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ORIGINAL ARTICLE

High-intensity focused ultrasound for the treatment of prostate cancer: A prospective trial with long-term follow-up

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Abstract

Objective. High-intensity focused ultrasound (HIFU) is a minimally invasive treatment for prostate cancer. Data from the literature show promising oncological outcomes with a favourable side-effect profile. The aim of this study was to re-evaluate and bring up to date the follow-up of a previously published, prospective trial on HIFU as the primary treatment for prostate cancer. *Materials and methods.* Between 2004 and 2007, 163 consecutive men with T1–T3N0M0 prostate cancer underwent HIFU with the Sonablate® 500. Follow-up included prostate-specific antigen (PSA) tests every 3 months after treatment and a random prostate biopsy at 6 months. Failure was defined according to positive findings at the 6 month biopsy and biochemical failure was defined according to the Phoenix criteria. Biochemical-free survival, metastasis-free survival and cancer-specific survival were calculated by Kaplan–Meier curves. *Results.* Median follow-up was 72.0 months. Of the 160 evaluable patients, 104 (65%) were biochemically disease free; in low- to intermediate-risk disease, on Kaplan–Meier analysis the 8 year biochemical-non-evidence of disease (bNED), metastasis-free survival and cancer-specific survival rates were 69.6%, 81.3%, 100% and 40.5%, 60.6%, 100%, respectively. A PSA nadir below 0.40 ng/ml and risk stratification have an independent predictive value for bNED and metastasis-free survival. *Conclusions.* A long-term favourable outcome of HIFU is associated with careful patient selection, with low- to intermediate-risk disease being the ideal case. A low postoperative PSA nadir is a predictor of long-term bNED.

Keywords:

Biochemical-free survival, cancer-specific survival, HIFU, high-intensity focused ultrasound, prostate cancer

History

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Introduction

Prostate cancer is the most common cancer in men [1]. Thanks to prostate-specific antigen (PSA) testing, most patients harbour localized prostate cancer at diagnosis and therefore are suitable candidates to undergo a curative procedure. The choice of adequate therapy depends on several factors, both disease related (tumour stage, PSA, Gleason score) and patient related (age and life expectancy, presence of concomitant diseases, patient preference).

High-intensity focused ultrasound (HIFU) [2,3] has been tested in many clinical trials since its introduction for the treatment of prostate cancer in 1995 [4].

Despite many clinical trials [5], the recommendations concerning HIFU in international guidelines are still conflicting. The 2013 European Association of Urology guidelines [6] state that HIFU has emerged as an alternative therapeutic options in patients with clinically localized prostate cancer who are not suitable for radical prostatectomy. However, data from HIFU are not extensive enough to be considered in treatment recommendations, since the available evidence on the efficacy and safety of HIFU is of very low quality. Similarly, the American Urological Association guidelines on prostate cancer [7] do not include HIFU in the treatment options for organ-confined prostate cancer owing to a combination of factors, including limited published experience and short-term follow-up.

In general, the lack of approval comes from the paucity of evidence concerning long-term survival, the lack of long-term follow-up data and the lack of randomized trials. Moreover, data come from the use of two different HIFU devices, the Ablatherm (EDAP-TMS, Vaulx-en-Velin, France) and the Sonablate device (Focus Surgery, Indianapolis, IN, USA), thus increasing the overall variability in efficacy. The Sonablate® 500 was developed by Focus Surgery to treat prostate cancer, and since its introduction in the clinical setting some good-sized clinical trials with intermediate-term follow-up have been reported [8].

In a preliminary report [9], the present authors tested the safety and efficacy of primary HIFU, demonstrating that careful patient selection and PSA nadir are the best predictors of short-term disease control.

This study reports on the updated follow-up of the prospective trial of the Italian experience with the Sonablate 500 device.

Materials and methods

Patient selection

The study design and inclusion and exclusion criteria are described in detail in the previous report [9]. In brief, all

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patients had a histological diagnosis of prostate cancer, staged by mean of a digital rectal examination (DRE), transrectal ultrasound (TRUS), computed tomography (CT) scan and bone scan, or endorectal magnetic resonance when deemed beneficial on the basis of D'Amico risk stratification [10]. The CT scan and bone scan were scheduled only if the PSA level was greater than 10 ng/ml, the Gleason score was greater than 8, or the clinical stage was T3 or higher.

The inclusion criteria were patients with T1c–T2 and limited cT3a N0M0 disease. Exclusion criteria were prostate volume exceeding 50 ml, intraprostatic calcification greater than 1 cm and concomitant anal stricture. None of the patients underwent transurethral resection of the prostate (TURP) before HIFU treatment. Patients who received neoadjuvant hormone therapy were excluded from data analysis. All patients were informed of the details of this treatment and provided written informed consent. The institutional review board approved the study.

High-intensity focused ultrasound device and procedure

The Sonablate 500 (Focus Surgery, Indianapolis, IN, USA) HIFU device was used in this study. HIFU was delivered as a whole-gland treatment under ultrasound guidance. Before the treatment, the operator uses longitudinal and transverse ultrasound images of the prostate, selecting the prostate tissue volume to be ablated; each focused ultrasonic beam ablates a volume of $3 \times 3 \times 10$ mm, producing a coagulative necrosis of the entire targeted prostate. The HIFU treatment was delivered in a day-surgery setting. At the end of the procedure, a transurethral catheter or a percutaneous suprapubic cystostomy was inserted.

Patients were discharged on the next day, and received antibiotics and anti-inflammatory drugs for at least 21 days. The catheter was removed as soon as possible. All procedures were carried out according to the proposed standard [11,12].

Follow-up

Visits were scheduled at 1, 3 and 6 months and then every 6 months, including DRE, uroflowmetry and TRUS at 3 and 6 months, and self-administered questionnaires on urinary function [International Prostate Symptom Score (IPSS)] and sexual function [International Index of Erectile Function-5 (IIEF-5)]. PSA was tested at 1, 3 and 6 months and then every 6 months, while prostate biopsy was scheduled at 6 months, taking a minimum of eight cores.

Local failure was defined according to positive findings at the 6 month prostate biopsy. Biochemical failure was defined according to the Phoenix criteria [13], i.e. an increase in post-treatment PSA of at least 2 ng/ml above the PSA nadir.

No patients received hormonal or any other anticancer therapy (with the exception of another HIFU session for local relapse) before the documentation of disease recurrence by means of CT scan and bone scintigraphy (scheduled for PSA >10 ng/ml and high-PSA velocity or symptoms), compared with baseline. The definition of metastatic status also included the presence of regional lymph-node enlargement (with a threshold >10 mm) on the CT scan.

Statistical analysis

Frequencies are presented as the median and interquartile range (IQR).

In univariate analysis, the Mann–Whitney and Wilcoxon tests were used to compare ordinal and non-normally distributed continuous variables. Deviations from the Gaussian distribution were checked using the Shapiro–Wilk test. Categorical data were analysed by the chi-squared test or Fisher's exact test.

For adjusting predictive variables of post-HIFU local failure, multiple logistic and regression models were applied, with subjects subdivided according to their status at 6 months of follow-up. The goodness of fit of the logistic model was tested using the Hosmer–Lemeshow test. Odds ratios (ORs) with 95% confidence intervals (CIs) were also calculated.

The Kaplan–Meier estimator with log-rank test was used to estimate biochemical-free survival, metastasis-free survival (MFS) and cancer-specific survival (CSS) rates, according to risk classification. To investigate the effect of variables, Cox regression was used and hazard ratios (HRs) with 95% confidence intervals were calculated.

The level of statistical significance was set at $p < 0.05$. All calculations were carried out with MedCalc version 12.5.0.0 (MedCalc Software).

Results

In total, 163 patients were included. The prostate was treated in one HIFU session (135 patients) or two HIFU sessions (28), making a total of 191 procedures (mean 1.17 sessions/patient). The HIFU treatment was repeated as whole-gland treatment in 22 cases for residual tumour detected at the 6 month follow-up biopsy.

There were no intraoperative or perioperative complications. There were two cases of rectal fistula (1.2%), occurring 2 and 7 months later, related to concomitant urinary obstruction and latent infection.

Table 1 describes the clinical characteristics. Median operative time was 189.5 min (range 165–210 min), median hospitalization time was 1.4 days (1–4 days) and the urinary drainage was removed in a median of 13 days (7–20 days). Of the 163 patients, 160 (98.2%) were followed up for a median time of 71.5 months (66.1–73.2 months) and three patients were lost to follow-up.

The median PSA nadir was 0.15 ng/ml (0.05–0.59 ng/ml) and was reached in a median of 2.3 months (1–3 months). The PSA nadir was less than or equal to 0.40 ng/ml in 70.2% of cases. Table 2 shows the median PSA value over time, including the last PSA determination.

Local failure

The 6 month positive prostate biopsy rate was 33.9% after a single treatment; on logistic regression analysis, only a PSA nadir greater than 0.40 ng/ml (OR 6.393, $p < 0.01$, 95% CI 2.312–17.681) had an independent predictive value for local failure. According to risk stratification, the negative biopsy rates for low, intermediate, high and very high risk were 75.5%, 77.4%, 35.7% and 18.7%, respectively ($p < 0.01$).

Table 1. Clinical characteristics.

Age (years)	72 (68–75)
PSA (ng/ml)	7.3 (5.2–10)
Prostate volume (ml)	32.4 (24.7–40)
Clinical stage	
T1	72 (44.1)
T2	69 (42.5)
T3	22 (13.4)
Gleason score	
≤6	100 (61.3)
7	48 (29.5)
8–10	15 (9.2)
Risk group	
Low	80 (49.1)
Intermediate	47 (28.8)
High	14 (8.6)
Very high	22 (13.5)
Follow-up (months)	71.5 (66.1–73.2)

Data are shown as median (interquartile range) or *n* (%).
PSA = prostate-specific antigen.

A new HIFU session was proposed to all patients with local failure only. Two patients were treated by external beam radiotherapy, whereas six were treated by salvage radical prostatectomy, which was challenging but feasible.

Biochemical failure

Of the 160 evaluable patients, 104 (65%) were biochemically disease free [biochemical non-evidence of disease (bNED)] at follow-up. On Kaplan–Meier analysis and according to risk stratification, the 5 year bNED survival rates for low, intermediate, high and very high risk were 85.7%, 74.5%, 39.3% and 46.2%, respectively ($p = 0.001$). The overall 8 year bNED was 48.1%; according to risk stratification, the 8 year bNED survival rates for low, intermediate, high and very high risk were 69.6%, 40.5%, 0% and 20.2%, respectively ($p = 0.001$) (Figure 1).

On univariate analysis, bNED was significantly associated with baseline PSA, stage, Gleason score, risk stratification and PSA nadir less than 0.40 ng/ml. On Cox regression analysis, risk stratification and PSA nadir less than 0.40 ng/ml had an independent predictive value for bNED (Table 3).

Metastasis-free survival and cancer-specific survival

Of the 160 evaluable patients, 125 (78.1%) were metastasis free at follow-up. In particular, there were one positive bone scan in the low-risk group (1.2%), and there were four cases in the intermediate-risk (8.5%), three in the high-risk (21.4%) and eight in the very high-risk group (36.3%).

On Kaplan–Meier analysis and according to risk stratification, the 5 year MFS rates for low, intermediate, high and very high risk were 98.7%, 95.3%, 77.4% and 63.6%, respectively ($p = 0.001$). The overall 8 year MFS rate was 69.0%; according to risk stratification, the 8 year MFS rates for low, intermediate, high and very high-risk were 81.3%, 60.6%, 38.7% and 46.3%, respectively ($p = 0.001$) (Figure 2).

On univariate analysis, MFS was significantly associated with baseline PSA, stage, Gleason score, risk stratification and PSA nadir less than 0.40 ng/ml. On Cox regression analysis, risk stratification had an independent predictive value for MFS (Table 3).

Thirty-nine patients (24.3%) received salvage adjuvant hormone therapy upon the occurrence of metastasis and/or progressive PSA increases.

For the 160 evaluable patients, CSS was 98.1% at follow-up. On Kaplan–Meier analysis and according to risk stratification, the 5 year CSS rates for low, intermediate, high and very high risk were 100%, 100%, 84.6% and 90.0%, respectively ($p = 0.001$). The overall 8 year CSS was 93.1%; according to risk stratification, the 8 year CSS rates for low, intermediate, high and very high risk were 100%, 100%, 84.6% and 77.1%, respectively ($p = 0.001$) (Figure 3).

On univariate analysis, CSS was significantly associated with baseline PSA, stage, Gleason score and risk stratification. On Cox regression analysis, baseline PSA and Gleason score had an independent predictive value for CSS (Table 3).

Functional data

Eighteen patients (16%) had mild mixed urinary incontinence and only one patient had grade 3 stress incontinence (after two HIFU sessions).

Thirty-one patients (19.3%) developed a urethral stricture, which was treated by simple dilatation in nine and by endoscopic incision in 22 patients (13.4%).

Two patients developed a rectourethral fistula requiring, after a failed attempt at a complex reconstructive surgical repair, a urinary diversion in one patient; in the other case, conservative management with a long-lasting suprapubic tube and long-term antibiotics permitted the spontaneous resolution of the fistula.

Median prostate volume when biopsy was performed was 25.0 ml (range 13.5–32.5 ml), with a median reduction of 22.8% with respect to baseline ($p < 0.05$). Median last IPSS score was 7 (range 1–29), a 30% decreases compared to baseline ($p < 0.05$) (Table 4).

Median baseline IIEF-5 score was 13 (0–25); considering a score 22–25 as indicative of normal erectile function, only 25 patients (15.3%) were potent. Last median IIEF-5 score was 12.7 (range 0–25); considering only the preoperative potent patients, only 11 (44%) were still potent, while an

Table 2. Median prostate-specific antigen (PSA) values over time.

	Baseline	Nadir	1 month	3 months	6 months	Last determination
PSA (ng/ml)	7.3 (5.2–10)	0.15 (0.05–0.59)	0.18 (0.06–0.6)	0.30 (0.1–1.2)	0.54 (0.15–1.52)	0.62 (0.0–19.2)

Data are shown as median (interquartile range).

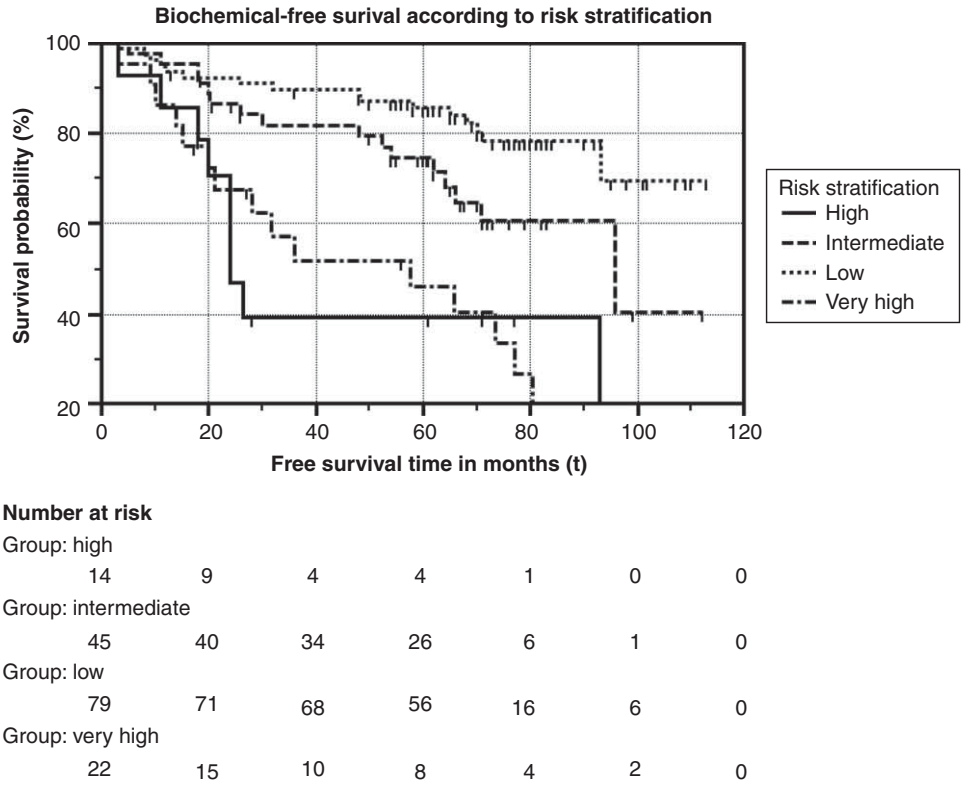


Figure 1. Kaplan–Meier biochemical-free survival according to risk stratification: low-, intermediate-, high- and very-high-risk disease.

overall reduction in IIEF-5 score was detected in 70.8% of cases.

Discussion

In organ-confined prostate cancer, radical prostatectomy and external beam radiotherapy are the gold-standard form of therapy; however, surgery and radiotherapy are associated with significant morbidity. As alternatives, recognized options include watchful waiting, active surveillance, brachytherapy, cryotherapy and hormonal therapy [14–17].

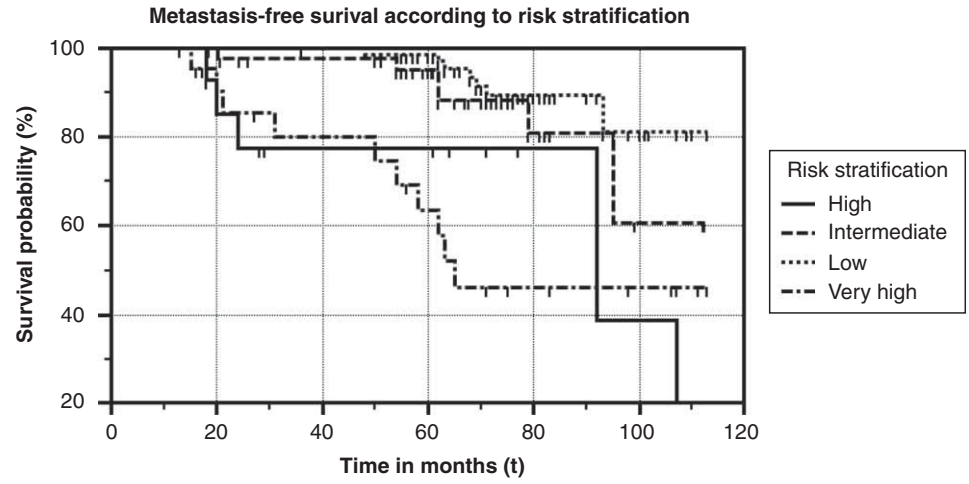
HIFU is a non-invasive technique for the thermal ablation of tissue. Despite its possibilities and more than 15 years of clinical use, its role is still a matter of debate. Discussions focus upon patient selection and indications, the definition of failure, and long-term oncological and functional outcomes.

With regard to patient selection, the current series confirmed, in the long term, the results of the preliminary experience. The ideal candidate for primary HIFU is a patient with low- to intermediate-risk disease according to D'Amico risk stratification. This was demonstrated by the low rate of local failure in low- and intermediate-risk patients (75.5% and 77.4%, respectively) and the 8 year bNED rates (69.6% and 40.5%, respectively) obtained by HIFU alone. These data are supported by the Cox regression analysis, confirming that D'Amico risk stratification has an independent predictive

Table 3. Factors affecting biochemical non-evidence of disease (bNED), metastasis-free survival (MFS) and cancer-specific survival (CSS).

		Univariate			Multivariate		
		HR	95% CI	*p*	HR	95% CI	*p*
bNED	Baseline PSA	1.006	1.001–1.010	< 0.001	–	–	–
	Stage	1.652	1.129–2417	< 0.01	–	–	–
	Gleason score	1.602	1.289–1.991	< 0.001	–	–	–
	Risk stratification	1.713	1.385–2.118	< 0.001	1.883	1.595–3.058	< 0.01
	PSA nadir <0.40 ng/ml	1.352	1.198–1.520	< 0.001	1.343	1.190–1.618	< 0.01
MFS	Baseline PSA	1.009	1.003–1.014	< 0.001	–	–	–
	Stage	1.867	1.082–3.222	< 0.05	–	–	–
	Gleason score	1.767	1.290–2.420	< 0.001	–	–	–
	Risk stratification	1.882	1.393–2.542	< 0.001	2.047	0.984–4.257	< 0.05
	PSA nadir <0.40 ng/ml	1.277	1.086–1.502	< 0.001	–	–	–
CSS	Baseline PSA	1.013	1.006–1.021	< 0.001	1.016	1.004–1.028	< 0.01
	Stage	3.730	0.972–14.316	< 0.05	–	–	–
	Gleason score	4.013	2.066–7.792	< 0.001	6.439	1.793–23.121	< 0.01
	Risk stratification	4.062	1.361–12.122	< 0.001	–	–	–

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.



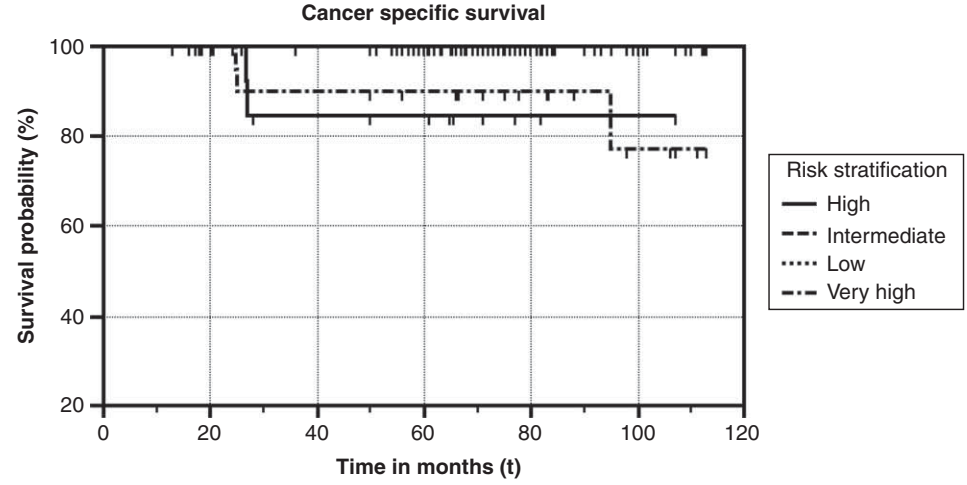
Number at risk

Group: high						
14	11	8	7	2	1	0
Group: intermediate						
45	45	41	30	9	2	0
Group: low						
79	77	76	60	17	6	0
Group: very high						
22	18	15	11	6	4	0

Figure 2. Kaplan–Meier metastasis-free survival according to risk stratification: low-, intermediate-, high- and very-high-risk disease.

value for bNED. This reinforces data coming from most series [8,18–20] indicating HIFU for patients with low- to intermediate-risk prostate cancer.

A direct comparison of outcomes between patients undergoing conventional treatment for low- or intermediate-risk prostate cancer such as radical prostatectomy, radiotherapy and active surveillance and those undergoing HIFU is not possible owing to a lack of comparative studies. Regarding low-risk prostate cancer, active surveillance is a valuable alternative; however, inclusion criteria for active surveillance



Number at risk

Group: high						
14	13	10	9	3	2	0
Group: intermediate						
45	45	41	30	10	2	0
Group: low						
79	77	76	61	18	7	0
Group: very high						
22	20	17	15	10	5	0

Figure 3. Kaplan–Meier cancer-specific survival according to risk stratification: low-, intermediate-, high- and very-high-risk disease.

Table 4. Functional data according to the International Prostate Symptom Score (IPSS) and International Index of Erectile Function-5 (IIEF-5) questionnaires.

	n	Mean	SD	Median	Min.	Max.
IPSS score						
Baseline IPSS	163	11.2	6.7	10.0	0.0	34.0
IPSS at follow-up	93	9.1	6.0	7.0	1.0	29.0
IIEF-5 score						
Baseline IIEF	163	13.0	7.2	12.0	0.0	25.0
Potent[a]	25 (15.3%)					
Follow-up IIEF	85	12.7	7.5	12.0	0.0	25.0
Potent[a]	11 (12.9%)					
Reduction	17 (70.8%)					

[a]Absence of erectile dysfunction was defined as a score of 22–25.

are more selective than the low-risk criteria of D'Amico risk classification. The relatively high incidence of positive rebiopsy (33.9% overall) depends on many factors, including the fact that the 6 month biopsy was carried out in all subjects after a single HIFU session; some patients had a high-volume prostate, for which a second HIFU session was scheduled. Finally, in some cases, owing to different prostatic impedance and the "popcorn" effect, the power of the HIFU beam was reduced, thus increasing the percentage of local persistence of disease. Moreover, the clinical value of a small, low-grade residual cancer is unknown.

The lower incidence of local relapse and bNED translate into the acceptable 8 year MFS and CSS in low-risk disease (81.3% and 100%, respectively) and in intermediate-risk disease (60.6% and 100%, respectively), in accordance with other long-term follow-up series [21–23].

Regarding intermediate-risk prostate cancer, at least in the authors' experience, the relatively high rate of metastatic disease is partly attributable to the fact that salvage therapy was administered upon clinical evidence of disease recurrence. Moreover, the rather high rate of metastatic disease may be influenced by adding CT findings when assessing the metastatic rate and considering the threshold used for the definition of pathological nodal status.

A criticism in patient selection comes from the definition of bNED, since different definitions have been used. The first accepted definition of bNED was the American Society for Radiation Oncology (ASTRO) criteria. According to this definition, Uchida et al. [24] reported an overall bNED rate of 75% (84% and 69% for low- and intermediate-risk disease, respectively]. Most authors have used the ASTRO–Phoenix definition of biochemical failure (i.e. PSA nadir plus 2 ng/ml) [8,21]. More recently, the so-called Stuttgart definition (a PSA increase of 1.2 ng/ml above the PSA nadir value) has been suggested to judge PSA failure following HIFU treatment [25]. Using this new definition, studies reported inferior bNED, translating into ineffective cancer control [19] or inferior cancer control with respect to the Phoenix definition of failure [26]. A criticism of the Stuttgart definition of biochemical failure is that it comes from a study in which 92.4% of patients underwent TURP before HIFU, and consequently the fake PSA bounce has not been compared with HIFU alone. Moreover, it is not clear whether the Stuttgart definition is a predictor of failure or is correlated with CSS. Therefore, the present authors continue to express bNED according to the Phoenix criteria, confirming their validity [27].

The identification of a surrogate able to predict outcomes is more convincing. Most authors [19,28] agree that the PSA nadir can be used to predict the risk of biochemical failure or local relapse. The correct PSA nadir cut-off has not yet been defined, although a value below 0.20 ng/ml seems to be the best predictor of treatment failure. In the authors' experience, using a PSA nadir cut-off of less than 0.40 ng/ml, PSA nadir is an independent predictor of positive biopsy in multiple logistic regression analysis; in the long term, PSA nadir is an independent predictor of bNED and MFS in univariate analysis. Regarding CSS, PSA nadir did not reach a predictive value, probably because of the overall low mortality rate.

Perioperative and short-term side-effects following HIFU have been extensively described. Acute urinary retention is an expected effect of thermal injury, oedema and swelling of the prostate [29], with the prostate volume increasing by up to 30% from baseline. Sloughing (by elimination of necrotic tissue) is another lower urinary tract problem. During sloughing, patients complain of dysuria, with urgency as well as irritative or obstructive symptoms, or both. Another frequent complication is bladder outlet obstruction due to bladder neck stenosis or urethral stenosis, or both.

In the authors' experience, in the long term the impact on urinary function is at least positive, owing to the progressive reduction in prostate volume. This has been demonstrated by the IPSS questionnaire showing a 19% decrease compared to baseline. The overall rate of urethral stricture, although significant, was more frequent in patients after a second HIFU session and in most cases it was solvable by simple dilatation. In 22 cases, in whom a bladder neck stenosis was found, endoscopic incision was performed.

Two patients developed a rectourethral fistula, requiring urinary diversion in one case; in the other case, a long-lasting suprapubic tube and long-term antibiotics permitted the spontaneous resolution of the fistula. What is remarkable is that, in both cases, the patients had received two HIFU sessions and presented with an undiscovered, early prostatic fossa stricture, above which the fistula originated.

No patients showed *de novo* stress incontinence, whereas 16.7% of patients suffered from urge incontinence at 6–12 months.

The incidence of erectile dysfunction following whole-gland HIFU was reported to range from 18.4% to 53.4% [30]. In the present cases and according to their IIEF-5 scores (Table 4), 70% of these patients showed impaired sexual function at the last follow-up.

The present study has several limitations. First, it is a single-arm study without any comparison to a group of patients treated with other forms of curative therapy or active surveillance. Other limitations are the low number of included patients, the short follow-up and the overall low incidence of cancer-specific death, thus weakening the strength of any conclusions that may be drawn. Finally, current data come from the original Sonablate 500; this instrument is now undergoing technical improvements to increase its efficacy and safety.

In conclusion, HIFU is no longer a new procedure for the treatment of prostate cancer. It is definitively clear that: (i) as for other non-invasive treatments, careful selection of well-informed patients is fundamental, reserving HIFU for those with low- or intermediate-risk disease; (ii) a low PSA nadir is a strong surrogate to predict disease control (local relapse and bNED); (iii) in intermediate-risk patients, careful follow-up is mandatory, and patients should be informed about the further need for adjuvant or early salvage treatments, thus increasing the long-term MFS.

HIFU is a valid alternative especially in low-risk disease, filling the gap between an active surveillance strategy and whole-gland radical treatment, and providing a reasonable balance between cancer control and quality of life.

Despite some evidence, the lack of prospective controlled studies means that there is little information on comparative overall survival and CSS.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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