BJUI
BJU International

Salvage high-intensity focused ultrasound (HIFU) for locally recurrent prostate cancer after failed radiation therapy: Multi-institutional analysis of 418 patients

Sebastien Crouzet*, Andreas Blana†, Francois J. Murat‡, Gilles Pasticier§, Stephen C. W. Brown¶, Giario N. Conti**, Roman Ganzer††, Olivier Chapet‡‡, Albert Gelet*, Christian G. Chaussy††, Cary N. Robertson§§, Stefan Thuroff¶¶ and John F. Ward***

*Department of Urology, Edouard Herriot Hospital, Lyon, France, †Department of Urology, Fuerth Hospital, Fürth, Germany, ‡Urology Department, Val d'Ouest Hospital, Ecully , §Department of Urology, CHU Pellegrin, Bordeaux, France, ¶Department of Urology, Stepping Hill Hospital, Stockport, UK, **Department of Urology, St. Anna Hospital, Como, Italy, ††Department of Urology, University of Regensburg, Regensburg, Germany, ‡‡Department of Radiation Oncology, Lyon Sud Hospital, Pierre Bénite, France, §§Department of Urology, Duke University, Durham, NC, USA, ¶¶Department of Urology, Harlaching Hospital, Munich, Germany, and ***Department of Urology, M. D. Anderson Cancer Center, Houston, TX, USA

S.C and A.B. shared first author.

Objective

To report the oncological outcome of salvage high-intensity focused ultrasound (S-HIFU) for locally recurrent prostate cancer after external beam radiotherapy (EBRT) from a multicentre database.

Patients and Methods

This retrospective study comprises patients from nine centres with local recurrent disease after EBRT treated with S-HIFU from 1995 to 2009. The biochemical failure-free survival (bFFS) rate was based on the 'Phoenix' definition (PSA nadir + 2 ng/mL). Secondary endpoints included progression to metastasis and cancer-specific death. Kaplan–Meier analysis was performed examining overall (OS), cancer-specific (CSS) and metastasis-free survival (MFS). Adverse events and quality of life status are reported.

Results

In all, 418 patients with a mean (SD) follow-up of 3.5 (2.5) years were included. The mean (SD) age was 68.6 (5.8) years and the PSA level before S-HIFU was 6.8 (7.8) ng/mL. The median PSA nadir after S-HIFU was 0.19 ng/mL. The OS, CSS and MFS rates at 7 years were 72%, 82% and 81%, respectively. At 5 years the bFFS rate was 58%, 51% and 36% for pre-EBRT low-, intermediate- and high-risk patients, respectively. The 5-year bFFS rate was 67%, 42% and 22% for pre-S-HIFU PSA level ≤4, 4–10 and ≥10 ng/mL, respectively. Complication rates decreased after the introduction of specific post-RT parameters: incontinence (grade II or III) from 32% to 19% ($P = 0.002$); bladder outlet obstruction or stenosis from 30% to 15% ($P = 0.003$); recto-urethral fistula decreased from 9% to 0.6% ($P < 0.001$). Study limitations include being a retrospective analysis from a registry with no control group.

Conclusion

S-HIFU for locally recurrent prostate cancer after failed EBRT is associated with 7-year CSS and MFS rates of >80% at a price of significant morbidity. S-HIFU should be initiated early following EBRT failure

Keywords

high-intensity focused ultrasound, PSA, biochemical failure, follow-up, salvage therapy, #ProstateCancer

Introduction

A significant proportion of patients experience a recurrence after external beam radiotherapy (EBRT) [1,2]. The recurrence rate after EBRT at 5 years in a multicentre study was reported to be 39% and 28% for 70 and 80 Gy, respectively [3]. After intensity-modulated RT, with a median dose of 7.6 Gy, biochemical survival rates at 9 years were 77.4%, 69.6% and 53.3% for low-, intermediate- and high-risk patients, respectively [4]. In the Cancer of the Prostate

Strategic Urologic Research Endeavor (CaPSURE) population, >90% of patients with recurrent prostate cancer received palliative androgen-deprivation therapy (ADT), which suppresses PSA levels but with absolutely no chance of cure [5]. Salvage radical prostatectomy (SRP) series have reported 10-year biochemical failure-free (bFFS), metastasis-free (MFS), and cancer-specific (CSS) survival probabilities of 37%, 77%, and 83%, respectively [6]. However, SRP is associated with significant morbidity especially urinary incontinence [7].

High-intensity focused ultrasound (HIFU) has been used as a primary treatment for prostate cancer for over a decade [8–10]. More recently, the technology was evaluated as a salvage therapy for locally recurrent prostate cancer after EBRT in patients without evidence of metastasis [11]. Based on data from 290 consecutive patients, the 7-year estimated CSS rate after salvage HIFU (S-HIFU) was 80%. The progression free-survival rates were 53%, 42% and 25% for low-, intermediate-, and high-risk patients (D'Amico), respectively, suggesting that S-HIFU is a valuable therapy for radio-recurrent prostate cancer [12]. S-HIFU is intended to completely ablate all prostate tissue that remains after primary EBRT. In the present multicentre, registry study, we evaluated the oncological outcomes and the associated morbidity of S-HIFU along with the preoperative prognostics that predict oncological success for the first time in a large cohort.

Patients and Methods

The Ablatherm (EDAP-TMS, Lyon, France) treatment registry (@-Registry™) is a secure on-line database for patients who have undergone prostate HIFU using the Ablatherm device. The @-Registry was specifically designed to collect de-identified pre- and post-treatment information. Data from 3218 consecutively treated patients entered in the @-Registry between December 2005 and June 2009 were reviewed for this retrospective analysis.

Patients who underwent total gland S-HIFU for locally recurrent prostate cancer (T1–2) after EBRT were included in the analysis. The inclusion criteria were a biochemical failure [American Society for Therapeutic Radiology and Oncology (ASTRO) before 2006 and then Phoenix definition) [13,14], a positive post-EBRT biopsy, and a negative metastatic evaluation. Metastatic evaluation included a bone scan and an abdominopelvic CT, and most patients also received a prostatic MRI. All patients who received ADT within 90 days of S-HIFU were excluded from the analysis.

Contraindications for S-HIFU included anal/rectal stenosis and a rectal wall thickness >6 mm measured in by TRUS.

Total gland S-HIFU was performed using the Ablatherm HIFU device. The prostate was treated in two to four overlapping blocks from the apex to the base. Between 1995 and March 2002, standard treatment parameters were used. This entailed 100% acoustic power with a 6-s pulse of energy to create each discrete HIFU lesion with a 4-s delay between each shot. Starting in March 2002, specific post-RT parameters were adopted (4-s pulse, 6-s waiting period, 90% of the acoustic power) due to the high rate of morbidity with the protocol before 2002. These were developed considering the decreased vascularity of the previously irradiated tissue. The goal was to optimise the thermal dose delivered within the gland while minimising the possible damage probability to surrounding tissues, especially the rectal wall, which is caused by conductive heat transfer.

S-HIFU treatments were usually performed under spinal anaesthesia or general anaesthesia. Most of the patients underwent a bladder neck incision to reduce the risk of urinary retention and BOO after S-HIFU. TURP was performed if a median lobe was present. TURP and S-HIFU were performed during a single session, and patients were usually discharged from hospital 3–5 days after the procedure with or without a urinary catheter. No adjuvant ADT was used after S-HIFU.

Patient follow-up included clinical and biochemical evaluations every 3 months for the first year and every 6 months thereafter. Initially, treated patients first underwent systematic biopsies at 3 months. Additional biopsies were taken in cases of rising PSA during follow-up. Since 2008, when the PSA nadir was <0.2 ng/mL, systematic control biopsies have not taken [15]. Control biopsies were taken only in cases of rising PSA. A complete diagnostic evaluation was conducted in cases of biochemical relapse after S-HIFU. A second S-HIFU session was offered when an exclusively local recurrence was identified. Side-effects were systematically evaluated and recorded. Urinary incontinence was graded according to the Ingelman–Sundberg score (strong, moderate, minimal effort: grade I, grade II and grade III, respectively) [16].

The CSS, MFS and bFFS rates were estimated using the Kaplan–Meier method. Biochemical failure was defined as an increase of ≥2 ng/mL above the PSA nadir (Phoenix definition) [14]. The salvage treatment-free survival rate was defined as the time of ADT initiation. The bFFS was stratified according to the pre-radiotherapy D'Amico's risk group, the pre-S-HIFU PSA level (≤4, 4.1–10, or >10 ng/mL), the pre-S-HIFU estimated Gleason score (≤6, 7, ≥8) and the administration of ADT prior or during EBRT. The Kaplan–Meier method was also used to estimate the bFFS curves according to the different categories of each factor compared when using the log-rank test. A Cox model was used for multivariate analysis to identify independent factors linked to the risk of failure. Analysis was performed using the statistical software S-plus version 6.2. A $P < 0.05$ was chosen to identify statistically significant differences.

Results

Of the 3218 datasets collected in the @-Registry between December 2005 and June 2009, 418 patients met the inclusion criteria for the analysis (Table 1). The mean (SD) RT dose was 69.2 (6.5) Gy (median 70 Gy) and the mean (SD) time between EBRT and S-HIFU was 5.1 (2.7) years. The mean (SD) age at S-HIFU was 68.6 (5.8) years and the PSA level before S-HIFU was 6.8 (7.8) ng/mL. In all, 191 patients (45.7%) had a history of ADT (neoadjuvant, concomitant or adjuvant). No patients continued ADT after S-HIFU treatment.

The mean (SD) prostate volume before S-HIFU was 20.6 (7.9) mL and the treated volume was 22.2 (8.5) mL (average 108% of the prostate volume due to an overlap between the treated zone inside the prostate). The total number of S-HIFU sessions was 476 [one session: 364 (87.1%), two sessions: 51 (12.2%), and three sessions: three (0.7%)].

The median (range) follow-up after S-HIFU was 3.3 (1.5–5.2) years. The mean (SD) prostate volume after S-HIFU was 15.0 (8.8) mL. Due to the small prostate volume after S-HIFU, a minimum of six control biopsies were usually taken to evaluate the local control of the prostate cancer. In all, 254 patients (60.8%) underwent biopsy of which 187 (73.6%) were negative. Of the 164 patients without control biopsy, 88 (53.6%) did not have biochemical recurrence, while 76 (46.4%) did and were placed on ADT.

Table 1 Baseline characteristics of 418 patients treated with S-HIFU after EBRT failure.

Variable	Value
Age, years	
Mean (SD)	68.6 (5.8)
Median (range)	69 (42–83)
PSA, ng/mL	
Mean (SD)	6.8 (7.8)
Median (range)	4.6 (0.0-62.0)
Prostate volume, mL	
Mean (SD)	20.6 (7.9)
Median (range)	19.0 (4.3–53.1)
Delay between Pre-EBRT and S-HIFU, years	
Mean (SD)	5.1 (2.7)
Median (range)	4.7 (0.1–17.5)
N (%)	
Previous ADT	
Yes	191 (45.7)
No	227 (54.3)
Pre-EBRT risk	
Low	48 (11.5)
Intermediate	77 (18.4)
High	119 (28.5)
Undefined	174 (41.6)
Pre-S-HIFU Gleason score	
≤6	121 (28.9)
=7	114 (23.3)
≥8	112 (26.8)
Undefined	71 (17.0)
Pre-S-HIFU PSA level, ng/mL	
≤4	173 (41.4)
4–10	166 (39.7)
≥10	76 (18.2)
Undefined	3 (0.7)

In all, 222 patients (53.1%) did not receive any salvage treatment after S-HIFU, while 196 patients (46.9%) received ADT for recurrent local prostate cancer or metastases after S-HIFU. Of the 196 patients that received ADT after S-HIFU, 45 (23%) had positive biopsies, 75 (38.3%) had negative biopsies, and 76 (38.8%) did not have biopsies taken. Of the 222 patients that did not receive ADT after S-HIFU, 22 (9.9%) had positive biopsies, 112 (50.5%) had negative biopsies, and 88 (39.6%) did not have biopsies taken. The OS, CSS and MFS rates at 7 years were 72%, 82% and 81%, respectively (Fig. 1).

The mean (SD) PSA nadir was 1.9 (5.2) ng/mL (median 0.19, range 0–54.9 ng/mL) and was reached at a mean (SD) time of 10.1 (10.7) weeks after S-HIFU. In all, 225 patients (53.8%) reached a nadir PSA level of ≤0.3 ng/mL and 203 (48.6%) ≤0.2 ng/mL.

The bFFS rate at 5 years was 49%. At 5 years the bFFS rate was 58%, 51% and 36% for pre-EBRT low-, intermediate- and high-risk patients, respectively. The 5-year bFFS rate was 67%, 42% and 22% for pre-S-HIFU PSA levels of ≤4, 4–10 and ≥10 ng/mL respectively and 59%, 41% and 39% for pre-S-HIFU Gleason score of ≤6, equal to 7 and ≥8, respectively. The bFFS rate was 59% for patients without any previous ADT and 38% for those with a history of ADT (Fig. 2).

The salvage treatment-free survival rate at 5 years was 37%, and was 54%, 37% and 23% for pre-EBRT low-, intermediate- and high-risk patients, respectively. The 5-year salvage treatment-free survival rate was 49%, 33% and 20% for pre-S-

Fig. 1 OS, CSS and MFS rates in patients treated after S-HIFU

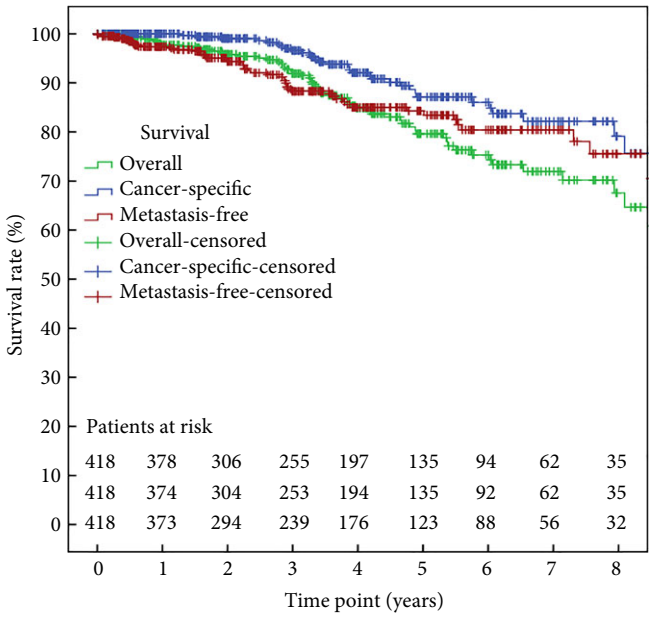
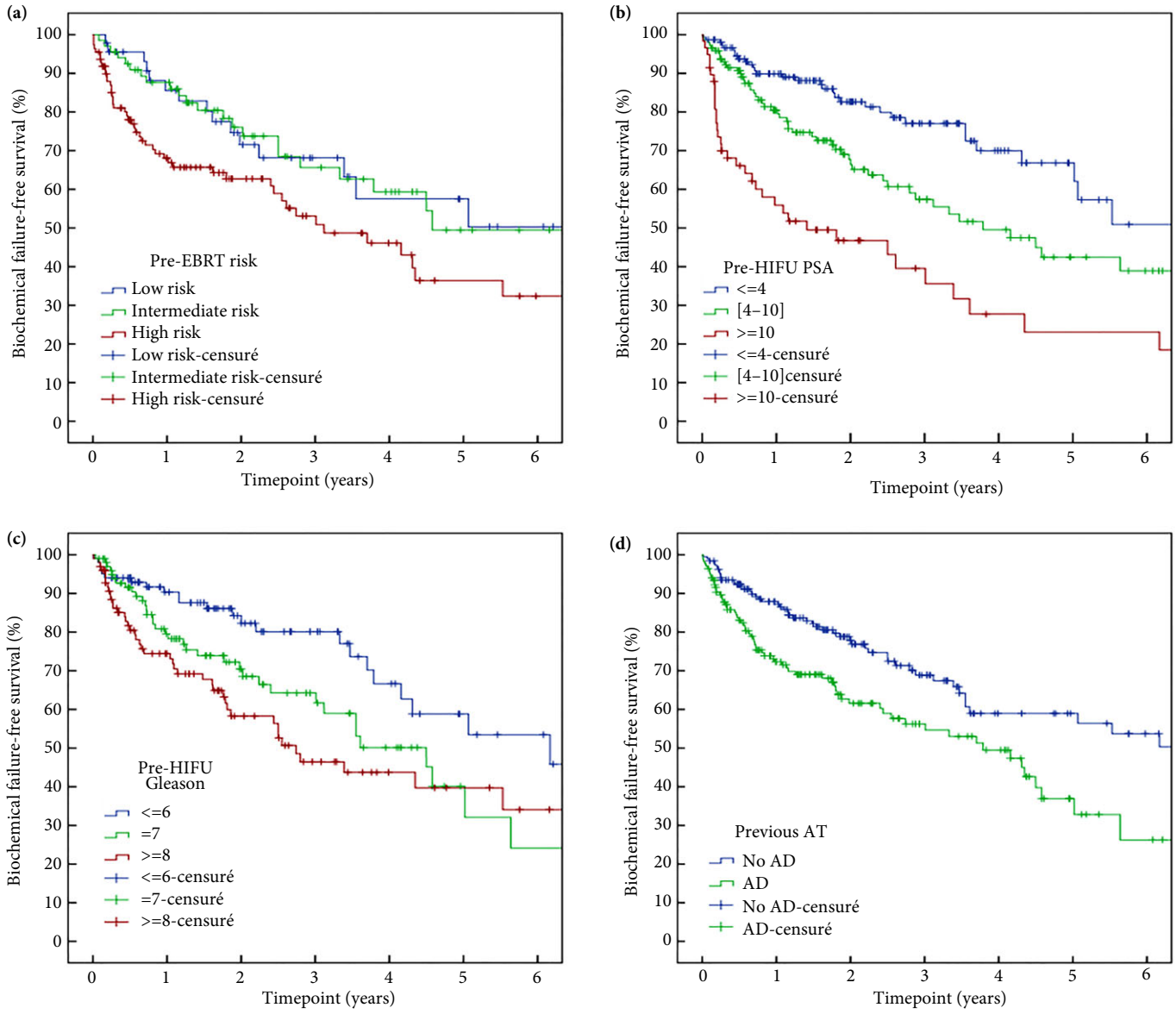


Fig. 2 bFFS rates. (**a**) influence of initial risk; (**b**) influence of pre-S-HIFU PSA level; (**c**) influence of pre-S-HIFU Gleason score; (**d**) influence of post-S-HIFU nadir PSA.



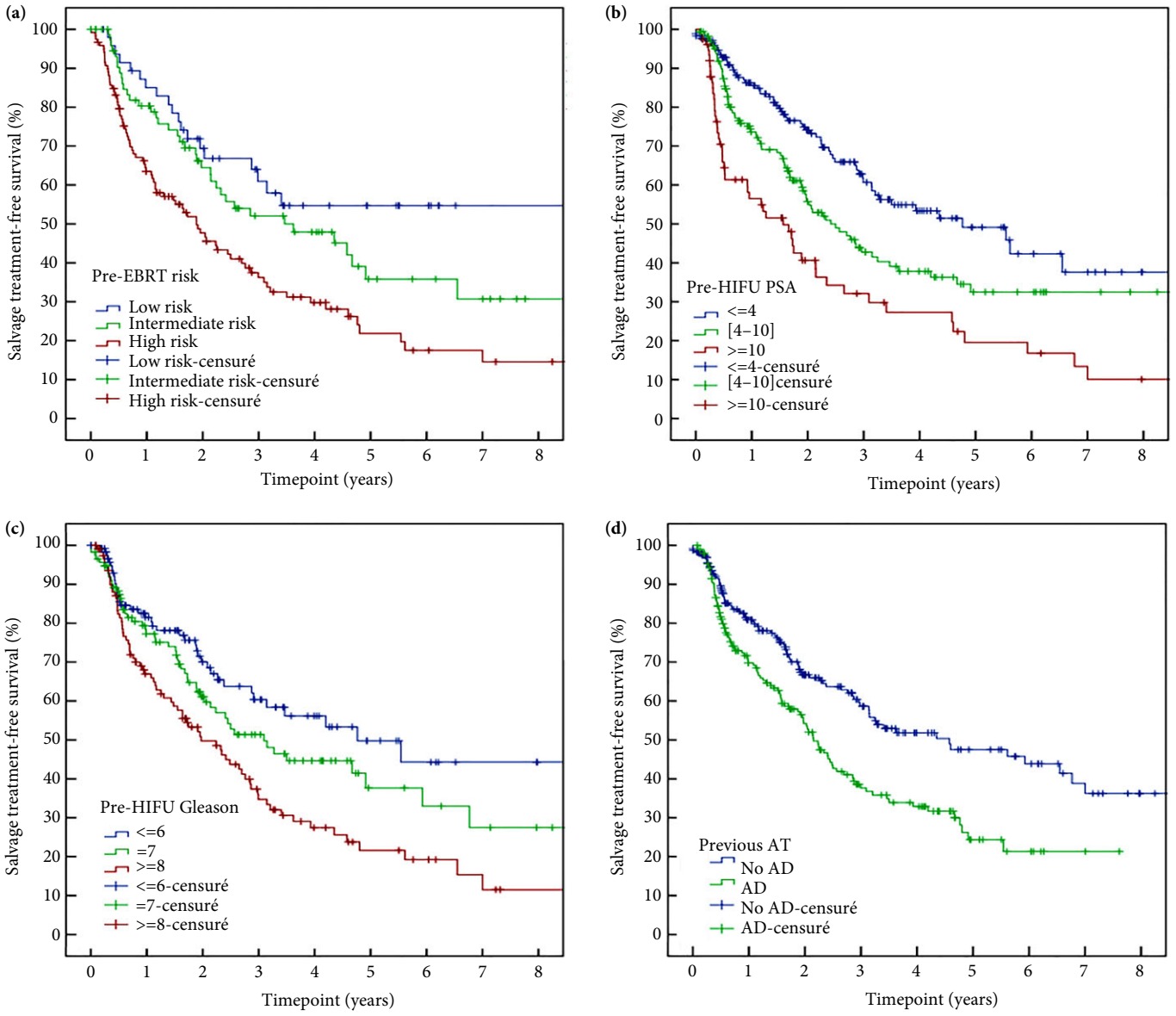
HIFU PSA levels of ≤4, 4–10 and ≥10 ng/mL respectively and 50%, 38% and 22% for pre-S-HIFU Gleason score of ≤6, equal to 7 and ≥8, respectively. The 5-year salvage treatment-free survival rate for patients without any previous ADT was at 48% vs 26% for those with a history of ADT (Fig. 3).

In the multivariate analysis three factors (history of ADT, pre-S-HIFU Gleason score and pre-S-HIFU PSA level) were significantly linked to biochemical recurrence and initiation of a salvage treatment (Table 2).

The PSA nadir was a major predictive factor for salvage treatment-free survival rate (Fig. 3). The salvage treatment-free survival rate at 5 years was 56%, 16% and 8% for PSA nadir of ≤0.3, 0.31–1 and >1 ng/mL, respectively.

The specific post-RT parameters introduced in 2002 decreased the rate of many long-term complications (Table 3). Moderate and severe incontinence (grade II or III) decreased from 32% to 19%. The incidence of artificial urinary sphincter implantation was significantly reduced with the specific post-RT parameters when compared to standard parameters (15% vs 5%; $P < 0.001$). The incidence of BOO or stenosis incidence dropped from 30% to 15% ($P = 0.001$). The rate of recto-urethral fistula decreased from 9% to 0.6%.

Fig. 3 Salvage treatment-free survival rates. (**a**) influence of initial risk; (**b**) influence of pre-S-HIFU PSA level; (**c**) influence of pre-S-HIFU Gleason score; (**d**) influence of post-S-HIFU nadir PSA.



Erectile function was not evaluated. Of the nine recto-urethral fistulae, only two were successfully closed with a York-Masson procedure. The other seven, were managed with colostomy and Bricker (four) or colostomy alone (three). Osteitis was managed with prolonged antibiotics in six patients, retropubic muscular interposition in two, colostomy and Bricker in one.

Discussion

Most men with radio-recurrent prostate cancer are treated with systemic ADT [5,17]. ADT is also associated with adverse effects, including cardiac and thromboembolic complications [18]. Patients treated with ADT or ADT followed by chemotherapy have poor outcomes. In the Zumsteg et al. [19] study, the date of biochemical failure to distant metastasis and cancer-specific mortality were 5.4 and 10.5 years respectively, despite the use of medical therapies, the estimated 5-year post-biochemical failure distant metastasis rate was 47% and the 5-year cumulative incidence of cancer-specific mortality was 18%. In our present study, after S-HIFU, the estimated MFS rate was 81% at 7 years.

The CSS rate after SRP at 10 years was reported to be 77% [20]. More recently, in a series of 404 patients undergoing SRP, at 10 years, the bFFS rate was

Table 2 Initiation of salvage treatment after S-HIFU failure and biochemical failure (Phoenix definition): result of the Cox-multivariate analysis.*

Prognostic factors	Univariate		Multivariate	
	Risk ratio (95% CI)	*P*	Risk ratio (95% CI)	*P*
Initiation of salvage treatment after S-HIFU failure				
ADT	1.71 (1.29–2.27)	<0.001	2.09 (1.42–3.08)	<0.001
Pre-S-HIFU Gleason score				
≤6	1	–	1	–
=7	1.36 (0.90–2.06)	0.139	1.23 (0.73–2.07)	0.441
≥8	2.06 (1.40–3.02)	<0.001	1.82 (1.12–2.98)	0.016
Pre-S-HIFU PSA level, ng/mL				
≤4	1	–	1	–
4–10	1.59 (1.14–2.20)	0.006	1.62 (1.08–2.44)	0.021
>10	2.68 (1.85–3.88)	<0.001	2.24 (1.34–3.75)	0.002
Biochemical failure (Phoenix) after S-HIFU				
ADT	1.80 (1.25–2.59)	0.002	2.42 (1.46–4.00)	0.001
Pre-S-HIFU Gleason score				
≤6	1	–	1	–
=7	1.70 (1.01–2.85)	0.044	1.24 (0.64–2.39)	0.529
≥8	2.26 (1.37–3.71)	0.001	1.94 (1.05–3.58)	0.035
Pre-S-HIFU PSA level, ng/mL				
≤4	1	–	1	–
4–10	1.89 (1.21–2.93)	0.005	1.58 (0.92–2.72)	0.100
>10	4.12 (2.56–6.64)	<0.001	3.26 (1.76–6.05)	<0.001

**Pre-EBRT risk was not significant and was removed from the model (Cox backward stepwise method).*

Table 3 Morbidity.

Adverse event	Standard HIFU parameters, % (*n*) (*n* = 74)	Post-RT HIFU parameters, % (*n*) (*n* = 314)	Overall, % (*n*) (*n* = 388)	*P*
Urinary incontinence, % (at risk)				
No pads	51.4 (38)	59.2 (186)	57.7 (224)	
grade 1	16 (12)	22 (69)	21 (81)	N.S.
grade 2	23 (17)	10 (31)	12 (48)	0.002
grade 3	9 (7)	9 (28)	9 (35)	N.S.
AUS	15 (11)	5 (16)	7 (27)	0.003
BOO/stenosis	30 (22)	15 (47)	18 (69)	0.003
Fistula	9 (7)	0.6 (2)	2.3 (9)	<0.001
Pubic bone osteitis	3 (2)	2 (6)	2 (8)	N.S.

AUS, artificial urinary sphincter.

77% and the CSS rate was 83% [6]. Definitive surgery for local recurrent prostate cancer after EBRT is associated with severe morbidity. The average rate of rectal injury was 4–7%, of bladder neck stricture was 24%, and the average urinary incontinence rate was 41% [21]. In a recent study, the rate of urinary incontinence was found to be 45.5% with 25.5% using 1 pad/day and 20% with ≥2 pads/day [7]. The rate of rectal injury was 3.6%. Those survival and complication data seem similar to those achieved with S-HIFU. But if only patients with specific S-HIFU parameters are evaluated, S-HIFU compares favourably with SPR. Results achieved after a robotic procedure seem similar to those of open surgery. In 2013, Yu et al. [22] reported complications and oncological outcomes of 51 robot-assisted SRPs: the estimated 3-year bFFS or progression-free survival rate was 57%. The overall complications rate was 47% with a 35% major complications rate (Clavien–Dindo III–V): 16% bladder neck contractures, 4% thromboembolic events and 4% urosepsis. Return to urinary continence was achieved in 45% of patients.

Salvage cryotherapy is another option for this patient group. The disease-free survival rate at 10 years was 39% and the CSS rate was 87% in a report by Williams et al. [21]. The predictive factors of recurrence for salvage cryotherapy and for S-HIFU are similar (pre-salvage treatment PSA level, Gleason score, and PSA nadir). The morbidity for salvage cryotherapy is significant: recto-urethral fistula, 1–2%; obstruction/retention, 3.2–67%; chronic perineal pain, 4–14%; severe incontinence, 2–4%; and mild incontinence, 6–13% [23,24].

One concern with the localisation of the recurrence after EBRT is the localisation close to the urethra. Leibovici et al. [25] found 74% of recurrences are located within 5.0 mm of the urethra. The advantage of S-HIFU is the complete treatment without preservation of the urethra as opposed to cryotherapy.

Pisters et al. [26] compared the treatment outcomes of SRP and salvage cryotherapy for patients with locally recurrent prostate cancer after initial RT. Compared to salvage cryotherapy, SRP resulted in superior biochemical survival. In previously reported data, the progression-free survival rates after salvage cryotherapy at 5 years ranged from 40% [27] to 59% [28].

Few data are available for salvage brachytherapy with short follow-ups. The rate of morbidity was found on average for

incontinence to be 36%, recto-urethral fistula 3.4% and rectal grade 3–4 toxicity 5.6% [29]. Gomez-Veiga et al. [30] reported the main results of 10 trials of salvage brachytherapy for EBRT failure: the 5-year biochemical disease-free survival (bDFS) rates ranged from 20% to 87%. One study reported a 10-year bDFS rate of 54%. The incidence of gastrointestinal complications ranged from 5.4% to 65% and 2.7% to 20% for grade 1–2 and grade 3–4 complications, respectively.

In the present analysis, we evaluated survival rates after S-HIFU therapy for locally radio-recurrent prostate cancer in the largest case series to date. At a mean follow-up of 7 years after S-HIFU, the CSS and MFS rates were 72% and 82%, respectively. Our present results appear similar to those obtain after salvage surgery with a lower rate of severe complications using specific post-RT S-HIFU parameters. The present results support the use of S-HIFU as a definitive treatment for local recurrence after EBRT. Another series of S-HIFU performed with the Sonablate® device with a shorter follow-up (19.8 months) found a bFFS rate at 2 years of 43%, with 62% of patients being pad free [31]. The rate of BOO was 20% and the rate of recto-urethral fistula was 2.4% after one treatment.

In 2002, treatment-specific parameters for post-RT S-HIFU with Ablatherm® device were introduced to account for the vascularisation of the prostate gland and peri-prostatic tissue, resulting from RT-induced fibrosis. The incidence of side-effects dropped significantly when the dedicated acoustic parameters of the S-HIFU device were implemented. With the latest Ablatherm device the rate of recto-urethral fistula is now <1% and the rate of severe incontinence is <20%. These data compare favourably with recent data on salvage surgery [7]. The main side-effect in our present series was BOO caused by urethral stricture, bladder neck stenosis or an accumulation of captive necrotic tissue in the treated area. The decrease of BOO achieved with dedicated parameters is probably due to reduction of the shots duration and acoustic intensity (i.e. thermal dose).

An important prognostic factor was the pre-S-HIFU PSA level, which can serve as a very early identifier of local recurrence after EBRT. This suggests that, to increase the chances of a successful treatment, control biopsies should be taken as soon as a biochemical relapse is identified. The pre-S-HIFU estimated Gleason score and previous ADT are also predictive factors of success.

Early identification of local recurrence after EBRT allows the option of focal therapy using S-HIFU or salvage cryotherapy [32]. In the Ly et al. [33] study, 91 patients with biopsy confirmed radio-recurrent prostate cancer underwent salvage focal cryoablation with curative intent. The bDFS rates was 46.5% at 5 years, and there were positive biopsies after salvage focal cryoablation in four of 14 patients who underwent biopsy. Recto-urethral fistula occurred in three patients (3.3%), urinary retention in six (6.6%), and incontinence in five (5.5%). In the Ahmed et al. [34] study, 39 patients received focal S-HIFU for localised recurrence after EBRT. The estimated progression-free survival rate was 49% at 2 years according to the Phoenix criteria and the pad-free rate was 87.2% at the last follow-up. In the two-centre study of Baco et al. [35], 48 patients received hemi-S-HIFU for unilateral radio-recurrent prostate cancer. The progression-free survival rate at 24 months was 52% and severe incontinence occurred in 8% of the patients, 17% required 1 pad/day and 75% were pad free. Focal therapies (cryoablation or HIFU) in patients with unilateral radio-recurrent prostate cancer results in less morbidity than whole gland salvage therapies. Accurate imaging and targeted biopsy are essential for identifying patients suitable for focal salvage procedures.

The present study has limitations: it is a retrospective analysis of registry data with a relatively short follow-up period. We did not evaluate PSA-doubling time, and the influence of the interval between EBRT and recurrence. The pre-EBRT D'Amico risk group was unknown in 41.6% of the patients and could represent a bias for the statistical analysis. Furthermore, the absence of a control group could have overestimated the effect of S-HIFU on the salvage treatment-free survival rate and CSS rate.

The lack of patient-reported outcome measures in the @registry is a drawback for quality of life evaluation. Concerning biochemical failure, the Phoenix definition was used in the present study, although it is not validated for HIFU treatment. To overcome this limitation we presented the results of the salvage treatment-free survival rate after S-HIFU.

In the present retrospective study, the locoregional and metastatic evaluation was not optimal for the first set of patients as positron emission tomography-choline and bone-MRI were not routinely available. Careful patient selection should be performed and the prospect of salvage treatment should be carefully weighed in the absence of level I evidence. Rectal stenosis after EBRT can represent an issue for S-HIFU. An MRI with an endorectal balloon can evaluate the size of the rectum and the rectal wall thickness before treatment.

Nonetheless, these data represent the largest case series of S-HIFU after RT failure to date, and the CSS, MFS and bFFS rates, add to the growing body of evidence that supports the expanded use of this procedure.

Conclusion

S-HIFU for locally recurrent prostate cancer after failed EBRT is associated with favourable 7-year survival rates at a price of significant morbidity, which patients should be made aware

of. Longer-term survival rates are needed, although the data presented supports the view that S-HIFU should now be considered as a definitive treatment option for patients with sufficient life expectancy to justify a salvage curative treatment.

Conflicts of Interest

Dr Crouzet is a consultant for EDAP TMS; Dr Blana, Dr Gelet and Dr Chaussy report personal fees from EDAP TMS.

References

1 **Zelefsky MJ, Reuter VE, Fuks Z, Scardino P, Shippy A.** Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. *J Urol* 2008; 179: 1368–73

2 **Zapatero A, Minguez R, Nieto S, Martin De Vidales C, Garcia-Vicente F.** Post-treatment prostate biopsies in the era of three-dimensional conformal radiotherapy: what can they teach us? *Eur Urol* 2009;55:902–9.

3 **Beckendorf V, Guerif S, Le Prise E et al.** 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys* 2011; 80: 1056–63

4 **Vora SA, Wong WW, Schild SE et al.** Outcome and toxicity for patients treated with intensity modulated radiation therapy for localized prostate cancer. *J Urol* 2013; 190: 521–6

5 **Jones JS.** Radiorecurrent prostate cancer: an emerging and largely mismanaged epidemic. *Eur Urol* 2011; 60: 411–12

6 **Chade DC, Shariat SF, Cronin AM et al.** Salvage radical prostatectomy for radiation-recurrent prostate cancer: a multi-institutional collaboration. *Eur Urol* 2011; 60: 205–10

7 **Heidenreich A, Richter S, Thuer D, Pfister D.** Prognostic parameters, complications, and oncologic and functional outcome of salvage radical prostatectomy for locally recurrent prostate cancer after 21st-century radiotherapy. *Eur Urol* 2010; 57: 437–43

8 **Thüroff S, Chaussy C.** Evolution and outcomes of 3 intensity focused ultrasound therapy for localized prostate cancer during 15 years. *J Urol* 2013; 190: 702–10

9 **Ganzer R, Fritsche HM, Brandtner A et al.** Fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localized prostate cancer. *BJU Int* 2013; 112: 322–9

10 **Crouzet S, Chapelon JY, Rouvière O et al.** Whole-gland ablation of localized prostate cancer with high-intensity focused ultrasound: oncologic outcomes and morbidity in 1002 patients. *Eur Urol* 2014; 65: 907–14

11 **Murat FJ, Poissonnier L, Rabilloud M et al.** Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. *Eur Urol* 2009; 55: 640–7

12 **Crouzet S, Murat FJ, Pommier P et al.** Locally recurrent prostate cancer after initial radiation therapy: early salvage high-intensity focused ultrasound improves oncologic outcomes. *Radiother Oncol* 2012; 105: 198–202

13 **American Society for Therapeutic Radiology and Oncology Consensus. Panel.** Consensus statement: guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 1997; 37: 1035–41

14 **Roach M 3rd, Hanks G, Thames H Jr et al.** Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006; 65: 965–74

15 **Ganzer R, Rogenhofer S, Walter B et al.** PSA nadir is a significant predictor of treatment failure after high-intensity focussed ultrasound (HIFU) treatment of localised prostate cancer. *Eur Urol* 2008; 53: 547–53

16 **Ingelman-Sundberg A, Ulmsten U.** Surgical treatment of female urinary stress incontinence. *Contrib Gynecol Obstet* 1983; 10: 51–69

17 **Grossfeld GD, Li YP, Lubeck DP, Caroll PR.** Patterns of failure after primary local therapy for prostate cancer and rationale for secondary therapy. *Urology* 2002;60:57–62.

18 **Ehdaie B, Atoria CL, Gupta A et al.** Androgen deprivation and thromboembolic events in men with prostate cancer. *Cancer* 2012; 118: 3397–406

19 **Zumsteg ZS, SPratt DE, Romesser PB et al.** The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. *Eur Urol* 2015;67:1009–16.

20 **Ward JF, Sebo TJ, Zincke H, Blute ML.** Salvage surgery for radiorecurrent prostate cancer: contemporary outcomes. *J Urol* 2005; 173: 1156–60

21 **Williams AK, Martinez CH, Lu C et al.** Disease-free survival following salvage cryotherapy for biopsy-proven radio-recurrent prostate cancer. *Eur Urol* 2011; 60: 405–10

22 **Yuh B, Ruel N, Muldrew S et al.** Complications and outcomes of salvage robot-assisted radical prostatectomy: a single-institution experience. *BJU Int* 2014; 113: 769–76

23 **Nguyen PL, D'Amico AV, Lee AK, Suh WW.** Patient selection, cancer control, and complications after salvage local therapy for postradiation prostate-specific antigen failure: a systematic review of the literature. *Cancer* 2007; 110: 1417–28

24 **Mouraviev V, Spiess PE, Jones JS.** Salvage cryoablation for locally recurrent prostate cancer following primary radiotherapy. *Eur Urol* 2012; 61: 1204–11

25 **Leibovici D, Chiong E, Pisters LL et al.** Pathological characteristics of prostate cancer recurrence after radiation therapy: implications for focal salvage therapy. *J Urol* 2012; 188: 98–102

26 **Pisters LL, Leibovici D, Blute M et al.** Locally recurrent prostate cancer after initial radiation therapy: a comparison of salvage radical prostatectomy versus cryotherapy. *J Urol* 2009; 182: 517–27

27 **Izawa JI, Morganstern N, Chan DM, Levy LB, Scott SM, Pisters LL.** Incomplete glandular ablation after salvage cryotherapy for recurrent prostate cancer after radiotherapy. *Int J Radiat Oncol Biol Phys* 2003; 56: 468–72

28 **Bahn DK, Lee F, Silverman P et al.** Salvage cryosurgery for recurrent prostate cancer after radiation therapy: a seven-year follow-up. *Clin Prostate Cancer* 2003; 2: 111–14

29 **Grado GL, Collins JM, Kriegshauser JS et al.** Salvage brachytherapy for localized prostate cancer after radiotherapy failure. *Urology* 1999; 53: 2–10

30 **Gomez-Veiga F, Mariño A, Alvarez L et al.** Brachytherapy for the treatment of recurrent prostate cancer after radiotherapy or radical prostatectomy. *BJU Int* 2012; 109(Suppl. 1): 17–21

31 **Ahmed HU, Cathcart P, Chalasani V et al.** Whole-gland salvage high-intensity focused ultrasound therapy for localized prostate cancer recurrence after external beam radiation therapy. *Cancer* 2012; 118: 3071–8

32 **Bahn D, de Castro Abreu AL, Gill IS et al.** Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. *Eur Urol* 2012; 62: 55–63

33 **Li YH, Elshafei A, Agarwal G, Ruckle H, Powsang J, Jones JS.** Salvage focal prostate cryoablation for locally recurrent prostate cancer after radiotherapy: initial results from the cryo on-line data registry. *Prostate* 2015; 75: 1–7

34 **Ahmed HU, Cathcart P, McCartan N et al.** Focal salvage therapy for localized prostate cancer Recurrence after external beam radiotherapy. *Cancer* 2012; 118: 4148–55

35 **Baco E, Gelet A, Crouzet S et al.** hemisalvage hig-intensity focused ultrasound (HIFU) in unilateral radiorecurrent prostate cancer: a prospective two centre study. *BJUI Int* 2014; 114: 532–40

Correspondence: Sebastien Crouzet, Urology and Transplantation Department, Edouard Herriot Hospital, 5 Place d'Arsonval, 69437 Lyon Cedex 03, France.

e-mail: sebastien.crouzet@chu-lyon.fr

Abbreviations: ADT, androgen-deprivation therapy; bDFS, biochemical disease-free survival; bFFS, biochemical failure-free survival; CSS, cancer-specific survival; HIFU, high-intensity focused ultrasound; MFS, metastasis-free survival; OS, overall survival; SRP, salvage radical prostatectomy; (EB) RT, (external beam) radiotherapy.

