Original article

Experience with high-intensity focused ultrasound therapy for management of organ-confined prostate cancer: critical evaluation of oncologic outcomes

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Abstract. *Objectives:* To assess the oncologic results of high-intensity focused ultrasound therapy (HIFU) as treatment for clinically localized prostate cancer. *Methods:* A total of 180 patients with clinically localized prostate cancer underwent HIFU and were retrospectively reviewed. Of those 171 patients primarily treated with HIFU were included in the analysis. They were stratified by prostatic volume, neoadjuvant hormonal ablation (NHA), and post-treatment PSA nadir. PSA level was monitored every month during the first 6 months after the treatment and every 3 months thereafter. According to the latest Phoenix criteria, biochemical failure was defined by a PSA rise of 2 ng/ml or more above the PSA nadir. Seventy-six (44.4%) patients were offered preoperative NHA in median duration of 3 months (IQR: 3 – 5.75). Preoperative transurethral resection of the prostate (TURP) was performed in 56 (32.7%) patients having the calcification within the prostatic gland. *Results:* Mean patient age was 68.3 ± 7.0. The median follow-up time was 43 months (IQR: 30 - 55). According to D'amico risk groups 52 (30.4%) patients were identified with low risk, 47 (27.5%) patients with intermediate risk, and 72 (42.1%) with high risk. The overall and cancer-specific survival rates at 5 years were 98.8% and 100%. The metastasis-free survival rate at 5 years was 99.4%. No significant differences were seen in biochemical failure-free survival when stratified according to preoperative prostatic volume and administration of preoperative NHA (p = 0.931 and p = 0.712, respectively). Regardless NHA administration, patients with smaller PSA nadir (0.2 ng/ml) achieved better biochemical failure-free survival ratio. *Conclusion:* High-intensity focused ultrasound therapy provides sufficient oncologic control only in patients with low-risk prostate cancer. However, our data could be used to improve the selection of patients who are potential candidates for HIFU therapy. (www.actabiomedica.it)

Key words: HIFU, prostate cancer, PSA nadir

Introduction

Due to the increased use of PSA testing and increasing life-expectancy, more patients are being diagnosed with localized prostate cancer. The mainstay of treatment remains radical surgery or radiation therapy (RT). However, these established therapies can be associated with significant complications and risks. There are patients who are not willing or are unsuitable for radical surgery or RT. Several minimally invasive treatments are now under evaluation that may prove to be of equivalent oncologic results in the long term. Transrectal high-intensity focused ultrasound (HIFU) application has been used for more than 15 years to treat clinically localized prostate cancers with results challenging those of RT. HIFU is now accept-

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ed as a new minimally invasive therapeutic method to be able to transdermally and/or transmucosally coagulate, so that it destroy tissue in various conditions that have clinical applications, including the breast, uterus, kidney, spleen, liver, and bone. HIFU has been evaluated as primary therapy for patients with localized prostate cancer or as salvage therapy in patients with recurrence after RT. In clinically localized disease, the identified negative prognostic factors that influence the outcome after HIFU therapy are high PSA levels (>10 ng/ml), high Gleason scores (>6), and a high number of positive sextants at pretreatment biopsy (>4).

The aim of the present study was to report the oncologic outcome in patients with low-, intermediate-, and high-risk prostate cancer treated by HIFU and examine factors that could influence disease recurrence after HIFU.

Materials and methods

Equipment

All patients were treated with the Sonablate HIFU device (Focus Surgery, Indianapolis, IN, USA). From 2004 to 2007, the patients were treated with Sonablate 500 device, and thereafter with Sonablate 500 version 4 device. This treatment module includes the ultrasound power generator, transrectal probes, the probe positioning system, and a continuous cooling system (Sonachill™). The transrectal HIFU probe uses double transducer technology with low-energy ultrasound (4 MHz) for real-time imaging of the prostate and delivery of high-energy ablative pulses (site intensity, 1300-2200 W/cm^2). The two-dimensional STACK feature was added for the Sonablate 500 version 4, which allowed the physician to quickly review and refine a complete prostate treatment plan for more thorough and improved treatment planning during ongoing treatment.

Patients

The inclusion criteria for treatment were as follows: clinical stage T1-T2N0M0 biopsy-proven localized prostate cancer, prostate volume at diagnosis ≤ 50 ml, no previous radical treatment for prostate cancer, and at least 12 months of follow-up defined as the interval between the last HIFU treatment and the most recent PSA measurement. All patients were treated after providing informed consent. The present study was approved by the lRB. Between 2004 and 2008, 180 consecutive patients undergoing HIFU at our institution were enrolled into a database. We analyzed the data of 171 patents who underwent HIFU as the primary therapy and no previous radical treatment including radical prostatectomy, external-beam radiation therapy, or brachytherapy, excluding the data of 9 patients who were treated for salvage. Treatment in all patients was performed under epidural or spinal anesthesia, and in lithotomy position.

Follow-up

The follow-up examinations included digital rectal examinations (DRE), transrectal ultrasonography (TRUS), and PSA measurement every month during the first 6 months after treatment and every 3 months thereafter. A follow-up control octant biopsy was recommended to all patients 3-6 months after the treatment and was also performed if biochemical relapse was suggested by PSA rise. Patients with a rising PSA but negative biopsy underwent a bone scan and a computed tomography scan to exclude metastatic disease. Biochemical failure was defined according to the Phoenix definition (a rise of 2 ng/ml or more above the nadir PSA) (1-2) derived from the experience with external radiotherapy. The disease-free survival rate (DFSR) was evaluated using the definition for disease failure, which was defined according to the Phoenix criteria: a rise of 2 ng/ml or more above the nadir PSA (biochemical failure), positive follow-up biopsy or the administration of salvage treatment. In the present study, no patient received adjuvant hormonal therapy or any other salvage therapy before the diagnosis of biochemical failure and positive follow-up biopsy. Therefore, disease failure was simply defined as PSA nadir + 2 ng/ml or positive follow-up biopsy. Patient status and treatment-related complications were followed up by self-administered questionnaires and regular checkup at outpatient care. Treatment toxicity

and adverse events were defined according to the Common Toxicity Criteria of the National Cancer Institute version 3.0 (CTC-NCI ver 3.0) (3). Sexual function before and after HIFU treatment was assessed by posing a set of short questions exploring erectile function, sexual activity and ability to have sexual intercourse (non-validated questionnaire). Postoperative erectile dysfunction (ED) was defined as the inability to have sexual intercourse. The following clinical variables were evaluated: age, preoperative PSA level, Gleason score, clinical stage, risk groups (4-6), preoperative prostatic volume, NHA, TURP before HIFU. We applied the two risk classification (i.e. D'amico risk groups and National Comprehensive Cancer Network (NCCN) risk groups) to compare the treatment outcome with previous studies. The T stage was based on digital rectal examination, prostatic biopsy, and transrectal ultrasound findings. Patients were offered NHA to reduce the prostatic volume when the initial size of the prostate was greater than 35 ml. Any hormonal therapy was discontinued at the time of the HIFU. The prostatic volume was evaluated again in prior to HIFU therapy. TURP was performed before HIFU to resect calcifications within the prostate and reduce the prostatic volume. The PSA nadir was defined as the lowest recorded PSA level during follow-up after the HIFU.

Statistical analysis

Continuous parametric variables were reported as the mean value ± standard deviation (SD). Continuous nonparametric variables were presented as the median value and interquartile range (IQR). The unpaired t test and the Mann-Whitney U test were used for quantitative parametric and nonparametric variables, respectively. Chi-square tests were conducted to assess the differences of the distributions between the clinicopathological parameters. Estimates for survival were calculated with the use of life table methods. The log-rank test was used to compare the curves based on Kaplan-Meier models. A multivariate Cox proportional hazards regression model was used to estimate the prognostic relevance of clinicopathological variables. Associations were regarded as significant if $p < 0.05$ and all p values were 2-sided. All data were analyzed with the use of the Statistical Package for the Social Sciences software, version 12.0 (SPSS Inc, Chicago, IL).

Results

Patients characteristics

Table 1 summarizes the clinical and pathologic characteristics of 171 patients included in the analysis. The median follow-up time was 43 months (IQR: 30 - 55). The first 130 patients (treated before 2008) received HIFU using Sonablate 500, the subsequent 41 patients were treated using Sonablate 500 ver4.

Table 1. Patient characteristics

No. of patients	171
Mean ± SD age	68.3 ± 7.0
Median PSA [ng/ml] (IQR)	7.7 (5.8 - 12.6)
Gleason score (%)	
5 or less	9 (5.3)
6	83 (48.5)
7	37 (21.6)
Greater than 7	42 (24.6)
Clinical stage (%)	
cT1c	47 (27.5)
cT2a	51 (29.8)
cT2b	40 (23.4)
cT2c	33 (19.3)
D'amico risk groups (%)	
Low risk	52 (30.4)
Intermediate risk	47 (27.5)
High risk	72 (42.1)
NCCN risk groups (%)	
Low risk	52 (30.4)
Intermediate risk	66 (38.6)
High risk	53 (31.0)
Mean ± SD prostatic volume [ml]	20.1 ± 7.6
NHA (%)	
No	95 (55.6)
Yes	76 (44.4)
Median duration of NHA [month] (IQR)	3 (3 - 5.75)
TUR before HIFU (%)	
No	115 (67.3)
Yes	56 (32.7)

SD, standard deviation; PSA, prostate-specific antigen; IQR, interquartile ranges; NCCN, National Comprehensive Cancer Network; NHA, neoajuvant hormonal ablation; HIFU, high-intensity focussed ultrasound; TUR, transurethral resection

The mean number of HIFU sessions was 1.1 ± 0.3 (1 session: 158 patients, 2 sessions: 12 patients, 3 sessions: 1patients) for a total of 185 procedures in 171 patients. Mean ± SD patient age was 68.3 ± 7.0 years. Median baseline PSA level was 7.7 ng/ml (IQR: 5.8 - 12.6). According to D'amico risk groups 52 (30.4%) patients were identified with low risk, 47 (27.5%) patients with intermediate risk, and 72 (42.1%) with high risk. When applying the NCCN risk groups 52 (30.4%) patients presented with low risk, 66 (38.6%) patients with intermediate risk, and 53 (31.0%) with high risk cancer (Table 2). Seventy-six (44.4%) patients were offered preoperative NHA in median duration of 3 months (IQR: 3 - 5.75) and mean ± SD prostatic volume at the time of HIFU is 20.1 ± 7.6 ml (Table 3). Preoperative TURP was performed in 56 (32.7%) patients having the calcification within the prostatic gland. The median operating time was 149 minutes (range: 90 - 340). There were no perioperative or intraoperative complications, which achieved excellently short hospitalization time of median 1.0 day (range: 1 - 3). The urethral catheter was removed at a median of 11.5 days (range 5 - 21).

Survival rates, biochemical failure-free survival, and disease-free survival

The overall and cancer-specific survival rates at 5 years were 98.8% and 100%. The metastasis-free survival rate at 5 years was 99.4%. Table 2 summarized biochemical failure-free survival rates at 3 year and 5 year including Phoenix definition according to risk groups including D'amico and NCCN. We also analyzed the disease-free survival rate for each risk

Table 2. BFS and DFS probability in 171 patients after HIFU according to risk groups

Variables	Mean ± SE BFS probability			Mean ± SE BFS probability		
	3 yrs	5 yrs	p Value	3 yrs	5 yrs	p Value
All cohort	0.77 ± 0.04	0.69 ± 0.05		0.73 ± 0.03	0.63 ± 0.05	
D'amico risk groups						
Low	0.85 ± 0.05	0.85 ± 0.05		0.82 ± 0.06	0.79 ± 0.07	
Intermediate	0.82 ± 0.07	0.73 ± 0.09	0.404	0.80 ± 0.07	0.72 ± 0.09	0.528
Low + Intermediate	0.83 ± 0.02	0.80 ± 0.05		0.81 ± 0.03	0.76 ± 0.05	
High	0.68 ± 0.06	0.51 ± 0.08	<0.001	0.62 ± 0.06	0.47 ± 0.08	<0.001
NCCN risk groups						
Low	0.85 ± 0.05	0.85 ± 0.05		0.82 ± 0.06	0.79 ± 0.07	
Intermediate	0.78 ± 0.06	0.69 ± 0.08	0.159	0.72 ± 0.07	0.63 ± 0.08	0.102
Low + Intermediate	0.81 ± 0.04	0.77 ± 0.05		0.77 ± 0.04	0.71 ± 0.05	
High	0.67 ± 0.07	0.48 ± 0.10	0.002	0.64 ± 0.07	0.46 ± 0.09	0.007

BFS, biochemical failure-free survival; DFS, disease-free survival; HIFU, high-intensity focussed ultrasound; SE, standard error

Table 3. Prostate-specific antigen nadir values after high-intensity focused ultrasound between patients receiving and not receiving neoadjuvant hormonal ablation

	Overall cohort	NHA (-)	NHA (+)	p value
n (%)	171	95 (55.6)	76 (44.4)	
Median nadir PSA [ng/ml] (IQR)	0.03 (0.01 - 0.30)	0.09 (0.02 - 0.47)	0.01 (0.01 - 0.03)	<0.001
Median time to PSA nadir [month] (IQR)	2.5 (1.0 - 3.0)	3.0 (2.0 - 3.0)	2.0 (1.0 - 3.0)	<0.001
Nadir PSA [ng/ml] (%)				
≤ 0.2	120 (70.2)	55 (57.9)	65 (85.5)	
>0.2	51 (29.8)	40 (42.1)	11 (14.5)	<0.001

PSA, prostate-specific antigen; NHA, neoadjuvant hormonal ablation

groups. For all categories of survival definitions the high risk patients were significantly likely to have poor cancer control compared with low and intermediate risk patients, whereas no statistical differences for all survival definitions were seen between low and intermediate risk patients.

We also analyzed additional subgroup analysis, estimating Kaplan-Meier curves using Phoenix definition (nadir +2 ng/ml) based on preoperative variables including prostatic volume immediately before HIFU (cut off of 20ml), TURP before HIFU, and preoperative NHA (Fig. 1). No significant differences were seen when stratified according to preoperative prostatic volume and administration of preoperative NHA (p = 0.931 and p = 0.712, respectively) (Fig. 1. a and b). There was a tendency that administration of TURP before HIFU favorably affected cancer control after HIFU, but this tendency did not achieve statistical significance (p = 0.149) (Fig. 1. c).

PSA nadir value after HIFU

The PSA nadir values are summarized in Table 3. Of all cohort median nadir PSA was 0.03 ng/ml (IQR: 0.01 - 0.30) with median time to PSA nadir of 2.5 months (IQR: 1.0 - 3.0). Seventy-six patients (44.4%) were offered administration of NHA, which would affect the course of PSA value after HIFU. Therefore, we stratified the patients according to administration of NHA, in which the median nadir PSA level in patients offered NHA was significantly lower than those in patients not offered NHA (0.01 and 0.09 ng/ml, respectively) (p = <0.001) and median time to PSA nadir was also significantly shorter in the cohort offered NHA (2.0 months) compared with those not offered NHA (3.0 months) (p = <0.001). For the overall cohort 120 (70.2 %) patients achieved PSA nadir level of ≤ 0.2 ng/ml, whereas administration of NHA significantly contributed to achievement of PSA nadir level of ≤ 0.2 ng/ml (p = <0.001). Log-rank test demonstrated a significant association (p = <0.001) between the value of PSA nadir and the risk of biochemical failure inpatients without preoperative NHA (Fig. 2. a). Similary, log-rank test demonstrated a significant association (p = <0.001) between the value of PSA nadir and the risk of biochemical failure in the group who offered preoperative NHA (Fig. 2. b). These results showed that patients whose PSA nadir was ≥ 0.2 ng/mL had the strongest association

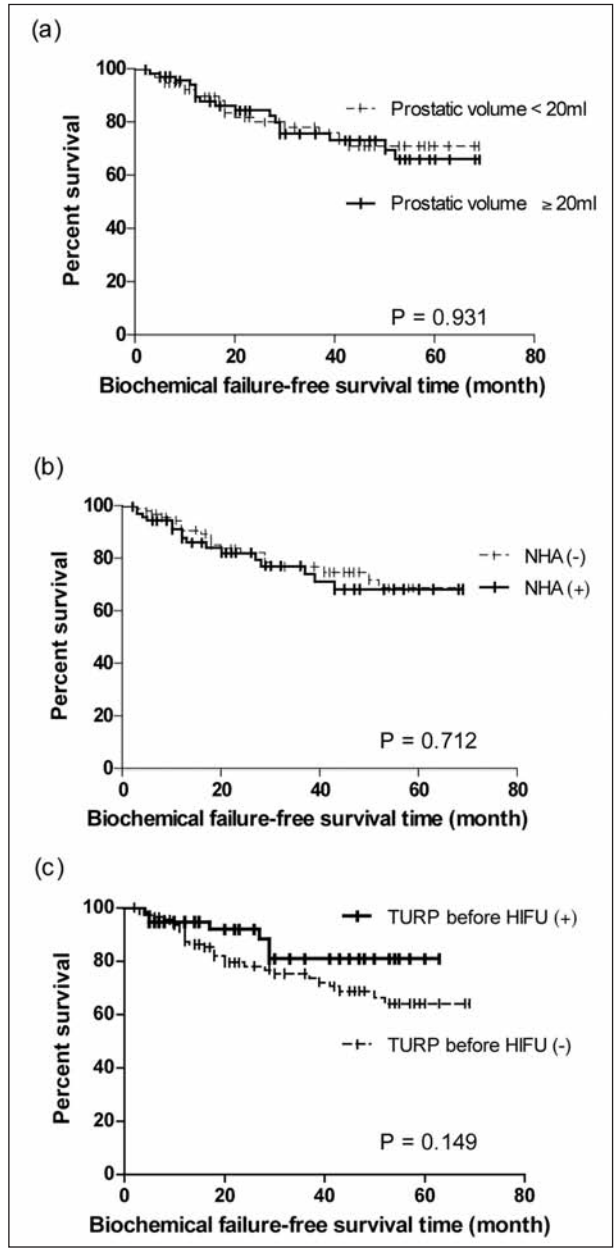

Figure 1. Biochemical failure-free survival curve of all patients underwent HIFU treatment. (a) Curve stratified according to preoperative prostatic volume (cut-off: 20cc). (b) Comparison of biochemical failure-free survival in patients with or without neoadjuvant hormonal ablation (NHA). (c) Comparison of biochemical failure-free survival in patients with or without preoperative TUR-P

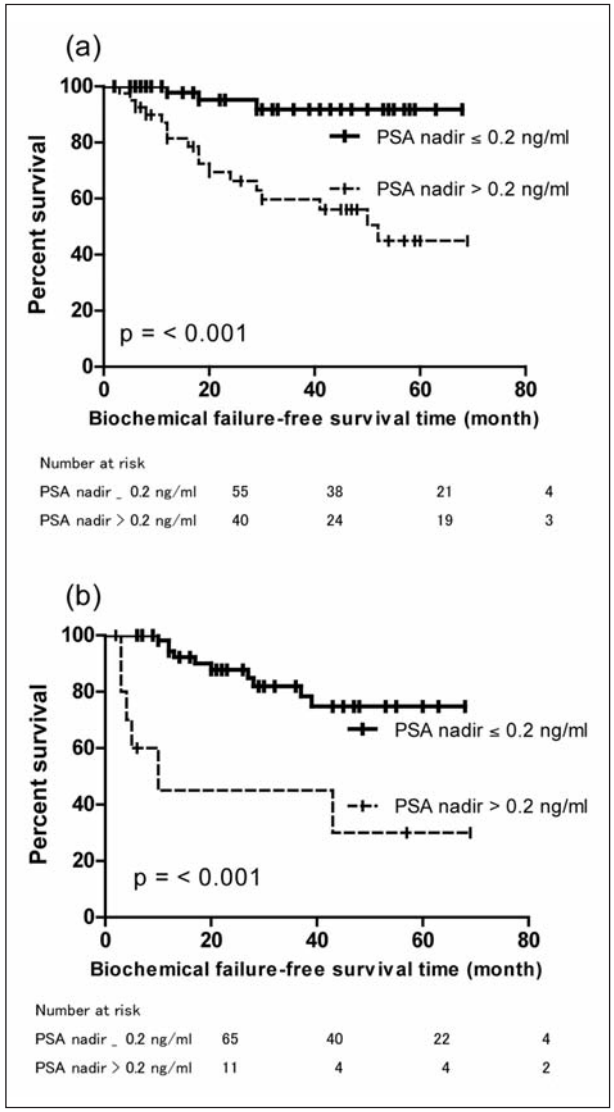

Figure 2. Biochemical failure-free survival curve of the patients underwent HIFU treatment. (a) Biochemical failure-free survival in patients without neoadjuvant hormonal ablation (NHA) stratified according to PSA nadir value (cut-off: 0.2ng/ml). (b) Biochemical failure-free survival in patients with neoadjuvant hormonal ablation (NHA) stratified according to PSA nadir value (cut-off: 0.2ng/ml)

amongst other clinical factors with clinical failure regardless the NHA.

Clinical outcomes

A total of 44 patients were diagnosed as disease failure with Phoenix definition (nadir + 2 ng/ml) in 36 patients and positive follow-up biopsy in 8 patients. After undergoing a bone scan and a computed tomography scan to exclude metastatic disease, salvage therapies were proposed for those patients with considering their each cancer characteristics and general status. A new HIFU session were offered as salvage therapy in 13 patients, hormone deprivation in 26 patients, and external beam radio therapy (EBRT) in 5 patients, respectively.

Discussion

Among newly diagnosed prostate cancer cases, almost 70% are organ-confined and may be treated by varying therapies with curable intent. Among the several new therapeutic options available, HIFU appears to be an attractive and promising therapy in the treatment of organ-confined prostate cancer. A growing number of studies have reported the oncologic outcome of HIFU therapy in the treatment of organ-confined prostate cancer. The 5-year disease-free survival has been reported in the range of 54–84%. According to the latest ASTRO phoenix criteria, we have reported herein a 77% 3-year BFS and 69% 5-year BFS, respectively. Using the same definition, Blana et al. reported 77% 5-year BFS (7). From the most recent data on the Ablatherm HIFU device from an international registry (@-Registry), reported a good oncologic control with a 85% BFS at 5 years (8). We believe that our BFS survival was lower than expected given that nearly two-thirds of these patients belonged to the intermediate- or high-risk group. In fact, repeat HIFU treatments were needed in 13 patients (2 sessions: 12 patients, 3 sessions: 1patients). Patients in D'Amico low risk features had 85% 3-year BFS and 85% 5-year BFS, respectively, which showed marked contrast to worsened BFS of patients in D'Amico high risk features (68% 3-year BFS and 51% 5-year BFS, respectively). NCCN risk stratification exhibited the similar tendency with D'Amico risk classification.

Among other indicators which affect oncologic control after HIFU, PSA nadir seems to be the best predictor for disease control. Ganzer et al. were able to stratify outcomes in 103 patients according to PSA

nadir, which was defined as low (<0.2 ng/ml), intermediate (0.2 - 1 ng/ml), and high (>1 ng/ml) (9). Similarly, we observed a significant correlation between the PSA nadir and disease free survival after HIFU. Blana et al. have found on multivariate analysis, the pretreatment PSA level was the only statistically significant predictive factor of recurrence (10). More recently, Sung et al. have reported that age, PSA nadir, time to PSA nadir and the NCCN risk classification were significant factors for the prediction of biochemical recurrence after HIFU therapy (11). Unlike radical prostatectomy, HIFU therapy does not have specimen-based pathological evaluation, which would help predicting the subsequent oncologic outcome and the need for salvage therapy. Therefore, novel prognostic factors to predict treatment outcome for HIFU are urgent necessity. We have recently identified that post-HIFU urethral stricture is a negative prognostic outcome factor (12). We found a significant correlation between development of post-HIFU urethral stricture and favorable survival was valid in patients with a PSA nadir of 0.2 ng/ml or less but was no longer detectable in patients with a PSA nadir of greater than 0.2 ng/ml (12). Also, there was a significant association with development of post-HIFU urethral stricture and decreased PSA nadir level (12). It is conceivable that enhanced BFS and urethral stricture are linked by improved PSA nadir.

Contraindications should be considered before offering HIFU to a patient with organ-confined prostate cancer. The prostate volume is one of a limitation of this procedure and it is not recommended if the prostate size excesses over 40 cc. TUR-P or hormonal therapy prior to HIFU therapy help to reduce the prostate volume. Actually TUR-P inprior to HIFU is increasingly used, amongst other methods, to reduce the size of the prostate, which potentially reduces prolonged urinary retention which require transurethral catheterization. In our series, we took advantage TUR-P before HIFU for removing calcifications, and used hormonal therapy to reduce the prostate size, so that we could gain optimal prostate volume for the procedure. The duration of hormonal therapy before HIFU is under discussion. In a retrospective cohort, Uchida et al showed that the probability of being free of disease on prostate biopsies 6 months after the HIFU therapy appeared to be independent of whether the patients received or did not receive hormonal therapy before the procedure (13). Similarly, we used short term NHA for median 3 months (IQR 3 - 5.75) for almost half of the whole cohort, which significantly affected PSA nadir value, along with time to nadir. Importantly, we did not observe any impact of NHA for biochemical failure-free survival of patients. Usage of HIFU is challenging for high-risk and locally advanced stages of prostate cancer. Ficarra et al. suggested the possible application of HIFU in association with hormonal therapy for high-risk prostate cancer (14). Their oncologic outcome at one year of follow-up is acceptable, in which 23% was biopsy positive (14). However, these results require reassessment over a longer follow-up.

Conclusions

PSA nadir level was found to be an effective tool to predict biochemical failure. Our findings may contribute the selection and the follow-up of candidates

for HIFU therapy and suggest that patients in the low- and intermediate-risk group should be considered for HIFU therapy.

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