High-Intensity Focused Ultrasound and Localized Prostate Cancer: Efficacy Results from the European Multicentric Study*

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ABSTRACT

Purpose: To describe the safety and efficacy of high-intensity focused ultrasound (HIFU) for the treatment of prostate cancer as assessed in a Phase II/III prospective multicentric clinical trial.

Patients and Methods: Patients (N = 402) presenting with localized (stage $T_{1-2}N_{0-x}M_0$) prostate cancer between 1995 and 1999 at six European sites who were not candidates for radical prostatectomy were treated with HIFU under general or spinal anesthesia. Their mean age was 69.3 ± 7.1 (SD) years, the mean prostate volume 28.0 ± 13.8 cc, and the mean serum prostate specific antigen (PSA) concentration 10.9 ± 8.7 ng/mL. Nearly all (92.2%) of the patients had one to four positive biopsy samples at baseline. The Gleason scores were 2 to 4 for 13.2% of the patients, 5 to 7 for 77.5%, and 8 to 10 for 9.3%. During the follow-up, random sextant biopsies and serum PSA measurements were performed. Any positive sample in biopsies performed after the last treatment session resulted in a "HIFU failure" classification.

Results: The patients received a mean of 1.4 HIFU sessions. The mean follow-up duration was 407 days (quartile 1 135 days, median 321 days, quartile 3 598 days). The negative biopsy rate observed in the T1-2 primary-care population was 87.2%. These results were also stratified according to the usual disease-related risk classification, and as much as a 92.1% negative biopsy rate was observed in low-risk patients. Nadir PSA results correlated with prostate size and the clinical procedure.

Conclusion: These short-term results obtained on a large cohort confirm that HIFU is an option to be considered for the primary treatment of localized prostate cancer.

INTRODUCTION

NEW NONSURGICAL TREATMENT OPTIONS for localized prostate cancer are emerging in our daily practice. This trend results from several factors, including the sharp increase in early diagnoses thanks to screening with serum prostate specific antigen (PSA) assay and the role of the patient in choosing his treatment. Indeed, patients are more and more concerned with the post-treatment quality of life; i.e., the recovery time and the treatment-related acute and chronic morbidity.

Beside the large experience in the U.S.A. with brachytherapy for localized prostate cancer, using iodine or palladium permanent implants, a minimally invasive option using high-intensity focused ultrasound (HIFU) has been developed in Europe. It was first demonstrated that HIFU may destroy prostate cancer by coagulative necrosis of the tissue[1] without damaging the intervening structures passed by HIFU[2] and without an in-

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crease in metastasis formation.[3] The transrectal approach was validated initially with an animal model[4] and then with the first clinical trials.[5,6]

In order to evaluate the results of the HIFU treatment for prostate cancer on a larger patient population, the European Multicentric Study was carried out at six investigational sites.

PATIENTS AND METHODS

The European Multicentric Study is a prospective, multi-center, open-labeled, uncontrolled clinical trial. The study was approved by local ethics committees, and all the patients signed an informed consent form for participation prior to their enrollment.

From November 1995 to October 2000, 652 patients were included, which is still ongoing in most of the sites for patient follow-up. In November 1999, an interim statistical analysis was performed, including all the patients enrolled and treated up to that time. The results of this interim analysis are presented herein.

In this 4-year period (November 1995–November 1999), 559 patients were selected and treated with HIFU. All of the patients had biopsy-proven prostate cancer and were not suitable candidates for radical prostatectomy. Of them, 402 patients presented with localized prostate cancer ($T_{1-2}N_{0-x}M_0$) and were treated with HIFU as primary management. The results are focused on this group. The other subpopulations (patients enrolled but excluded from this analysis) were 8 patients who underwent previously a radical prostatectomy, 35 patients with previous external-beam radiation therapy, 104 patients with a previous orchiectomy or hormone deprivation, and 10 patients with locally advanced disease or distant metastases (T_{3-4} and/or N^+ and/or M^+).

At baseline, the patients had the characteristics shown in Table 1. Baseline characteristics were also considered for the patient classification according to the disease-related risk level using the usual definition:

Low risk = stage T_{1-2a} **and** PSA ≤ 10 ng/mL
and Gleason score ≤ 6;
Intermediate risk = T_{2b} or $10 < PSA \leq 20$ ng/mL
or Gleason score = 7;
High risk = T2c **or** PSA >20 ng/mL **or** Gleason score ≥ 8.

This classification resulted in 114 low-risk patients (28.4%), 193 intermediate-risk patients (48.0%), and 95 high-risk patients (23.6%).

All the patients were treated using the Ablatherm® HIFU device (EDAP Technomed, Lyon, France), generally under spinal anesthesia. Several device prototypes were used during the course of the study, and the technical parameters evolved over time. There was a progressive increase in frequency from 2.25 to 3 MHz and a progressive increase in the shot duration from 4 to 5 seconds. In parallel, a cooling system and additional safety features were implemented. For statistical analysis, four major technical protocols (TP) were identified: TP1 with a 2.25-MHz frequency and a shot duration ≤ 4.5 seconds (no cooling system), TP2 with a frequency <3 MHz and a 4.5-second shot duration, TP3 with a 3-MHz frequency and a 4.5-second shot duration, and TP4 with a 3-MHz frequency and a 5-second shot duration.

Patients were systematically treated in two HIFU sessions (one session/lobe) from 1995 to 1998. Thereafter, the prostate was targeted in a single session. In case of residual positive biopsies or local recurrence during follow-up, HIFU retreatment was considered. The patients who were no longer candidates for HIFU were generally managed with external-beam radiotherapy or hormone deprivation and were therefore considered HIFU failures.

Efficacy was assessed through sextant biopsies and PSA measurements. Any positive core, whatever the cancer size, among the biopsies performed 6 weeks or more after the last treatment session led to patient classification as "positive biopsy." Nadir PSA was defined as the lowest concentration measured after the last HIFU session. Only patients with 6 months' follow-up or more were considered for PSA nadir determination. Biopsy and PSA results were assessed for the overall localized prostate cancer population (N = 402) and were then stratified according to factors that might influence the results; i.e., patient baseline characteristics and the different technical protocols. For the HIFU safety evaluation, all adverse events were collected.

RESULTS

In total, 602 HIFU sessions were performed for the 402 patients (1.47 session/patient), with 62.4% of the patients treated with a single session and 27.9% treated with two sessions. The retreatment rate is not interpretable because of the change in the clinical procedure during the course of the trial, moving from one session/lobe to a single session for the entire prostate. At the first treatment session, 49 patients (12.2%) were treated with TP1, 59 patients (14.7%) with TP2, 184 patients (45.8%) with TP3, and 110 patients (27.4%) with TP4.

TABLE 1. PATIENT CHARACTERISTICS

	Age (years)	Prostate volume (cc)	PSA (ng/mL)	Gleason score
No.	396	389	397	369
Mean (SD)	69.3 (7.1)	28.0 (12.7)	10.9 (8.7)	6.0 (1.3)
Q1	65.0	19.0	5.8	5.0
Median	70.0	25.0	8.9	6.0
Q3	75.0	34.0	41.0	7.0
Minimum	51.0	4.2	0.1	2.0
Maximum	88.0	120.0	78.0	9.0

For each patient, follow-up time was defined from the first treatment session to the last histologic analysis or PSA measurement available. At the time of the statistical analysis, the mean follow-up was 407.3 days, ranging from 0 to 1541 days. The quartile distribution (Q1 135 days, median 321 days, Q3 598 days) reflects the patient accrual rate during the course of the study: a low rate during the first year of the study, then a progressive increase and about half of the patients included in the last year of the period being considered for analysis.

In total, 288 patients were assessable for sextant biopsy results, and an 87.2% negative biopsy rate was observed. Biopsy results were stratified according to the prostate size; i.e., for patients with a prostate volume $\leq$40 cc v >40 cc: 88.4% and 85.0% negative biopsy rates were observed, respectively (P = 0.599 [NS]; Fisher's exact test) (Table 2). Similarly, biopsy results were stratified according to the anteroposterior (AP) prostate diameter, considering the limitation of the unitary lesion length. For prostates with AP diameters $\leq$25 mm v >25 mm, 85.4% and 88.1% negative biopsy rates were observed, respectively (P = 0.622; χ^2 test). When stratified according to the disease-related risk, the following negative biopsy rates were observed: 92.1% in low-risk patients, 86.4% in intermediate-risk patients, and 82.1% in high-risk patients (P = 0.167; χ^2 test). When considering only the number of positive cores in pretreatment sextant biopsies among prognostic factors, the comparison reached the significance level: 88.1% negative biopsy rate in patients presenting with one to four positive cores v 70.8% in patients with more than four positive cores (P = 0.017; Fisher's exact test). Whether the HIFU was considered to be partial or complete treatment of the gland because of the treatment strategy or the prostate size was without statistically significant impact on the negative biopsy rate: 91.7% after complete treatment v 87.2% after partial treatment (P = 0.321; Fisher's exact test). Finally, the negative biopsy results were stratified according to the technical protocols: 44.4% in TP1,

82.1% in TP2, 91.2% in TP3, and 94.8% in TP4 (P < 0.0001; χ^2 test). These results are possibly biased by the time effect, the different technical protocols being used successively during the course of the study, and the first patients treated having had more time to reveal a residual or recurrent cancer. In order to reduce this bias, the negative biopsy results at 1 year were also calculated for each TP group: 66.7% in TP1, 76.5% in TP2, 91.2% in TP3, and 100.0% in TP4 (P = 0.021; Fisher's exact test). However, but there were only nine patients in the TP4 group with 1-year biopsy results.

All the patients with at least 6-month follow-up were assessed for PSA nadir (Table 2). In these 212 patients, the nadir was generally obtained within 3 to 4 months after HIFU treatment (mean 163.5 days; median 111.5 days). The quartile distribution of the nadir median PSA results was Q1 0.1 ng/mL, Q2 0.6 ng/mL, and Q3 2.1 ng/mL. The mean nadir PSA value, at 1.8 ng/mL, was relatively high because of the nonresponders (range 0–27 ng/mL). As with the biopsy results, nadir PSA results were stratified according to the prostate volume (mean 1.5 ng/mL and median 0.4 ng/mL in prostates $\leq$40 cc v mean 2.9 ng/mL and median 2.0 ng/mL in prostates >40 cc; P = 0.0001; Wilcoxon test); according to the AP diameter (mean 1.4 ng/mL and median 0.4 ng/mL in AP $\leq$25 mm v mean 1.3 ng/mL and median 0.5 ng/mL in AP >25 mm; P = 0.453; Wilcoxon test); according to the clinical procedure (mean 1.4 ng/ml and median 0.1 ng/mL after complete treatment v mean 1.8 ng/mL and median 0.6 ng/mL after partial treatment; P = 0.016; Kruskal-Wallis test); according to the disease-related risk level (mean 1.3 ng/mL and median 0.5 ng/mL in low-risk patients v mean 1.4 ng/mL and median 0.7 ng/mL in intermediate-risk patients v mean 3.1 ng/mL and median 0.5 ng/mL in high-risk patients; P = 0.793; Kruskal-Wallis test); and according to the technical protocols (mean 5.1 ng/mL and median 1.2 ng/mL in patients treated with TP1 v mean 3.3 ng/mL and median 2.0 ng/mL in TP2 v mean 1.3 ng/mL and median 0.5 ng/mL in TP3 v mean

TABLE 2. BIOPSY AND NADIR PSA RESULTS

| | Negative biopsy | | Nadir PS (ng/mL) | | |
	%	P	Median	Mean	P
Overall result	87.2		0.6	1.8	
Prostate volume (cc)					0.0001
$\leq$40	88.4		0.4	1.5	
>40	85.0	NS	2.0	2.9	
AP diameter (mm)					
$\leq$25	85.4		0.4	1.4	
>25	88.1	NS	0.5	1.3	NS
Risk					
Low	92.1	NS	0.5	1.3	NS
Intermediate	86.4		0.7	1.4	
High	82.1		0.5	3.1	
Treatment					
Partial	87.2		0.6	1.8	
Complete	91.7	NS	0.1	1.4	0.016
Protocol					
TP1	44.4		1.2	5.1	
TP2	82.1		2.0	3.3	
TP3	91.2	<0.0001	0.5	1.3	0.0001
TP4	94.8		0.3	0.9	

0.9 ng/mL and median 0.3 ng/mL in TP4; $P = 0.0001$; Kruskal Wallis test). The PSA level stability was not assessed because of the high proportion of patients with <1-year follow-up. Indeed, when considering the ASTRO definition, time to nadir plus at least 9 months is needed in order to evidence rising PSA on three successive measurements taken at least 3 months apart. So, after HIFU, patients should have at least 1 year of follow-up to be considered for such an analysis.

The most serious adverse event reported was urethrorectal fistula, which occurred in 5 patients in the following situations: before the implementation of the rectal cooling system (N = 2); in patients with a rectal wall thickness >6 mm, which is now considered a contraindication to HIFU treatment (N = 2); and after a repeated HIFU session with only a 2-month interval in between (N = 1). These fistulas resolved after urinary catheter placement (N = 3), fibrin glue injection (N = 1), or surgery (N = 1). Stress incontinence grade I and grade II was observed in 10.6% and 2.5% of the patients, respectively. These mild to moderate cases of stress incontinence generally resolved spontaneously or after appropriate management with medication, pelvic floor muscle training, or both. Grade III stress incontinence was reported in 6 patients but ceased after pelvic floor muscle training (N = 1), artificial sphincter placement (N = 4), or collagen injection (N = 1). Urinary tract infections were reported in 13.8% of the patients and were easily managed with the usual antibiotics. Immediate post-treatment retention was observed in all patients, for a median of 5 days when the retention was managed with a Foley urethral catheter and for a median of 34 days when managed with a suprapubic tube. Prolonged retention was reported in 8.6% of the cases, mainly as a consequence of tissue sloughing, and generally resolved with the evacuation of the necrotic debris. Later during follow-up, 3.6% of the patients presented urethral stenosis, usually treated with urethrotomy. Of the patients, 35 spontaneously reported partial or total loss of potency, but the pretreatment potency status was not systematically recorded at all the sites.

DISCUSSION

The observed short-term efficacy analysis demonstrate good local control of the disease after HIFU treatment, even considering the high proportion of high-risk patients, better results being observed in patients properly selected as suitable candidates for a local treatment. When considering longer-term results, as described by Gelet and associates,[7,8] a plateau in the disease-free rates survival curves calculated with the Kaplan-Meier method is observed from 20-month follow-up. The time for this plateau occurrence should be confirmed with an updated statistical analysis of the European Multicentric Study cohort.

The prostate size or the clinical procedure does not affect the biopsy results, while it directly impacts the residual PSA concentration. Moreover, prostate size is not an actual limitation to HIFU considering that the treatment may be repeated.

The progressive optimization of the technical parameters led to better efficiency of the treatment delivered, and the last technical protocol studied (3-MHz frequency, 5 seconds for the shot duration) was implemented with the standard device. In daily practice, the retreatment rate using these technical parameters does not exceed 10% to 20% according to the first-choice treatment strategy, from treatment including the prostate capsule to nerve-sparing treatment excluding 5 mm of tissue near the neurovascular bundle.[10–12]

The now-standardized clinical procedure for HIFU treatment, as well as the safety features implemented, sharply reduced the treatment-related morbidity. In patients treated with HIFU as a primary management, and with a safety margin for the treatment of the apex, the fistulae and grade III stress incontinence disappeared without an increase in apical residual cancer.[9–12] In order to reduce post-treatment retention, we are now combining a transurethral resection of the prostate (TURP) immediately prior to the HIFU treatment under the same spinal anesthesia; this procedure leads to a significant reduction in the catheter time, from 2 days with the transurethral tube to 7 days when a suprapubic tube is placed. The patient management after the combined TURP + HIFU treatment is similar to that after a classical TURP.

Following this multicenter experience, HIFU treatments may be efficiently performed with an established procedure and with a short learning curve (approximately 10 patients for a new user with technical skill in ultrasound prostate imaging). As a minimally invasive treatment option, it may be delivered under spinal anesthesia. The HIFU-related morbidity is low, and the post-treatment management is simple. The evening after the HIFU session, the patient returns to normal dietary intake, does not need any analgesic medication, and may be discharged either the day after with a catheter placed or a few days later without a catheter according to the country and cultural context. Patients with a TURP history or presenting with a local recurrence after external radiotherapy or surgery are suitable candidates for HIFU. In case of local recurrence after primary HIFU, the patient may benefit from a further HIFU session or may still receive external-beam radiation.

In our practice, we select for HIFU treatment the patients who are not candidates for surgery because of their age or comorbidities, patients who are poor candidates for surgery because of the local conditions or at high risk for positive margin, and patients refusing surgery.

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