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Single-session primary high-intensity focused ultrasonography treatment for localized prostate cancer: biochemical outcomes using third generation-based technology

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Study Type – Therapy (case series)
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OBJECTIVE

- To assess 4-year biochemical failure (BCF) rates in patients after high-intensity focused ultrasonography (HIFU) treatment using the Horwitz and Stuttgart definitions.

PATIENTS AND METHODS

- A total of 447 consecutive patients were treated with a single session of HIFU between May 2005 and December 2010.
- Follow-up included prostate-specific antigen (PSA) measurement every 3 months during the first year and every 6 months thereafter.
- Patients who had previously received radiation, androgen deprivation or HIFU therapy, and patients with <2 consecutive PSA measurements were excluded.
- BCF was reported using the Stuttgart (PSA nadir + 1.2 ng/mL rising) and the Horwitz (two consecutive increases of at least 0.5 ng/mL) definitions.

RESULTS

- In all, 402 patients met the inclusion criteria and the median (range) follow-up was 24 (6–48) months.
- Of these patients, 183 (45.5%) had low and 219 (54.5%) had intermediate D'Amico's risk stratification disease.
- Mean and median absolute PSA nadir levels were 0.36 ± 0.69 and 0.1 ng/mL (Q_1:0, Q_3:0.37), respectively and these were achieved in median time of 3 months.
- Overall 4-year mean (range) BCF-free rates were 68 (61–75)% and 72 (68–77)% according to the Stuttgart and Horwitz definitions at 4 years, respectively.
- Mean (range) BCF-free rates were significantly higher for a PSA nadir ≤0.5 ng/mL and prostate volume ≤30 mL for both definitions at 4-year follow-up [Stuttgart: 79 (72–86)% vs. 25 (13–38)%; Horwitz: 82 (77–87)% vs. 33 (21–44)%] and [Stuttgart: 72 (64–79)% vs. 56 (42–69)%; Horwitz: 75 (69–80)% vs. 63 (53–74)%], respectively.
- Pre-treatment PSA and PSA nadir of >0.5 ng/mL were the predictors of BCF using both definitions.

CONCLUSIONS

- Primary HIFU appears to result in promising 4-year BCF-free rates in individuals with low- and intermediate-risk prostate cancer who achieve PSA nadir <0.5 ng/mL.
- A prostate volume <30 mL is associated with PSA nadir levels of <0.5 ng/mL suggesting a potential role for pretreatment volume reduction (medically or surgically) in larger prostates.

KEYWORDS

biochemical failure, HIFU, outcome, prostate cancer

What's known on the subject? and What does the study add?
The experience with HIFU as a minimally invasive treatment for localized prostate cancer is relatively new and most reports are from European centres.

Our study is unique in five regards: 1. Data was collected prospectively. 2. All patients were treated with contemporary technology. 3. Outcomes are reported after a single HIFU session using two definitions of biochemical failure that have the ability to predict longer-term clinical failure after primary ablative therapies for prostate cancer (Stuttgart definition for HIFU and Horwitz definition for radiation). 4. All patients were treated in a single centre. 5. No patients underwent peri-HIFU TURP. The present study represents the largest North American prospective cohort of primary HIFU for prostate cancer with mid-term oncological outcome data.

INTRODUCTION

With the advent of PSA screening most prostate cancer (PC) cases are now diagnosed at an early localized state. In parallel, novel treatment methods for organ-confined PC have emerged, which, it is hoped, will decrease treatment burden and side effects in comparison with radical prostatectomy and radiotherapy. High-intensity focused ultrasonography (HIFU) is an ablative technology that converts the

energy from ultrasound waves to heat resulting in coagulation necrosis, cavitations [1] and potentially in delayed immune response in the target tissue [2]. The clinical application of HIFU in the treatment of localized PC began 15 years ago, and significant improvements in energy delivery, safety features, and treatment protocol standardization have since been integrated into the new models of HIFU [3,4]. Nonetheless, few data on the oncological outcomes of contemporary HIFU treatment technology are currently available. In particular, data are sparse for HIFU as a primary therapy for PC [3–5].

In the present study, we aimed to evaluate the mid-term biochemical outcomes of HIFU in a large cohort of patients with localized PC treated with the latest HIFU technology at a single North American centre. The specific objectives were to assess the biochemical failure (BCF) rates according to post-radiation therapy (Horwitz) [6] and the recently introduced post-HIFU (Stuttgart) [7] definitions. These criteria were chosen for their ability to predict longer-term clinical failures. The present study is unique in five regards: data was collected prospectively; all patients were treated with contemporary technology; outcomes are reported after a single HIFU session; all patients were treated in a single centre; and no patients underwent peri-HIFU TURP. To our knowledge, the present study represents the largest North American prospective cohort of primary HIFU for PC with mid-term oncological outcome data.

MATERIALS AND METHODS

We retrospectively analysed prospectively collected data for 447 consecutive patients who underwent HIFU treatment at Maple Leaf HIFU LLP (Limited Liability Partnership) (Toronto, ON, Canada) between May 2005 and December 2010. Eligibility criteria for treatment were patients with a clinical stage of T1 and T2, Gleason score of ≤7 and serum PSA of <20 ng/mL. Patients with a prostate volume of >40 mL (based on their pre-treatment TRUS at the time of the diagnostic prostate biopsy) were not eligible for therapy.

For the purposes of this analysis, we excluded patients who had previously received radiation or HIFU therapy, patients who had received androgen deprivation therapy, and patients for who had <2 consecutive PSA measurements. Thus, a total of 402 patients were included in the present analysis. The study fulfilled the principles of the Declaration of Helsinki and was approved by the Research Review Board Inc., Waterloo, ON, Canada. Patients were treated with a planned single session of HIFU using the Ablatherm® integrated imaging model system (Ablatherm, EDAP, Lyon, France) under spinal anaesthesia and i.v. sedation. All patients were treated with average power ranging from 41 to 48 watts with an equivalent 6 s on, 4 s off pulse cycle. The mean (range) treatment duration was 122 (85–142) min per patient. Patients were discharged home the same day with a urethral catheter that was removed after 2 weeks. Patients were followed up every 3 months for the first year and every 6 months thereafter with PSA measurements. The overall follow-up period was defined as the interval between the HIFU treatment and the last follow-up time for each patient.

Patients were stratified according to D'Amico risk definitions [8]. PSA nadir was defined as the lowest value of PSA at any time during the follow-up period. The following definitions of BCF were used in this study: Horwitz definition (2 consecutive increases of at least 0.5 ng/mL, backdated) [6] and Stuttgart definition (nadir + 1.2 ng/mL 'at call') [7].

Prostate biopsies after treatment were offered to patients who had a rising PSA level from a nadir >0.5 ng/mL.

Categorical data are reported as percentages and continuous data as mean (SD) values or median and quartiles (Q1, Q3). Between-group comparison of continuous variables such as PSA nadir and prostate volume were achieved using an independent samples *t*-test. BCF events for each definition were determined and time to BCF for each definition was calculated. Probability curves of BCF-free survival were constructed using the Kaplan – Meier method, compared using a log-rank test and reported as percentages with 95% CIs. Cox's regression analysis was undertaken for proportional hazards (PH) modelling to explore the association of various prognostic factors (age, D'Amico risk [low/intermediate]), pre-treatment PSA, number of positive biopsies, the ratio of prostate volume treated to prostate volume and PSA nadir of >0.5 on BCF. The PH assumptions were tested using Schoenfeld's goodness-of-fit method for Stuttgart and Horwitz BCF definitions. The PH assumption was met for all variables with a *P* value of >0.1 and the *P* value for global test was 0.4085 for Stuttgart and 0.6290 for Horwitz definitions. One-step and stepwise approaches using the Wald statistic were performed for consistency. Hazard ratios (HRs) and 95% CIs are reported. The curves are truncated to 4 years owing to the small number patients after 4-year follow-up. All tests are two-sided and a *P* value of <0.05 was considered to indicate statistical significance. Data were analysed using STATA (STATA Corp LP, Texas, USA) and Minitab 14.0 (Minitab Inc., State College, PA, USA).

RESULTS

Between May 2005 and December 2010, 447 consecutive patients with PC were enrolled onto the study. We excluded 45 patients who had previously received radiation therapy or HIFU treatment or those who had <2 consecutive PSA measurements. We also excluded patients who had received androgen deprivation therapy. No patients received adjuvant hormonal therapy. A total of 402 patients were included in the analysis. Demographics and clinical characteristics for the 402 patients examined are shown in Table 1. The follow-up period varied from 6 to 48 months with a median of 24 (Q_1:15, Q_3:36) months. The mean (SD) ratio of prostate volume treated to calculated prostate volume at presentation was 1.5 (0.3). Of the 402 patients, one died of unrelated causes, there were no deaths attributed to PC, 183 (45.5%) patients had low-risk disease and 219 (54.5%) patients had intermediate-risk disease. Mean (SD) and median PSA nadir were 0.36 (0.69) ng/mL and 0.1 ng/mL (Q_1: 0, Q_3: 0.37), respectively. PSA nadir levels were achieved at a median time of 3 months (Q_1: 3, Q_3: 3). Mean (SD) PSA nadirs were 0.38 (0.7) ng/mL in low-risk and 0.35 (0.68) ng/mL in intermediate-risk groups ($P = 0.658$), respectively. A total of 324 (80.6%) patients had PSA nadir levels of ≤0.5 ng/mL. These patients had a significantly lower mean (SD) prostate volume than patients who reached a PSA nadir >0.5 ng/mL [24.3 (6.3) mL vs. 29.6 (8.5), $P < 0.001$].

There were 81 (29 low-risk, 52 intermediate-risk) and 99 (40 low-risk, 59 intermediate-

TABLE 1
Baseline characteristics of included patients (N = 402)

Clinical stage, *n* (%)	
T1c	307 (76.4)
T2a	74 (18.4)
T1b	2 (0.5)
T2b	19 (4.7)
T2c	0 (0)
Gleason score, *n* (%)	
5	4 (1.0)
6	205 (51.0)
3 + 4	130 (32.3)
4 + 3	63 (15.7)
Year of treatment, *n* (%)	
2005	34 (8.5)
2006	88 (21.9)
2007	96 (23.9)
2008	94 (23.4)
2009	63 (15.7)
2010	27 (6.7)
Risk group, *n* (%)	
Low	183 (45.5)
Intermediate	219 (54.5)
Gleason 3 + 4	130 (59.4)
Gleason 4 + 3	63 (28.8)
Gleason <7	26 (11.9)
Mean (SD) age	62.7 (7.5)
Mean (SD) baseline PSA ng/mL	6.6 (3.1)
Median (min, max) no. of biopsy cores	10 (3, 24)
Median (min, max) no. of positive biopsy cores	3 (1, 15)
Mean (SD) prostate volume mL	36.7 (7.6)

risk) BCF events according to Stuttgart and Horwitz definitions, respectively. The BCF-free survival rates were 68% (95% CI: 61–75%) for Stuttgart and 72% (95% CI: 68–77%) for Horwitz at 4 years follow-up time. According to the Stuttgart definition, BCF-free survival rates were 75% (95% CI: 67–84%) for low-risk patients and 62% (95% CI: 52–71%) for intermediate-risk patients at 4 years (Fig. 1A), with a statistically significant difference (log-rank $P = 0.047$). Using the Horwitz definition, BCF-free survival rates were 76% (95% CI: 69–83%) for low-risk patients and 69.5% (95% CI: 63–76%) for intermediate-risk patients at 4 years with no statistically significant differences (log-rank $P = 0.258$ [Fig. 1B]).

The PSA nadir value also had a substantial influence on cancer control. Using the Stuttgart definition, BCF-free survival at 4-year follow-up was 79% (95% CI: 72–86%) for a PSA nadir ≤0.5 ng/mL and 25% (95% CI: 13–38%) for PSA nadir > 0.5 ng/mL (log- rank $P < 0.001$ [Fig. 2A]).

Similarly, using the Horwitz definition, BCF-free survival at 4-year follow-up was 82% (95% CI: 77–87%) for a PSA nadir ≤0.5 ng/mL and 33% (95% CI: 21–44%) for PSA nadir > 0.5 ng/mL (log-rank $P < 0.001$ [Fig. 2B]).

Patients with a prostate volume of ≤30 mL had significantly higher BCF-free rates. Using the Stuttgart definition, BCF-free survival at 4-year follow-up was 72% (95% CI: 64–79%) for a prostate volume ≤30 mL, and 56% (95% CI: 42–69%) for prostate volume >30 mL, (log-rank $P = 0.002$ [Fig. 3A]). Similarly, using the Horwitz definition, BCF-free survival at 4-year follow-up was 75% (95% CI: 69–80%) for a prostate volume ≤30 mL, and 63% (95% CI: 53–74%) for prostate volume >30 mL (log-rank $P = 0.014$ [Fig. 3B])

Using Cox regression analysis (Table 2), the predictors of the Stuttgart definition for BCF were Nadir > 0.5 ng/mL (HR = 6.8 [95% CI: 4.3, 10.6], $P < 0.001$) and pre-treatment PSA value (HR = 1.11 [95%CI: 1.05, 1.18], $P < 0.001$). The predictors of the Horwitz definition for BCF were nadir > 0.5 ng/mL (HR = 5.6 [95% CI: 3.7, 8.5], $P < 0.001$) and pre-treatment PSA value (HR = 1.12 (95% CI: 1.06, 1.20), $P < 0.001$). Age, number of positive biopsies, prostate volume, D'Amico risk classification group (low/intermediate) or the ratio of prostate volume treated to prostate volume were not significant indicators of BCF in these patients.

Table 3 shows the timing of the biochemical events during the study period. For the Horwitz definition, 90% of the BCF events occurred during the first year with no events during the third and fourth year, respectively. According to the Stuttgart definition, 82.7% of failures occurred in the first 2 years.

Prostate biopsy was offered to the 78 patients who had a rising PSA level over a nadir > 0.5 ng/mL of whom 50 (64%) underwent biopsy. Thirty-four patients (68%) had positive biopsy results of whom 12 (35.3%) had repeat HIFU, six (17.6%) radical prostatectomy, four (11.8%) external beam radiation therapy, four (11.8%) androgen deprivation therapy, seven (20.6%) were considering their treatment options and are currently under surveillance and one patient (2.9%) was lost to follow-up. Overall 28 patients (7%) had some sort of salvage therapy.

DISCUSSION

The present study indicates that primary HIFU has therapeutic efficacy in the treatment of low- and intermediate-risk patient groups with PC. Clearly, local and distant failures are the most meaningful oncological outcomes by which any type of primary PC therapy should be evaluated; however, the follow-up needed for their appearance is significantly longer than that reported in the currently available prostate HIFU literature [3–5]. Two different definitions of BCF were thus used: the Stuttgart definition [7] and the Horwitz definition [6]. We chose to use these two definitions because of their ability to predict longer-term clinical failure after primary ablative therapies for PC (Stuttgart definition [7] for HIFU and Horwitz definition [6] for radiation). In addition, patients receiving any type of secondary treatment were considered to have BCF at the time of their treatment.

Blana *et al.* [7] retrospectively analysed a prospectively collected dataset of 285 patients who underwent HIFU as a primary therapy for low- and intermediate-risk localized PC. Clinical failure was defined as having positive post-HIFU biopsy, initiation of secondary treatment (including repeat HIFU), radiographic evidence of metastasis or PC-related deaths. With a median (range) follow-up of 4.7 (2–10.9) years, the biochemical events that best predicted clinical failure were PSA velocities of >0.2 ng/mL/year and reaching a threshold of nadir + 1.2 ng/mL (Stuttgart definition). Using this definition in the present cohort the 4-year BCF-free survival rate was significantly higher for patients with low-risk PC (75%, 95% CI: 67, 84%) than for patients with intermediate-risk PC (62% [95% CI: 52, 71%] $P = 0.047$; Fig. 1A).

Other studies reporting PSA outcomes after HIFU used the ASTRO or Phoenix definitions [9] that apply to post-radiation therapy. These criteria may not be accurate as they depend on relatively long follow-ups that were not achieved in these studies [3–5] or in the present study. We adopted the Horwitz definition, therefore, which requires only 2 consecutive rises in PSA of at least 0.5 ng/mL above nadir [6] to better fit to our

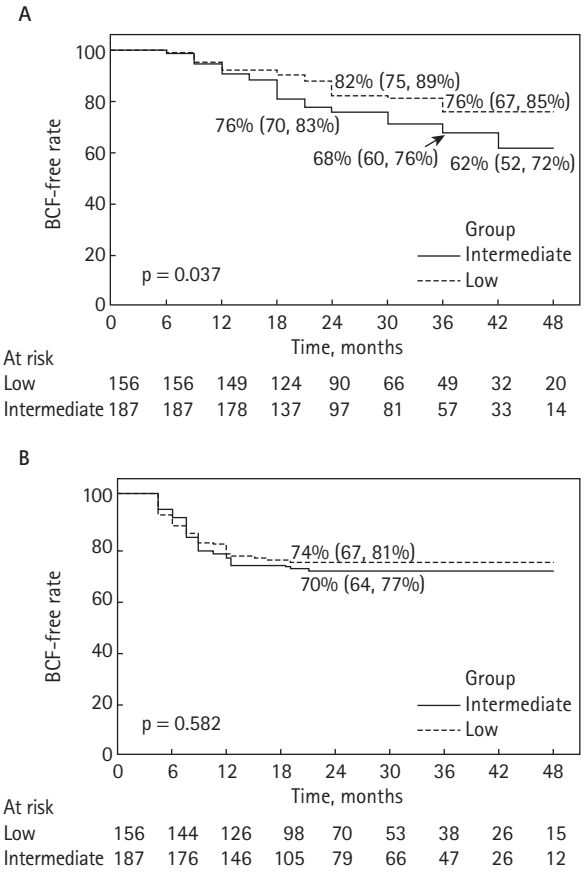

FIG. 1.
BCF-free rates in 402 patients with localized prostate cancer after HIFU treatment by risk group stratification. A = Stuttgart, B = Horwitz.

TABLE 2 Univariable and multivariable Cox regression analysis of BCF predictors

Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Stuttgart definition	Univariable		Multivariable	
Risk group	1.56 (0.99, 2.47)	0.053	–	0.134
Stage	1.66 (0.73, 3.91)	0.232	–	
Gleason score	1.33 (0.86, 2.06)	0.198	–	
Age	1.01 (0.98, 1.04)	0.485	–	
Prostate volume	1.04 (1.02, 1.07)	<0.001	–	0.679
Prostate volume treated to calculated prostate volume	0.40 (0.20, 0.81)	0.012	–	0.693
Pretreatment PSA	1.15 (1.10, 1.22)	<0.001	1.11 (1.05, 1.18)	<0.001
No. of positive biopsy cores	1.06 (0.97, 1.15)	0.204	–	
PSA nadir > 0.5 ng/mL	7.69 (4.93, 12.0)	<0.001	6.88 (4.39, 10.77)	<0.001
Horwitz definition	Univariable		Multivariable	
Risk group	1.25 (0.83, 1.90)	0.269	–	
Stage	1.25 (0.54, 2.85)	0.596	–	
Gleason score	1.01 (0.68, 1.50)	0.945	–	
Age	1.01 (0.98, 1.04)	0.400	–	
Prostate volume	1.04 (1.01, 1.07)	<0.001	–	0.773
Prostate volume treated to calculated prostate volume	0.33 (0.18, 0.61)	<0.001	–	0.101
Pretreatment PSA	1.13 (1.07, 1.20)	<0.001	1.12 (1.06, 1.18)	<0.001
No.of positive biopsy cores	1.00 (0.92, 1.10)	0.933	–	
PSA nadir > 0.5 ng/mL	7.92 (5.08, 12.36)	<0.001	5.76 (3.84, 8.61)	<0.001

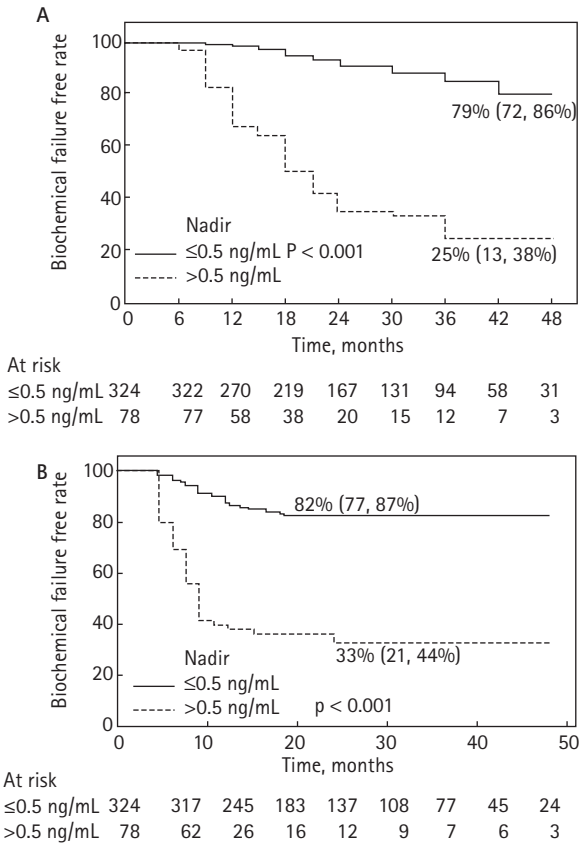

FIG. 2.
BCF-free rates in 402 patients with localized prostate cancer after HIFU treatment by PSA nadir. A = Stuttgart, B = Horwitz.

TABLE 3 Timing of biochemical events during the study period

	BCF Stuttgart, *n* (%)	BCF Horwitz, *n* (%)
Year 1	33 (40.7)	89 (90)
Year 2	34 (42.0)	10 (10)
Year 3–4	14 (17.3)	0
Total	81 (100)	99 (100)

mid-term follow-up. This approach further minimizes the potential of bias in underestimating PSA relapse rates. Additionally, when compared with other definitions of BCF after external beam radiation therapy for localized PC, the Horwitz criteria were shown to have the highest sensitivity and specificity for predication of distant failures alone or clinical failures [6]. Using this definition, we reported an overall 4-year BCF-free survival rate of 76% (95% CI: 69, 83%) in low-risk and 69.5% (95% CI: 63, 76%) in intermediate-risk groups, with no significant differences (Fig. 1B). Since most failures (90%) occurred during the first year (Table 3), we believe that the present results reflect a genuine rate of mid-term BCF failure after primary HIFU therapy for PC.

Our relatively low mid-term BCF rates can probably be attributed to our ability to achieve low PSA nadir levels. Low PSA nadir levels were shown in several studies to be the most important prognostic factor for biochemical success and post-HIFU negative biopsies [10,11]. Indeed, patients with both low- and intermediate risk-disease who attain PSA nadir levels <0.5 ng/mL are expected to have 82% (95% CI: 77, 87%) 4-year BCF-free survival (Fig. 2B), while those who fail to achieve this PSA nadir do poorly after a single session of HIFU and no other therapy (33%, 95% CI: 21, 4%). Thus, Nadir PSA after primary HIFU serves as a highly significant predictor of biochemical progression. Given that nadir PSA is achieved at a median time of 3 months, this variable can be used as an early indicator for post-treatment biopsy, and salvage treatment by other treatment methods. In fact, the PSA nadir of >0.5 and pre-treatment PSA value were the best predictors of BCF by both definitions in the present series (Table 2).

A unique feature of the present series is that we did not perform TURP in any of our patients. Chaussy *et al.* [10] recommended the use of concomitant or pre-HIFU TURP. The mean (SD) prostate volume in the present series was 36.7 (7.6) mL enabling adequate coverage of the gland. Accordingly, the mean ratio of treated volume/calculated prostate volume was 1.5 (0.3) implicating complete targeting of the prostate within the treatment boundaries. Nevertheless, given the fact that patients with a prostate volume >30 mL had a higher rate of BCF than patients with prostate volume <30 mL warrants re-examination of the role of 5α-reductase inhibitors, LHRH agonists or, in very large prostates, even TURP for prostate size reduction.

Our results were obtained after treatment with the Ablatherm® integrated imaging model system and thus may not be generalized to the application of other HIFU operating systems. Nevertheless, using the Sonablate devices (Focus Surgery, Indianapolis, IN, USA) in a different treatment protocol, Uchida *et al.* [11] reported 5-year biochemical disease-free rates (according to the Phoenix definition) of 84%, and 64% in patients with low- and intermediate-risk disease, respectively. Moreover, similar high rates of negative post-HIFU prostate biopsies were reported using both the Ablatherm® [3] and the Sonablate® [12] devices.

The present study has several limitations. Similar to all other studies of primary HIFU therapy for PC [5], it is a retrospective analysis of prospective data and subject to biases inherent with observational studies such as selection bias. Ideally, a well-designed prospective randomized trial would address this question; however, studies that randomize localized PC patients to different treatment methods typically suffer from lack of accrual [13]. A further limitation of the present study is lack of post-treatment biopsy data for most patients as biopsies were performed only in 50/78 patients (64%) who had rising PSA over a nadir > 0.5 ng/mL; however, the reported rates of

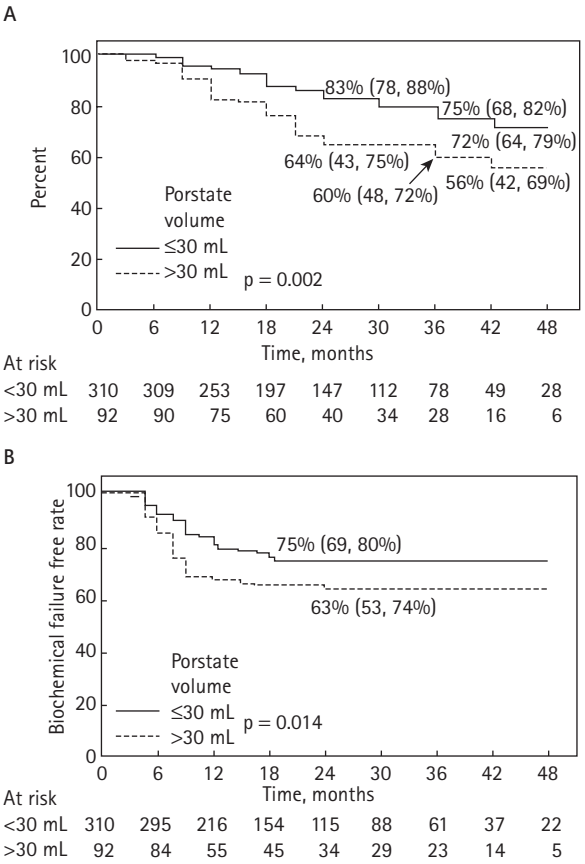

FIG. 3.
BCF-free rates in 402 patients with localized prostate cancer after HIFU treatment by prostate volume. A = Stuttgart, B = Horwitz.

negative biopsies after treatment with the Ablatherm® device reaches 90% in patients with low- or intermediate-risk disease who undergo routine post-HIFU prostate biopsy [3].

In conclusion, 4-year oncological efficacy of single-session primary HIFU is promising in patients with low- and intermediate-risk PC. Most cases of BCF occur in the first 2 years and are progressively less common thereafter within the timeline of study. Patients with low- and intermediate-risk PC who achieve a PSA nadir < 0.5 ng/mL have excellent 4-year biochemical failure free progression after a single session of primary HIFU therapy. A prostate volume <30 mL is associated with PSA nadir levels of <0.5 ng/mL which raises the question of whether planned pretreatment prostate volume reduction (medically or surgically) should be considered in larger prostates.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **HIFU**, high-intensity focused ultrasonography; **BCF**, biochemical failure; **PC**, prostate cancer; **PH**, proportional hazards; **HR**, hazard ratio.