

Transrectal High-Intensity Focused Ultrasound in the Treatment of Localized Prostate Cancer

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ABSTRACT

The literature concerning the efficacy and safety of transrectal high-intensity focused ultrasound (HIFU) for the treatment of localized prostate cancer still comprises a relatively small number of articles. The main studies have been published by four teams using an apparatus available in Europe for several years. The recently presented results of the European Multicentre Study and the study by Gelet and associates based on 242 patients with a follow-up of more than 1 year show that HIFU is a valid alternative for the management of well-differentiated and moderately differentiated localized prostate cancer with an initial PSA ≤ 15 ng/mL in men with a life expectancy >10 years. In two studies, the combination of transurethral resection of the prostate and HIFU limited the risk of postoperative urinary retention without inducing a higher complication rate. In a series of patients presenting recurrence after external-beam radiotherapy, HIFU was found to be a useful therapy, with $>80\%$ negative biopsies. The best indications for HIFU are men over the age of 65, those who are not candidates for radical prostatectomy, obese patients, or patients with comorbidities likely to make surgery more difficult. The learning curve for this technique is relatively short, between 10 and 15 patients, for urologists experienced in transrectal ultrasonography. One of the advantages of HIFU is that it can be repeated in the case of recurrence or to re-treat a prostatic site, it involves no radiation, and patients do not suffer from long-term irritative urinary symptoms.

INTRODUCTION

SINCE 2000, PROSTATE CANCER has become the most frequent cancer in men in France (an estimated 40,000 new cases in 2000; i.e. 25% of all new cases of male cancer). This tendency is becoming more marked because of the aging of the population and improvement and more effective use of diagnostic methods (serum prostate specific antigen [PSA]).

Treatment of these localized cancers (total prostatectomy, radiotherapy, or brachytherapy) is not devoid of adverse effects. Treatment with high-intensity focused ultrasound (HIFU), which has been shown to be effective in localized prostate cancer, appears to provide interesting results at the cost of a low

continuous prospective morbidity. The purpose of this paper is to review the literature and define the indications for HIFU in prostate cancer.

MATERIALS AND METHODS

Principles of treatment

The focused ultrasound treatment system used in this study is the Ablatherm (Edap-TMS, Vaulx-en-Velin, France). The piezoelectric transducer produces bursts of convergent beams of high-intensity ultrasound.

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FIG. 1. Patient ready for Ablatherm session.

Tissue destruction in the target zone is attributable to three phenomena: coagulation, cavitation, and heat. **Coagulation necrosis** is induced by sudden hyperthermia (between 85°C and 100°C) at the focal point. The elementary zone destroyed with each shot is ellipsoid and measures several cubic millimeters. The short duration of the phenomenon limits diffusion of heat around the focal point. Repeated shots after displacement of the focal point allows juxtaposition of elementary lesions and destruction of prostatic volume. The **cavitation phenomenon**¹ results from vibration of microscopic gas bubbles dissolved in the tissues by successive ultrasound impulses. This cavitation explains why the ellipsoid lesion created by each shot is not centered on the focal point but drifts toward the transducer. Finally, a **temperature rise** gradually occurs within target volume by the summation of several shots over time and space (shot length 1.7 mm). The temperature rise is maximum at the center of the treated volume but spreads peripherally. This diffusion, calculated by a computer model, requires the use of safety margins at the prostatic apex to protect the striated sphincter and, when necessary, the neurovascular pedicles.

Equipment

The equipment comprises a treatment table and an ultrasound generator with a treatment head placed in a chilled balloon connected to transrectal ultrasonography (for identification of the target volume) and to a computer, which directs shots to the target volume determined by the urologist (Figs. 1 and 2). Safety devices have been gradually reinforced since the first clinical evaluations to ensure continuous control of the position of the transducer in relation to the rectal wall, detection of the patient's movement, and interruption of shots in the case of an abnormality. The rectal mucosa is cooled to between 12°C and 14°C.

The procedure is now standardized. It is based on progressive optimization of controllable technical parameters (ultrasound frequency, shot duration, and intershot latency) to ensure optimal efficacy of treatment. This standard currently proposes a frequency of 3 MHz, a latency and shot duration of 5 seconds for first-line standard treatment, and a shorter shot duration (4.5 seconds) for repeat treatments and failures or treatment of recurrence after radiotherapy. The volume of the elementary lesion is small (19 to 24 × 1.7 mm).

Technique

Transrectal resection of the prostate (TURP) or a bladder-neck incision is performed under the same anesthesia at the beginning of the procedure to reduce the risk of prolonged urinary retention. Then the firing head is placed in the rectum, and the prostate volume is calculated before starting the shots. An 18F bladder catheter is inserted before or after the procedure. From 350 to more than 1000 shots are delivered with an average of 100 minutes of treatment.

RESULTS

Experimental studies

Several experimental studies have demonstrated the efficacy of HIFU in destroying prostatic tissue by coagulation necrosis¹ without injuring surrounding tissues² or promoting the development of metastases.³ The transrectal approach has been validated in animal models and then by the first clinical trials in man. The complex mechanism of tissue destruction has been modeled.^{4,5}

Clinical results

The first **Phase I clinical trial**, conducted in 1992,⁶ involved application of transrectal HIFU to benign prostatic hyperplasia (BPH) tissue in 12 patients prior to prostatectomy to allow analysis of the lesions created. The mean volume of the prostate was 40 cc. The duration of HIFU was about 20 minutes. Histologic examination showed that the lesion size differed as a function of the ultrasound dose. Coagulation necrosis was homogeneous, with clearly defined limits in the case of high doses and less homogeneous limits in the case of low doses. No major complications were observed; one of four patients presented an abnormality of the rectal mucosa on systematic rectal examination. A total of 5084 HIFU treatment sessions (Ablath-

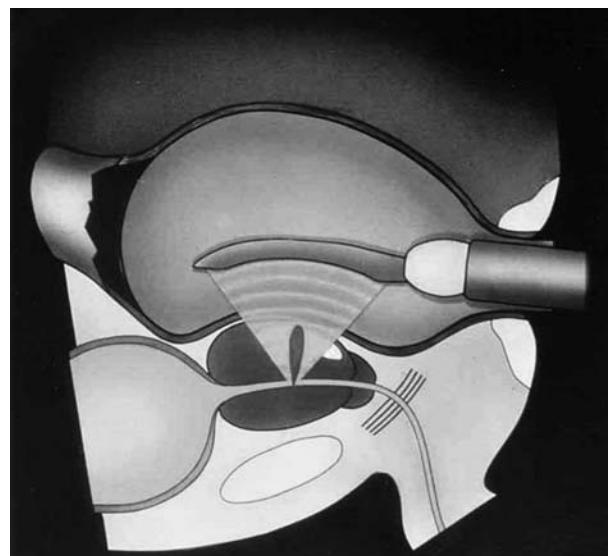


FIG. 2. Activated HIFU probe.

erm) had been performed up until 31 June 2003 and are listed in Table 1 by site. Results from teams who had performed only a small number of sessions by that date (<20) have been pooled.

In 2001, **Gelet and associates**⁷ published a series of 102 patients with a mean age of 70.8 ± 6.13 years who had clinically localized prostate cancer (46% T_{1b-c} and 46% T₂) or local re-

currence after external-beam radiotherapy (8%). A few (8%) of the patients had received neoadjuvant endocrine therapy, which was stopped before HIFU. These patients were not candidates for prostatectomy but had a life expectancy of at least 10 years or refused the other treatment options or simple surveillance. The mean follow-up was 19 months (range 7–76 months). Over

TABLE 1. NUMBER OF HIFU SESSIONS PERFORMED UP TO 1 JULY 2004

Center	Total sessions	Published/presented series (Ablatherm)
Harlaching (Munich)	1219	<ul style="list-style-type: none"> • Analysis of 65 patients $\leq T_2$, PSA <25 ng/mL treated before 1997 • Analysis of 184 patients • European Multicentre Study (402 localized tumors) • Impact of resection combined with HIFU (271 localized tumors) • Experience on 576 patients (T₁₋₂, T₃, salvage after surgery or radiotherapy, treatment post-endocrine therapy or for volume reduction of N+/M+ tumors)
Edouard Herriot (Lyon)	1227	<ul style="list-style-type: none"> • 102 patients (T₁₋₂ and recurrences after radiotherapy) • 120 T₁₋₂ patients, PSA <10 ng/mL • 245 T₁₋₃ patients • European Multicentre Study • 242 patients >1-year follow-up • 71 re-treated patients (with IMM) • Participation in AFU study
Institut Mutualiste Montsouris (IMM) (Paris)	445	<ul style="list-style-type: none"> • European Multicentre Study • Publication on re-treatments (with Lyon) • Feasibility of resection + HIFU: 30 patients • Complications in a 223-patient study
Caritas (Regensburg)	445	<ul style="list-style-type: none"> • Participation in AFU study • European Multicentre Study
AZ Middelheim (Antwerp)	293	<ul style="list-style-type: none"> • 146 patients with localized tumor
Santa Anna (Como)	261	<ul style="list-style-type: none"> • 220 patients T₁₋₃N₀M₀
St. Joseph (Marseille)	254	<ul style="list-style-type: none"> • 106 patients, tumors localized
S. Giov. Batt. (Torino)	170	
Pitié/Saint Louis (Paris)	132	<ul style="list-style-type: none"> • European Multicentre Study (St. Louis) • Participation in AFU study (Pitié)
Bari (Italie)	95	
Hôpital Côte de Nacre (Caen)	222	<ul style="list-style-type: none"> • Medicoeconomic study: 20 patients
Institut Bordet (Brussels)	79	
Montpellier (France)	95	
Other centres in France: Nice, Monaco, Lille, Rouen, Strasbourg, Nancy, Amiens, Paris Tenon, Paris Bichat, Paris Saint Louis, Tours, Reims, La Rochelle	147	<ul style="list-style-type: none"> • Participation in AFU study: 100 patients
Other centers: Hamburg, Jeddah, Rome, Madrid, Itzehoe (UMS), Geneva, Manila, Neustadt (UMS), Nimegen, Washington, Houston, San Francisco, Beyreuth, Gronau, Verona, Orenbourg, Zurich, Lausanne, Bale, Moscow, Nürenberg, Aachen, Mannheim, Stockport, Würzburg, Frankfurt, Seoul, Ufa	400	
Total	5084 sessions	

this period, 75% of the patients remained recurrence free (negative biopsy). The actuarial 5-year progression-free survival rate (negative biopsy, no PSA elevation) was 66%, and progression-free survival rate ranged from 73% for PSA <10 ng/mL to 50% with a higher level ($P = 0.02$), from 81% for a Gleason score <6 to 46% for higher scores ($P < 0.001$), and from 68% with one to four positive pretreatment biopsies to 40% with a larger number of positive biopsies ($P = 0.01$). No significant difference was observed according to the prostate volume treated.

A second study by the same authors, published in 2003,⁸ combined the results of 120 patients treated by HIFU since 1993 for localized prostate cancer ($T_{1-2}N_0M_0$) with a preoperative PSA concentration <10 ng/mL and a mean age of 71 years (range 56–86 years) who were not candidates for radical prostatectomy but had a life expectancy >10 years. The 5-year progression-free survival rate was 76.9%. It increased significantly ($P = 0.024$), to 85.4%, in patients with well-differentiated tumors (Gleason score 2–6) v 61.3% for poorly differentiated tumors (Gleason score 7–10). No significant difference was observed according to the volume of the prostate (71.5% if the volume was <40 cc v 72.3% if it was >40 cc), number of positive biopsies at diagnosis (78% for one or two v 77.2 for 3 to 6), or baseline PSA (88% if the PSA was <4 ng/mL v 73.1% if the PSA was >4 ng/mL). The nadir was a significant prognostic factor: a PSA nadir <0.5 ng/mL was associated with a 91% negative-biopsy rate and an 86% progression-free survival rate. Indeed, the progression-free survival rate was 93% when follow-up biopsies were negative and the PSA nadir was <0.5 ng/mL.

The third study by Gelet et al⁷ presented the results of 242 patients treated between 1993 and 2002 at Edouard Herriot Hospital in Lyon with a minimum follow-up of 1 year. This prospective study was the first to present actuarial recurrence-free survival rates for groups stratified according to their prognostic risk (25.6% low risk, 44.6% intermediate risk, 29.8% high risk) with a minimum follow-up of 1 year. The Ablatherm prototype was used from 1993 to 1999 (104 patients) and the standard apparatus since 2000 (138 patients). The patients enrolled, who had a mean age of 71 ± 5.43 years (median 71 years), essentially presented with localized prostate cancer (48.8% T_1 , 47.5% T_2 , and 3.7% T_3) with PSA <30 ng/mL (mean 9.22 ± 5.76 ng/mL). The mean prostate volume was 32.4 ± 16.6 cc. A few (12.8%) of the patients had a poorly differentiated tumor (Gleason score 2–4: 59.5%; 7: 27.7%; >7: 12.8%). An average of 1.6 ± 0.8 sessions was performed per patient overall, with a mean of 1.9 ± 0.9 sessions for the 104 patients treated with the prototype (corresponding to two systematic sessions; i.e. one session per lobe) and 1.3 ± 0.4 for the 138 patients treated with the standard device. All patients were followed for more than 1 year (mean 29 ± 21 months; range 1–9 years; median 24 months). The criteria for failure used for calculation of progression-free survival were a positive biopsy regardless of the PSA value or three consecutive PSA elevations with a velocity >0.75.

The median PSA nadir was 0.16 ng/mL; 72.7% of patients had a PSA nadir < 0.5 ng/mL; and 81.8% of the biopsies were negative after treatment. The actuarial 5-year negative-biopsy rate was 74% (82%, 71%, and 48% for Gleason 2–6, 7, and >7, respectively). The 5-year recurrence-free survival rate was 63% (low risk 78%, intermediate risk 61%, and high risk 47%). Some patients (16.5%) had received adjuvant therapy after

treatment failure (radiotherapy in one half of cases, endocrine therapy in one half, including two combined treatments). A few patients with failure (7%) did not receive any complementary treatment because of a low PSA with low velocity. The actuarial 5-year adjuvant treatment-free survival rate was 72% (low risk 94%, intermediate risk 62%, and high risk 65%; $P < 0.05$).

The **Institut Montsouris Paris** team¹⁰ presented the results of a feasibility study of resection (22 patients) or bladder-neck incision (8 patients) combined in a single session with HIFU (3 MHz, 5 seconds) and reported the benefits of this approach. Thirty patients with a localized tumor ($T_{1-2}N_0M_0$) without prior endocrine therapy received this combination therapy between April 1999 and November 2001 (age ≥ 60 years, prostate volume <45 cc, <4 positive biopsies, baseline PSA <10 ng/mL). The median age was 72 years (range 61–79 years), and the median prostatic volume was 30 cc (range 11–45 cc). An average of two biopsies were positive at the time of diagnosis, the median Gleason score was 6 (range 4–7), with a median baseline PSA of 7 ng/mL (range 1–10 ng/mL). Patients received one (25 patients) or two (5 patients) HIFU sessions. The median duration of the procedure (resection + HIFU) was 2 hours 48 minutes. Cancer cells were detected in the resection chips in 13% of the patients. The urethral catheter was removed on the second day after HIFU, and the mean length of the hospital stay was 3 days. Postoperative surveillance consisted of International Prostate Symptom Score (IPSS), PSA assay, and follow-up biopsies at 1 year or in the case of PSA elevation. After a mean follow-up of 20 months (range 3–38 months), 86% of the patients had negative biopsies after one or two sessions. Roughly three fourths of the biopsies (73.3%) were negative at 1 year after only one HIFU session, while 3 patients (10%) had a PSA value >4 ng/mL (mean 6.3 ng/mL; range 4.2–8.0 ng/mL). Three of these four patients received second-line treatment (radiotherapy in two cases, endocrine therapy in one). Biopsies showed persistent cancer in 16.7% (five patients), necessitating a second session and achieving 80% negative biopsies at 6 months. One subject with persistent failure was given endocrine therapy. The median PSA after HIFU was 0.9 ng/mL. The mean IPSS after HIFU was 6.7 (median at 1 year 8) compared with a pretreatment score of 7.5. Most (73%) of the sexually active patients remained sexually active after the operation.

Chaussy and Thüroff^{11,12} reported the results of a series of 184 patients with clinically localized prostate cancer and a life expectancy >5 years who were not candidates for total prostatectomy. One half (48%) had previously received androgen suppression. The results showed negative biopsies in 57% after treatment for the entire population and 79% for the 94 patients treated since November 1997 according to the standard procedure (optimized technical parameters and protection and alarm systems). One third of the patients required transurethral resection 6 to 8 weeks after HIFU for persistent urinary retention. The median value of the last postoperative PSA was 1.3 ng/mL (range 0–14.3 ng/mL).

Another study from the Munich team¹³ evaluated the benefit of transurethral resection of the prostate (TURP) combined with HIFU (3 MHz, 5 seconds) on patient comfort. It included 271 patients with localized prostate cancer and PSA <15 ng/mL regardless of the Gleason score. Patients were included in two successive steps from November 1996 to December 2002, which correspond to the procedures successively applied by this

team (HIFU alone until 1999 and HIFU after resection since 1999). None of the patients received radiotherapy, and only patients without endocrine therapy or who received endocrine therapy before HIFU for <6 months were included. The analysis concerned two groups of patients: 175 in whom prostatic resection was performed before HIFU and 96 patients without prostatic resection. The two groups were treated successively, as the Munich team has been systematically performing resections since 2000. The mean weight of resection was 15.7 g (range 2–110 g; median 12.5 g). Histopathologic examination did not reveal any signs of cancer in 51.6% of cases; <10% of the chips were invaded in 27.5%, 10% to 40% of the chips in 16.3% and >40% of the chips in 4.6% of the patients. The mean follow-up was 18.7 ± 12.1 months (range 3–46.3 months) in group 1 and 10.9 ± 6.2 months (range 2.9–26.9 months) in group 2. The retreatment rate was 25% in the HIFU-only group v 4% in the HIFU + TURP group. This tendency cannot be interpreted because of the different durations of follow-up in the two groups. The histologic results were similar in the two groups: 87.7% of patients had negative biopsies after HIFU only v 81.6% after HIFU + resection (NS). Patients in group 2 had a shorter follow-up and included some waiting for HIFU retreatment. The mean PSA nadir was 0.48 ± 1.10 ng/mL in group 1 (median 0.00 ng/mL) v 0.26 ± 0.90 ng/mL in group 2 (median 0.00 ng/mL) (NS). After the nadir, the PSA remained stable for 84.2% of the patients of the HIFU group (ASTRO criterion) v 80.0% of patients in the HIFU + resection group (NS). The median duration of suprapubic catheter drainage was longer in the non-resected group (40 days v 7 days).

In the **AFU 2001–2002** study, which is awaiting publication, eight urologic centers used the Ablatherm apparatus from January 2001 to January 2002 according to the same technique. Statistical analysis was based on 117 patients with localized prostate cancer (68 T₁, 49 T₂), a mean age of 69 years (range 47–79 years) with a mean baseline PSA of 8.5 ± 3.5 ng/mL (range 1–15 ng/mL), 2 ± 1 positive biopsies out of 8 ± 3 , a mean Gleason score of 6 ± 1 (range 2–7), a mean prostatic volume of 31 ± 10 cc (range 12–50 cc), and a mean IPSS of 7 ± 6 (range 0–30). Eighty patients reported sexual activity prior to treatment. Prostatic resection was associated in 92 cases, and the mean treated volume was 34 ± 9 cc. The mean hospital stay was 6.1 ± 1.5 days (range 3–10 days; median 6 days), and the mean duration of bladder drainage was 7.1 ± 10 days (range 1–64 days, with 90% catheter free before day 15; median 4 days). The mean duration of bladder drainage was 18 ± 21 days (median 10.5 days) in the patients having TURP and 8 ± 6 days (median 4 days) after resection. At 1 year, six patients had dropped out of the trial, including deaths at 5 and 8 months that were not attributable to treatment. The results at 6 months (N = 113) and 1 year (N = 102) were as follows: PSA 2.5 ± 3 ng/mL (median 1.3 ng/mL) and 2 ± 2.5 ng/mL (median 1.1 ng/mL) and IPSS 5.6 ± 6 and 4.4 ± 4 , respectively. At 6 months, follow-up biopsies were negative in 70 patients and positive in 32. A second treatment was performed in 35 patients (second HIFU session at 6 months in 31 patients; radiotherapy in 1 patient; endocrine therapy in 3 patients). Approximately two thirds (60%) of the patients who reported sexual activity before the procedure preserved this activity. Residual complications at 1 year were one case of moderate incontinence and four cases of urethral stricture treated by endoscopy. The complete and stable response rate, confirmed by follow-up biopsies, was 70% after one session.

The prospective **European Multicentre Study**¹⁴ included 652 patients from November 1995 to October 2000. These intermediate results concern the 402 patients with localized prostate cancer (T₁₋₂N_{0-x}M₀) out of the 559 patients treated between November 1995 and November 1999. All these patients received HIFU as first-line treatment and did not present indications for total prostatectomy. Patients previously treated by total prostatectomy (N = 8), external-beam radiotherapy (N = 35), or androgen suppression (N = 104) and 10 patients with locally advanced or metastatic disease (T₃₋₄ and/or N₁ and/or M₁) were excluded from the analysis. Treatment was administered in two sessions (one per lobe) until 1998. Another session could be proposed in the case of positive follow-up biopsy or local progression after HIFU. Recurrences after HIFU that were treated by other modalities (radiotherapy, androgen suppression) were considered to be failures of HIFU. Surveillance was by PSA assay and prostatic biopsies (>6 weeks after HIFU). Analysis of positive biopsies or a high PSA nadir was correlated with patient and tumor characteristics and successive technical protocols. These biopsy results were studied by classifying patients into three prognostic groups (low risk = T_{1-2a} and PSA = 10 ng/mL and Gleason score 6; intermediate risk = T_{2b} or PSA 10–20 ng/mL or Gleason 7; high risk = T_{2c} or PSA >20 ng/mL or Gleason score ≥ 8).

The 402 patients had a mean age of 69.3 ± 7.1 years. The mean prostate volume was 28 ± 13.8 cc; the initial PSA value was 10.9 ± 8.7 ng/mL. Most patients (90.7%) had a Gleason score ≤ 7 . A total of 602 sessions were performed (1.47 sessions/patient). The mean follow-up was 407.3 days (range 0–1541 days). After treatment, 87.2% of the 288 patients who underwent prostatic biopsy had negative findings. According to prognostic group, 92.1% of the biopsies were negative in patients presenting a low risk, 86.4% in the intermediate-risk group, and 82.1% in the high-risk group. Negative-biopsy rates were similar regardless of the prostatic volume (88.4% for prostatic volumes ≤ 40 cc v 85.0% for volumes >40 cc), the anteroposterior diameter of the prostate (85.4% for diameter ≤ 25 mm v 88.1% for diameter >25 mm), and complete or partial treatment of the prostatic volume (91.7% after complete treatment v 87.2% after partial treatment). The PSA nadir was usually obtained 3 to 4 months after HIFU (mean interval 163.5 days; median: 111.5 days). The mean PSA nadir was 1.8 ng/mL (range 0–27 ng/mL).

The **Saint Josef Hospital** team in Regensburg, Germany, presented the results of 146 consecutive patients (mean age 66.9 ± 6.7 years) with T₁₋₂N₀M₀ prostate cancer treated between October 1997 and November 2002.¹⁵ Almost half (43%) of the patients had already been given endocrine therapy. No adjuvant endocrine therapy was administered after HIFU. These patients presented a contraindication to total prostatectomy or refused this operation. The serum PSA concentration had to be <15 ng/mL (mean PSA 7.6 ± 3.4 ng/mL), and the Gleason score had to be <7 (mean score 5 ± 1.2). The mean prostatic volume was 23 ± 7.7 cc. All patients were treated under spinal anesthesia with Cystocath bladder drainage that was removed after an average of 12.7 days (range 1–59 days). A total of 171 sessions were performed in these 146 patients (1.17 sessions per patient). The mean follow-up was 22.5 months (range 4–62 months). Analysis of the results shows a median PSA nadir of 0.07 ng/mL (range 0–5.67 ng/mL), and 93.4% of patients had negative follow-up biopsies. The median PSA at 22 months was

0.15 ng/mL (range 0–12.11 ng/mL), and 87% of patients had a PSA value <1 ng/mL.

RESULTS OF HIFU IN SALVAGE THERAPY AFTER FAILURE OF RADIOTHERAPY

A recent publication¹⁶ analyzed the results of 71 patients treated at Edouard Herriot Hospital in Lyon and at the Institut Montsouris in Paris. Eight of the patients in this series were also included in the series of 102 patients in the article published in 2001. The tumor stage before radiotherapy was T₁, T₂, and T₃ for 21.1%, 39.5%, and 21.1% of the patients, respectively, and was unknown in 18.3% of cases. The mean PSA at diagnosis was 20.4 ng/mL (range 3.5–60 ng/mL), and the mean PSA nadir after radiotherapy was 1.46 ng/mL (range 0–4.3 ng/mL). The initial dose of radiotherapy was 64.6 Gy (range 56–88 Gy). Failure of radiotherapy was reflected by elevation of PSA and was confirmed by biopsy in each patient. No lymph-node or bone metastases were detected (N₀M₀). The mean interval before relapse was 38.5 months (range 6–120 months). One third of the patients had received endocrine therapy before HIFU, either as an adjuvant to radiotherapy or following the diagnosis of failure of radiotherapy. These treatments were stopped before HIFU. The mean age of the patients at the time of HIFU was 67 ± 5.86 years, the mean prostatic volume was 21.4 ± 11.1 cc, and the mean PSA was 7.7 ± 8.10 ng/mL. The Gleason score was between 2 and 6 in 33.8% of patients, 7 in 18.3%, and between 8 and 10 in 47.9%. The mean follow-up after HIFU was 14.8 months (range 6–86 months). Follow-up consisted of PSA assay and prostatic biopsies (systematic at 3 months and in the case of PSA elevation), CT, and bone scan in the case of PSA elevation. Most (80%) of post-HIFU prostatic biopsies were negative. The mean PSA nadir after HIFU was 1.97 ± 4.58 ng/mL, with a median of 0.20 ng/mL. A PSA nadir <0.5 ng/mL at 3 months was observed in 61% of patients. Slightly more than half of the patients (40; 56.3%) required adjuvant therapy after HIFU in the form of endocrine therapy alone (49.3%) or a combination of endocrine therapy and chemotherapy (7%) because of isolated PSA elevation (36.6%) or residual localized cancer (19.7%). Metastatic disease was diagnosed during follow-up in 9 patients (12.7%; bone 8.4%; lymph nodes 2.8%; lung 1.4%), and 4 patients died from it.

EVALUATION OF ONCOLOGIC EFFICACY OF HIFU IN PROSTATE CANCER

The oncologic efficacy of HIFU in prostate cancer has been homogeneously evaluated by various teams according to several methods:

- Analysis of total prostatectomy specimens
- Monitoring of PSA at 3, 6, and 12 months
- Systematic biopsies after treatment (usually at 3 months)
- Biopsy in the case of PSA elevation on three successive samples.

Analysis of prostatectomy specimens

The action of HIFU on the prostate and adjacent tissues was first described in 1995^{1,5} and was subsequently analyzed by

Beerlage in 1999¹⁷ in a series of 14 patients with clinically localized tumors (mean age 62 years [range 55–69 years], mean PSA 10.8 ng/mL) who were evaluated by total prostatectomy after HIFU treatment (Ablatherm) of one lobe or one prostatic zone (2.5 MHz; 4.5 seconds). Prostatectomy was performed 4 to 12 days (mean 8.5 days) after HIFU. A pelvic-tissue biopsy was performed in six patients. No complication related to HIFU or to the prostatectomy procedure was observed. Histologic examination consistently revealed hemorrhagic necrosis of the treated volume extending into the prostatic capsule (nine cases) or even further, into the periprostatic tissues and the proximal part of the seminal vesicles. Viable prostatic tissue persisted in the dorsal rim of the treated volume in all patients, with tumor being found in four cases. No residual cancer was detected in one case.

Analysis of clinical efficacy in localized prostate cancer

The results of HIFU therapy have also been assessed according to the ASTRO criterion (three successive PSA elevations indicate treatment failure) and the results of follow-up biopsies performed between 3 months and 1 year after HIFU. The most extensive series are the 402 patients of the European Multicentre Study¹⁴ and the prospective study by Gelet and colleagues on 242 patients with a minimum follow-up of 1 year.⁷ The Lyon study reported a median PSA nadir of 0.16 ng/mL, with 72.7% of the patients having a PSA nadir <0.5 ng/mL. In the European study, the mean PSA nadir with 6 months of follow-up was 1.8 ng/mL (range 0–27 ng/mL) and was influenced by prostatic volume, type of procedure, or technical treatment parameters, but not by prognostic group. In the Lyon study, 81.8% of the biopsies were negative after treatment. The actuarial 5-year negative-biopsy rate was 74% (82%, 71%, and 48% for Gleason 2 to 6, 7, and >7, respectively); 87.2% of the patients had negative biopsies. The negative-biopsy results in the European study (92.1% in the low-risk group, 86.4% in the intermediate-risk group, and 82.1% in the high-risk group) were influenced by the number of positive biopsies at diagnosis and the type of procedure. The Lyon study indicated a 5-year recurrence-free survival rate of 63%. The actuarial 5-year adjuvant treatment-free survival rate was 72% (low-risk: 94%, intermediate-risk: 62%).

COMPLICATIONS

Four studies have reported the complications of HIFU: one study based on 120 patients treated for localized prostate cancer with PSA ≤10 ng/mL, the European Multicentre Study published in 2003,¹⁴ Chaussy and Thüroff's paper comparing HIFU therapy alone with resection followed by HIFU,¹³ and the Lyon series of 242 patients with a minimum follow-up of 1 year.⁷

Asymptomatic urinary-tract infections detected by systematic post-treatment bacteriologic examinations were not taken into account in the analysis of the 120 patients treated for localized prostate cancer. Intermittent weekly preventive antiseptic treatment was maintained for 1 month. Urinary-tract infections were observed in 13% of patients in the European Multicentre Study and responded to the usual antibiotics. The study by Gelet and associates of 242 patients with a minimum follow-up of 1 year⁷ indicated a 1.4% rate of symptomatic urinary-tract infec-

tions in 138 patients treated according to current standards *v* 4.8% for patients treated with the prototype before 1999.

Urinary retention is frequent during the immediate post-operative period when resection is not systematically performed prior to HIFU. It is related to postoperative prostatic edema and elimination of necrotic debris. The prostatic volume increases by 20% to 40% after the HIFU session. The median duration of bladder drainage ranged from 5 days (urethral catheter) to 1 month (suprapubic catheter). The prolonged-retention rate was estimated to be 8.6% with a secondary resection rate of between 5% and 30%. Since January 2000, prostatic resection is performed systematically, which has considerably decreased the frequency of urinary retention (mean duration of post-HIFU catheterization 11 days without *v* 6 days with TURP). The duration of systematic bladder drainage is currently 3 to 4 days. Prolonged retention was observed in 3.6% of the 138 patients treated according to current standards *v* 4.8% for patients treated with the prototype in the analysis of 242 patients with a follow-up of at least 1 year.

The role and benefits of TURP before HIFU must be stressed. Vallancien and colleagues,¹⁰ in a series of 30 patients (22 resections, 8 bladder-neck incisions), reported prolonged retention in 6.6% of cases with improvement of the IPSS score after HIFU and only two patients with an IPSS score >12 after treatment. Half of the patients experienced urgency, which resolved over 3 weeks. Resection induces moderate hematuria in 75% of cases but does not accentuate the incontinence rate (3.3% grade 1 persisting at 1 year). Overall, 88% of patients are satisfied with their quality of life for a reason related to their urinary problems after HIFU *v* 63% before treatment (IPSS QoL). Chaussy and Thüroff^{12,13} compared the respective urinary complications of two patient groups: those treated by HIFU only during a first period (96 patients) and those receiving a combination of resection and HIFU from 2000 onward (175 patients). Those investigators likewise reported a benefit of associated resection on the patient's quality of life and the lower incidence of urinary adverse effects and even a decreased re-treatment rate for residual cancer (4% *v* 25% without resection). Prolonged retention was seen in 6.9% of patients. The drainage time after combined treatment was 7 days *v* 40 days after HIFU only, the IPSS score was 3.37 *v* 8.91 after HIFU only, and the risk of incontinence was reduced (6.9% after combined treatment *v* 15.4% after HIFU only).

Urethrorectal fistula is the main complication identified after transrectal prostatic HIFU (five patients in the European Multicentre Study). This risk has been eliminated for the treatment of localized lesions by integration of safety devices, essentially permanent control of the transducer-rectum distance, and the rectal-wall cooling achieved by circulation of fluid. The risk is still high after postradiotherapy salvage therapy. Two of the five fistulas reported in the European Multicentre Study were observed before integration of the rectal cooling system, two in patients with a very thick rectal wall (>6 mm) (which is currently considered to be a contraindication), and one during early re-treatment at 2 months. Treatment consisted of bladder drainage in three cases, collagen injection in one case, and surgical revision in one patient. In the series of 242 patients with a follow-up of at least 1 year,⁷ no urethrorectal fistula was observed when HIFU was performed according to current standards (since 2000) *v* 0.9% in patients treated up to 1999 with the prototype machine.

Strictures of the prostatic urethra or bladder neck have considerably decreased since systematic use of the TURP-HIFU combination (9% after resection *v* 26% after HIFU only). These strictures were corrected by bladder-neck incision (usually performed with a cold scalpel) an average of 6 months after the HIFU session. At long-term follow-up, 3.6% of patients presented a urethral stricture, treated simply by urethrotomy. A 8.7% rate of urethral strictures or bladder-neck sclerosis was reported in 138 patients treated according to current standards from 2000 to 2002 in the study of 242 patients with a minimum follow-up of 1 year *v* 25.9% for patients treated up until 1999 with the prototype equipment.

The risk of incontinence is not increased by associated transurethral resection: no cases of grade 3 incontinence were observed, and the rate of grade 1/2 incontinence has decreased (13% *v* 20%) among the 120 patients treated for localized prostate cancer. Grade 1 and grade 2 urinary incontinence were observed in 10.6% and 2.5% of cases, respectively, in the European Multicentre Study (Ablatherm prototype without associated resection). These moderate forms of incontinence resolved either spontaneously or after retraining by physiotherapy. Severe incontinence (grade 3) occurred in 6 patients (1.5%) and was treated by retraining (1 case), collagen injection (1 case), or artificial sphincter (4 cases). Gelet and associates, in their series of 242 patients with a minimum follow-up of 1 year,⁷ reported an incontinence rate of 7.9% for 138 patients treated according to current standards from 2000 to 2002 *v* 22% for patients treated with the prototype. The respective rates were 6.5% *v* 13.4% for grade 1, 1.4% *v* 6.7% for grade 2, and 0 for grade 3 *v* 3.8%. Urgency was also reported by 8% of patients.

Overall, the risk of incontinence after combined TURP and HIFU treatment of a localized tumor on the standard machine and according to the standard procedure is 4.6% to 6.5% for grade 1 incontinence, 1.4% to 2.3% for grade 2, and 0 for grade 3.

Chronic perineal pain, observed in 3.3% of patients, resembles internal pudendal neuralgia and is accentuated by sitting. It resolves spontaneously after 3 or 4 months. Perineal pain was observed in 1.4% of patients treated according to the current standard parameters by Gelet and associates after 2000 *v* 1.9% during treatments with the prototype.

TABLE 2. GOOD INDICATIONS FOR HIFU

Tumor characteristics
• Localized: clinical stage T _{1b} , T _{1c} , or T ₂
• Negative bone scan (M ₀)
• No lymphadenopathy (N ₀) on pelvic CT scan and/or MRI
• PSA ≤15 ng/mL
• Number of positive biopsies <4 in the case of sextant biopsies
• Gleason score no higher than 7 (3 + 4)
Prostate characteristics
• Volume <40 cc
• Transurethral resection can reduce prostatic volume
Patient characteristics
Not candidates for total prostatectomy because of
• Age
• Concomitant disease
• Obesity

The **impotence rate** was evaluated by questionnaire in the study of 120 patients: 70 patients achieved erections allowing penetration before treatment and 36% of patients retained erections allowing penetration after HIFU. Impotence was not studied in detail in the European Multicentre Study. Although 8.7% of patients spontaneously reported erectile dysfunction after treatment, the previous quality of erection was not established in all centers. The study by Gelet and associates of 242 patients with a minimum follow-up of 1 year⁷ showed an impotence rate of 66% in patients with no existing disorders (75 patients evaluated out of 242).

Overall, in the case of complete treatment of the prostatic volume for localized lesions, impotence occurs in 60% to 70% of patients. In the case of treatment preserving the neurovascular pedicles containing the nervi erigentes, impotence is observed in 20% to 30% of patients, with an increased risk of 15% when a complementary HIFU session needs to be performed because follow-up biopsy shows insufficient cancer control.

The Institute Montsouris team also presented an evaluation of the complications of HIFU therapy in 223 patients treated for localized prostate cancer between 1996 and 2003. Fifteen patients had previously been treated by radiotherapy, and 137 patients were treated by TURP or bladder-neck incision to decrease the risk of postoperative retention. The mean age in this series was 72 years (range 61–79 years). The median weight of the prostate was 30 g (range 11–45 g), and the median PSA was 7 ng/mL (range 1–10 ng/mL). The mean number of positive biopsies was 2 of 6, and the median Gleason score was 6 (range 4–7). No deaths were observed in this series. An obese patient developed pulmonary embolism as a complication of pelvic lymph-node dissection. Also, 80% of patients presented macroscopic hematuria that resolved spontaneously over a fortnight. Urinary-tract infection was diagnosed in 32 patients. Seven patients developed epididymo-orchitis secondary to an ineffective antibiotic protocol. Seven patients developed urethral stricture necessitating internal urethrotomy. In the group of 86 patients not treated by TURP or bladder-neck incision before the Ablatherm session, 8 required TURP between months 1 and 15, 2 presented dysuria related to elimination of necrotic fragments, and 1 developed bladder stones on a necrotic fragment. Fifteen patients presented stress incontinence, which was minimal without protection in 8 cases, moderate with 1 to 3 pads/day required in 6 cases, and severe in one case, necessitating an artificial sphincter at 1 year. A few patients (3%) reported urgency during the first month, but no patients had anal incontinence. Slightly more than half (60%) suffered from erectile dysfunction, and 35% of patients with preoperative erections reported impotence between the 1st and 18th months after Ablatherm treatment.

CONCLUSION

Recently presented results, derived from the European Multicentre Study and from single-center series, show that HIFU constitutes a valid alternative for the treatment of well- and moderately differentiated localized prostate cancer with a baseline PSA value ≤ 15 ng/mL in men with an estimated life expectancy between 5 and 15 years (Table 2). For patients with a localized tumor associated with an intermediate or low risk of recurrence, the preliminary results of HIFU are comparable

to those of other treatment options. The use of HIFU in the second-line treatment of a localized tumor after failure of radiotherapy appears to be promising.

The procedure is now standardized. The learning curve is short (about 10 to 15 patients) for urologists experienced in transrectal ultrasonography. The main advantages of HIFU remain its low morbidity and the possibility of repeated treatments, the absence of irradiation and special precautions, the possibility of treating patients with a history of TURP, early local control verified by biopsies, and the possibility, in the case of failure, of second-line treatment by radiotherapy without any increase in the complication rate.

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