knowledge, no publications to date have taken the complete Phoenix definition into account and reported the radiotherapy outcomes, with treatment failure defined as biochemical failure, positive biopsy findings, or the initiation of secondary treatment.

On multivariate analysis, the PSA level was the only statistically significant variable affecting disease-free survival in our analysis. Uchida et al.⁹ reported similar findings, and, in a study by Poissonnier et al.,⁵ only a greater preoperative PSA level was a negative prognostic outcome factor. Evidence has shown that because of the temperature levels achieved in the prostate by HIFU, all tissue is destroyed, regardless of the Gleason score.¹⁶

Obstruction due to necrosis or scarring of the prostate is the most common adverse effect after HIFU. In 181 patients treated with the Sonablate 500 (Focus Surgery, Indianapolis, IN), 22% developed bladder outlet obstruction during follow-up.⁹ Recently, Poissonnier et al.⁵ re-

ported on 227 patients treated with the Ablatherm, for whom the rate of bladder outlet obstruction in the 51 patients treated with HIFU alone was significantly greater (31%) than in the 176 patients in whom HIFU was combined with TURP (6%). Similar findings have been reported by Chaussy and Thuroff.¹⁷ In contrast, we observed no significant decrease in the rate of bladder outlet obstruction between those who underwent TURP before HIFU (26%) and those who underwent HIFU alone (19%). All patients with moderate to complete bladder outlet obstruction were treated with bladder neck incision or TURP. Although the implementation of TURP before HIFU did not reduce the rate of bladder outlet obstruction in our study, this concept offers the advantage of a shorter catheter time, removal of calcifications in the gland that might affect the ultrasound beam, and the downsizing of larger prostates.^{17,18}

Only a few patients (1.8%) experienced stress incontinence of a greater degree. Although the incontinence rates have been <1% after HIFU in some studies, most investigators have reported bother with urinary incontinence equivalent to our findings (ie, generally lower than after radical prostatectomy).¹⁹ Radiotherapy is associated with lower rates of urinary incontinence compared with radical prostatectomy, as well as compared with our results.²⁰ However, common adverse events after radiotherapy such as urinary irritation and bowel dysfunction were not found in our series.

A shortcoming of our study was that no validated questionnaires were used for the evaluation of erectile function, thus making our results barely comparable with other studies using validated instruments. A significant rate of 44.7% of preoperatively potent patients developed erectile dysfunction after HIFU. Because all patients were treated with the concept of ablation of the entire prostate, damage to the autonomic nerve fibers of the neurovascular bundle most probably resulted from heat diffusion.

This was a retrospective study from a single institution reporting on the results of HIFU in patients with low- or intermediate-risk localized prostate cancer. Although the design of the study might have been a limitation, it is the first report with longer follow-up after HIFU from a single center.

CONCLUSIONS

HIFU is a minimally invasive therapy for patients with localized prostate cancer. This study, with an average follow-up of 4.8 years, has provided evidence that HIFU can be an alternative in the treatment of localized prostate for patients who are not eligible for surgery.

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EDITORIAL COMMENT

These authors report on some of the longest follow-up available today in the use of high-intensity focused ultrasonography (HIFU) for the treatment of low- and intermediate-risk prostate cancer. With a mean follow-up of 4.8 years, these authors report what they believe are very favorable results with this technology. If one looks at these results objectively, the results of this technology are much less clear.

The most problematic issue is the use of PSA criteria in the analysis of the results. Because HIFU is a coagulative technology that results in complete cellular destruction, one could reasonably argue that it should achieve PSA efficacy results comparable to surgery, not those comparable to radiotherapy-based modalities. No scientific or even theoretical reason exists for why the Phoenix criteria would be an appropriate PSA endpoint for this type of treatment, and one could reasonably conclude that this endpoint was chosen to present the HIFU results in a favorable light.

The authors report that 36% of patients failed to achieve a PSA nadir of <0.2 ng/mL and 14% failed to achieve a PSA level <1.0 ng/mL. Ganzer et al.¹ previously reported that if the PSA nadir was 0.21-1.0 ng/mL after HIFU, 30% of patients experienced disease recurrence and if the PSA nadir was not <1.0 ng/mL, 100% of patients experienced disease recurrence. In a similar report, Uchida et al.² reported that 48% of patients experienced disease recurrence if the PSA nadir was <1.0 ng/mL.

Furthermore, the authors did not consider patients who had undergone repeat HIFU as having treatment failure. Potentially, many of these men who had negative biopsy findings but increasing PSA levels from recurrent or residual disease were not followed up long enough for it to be determined whether they had PSA failure according to the Phoenix criteria, were treated successfully, and thus were still considered a treatment success. The study was even further compounded by the use of TURP in 24% of patients and hormonal therapy in 37% of patients, both of which have significant effects on the PSA level, particularly if lax criteria are used.

The only valid endpoint in this study if the PSA endpoint is considered invalid would be either biopsies, which were under-sampled, or, alternatively, survival. Although the title of this report suggests 8 years of follow-up, the mean follow-up was only 4.8 years, a length of time during which even the most aggressive prostate cancers would be unlikely to result in mortality.

I believe that HIFU has great potential and could become a leading modality in the treatment of prostate cancer; however, until studies with appropriate endpoints are published, we will have no idea of its actual efficacy.

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