EUROPEAN UROLOGY XXX (2010) XXX–XXX

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journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
Editorial on pp. x–y of this issue

Multicentric Oncologic Outcomes of High-Intensity Focused Ultrasound for Localized Prostate Cancer in 803 Patients

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Article info

Article history:
Accepted June 22, 2010
Published online ahead of print on July 3, 2010

Keywords:
Ultrasound surgery
High-intensity focused ultrasound
Localized prostate cancer

Abstract

Background: High-intensity focused ultrasound (HIFU) is an emerging treatment for select patients with localized prostate cancer (PCa).
Objectives: To report the oncologic outcome of HIFU as a primary care option for localized prostate cancer from a multicenter database.
Design, setting, and participants: Patients with localized PCa treated with curative intent and presenting at least a 2-yr follow-up from February 1993 were considered in this study. Previously irradiated patients were excluded from this analysis. In case of any residual or recurrent PCa, patients were systematically offered a second session. Kaplan-Meier analysis was performed to determine disease-free survival rates (DFSR).
Measurements: Prostate-specific antigen (PSA), clinical stage, and pathologic results were measured pre- and post-HIFU.
Results and limitations: A total of 803 patients from six urologic departments met the inclusion criteria. Stratification according to d'Amico's risk group was low, intermediate, and high in 40.2%, 46.3%, and 13.5% of patients, respectively. Mean follow-up was 42 ± 33 mo. Mean PSA nadir was 1.0 ± 2.8 ng/ml with 54.3% reaching a nadir of ≤0.3 ng/ml. Control biopsies were negative in 85% of cases. The overall and cancer-specific survival rates at 8 yr were 89% and 99%, respectively. The metastasis-free survival rate at 8 yr was 97%. Initial PSA value and Gleason score value significantly influence the DFSR. The 5- and 7-yr biochemical-free survival rates (Phoenix criteria) were 83–75%, 72–63%, and 68–62% ($p = 0.03$) and the additional treatment-free survival rates were 84–79%, 68–61%, and 52–54% ($p < 0.001$) for low-, intermediate-, and high-risk patients, respectively. PSA nadir was a major predictive factor for HIFU success: negative biopsies, stable PSA, and no additional therapy.
Conclusions: Local control and DFSR achieved with HIFU were similar to those expected with conformal external-beam radiation therapy (EBRT). The excellent cancer-specific survival rate is also explained by the possibility to repeat HIFU and use salvage EBRT.

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0302-2838/$ – see back matter doi:10.1016/j.eururo.2010.06.037

Please cite this article in press as: Crouzet S, et al. Multicentric Oncologic Outcomes of High-Intensity Focused Ultrasound for Localized Prostate Cancer in 803 Patients. Eur Urol (2010), doi:10.1016/j.eururo.2010.06.037

1. Introduction

In absence of data from large randomized trials, men with clinically localized prostate cancer (PCa) meet a dilemma when selecting treatment. Many treatment options are available and the morbidity associated with radical treatments is significant. The three main strategies are radical surgery, radiation therapy, and active surveillance. Results of a Scandinavian randomized study of radical surgery versus surveillance concluded that radical prostatectomy results in a reduction in distant metastases and disease-specific death among patients with clinically localized PCa not detected by prostate-specific antigen (PSA) screening [1]. The subgroup analyses by age showed that the benefit of radical prostatectomy was limited to men <65 yr. Systematic control biopsies after three-dimensional conformal external-beam radiation therapy (EBRT) demonstrated that local control of the disease was achieved only in 68% of patients, although biochemical-free survival is ≤59% [2]. A well-defined protocol for active surveillance is still lacking and reliable criteria for active treatment are still unknown. High-intensity focused ultrasound (HIFU) is a minimally invasive option for localized PCa [3,4]. The goal of this study was to report the outcome of 803 consecutive patients who underwent HIFU as primary care option for localized PCa in six institutions and to determine the factors influencing the outcome. The morbidity was not analyzed in this study as it has already been published [5].

2. Materials and methods

HIFU propagates ultrasound waves generated by a spherical transducer placed in the rectum. HIFU works by focusing high-power acoustic waves on a specific focal point to produce temperatures of 85 °C [6]. These temperatures are high enough to cause cellular disruption and coagulative necrosis at the focal point of the HIFU acoustic waves.

All patients were treated using the Ablatherm HIFU device (EDAP SA, Vaulx-en-Velin, France). From 1993 to 1999, the patients were treated with prototype devices. After 2000, patients were treated with the first commercially available device (Ablatherm Maxis), and since 2005 treatment has been performed using the second commercially available device (Ablatherm Integrated Imaging), which allows a real-time control of the therapy [7].

To reduce duration of catheterization, the HIFU procedure was standardized in 2000: A transurethral resection of the prostate (TURP) is performed immediately prior to the HIFU session, under the same anesthesia in smaller glands (≤35 ml), and as a separate treatment 4–6 wk after TURP in larger glands [8,9]. The whole prostate gland is treated with a 4–6-mm safety margin for the treatment of the apex. This standardized HIFU procedure dramatically simplifies the outcome by reducing catheter time and rate of urinary infections [8,9].

The data were collected prospectively in a multicenter database approved by the Commission Nationale de l'Informatique et des Libertés (CNIL; an independent French administrative authority whose mission is to ensure that data privacy laws are applied to the collection, storage, and use of personal data). Patients treated consecutively between 1993 and January 2007 in six urologic departments were included in this database.

For this study, the patient selection was based on the following criteria: clinical stage T1–T2, N0, M0, no previous radical treatment for PCa (radical prostatectomy, EBRT, or brachytherapy), and at least 2 yr of follow-up. All patients were not suitable candidates for radical surgery according to the age and general status. Patients treated by neoadjuvant hormone therapy were excluded from the study.

All patients were regularly assessed based on the following criteria: baseline and post-HIFU PSA levels at 3, 6, and 12 mo, and then every 6 mo, and prostate sextant biopsies performed before inclusion and 6 mo after HIFU treatment, regardless of PSA level. Additional control biopsies were performed during follow-up in cases of rising PSA (three successive rises in PSA level). In case of positive prostate biopsy during follow-up without evidence of metastasis, HIFU retreatment was performed. The requirement for an additional treatment after repeated HIFU was defined depending on evidence of local relapse. EBRT or hormonal deprivation was administered according to the general status and the life expectancy of each patient.

For disease-free calculation, three different criteria were used to calculate Kaplan-Meier survival curves. We chose the Phoenix criteria for calculation of the biochemical disease-free survival rate (BFSR) to compare the HIFU results with the EBRT results [10]. We also calculated the additional treatment survival rate (the occurrence to define failure is the start of a salvage treatment). Finally, we present a survival curve using the combination of the two previous criteria because in this HIFU cohort, control biopsies were often performed before the PSA increase up to nadir plus 2 ng or at the time of a salvage treatment for local relapse evidenced by control biopsy.

Statistical analyses were carried out with SPSS statistical software v.16 (SPSS, Chicago, IL, USA). Depending on distributions, parametric and nonparametric tests were applied.

Survival curves were based on Kaplan-Meier models and the log-rank test was used for univariate comparisons. Actuarial survival rates were based on life table methods.

For multivariate analysis, the Cox proportional hazards regression model was used to estimate the prognostic relevance of age, prostate volume, PSA, clinical stage, positive biopsy rate, Gleason score, and nadir PSA on disease progression. All p values <0.05 reflected statistically significant differences.

3. Results

3.1. Patient characteristics

A total of 803 patients fulfilled the inclusion criteria and were considered for analysis (Montpellier: 99; Marseille: 20; Lyon: 579; Bordeaux: 19; Nice: 67; Toulouse: 19). Baseline characteristics are summarized in Table 1. The total number of cases analyzed was 1457 patients. Patients treated by neoadjuvant hormone therapy and were excluded from the study (n = 438). Another group of 216 patients was excluded from the study due to the following characteristics: T3 or higher, N+, M+, missing stage, PSA >50 ng/ml, missing Gleason, and follow-up <2 yr.

The mean follow-up period for the entire cohort was 42 ± 33 mo. The treatments were achieved with the prototypes in 80 patients, with the Ablatherm Maxis in 446 and with the Ablatherm Integrated Imaging in 277. In the two last subgroups, the HIFU session was combined with a TURP. The mean number of HIFU sessions was 1.4 ± 0.6 (one session: 521 (64.9%) patients; two sessions: 255 (31.7%) patients; three or more sessions: 27 (3.4%) patients). On average, 496 shots were delivered during the first HIFU session, corresponding to a treated volume of 26.8 ml (ie, an average of 109% of the prostate volume at the time of the treatment).

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Table 1 – Baseline characteristics of 803 patients with localized cancer following treatment with high-intensity focused ultrasound

Mean age, yr (median)	70.8 ± 5.6 (71)
Mean PSA, ng/ml (median)	9.1 ± 5.9 (7.7)
Mean prostate volume, ml (median)	24.5 ± 10.0 (23.0)
Stage, *n* (%)	
T1	481 (59.9)
T2	322 (40.1)
Gleason score, *n* (%)	
≤6	510 (63.5)
7	242 (30.1)
≥8	48 (6.0)
Undefined	3 (0.4)
Pre-HIFU d'Amico's risk group (2003), *n* (%)	
Low	323 (40.2)
Intermediate	372 (46.3)
High	108 (13.5)

PSA = prostate-specific antigen; HIFU = high-intensity focused ultrasound.

Table 2 – Prostate-specific antigen nadir after high-intensity focused ultrasound

	Overall
Mean nadir PSA, ng/ml (median)	1.0 ± 2.8 (0.25)
Mean time to nadir, wk (median)	12.9 ± 11.0 (9.0)
Nadir PSA, ng/ml (%)	
≤0.3	436 (54.3)
0.3–1	172 (21.4)
>1	179 (22.3)
Not determined	16 (1.9)

PSA = prostate-specific antigen; HIFU = high-intensity focused ultrasound.

3.2. *Pathologic and morphologic results*

After the HIFU treatment, the prostate volume (assessed by transrectal ultrasound) decreased sharply from 24.5 ± 10 ml to 13.6 ± 13.1 ml. The pre-HIFU prostate volume measurement was performed just before the HIFU treatment and after the TURP. According to the small prostate volume after HIFU, a minimum of 6 to 12 random control core biopsies were usually used to evaluate the local control of the cancer. Post-HIFU biopsies after the last HIFU sessions were only available in 589 (73.3%) patients. Control biopsies were negative in 459 patients (77.9%) and positive in 130 patients (22.1%). The negative control biopsy rate for low-, intermediate-, and high-risk patients were, respectively, 84.9%, 73.5%, and 72.0% ($p = 0.003$).

3.3. *Biochemical results*

The PSA nadir was reached within 6 mo after HIFU in all patients (mean nadir time achievement: 12.9 ± 11.0 wk). The mean PSA nadir was 1.0 ± 2.8 ng/ml, with a median of 0.25 ng/ml. PSA nadir values are summarized in Table 2. For the overall population, 436 patients (54.3%) presented a nadir PSA ≤ 0.3 ng/ml. Table 3 reports comparative outcome according to the development of HIFU technology between 1993 and 2006.

3.4. *Survival rates*

The overall and cancer-specific survival rates (CSSR) at 8 yr were 89% and 99%, respectively (Figs. 1 and 2). The metastasis-free survival rate was 97% at 8 yr (Fig. 3).

3.4.1. *Disease-free survival rates*

The 5-yr and 7-yr BFSR (Phoenix criteria) for low-, intermediate-, and high-risk patients were, respectively, 83–75%, 72–63%, and 68–62% ($p = 0.03$). In the same groups of patients, the 5-yr and 7-yr additional treatment-free survival rates were, respectively, 84–79%, 68–61%, and 52–54% ($p < 0.001$). By combining those two criteria, the DFSR at 5 yr and 7 yr were 72–62%, 56–46%, and 47–39% ($p < 0.001$) for low-, intermediate-, and high-risk patients, respectively (Figs. 4–6).

3.5. *Clinical outcome*

All patients presenting with a significantly rising PSA (Phoenix criteria) level received an additional treatment, whatever the local control and biopsy results. A total of 182 patients with relapse underwent salvage therapy, either with EBRT (84 patients) or androgen deprivation (98 patients). Hormone deprivation was used in patients without biopsy-proven local relapse or with poor general status; radiation therapy was performed in patients with demonstrated local recurrence and long life expectancy.

Table 3 – Comparative outcome according to the evolution of technology in patients treated with high-intensity focused ultrasound technology

	Before 2000	2000–2004	2005–2007	*p* value
Nb HIFU sessions	*n* (%)	*n* (%)	*n* (%)	
One session	26 (32.5)	259 (58.1)	236 (85.2)	$p < 0.001$
Two sessions	36 (45.0)	178 (39.9)	41 (14.8)	
Three or more sessions	18 (22.5)	9 (2.0)	0 (0.0)	
Total	80	446	277	
Nadir PSA, ng/ml	*n* (%)	*n* (%)	*n* (%)	
≤0.3	37 (46.3)	241 (54.0)	158 (57.0)	$p < 0.001$
0.3–1	18 (22.5)	101 (22.7)	53 (19.1)	
>1	25 (31.2)	100 (22.4)	54 (19.5)	
Not determined	0 (0.0)	4 (0.9)	12 (4.3)	

PSA = prostate-specific antigen; HIFU = high-intensity focused ultrasound.

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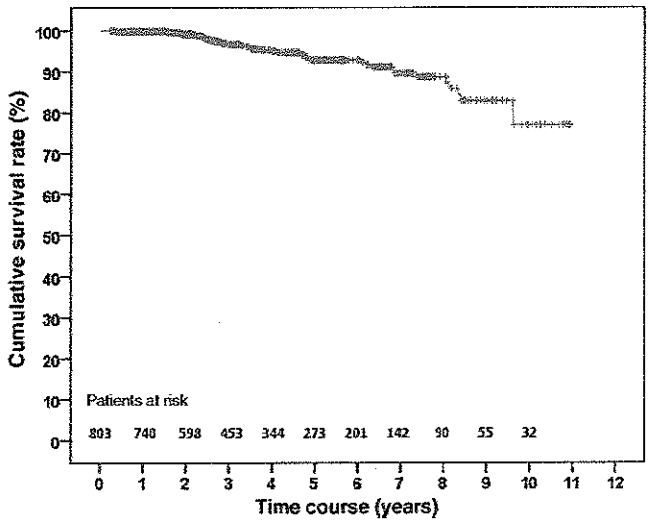

Fig. 1 – Overall survival rates in 803 patients with localized prostate cancer following treatment with high-intensity focused ultrasound.

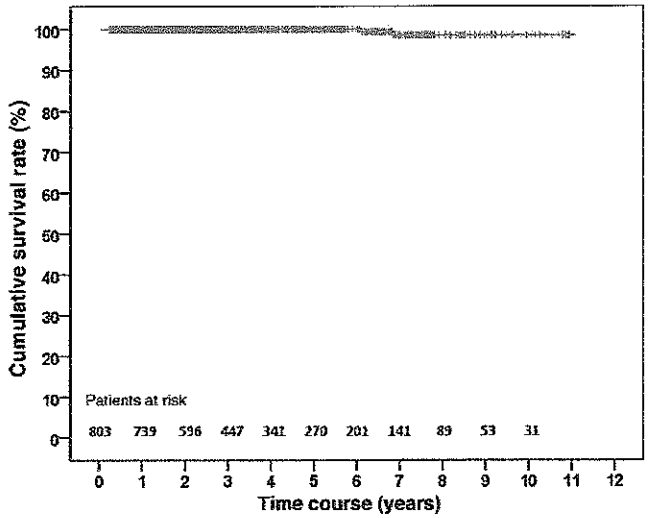

Fig. 2 – Cancer-specific survival rates in 803 patients with localized prostate cancer following treatment with high-intensity focused ultrasound.

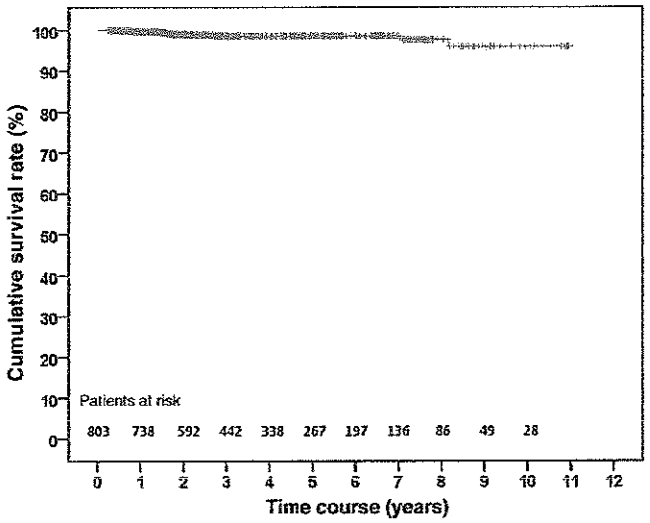

Fig. 3 – Metastasis-free survival rates in 803 patients with localized prostate cancer following treatment with high-intensity focused ultrasound.

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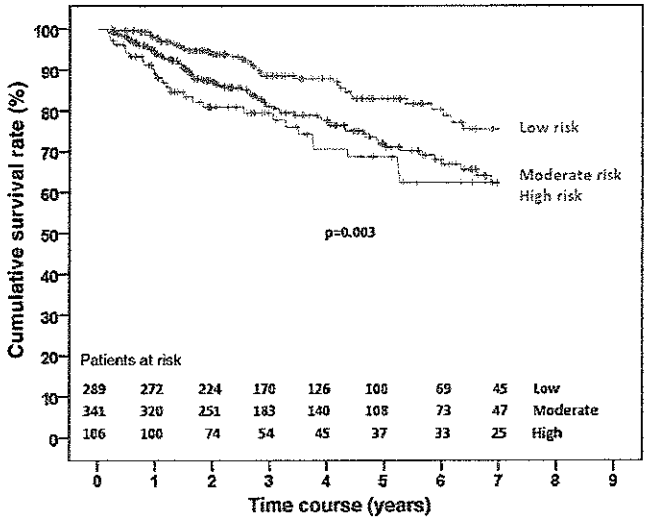

Fig. 4 – Biochemical-free survival rates in patients with localized prostate cancer following treatment with high-intensity focused ultrasound, according to D'Amico risk group.

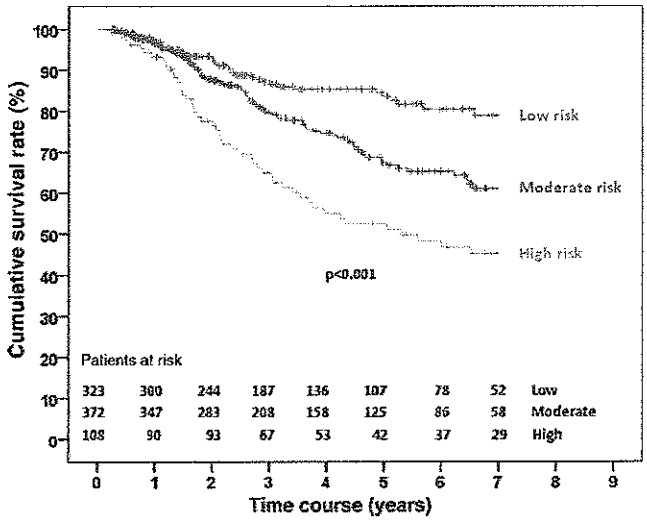

Fig. 5 – Adjuvant treatment-free survival rates in patients with localized prostate cancer following treatment with high-intensity focused ultrasound.

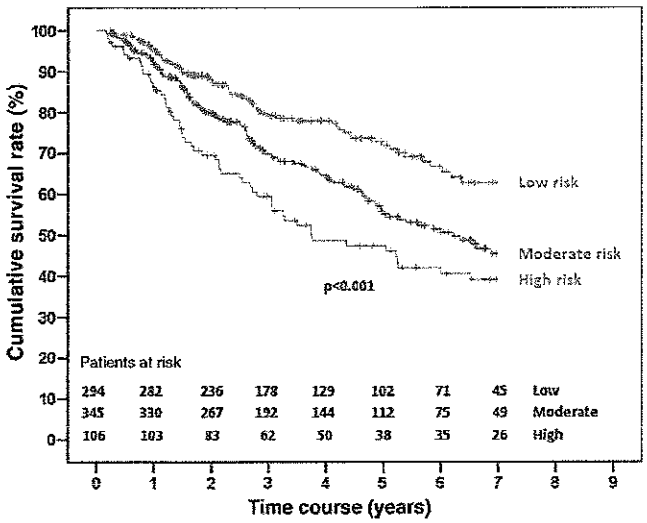

Fig. 6 – Disease-free survival rates using combined criteria in patients with localized prostate cancer following treatment with high-intensity focused ultrasound.

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Table 4 – Prognostic factors of disease progression (biochemical and adjuvant treatment) in patients treated with high-intensity focused ultrasound technology: results of the univariate analysis and Cox model

Prognostic factors	Univariate risk ratio	Univariate 95% CI	Univariate *p* value	Multivariate risk ratio	Multivariate 95% CI	Multivariate *p* value
Age	1.02	1.00–1.04	0.083	0.99	0.96–1.02	0.524
Gleason score						
≤6	1	–	–	1	–	–
7	1.25	0.95–1.64	0.109	1.11	0.77–1.60	0.564
≥8	2.25	1.52–3.31	<0.001	1.90	1.20–3.03	0.007
PSA, ng/ml						
≤4	1	–	–	1	–	–
4–10	2.91	1.68–5.06	<0.001	2.49	1.24–4.97	0.010
>10	4.93	2.82–8.60	<0.001	3.83	1.90–7.72	<0.001
Stage						
T1	1	–	–	1	–	–
T2	1.06	0.83–1.36	0.632	1.01	0.74–1.38	0.951
Prostate volume, ml						
≤25	1	–	–	1	–	–
>25	1.16	0.90–1.50	0.259	0.97	0.71–1.33	0.865
Positive biopsies						
≤33%	1	–	–	1	–	–
>33%	1.21	0.90–1.63	0.211	1.18	0.85–1.64	0.314

PSA = prostate-specific antigen; CI = confidence interval.

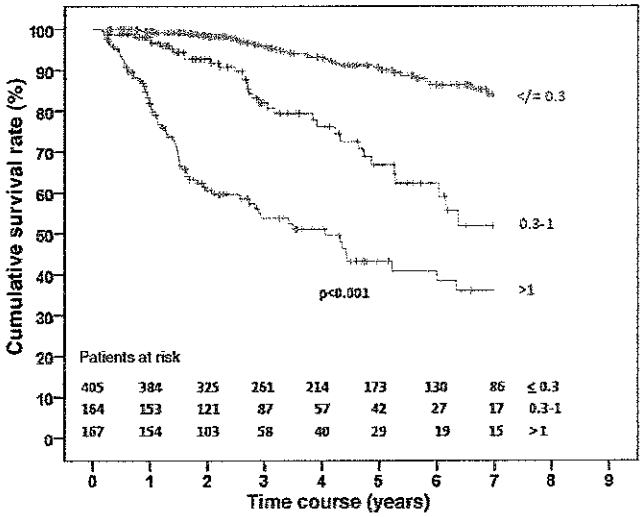

Fig. 7 – Biochemical-free survival rates in patients with localized prostate cancer following treatment with high-intensity focused ultrasound depending on prostate-specific antigen nadir levels.

3.6. *Outcome prognostic factors*

In the multivariate analysis (Table 4), only the PSA level and the Gleason score before the HIFU treatment was significantly linked to the rate of disease progression. Age, clinical stages, prostate volume, and percentage of positive biopsies before HIFU did not reach statistical significance. PSA nadir was a major predictive factor for HIFU success. The BFSR at 5 yr and 7 yr were 91% and 84%, respectively, for a PSA nadir ≤0.3 ng/ml, 67% and 51% for a PSA nadir of 0.31–1 ng/ml, and 42% and 35% for a PSA nadir >1 ng/ml ($p < 0.001$) (Fig. 7).

4. Discussion

The goal of PCa treatment is to reduce the risk of local recurrence, biochemical disease-free rate, distant metastasis, and, finally, to decrease the risk of cancer-specific death.

4.1. *Local control*

In this multicenter study, HIFU resulted in local control (negative biopsies) in 77.9% of our patients, which correlates well with previous published papers about both the Ablatherm device and the Sonablate device (Focus

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Surgery Inc, Indianapolis, IN, USA) [11–14]. This is similar to the results reported after radiation therapy. After conformal EBRT, relatively high positive biopsy rates (21–32%) were recently reported [2,15,16]. Local control of the tumor is a major predictor of long-term disease control. In the study of Zapatero et al, multivariate analysis showed that biopsy status after EBRT at 24–36 mo was an independent predictor of DFSR and of clinical failure-free survival [16]. Similarly, in the study of Zelefeski et al, multivariate analysis indicated that the strongest predictor of biochemical failure, distant metastasis, and PCa death was post-treatment biopsy status [2].

4.2. *Disease-free survival rate*

The BFSR after HIFU were similar to DFSR reported after conformal EBRT, especially for intermediate- and high-risk patients even with dose escalation [17,18]. However, only prospective studies or matched-pair analysis would allow a direct comparison between HIFU and EBRT. Similar to EBRT, the BFSR after HIFU was significantly influenced according to the d'Amico risk group [19]. The pre-HIFU prostate volume (<25 vs >25 ml) did not significantly influence the BFSR, even though the mean prostate volume before HIFU in this study was relatively small (median: 23 ml).

However, the Phoenix criteria are not very accurate for post-HIFU DFSR calculation: The Stuttgart criteria nadir plus 1.2 ng is certainly more sensitive [20]. In fact, in this HIFU cohort, control biopsies were often performed before the PSA increase to nadir plus 2 ng (usually at plus 1 ng above the nadir). The additional treatment survival rate is more accurate to present the real clinical outcomes after HIFU because the start of an additional treatment clearly defines clinical failure. The combination of the two previous criteria represents the real HIFU outcomes.

4.3. *Early detection of recurrence*

Unlike radiation therapy, HIFU allows an early feedback on treatment efficacy because the PSA nadir value was achieved within 3–6 mo after the treatment and, in addition, the phenomenon of PSA bounce is never observed after HIFU. Moreover, nadir was a major predictive factor for HIFU success [21,22]. Currently, in clinical practice in most institutions, the routine PSA cut-off value for early control biopsies is 0.3 ng/ml. Early detection of relapse significantly influenced the outcome of either the second HIFU session or post-HIFU salvage radiation therapy [23]. The predictive factor of PSA nadir value was also demonstrated after EBRT with an end point of 1.5 ng/ml, but the nadir after EBRT is usually achieved after 18 mo [24]. However, the use of control biopsy after EBRT is not common before a rise of PSA at a value of nadir plus 2, whatever the nadir value was. Color Doppler or dynamic contrast-enhanced magnetic resonance imaging have recently shown interesting results in detecting and localizing local recurrences after HIFU ablation. In the future these methods might improve treatment outcome by allowing early detection of recurrences [25–27].

4.4. *Distant metastasis and cancer-specific survival rate*

In this multicenter study, the metastasis-free survival rate was 97% and the CSSR was 99% at 8 yr. Those results may probably be explained by the good local control of the cancer achieved after HIFU and later using salvage radiotherapy in patients who presented a local relapse. Salvage EBRT after HIFU is able to improve the survival outcomes of a patient with a local recurrence after HIFU [23]. Patients with biopsy-proven local relapse after HIFU (84 patients) received a salvage radiation therapy that may explain these results. After conformal EBRT, Zelefski et al reported that 10-yr PSA relapse-free survival rates in patients with negative and severe treatment-effect biopsy outcomes were 59% and 49%, respectively; while in patients with positive biopsy, the corresponding outcome was only 3% [2]. Similarly, in the Zelefski et al study, the 10-yr metastasis-free survival rate in patients with negative/severe treatment-effect biopsy outcomes was 90% and the corresponding outcome in patients with positive treatment biopsy outcomes was 69%.

4.5. *Improvement of the results according to technical progress*

The current results were obtained in patients treated with prototypes, and the first and second generations of a commercialized HIFU device. It is difficult to compare the results achieved with the different devices because several technical improvements have been made. The last generation of the device allows real-time control of the treatment [7]. It is possible to define more accurately the apex and to determine a better treatment plan with an optimization of the targeted volume. The percentage of patients who reached a nadir value <0.3 ng increased progressively with a simultaneous reduction of the number of sessions and the number of patients with a nadir PSA >1 ng/ml, which favors better outcomes (Table 3). However, the implementation of a TURP prior to HIFU might contribute as much as technical developments to the improvement of the results. Preliminary data suggest that contrast-enhanced ultrasound can reliably show, immediately after the HIFU ablation, the location and amount of tissue that has not been destroyed after a first session of HIFU [28]. If these results are confirmed, this could allow an immediate retreatment of the incompletely destroyed areas.

5. Conclusions

Local control and DFSR achieved with HIFU were similar to those expected with conformal external beam radiation. HIFU can be repeated when necessary several months or several years after the first session and can also be followed by a salvage radiation therapy. This probably explains the excellent middle-term CSSR achieved in this multicenter study despite the presence of intermediate- and high-risk patients.

Author contributions: Sebastien Crouzet had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Study concept and design: Gelet, Crouzet.
Acquisition of data: Rebillard, Chevallier, Rischmann, Pasticier, Garcia, Gelet.
Analysis and interpretation of data: Crouzet, Gelet, Chapelon.
Drafting of the manuscript: Crouzet, Gelet, Rouviere.
Critical revision of the manuscript for important intellectual content: Gelet, Rouviere.
Statistical analysis: Crouzet, Gelet.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Gelet.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Albert Gelet is a lecturer and consultant for EDAP (Vaulx-en-Velin, France).

Funding/Support and role of the sponsor: None.

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Please cite this article in press as: Crouzet S, et al. Multicentric Oncologic Outcomes of High-Intensity Focused Ultrasound for Localized Prostate Cancer in 803 Patients. Eur Urol (2010), doi:10.1016/j.eururo.2010.06.037