

Visually Directed Transrectal High Intensity Focused Ultrasound for the Treatment of Prostate Cancer: A Preliminary Report on the Italian Experience

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Purpose: High intensity focused ultrasound is a minimally invasive treatment option for prostate cancer. Data from the literature show promising early oncological outcomes and a favorable side effect profile. This study is a preliminary report of the Italian experience (Perugia and Turin) of patients treated with the Sonablate®500 high intensity focused ultrasound device.

Materials and Methods: Between 2004 and 2007, 163 consecutive men with T1–T3 N0M0 prostate cancer underwent high intensity focused ultrasound with the Sonablate 500. Followup included prostate specific antigen tests at 1 month and then every 3 months after treatment, and a random prostate biopsy at 6 months. Failure was defined according to prostate specific antigen nadir, positive findings on followup biopsy and biochemical failure according to Phoenix criteria.

Results: Median patient age was 72 years old, median baseline prostate specific antigen was 7.3 ng/ml, and disease stage was T1 in 44.1%, T2 in 42.5% and T3a in 13.4% of patients. Median followup was 23.8 months. After high intensity focused ultrasound treatment prostate specific antigen decreased to a median nadir of 0.15 ng/ml. Median prostate specific antigen at 3 and 6 months was 0.30 and 0.54 ng/ml, respectively. At 6 months the negative biopsy rate was 66.1%. There was no biochemical evidence of disease in 71.9% overall. On multivariate analysis prostate specific antigen nadir became the only independent predictor of no biochemical evidence of disease and positive biopsy at a cutoff of 0.40 ng/ml.

Conclusions: A favorable outcome of high intensity focused ultrasound is associated with lower baseline prostate specific antigen, lower prostate specific antigen nadir, lower Gleason score and lower tumor stage. As with any novel technology long-term data will be required before this technique gains widespread clinical acceptance.

Key Words: prostatic neoplasms; ultrasound, high-intensity focused, transrectal

PROSTATE cancer is the most common cancer in men.¹ Widespread use of PSA testing has increased the number of patients diagnosed with localized prostate cancer who are suitable

candidates to undergo a curative procedure. Traditionally the aim of a curative procedure is to enhance quantity of life even if it is at the expense of quality of life (in terms of side effects,

Abbreviations and Acronyms

ASTRO = American Society for Therapeutic Radiology and Oncology
bNED = no biochemical evidence of disease
DRE = digital rectal examination
HIFU = high intensity focused ultrasound
IIEF-5 = International Index of Erectile Function
I-PSS = International Prostate Symptom Score
PSA = prostate specific antigen
Qmax = maximum urine flow rate
TRUS = transrectal ultrasound
TURP = transurethral resection of the prostate

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For another article on a related topic see page 354.

continence and potency). This has led to the increased popularity of minimally invasive treatments which may offer an improved side effect profile with comparable oncological efficacy. There is a wide range of techniques for local ablation of the prostate that cause minimal damage to the surrounding tissue such as 3-dimensional conformal radiotherapy, brachytherapy, intensity modulated external beam radiotherapy and laparoscopy, which have gained acceptance in the treatment of localized prostate cancer. Other experimental technologies (photodynamic therapy, microwave and radio frequency interstitial tumor ablation) are currently under investigation in early clinical trials.

Although it is not a new technology, high intensity focused ultrasound has recently become the subject of renewed interest in this field.² HIFU is capable of inducing coagulative necrosis in all biological tissue by thermal effects and cavitation. The focused ultrasound waves are absorbed in the target area with limited damage to the surrounding tissues.

Ultrasound parameters for treating the prostate gland were defined in 1992. In 1994 Madersbacher et al were the first to use HIFU for benign prostatic hyperplasia and in 1995 for prostate cancer.³ The first experience with organ confined prostate cancer was with Gelet et al in 1996.⁴

The first commercial HIFU machine, Ablatherm®, was developed by EDAP and launched in Europe in 2001. The Sonablate 500 originated at the Indiana University School of Medicine in Indianapolis in the 1970s and was further developed by Focus Surgery to treat prostate cancer. Each technology has been assessed for oncological and functional outcomes although the exact role, the ideal patient and the definition of success after HIFU procedures have not been completely defined. We report on the Italian experience in a prospective study of 163 consecutive patients treated with the Sonablate 500 device.

MATERIALS AND METHODS

Patient Selection

All patients had a histological diagnosis of prostate cancer, and disease was staged with DRE, TRUS, computerized tomography and bone scan, or endorectal magnetic resonance when deemed beneficial on the basis of D'Amico risk class.⁵ The inclusion criteria were T1c-T2 and limited cT3a N0M0 disease. All patients were fully informed of the details of this treatment and they provided written informed consent. Exclusion criteria were prostate volume greater than 50 cc (2 treatments scheduled), intraprostatic calcification of more than 1 cm and concomitant anal stricture. None of the patients underwent TURP before HIFU or received neoadjuvant hormone therapy.

HIFU Device

We used the Sonablate 500 HIFU device which includes a treatment module with an ultrasound power generator, transrectal probes, a mobile probe positioning system and a continuous cooling system (Sonachill™). This particular HIFU probe uses double transducer technology with a low energy (4 MHz) ultrasound for real-time imaging of the prostate and delivery of a high energy ablative pulse. The probe has 2 focal length probes with 4.0 and 3.0 cm of focus that limit the gland volume we could treat.

Procedure

HIFU treatment was delivered in a day surgery setting. All patients received an enema and antibiotic prophylaxis with a fluoroquinolone injection. Patients were anesthetized by spinal or general anesthesia and placed in the lithotomy position.

A Foley catheter was inserted to identify the bladder neck. The HIFU probe was inserted into the rectum and fixed using the mobile positioning system. After selection of the treatment zone the catheter was removed and the treatment was started. At the end of the procedure a transurethral catheter or a percutaneous suprapubic cystostomy was inserted.

Patients were discharged home the next day, receiving antibiotics and anti-inflammatory drugs for at least 21 days. The catheter was removed as soon as possible. All procedures were performed according to the proposed standards of Illing et al.⁶

Followup

Visits were scheduled at 1, 3 and 6 months, and then every 6 months. Followup included an accurate objective examination with DRE, uroflowmetry and TRUS at 3 to 6 months, and a self-administered questionnaire on urinary function (I-PSS) and sexual function (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 at least 8 samples customized to residual prostate volume.

Local failure was defined according to the findings of the prostate biopsy at 6-month followup. Biochemical failure was defined according to Phoenix criteria, ie posttreatment PSA + 2 ng/ml after a nadir was achieved.⁷ No patients received hormonal or any other anticancer therapy (except another HIFU session for local relapse) before documentation of a biochemical recurrence.

Statistical Analysis

Frequencies are presented as median and IQR.

Univariate analysis. The Mann-Whitney and Wilcoxon tests were used to compare ordinal and nonnormally distributed continuous variables. Deviations from Gaussian distribution were checked using the Shapiro-Wilk test. Categorical data were analyzed by the chi-square test or Fisher's exact test.

Multivariate analysis. For adjusting predictive variables of post-HIFU local failure multiple logistic and regression models were applied with subjects subdivided according to status at 6 months of followup (positive or negative biopsy). Goodness of fit of the logistic model was tested using the Hosmer and Lemeshow test. Odds ratios with 95% confidence intervals were also calculated.

Survival analysis. The Kaplan-Meier estimator with the log rank test was used to estimate biochemical-free survival rates according to risk classification. To investigate the effect of several variables as covariates on relapse, proportional hazards regression analysis (Cox regression) was used and hazard ratios with 95% confidence intervals were calculated. The level of statistical significance was set at $p < 0.05$. All calculations were performed with SPSS® release 13.0, 2004.

RESULTS

A total of 163 patients were included in the study. The prostate was treated in 1 (135 patients) or 2 (28) HIFU sessions for a total of 191 procedures in 163 patients (1.17 sessions per patient). Reasons for repeating HIFU treatments were technical problems in 1 case, a large prostate in 5 cases and residual tumor in the other cases. There were no intraoperative or perioperative complications. There was only 1 case (0.6%) of rectal fistula occurring 2 months later, supposedly related to concomitant urinary obstruction and latent infection.

Median patient age was 72.0 years (IQR 68 to 75). Median baseline PSA was 7.3 ng/ml (range 5.2 to 10). T stage was T1 in 44.1% of patients, T2 in 42.5% and T3 in 13.4%. Biopsy Gleason score was 2–4 in 14.2%, 5–7 in 76.7% and 8–10 in 9.2% of patients. According to D'Amico risk classification 80 patients presented with low risk, 47 with intermediate risk and 14 with high risk prostate cancer. The analysis included 22 patients with limited cT3a disease categorized as very high risk disease (table 1).

At baseline median prostate volume was 32.4 ml (range 24.7 to 40), median Qmax was 12.0 ml per second (range 11 to 14) and median I-PSS was 10 (range 6 to 15). Median IIEF-5 score was 16 (range 6 to 20). Median operative time was 189.5 minutes (range 165 to 210), median hospitalization time was 1.4 days (range 1 to 4) and the urinary drainage tube

was removed at a median of 13 days (range 7 to 20). Of 163 patients 160 (98.2%) were followed for a median of 23.8 months (range 11.8 to 40.8) and 3 were lost to followup.

Median PSA nadir was 0.15 ng/ml (range 0.05 to 0.59) and was reached in a median of 2.3 months (range 1 to 3). PSA nadir was 0.40 ng/ml or less in 70.2% of cases. Table 2 shows median PSA over time.

Local Failure

The 6-month positive prostate biopsy rate was 33.9% after a single treatment. On univariate analysis patients with a negative biopsy showed a significantly lower baseline PSA, lower PSA nadir values, lower PSA at followup, lower stage and lower Gleason score. On logistic regression analysis only PSA nadir greater than 0.40 ng/ml (OR 6.393, $p < 0.0001$, 95% CI 2.312–17.681) had an independent predictive value for local failure.

According to risk stratification the negative biopsy rate for low, intermediate, high and very high risk disease was 75.5%, 77.4%, 35.7% and 18.7%, respectively ($p = 0.001$). A new HIFU session was proposed to all patients with local failure only. There were 2 patients who preferred and were treated with external beam radiotherapy.

Biochemical Failure

Of the 160 evaluable patients 125 (78.1%) were biochemically disease-free during followup (fig. 1). On univariate analysis bNED was significantly associated with low baseline PSA, low PSA nadir, low PSA at followup, low disease stage and low Gleason score. On Cox regression analysis only PSA nadir greater than 0.40 ng/ml (HR 2.521, $p = 0.017$, 95% CI 1.180–5.386) and risk stratification (HR 1.764, $p = 0.047$, 95% CI 1.007–3.090) as covariates had an independent predictive value for biochemical relapse (fig. 2).

According to risk stratification the 3-year biochemical-free survival rate for low, intermediate, high and very high risk disease was 86.1%, 79.6%, 56.4% and 19.6%, respectively ($p = 0.001$, fig. 3). A total of 28 patients received androgen deprivation therapy.

Median prostate volume when biopsy was performed was 25.0 ml (range 13.5 to 32.5) with a median reduction of 22.8% with respect to baseline ($p < 0.05$). At 6 months median Qmax was 16.0 ml per second (range 12.5 to 20), a significant improvement of 25% compared to baseline ($p < 0.05$). Median I-PSS was 7 (range 5 to 12), a 30% decrease compared to baseline ($p < 0.05$).

There were 18 patients (16%) who presented with mild mixed urinary incontinence and only 1 had grade 3 stress incontinence (2 HIFU sessions). Urethral stricture developed in 24 patients (15%), and

Table 1

Median pt age (IQR)	72	(75–68)
Median ng/ml PSA (IQR)	7.3	(5.2–10)
Median ml prostate vol (IQR)	32.4	(24.7–40)
No. clinical stage (%):		
T1	72	(44.1)
T2	69	(42.5)
T3	22	(13.4)
No. Gleason score (%):		
2–4	23	(14.2)
5–7	125	(76.6)
8–10	15	(9.2)
No. risk group (%):		
Low	80	(49.1)
Intermediate	47	(28.8)
High	14	(8.6)
Very high	22	(13.5)
Median mos followup (IQR)	23.8	(11.8–40.8)

Table 2. Median PSA values over time

	Median ng/ml PSA (IQR)
Baseline	7.3 (5.2–10)
Nadir	0.15 (0.05–0.59)
1 Mo	0.18 (0.06–0.6)
3 Mos	0.30 (0.1–1.2)
6 Mos	0.54 (0.15–1.52)
Last determination	0.96 (0.0–55.3)

was treated with dilation in 5 and with endoscopic incision in 19. Rectourethral fistula developed in 1 patient at the beginning (less than 20 patients treated) after a failed attempt at a complex reconstructive surgical repair, and required urinary diversion. Median postoperative IIEF-5 score was 12 (range 6 to 20).

DISCUSSION

Radical prostatectomy is the gold standard form of therapy in patients with organ confined prostate cancer. Despite excellent long-term survival rates, surgery is associated with significant morbidity. In addition, surgery is not indicated for patients whose life expectancy is less than 10 years.

High intensity focused ultrasound is a noninvasive technique for the thermal ablation of tissue. Together with brachytherapy,⁸ cryosurgical ablation of the prostate,⁹ 3-dimensional conformal radiotherapy and intensity modulated external beam radio-

therapy,¹⁰ HIFU is one of the most attractive options for the noninvasive treatment of localized prostate cancer in patients with a life expectancy of less than 10 years but with a significant tumor or in patients with a life expectancy of more than 10 years who are not suitable candidates for surgery.

The first point is patient selection. In most series HIFU is recommended for patients with localized prostate cancer, Gleason score 7 or less and PSA 15 to 20 ng/ml or less.^{6,11} It has also been used for locally advanced disease, or radiation or brachytherapy failure.¹² Some authors advocate the use of HIFU plus hormone therapy for high risk prostate cancer (cT3a, or Gleason score 8–10 or total PSA greater than 20 ng/ml), reporting an interesting 77% rate of negative biopsy and good results at 1 year of followup.^{13,14} Especially for high risk patients, a policy of adjuvant treatment with androgen ablation could effectively improve biochemical-free survival.

In our experience we treated patients with low, intermediate and high risk prostate cancer as well as limited cT3a disease to identify the best candidates for HIFU treatment. As demonstrated by bNED survival rates and prostate biopsy findings the best results were achieved for low risk (3-year bNED 86.1%, negative biopsy 75.5%) and intermediate risk disease (bNED 79.6%, negative biopsy 77.4%), while high and very high risk disease presented an unacceptable risk of biochemical relapse (56.4% and 19.6%, respectively, expression of systemic disease) and/or positive biopsy findings (64.3%

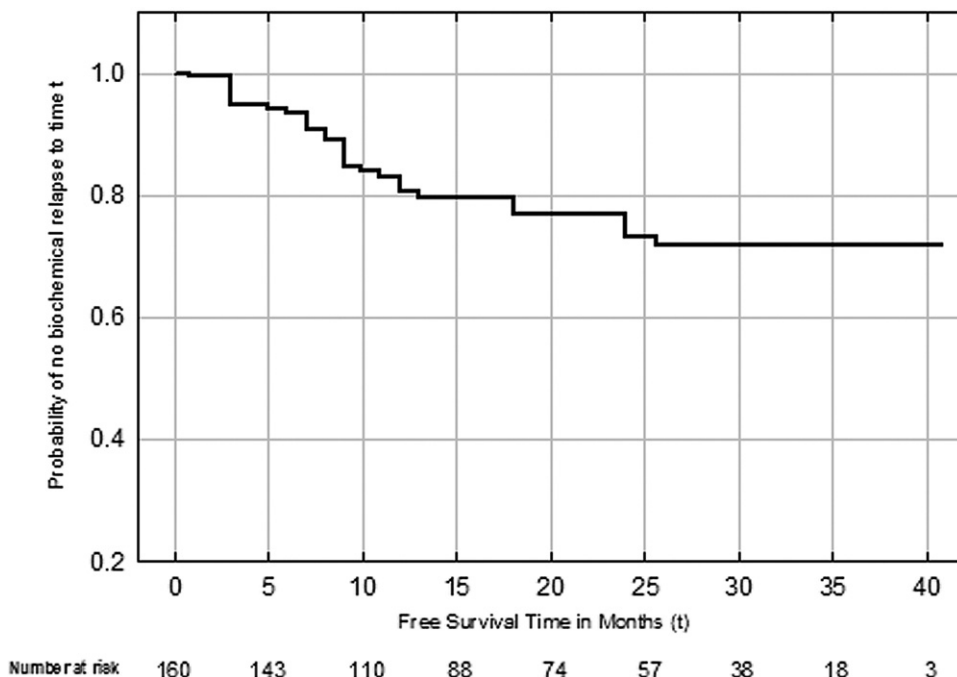


Figure 1. Kaplan-Meier curve: cumulative biochemical-free survival

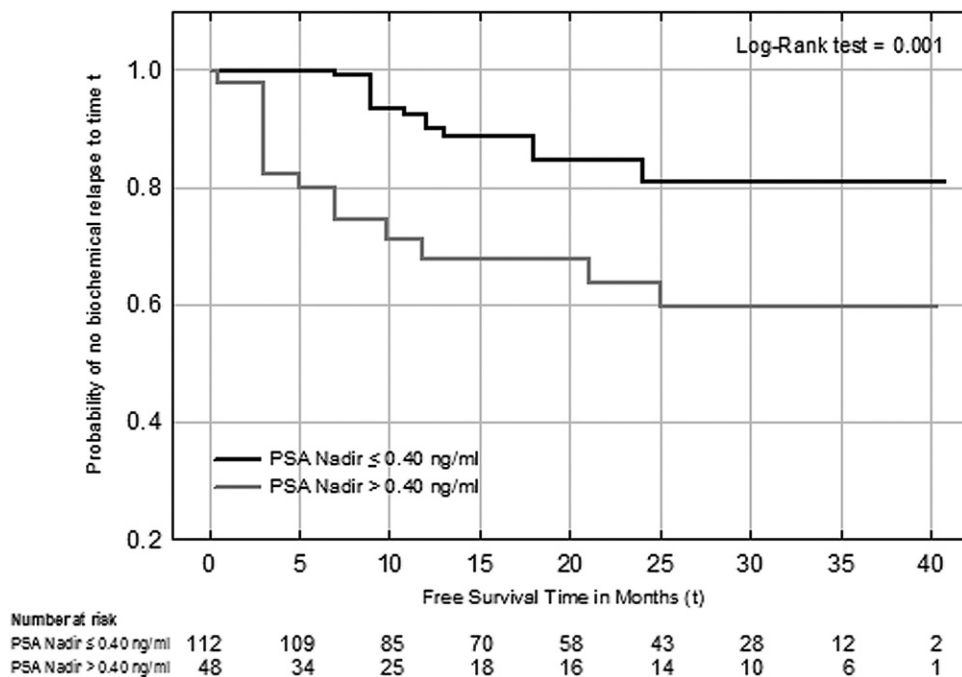


Figure 2. Kaplan-Meier curve: biochemical-free survival according to PSA nadir of 0.40 ng/ml or less, or greater than 0.40 ng/ml

and 81.2%, respectively). On Cox regression analysis D’Amico risk stratification has an independent predictive value for biochemical relapse together with PSA nadir.

The second point is definition of response. The most accepted definition of disease-free status is ASTRO criteria, ie 3 consecutive PSA increases after the PSA nadir has been reached.¹⁵ According to

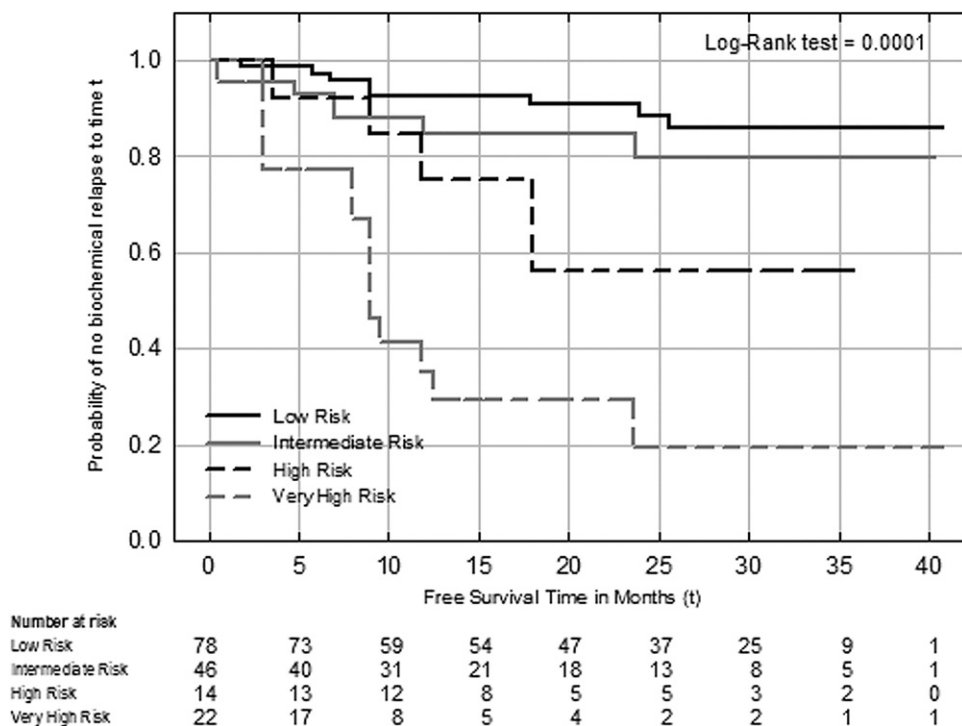


Figure 3. Kaplan-Meier curve: biochemical-free survival according to risk stratification

Table 3

	% Low Risk	% Intermediate Risk	% High Risk
Beyer (5 yrs) ¹⁸	88	79	65
Blasko et al (10 yrs) ²¹	94	82	65
Zelefsky et al (5 yrs) ²²	88	77	38
Uchida et al (3 yrs) ¹⁹	92	75	64
Blana et al (5 yrs) ¹⁷	90	84	
Present series (3 yrs)	86.1	79.6	56.4

these criteria Uchida et al reported an overall bNED rate of 75% with a clear distinction for low risk (84%) vs 69% and 51% for intermediate and high risk disease, respectively.¹⁶ Other authors have used the new Phoenix definition of biochemical failure (ie PSA nadir plus 2 ng/ml). According to this definition the overall 5-year biochemical disease-free rate was 77% in patients with low to intermediate risk prostate cancer.¹⁷

According to Phoenix criteria in our series overall bNED was 78.2%, and the results for the low and intermediate risk groups are comparable to the outcome of patients treated with brachytherapy (table 3).¹⁸ However, it is important to remember that ASTRO and Phoenix definitions of biochemical failure were created and applied only to patients treated with radiation.

The third point is the definition of a surrogate for predicting treatment failure. Most authors agree that PSA nadir (ie the lowest postoperative PSA) can be used to predict the risk of biochemical failure or residual disease.^{19,20}

Since HIFU is an ablative technology and complete prostatic ablation is being attempted, PSA nadirs should be at or near zero and any increasing PSA should be considered indicative of failure. However, HIFU is limited to the prostate gland with a proper size. PSA nadir was strongly associated with preoperative baseline PSA (higher PSA nadir should

be explained by the increasing probability of extra-prostatic disease) and prostate volume (prostate remnants will produce PSA).

The correct PSA nadir cutoff has not yet been defined even if, like for radical prostatectomy, a value less than 0.20 ng/ml seems to be the best predictor of treatment failure.^{16,19,20} Other authors used a PSA nadir cutoff of 0.50 ng/ml or less.¹⁷

In our experience using PSA nadir with a cutoff of 0.40 ng/ml, this criterion becomes the only independent predictor of positive biopsy on multiple logistic regression analysis (OR 6.393) and of bNED with Cox regression analysis (HR 3.842) together with risk stratification.

The procedure seems to be safe. The impact on urinary function is at least positive due to the progressive reduction of prostate volume. The rate of urethral stricture (15%) is low and this complication occurs more frequently in patients after a second HIFU session.

CONCLUSIONS

High intensity focused ultrasound is a relatively new procedure for prostate cancer treatment and surely it could become a choice for patients with localized prostate cancer. As with other minimally invasive treatments patients need to be carefully selected and it could be reserved for patients with low to intermediate risk disease. Prostate biopsy and PSA nadir are the best surrogates to define disease control. Phoenix criteria, even if originally created for the definition of bNED for patients treated with radiation, seem to be helpful even if flawed. However, only a more extensive followup study, and hopefully a randomized control trial comparing HIFU with other form of treatment, will definitively place HIFU in the armamentarium of prostate cancer control.

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EDITORIAL COMMENTS

This article clearly relates what we may expect with HIFU as a primary procedure for prostate cancer. One should not forget that HIFU is a recent technology and definitely not a mature one, even if long-term data are already promising (reference 17 in article). Many exciting developments and improvements are pending.^{1,2}

Dynamic focusing will allow for highly conformal therapy by making it possible to follow the prostate shape extremely precisely. Retroactive control of HIFU parameters using real-time magnetic resonance imaging thermometry will ensure a more uniform, precise and, subsequently, effective delivery of temperature.

HIFU focal therapy is another pathway to explore since HIFU toxicity correlates with the

treated volume. Neoadjuvant or concomitant chemotherapies have demonstrated a synergistic inhibitory effect in the development of aggressive tumors, thus raising hopes for patients with high risk disease.

Thus, HIFU potential is important, and advances in HIFU technology and refinements in delivery systems and imaging will continue to improve this technology, extending its indications.

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The feasibility of HIFU to necrotize prostate tissue was clearly demonstrated, thus justifying its use for prostate cancer. Apart from cancer specific and progression-free survival rates, the important question could arise of when to re-treat? In radical prostatectomy if PSA has not decreased to nil, re-treatment must be considered. With radiation therapy enough

viable prostate tissue may remain to produce PSA. Since re-biopsies are not capable of distinguishing the cured patients from those with recurrence, recurrence was defined by 3 consecutive increases in PSA. In HIFU only a nadir of PSA close to nil can be the measure of success, together with no relevant increase in the followup.

For one of the current HIFU systems TURP before HIFU is suggested. The authors of the current study have proven that HIFU treatment of prostate cancer does not require TURP in general and that urinary retention is not a frequent complication. On balance HIFU seems to have promise,

but further long-term and randomized studies are essential.

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REPLY BY AUTHORS

This new technology needs long-term randomized studies to place HIFU in the minimally invasive armamentarium for prostate cancer treatment. We agree that future interest will focus on who and when to re-treat prostate cancer. PSA nadir is a good

surrogate of success but which cutoff value will be the best remains controversial. If we want to decide who and when to re-treat, we need to correctly define local relapse, which is the only indication for a second HIFU session.