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Prostate Cancer

# First Analysis of the Long-Term Results with Transrectal HIFU in Patients with Localised Prostate Cancer

*Andreas Blana* [a,*,1], *François J. Murat* [b,1], *Bernhard Walter* [a], *Stefan Thuroff* [c], *Wolf F. Wieland* [a], *Christian Chaussy* [c], *Albert Gelet* [b]

[a] *Department of Urology, University of Regensburg, St Josef Hospital, Regensburg, Germany*
[b] *Department of Urology, Edouard Herriot Hospital, Lyon, France*
[c] *Department of Urology, Klinikum München-Harlaching, München, Germany*

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**Abstract**

***Objective:*** To evaluate the long-term efficacy of high-intensity focused ultrasound (HIFU) therapy for patients with localised prostate cancer.
***Material and methods:*** Patients included in this multicentre analysis had T1–T2 NxM0 prostate cancer, a PSA $< 15$ ng/ml, and a Gleason score (GS) $\leq 7$, and were treated with prototypes or first-generation Ablatherm$^{TM}$ HIFU devices between October 1997 and August 2001. The Phoenix definition of biochemical failure was used (PSA nadir + 2). Treatment failure was defined as: biochemical failure or positive biopsy.
***Results:*** A total of 140 patients with a mean (SD) age 69.1 yr (6.6) were included. Mean (SD) follow-up was 6.4 yr (1.1). Control prostate biopsies were negative in 86.4% of patients. Median PSA nadir of 0.16 ng/ml (range, 0.0–9.1) was achieved at a mean (SD) of 4.9 mo (5.2). A PSA nadir $\leq 0.5$ ng/ml was recorded in 68.4% of patients. The actuarial biochemical failure–free survival rates (SR) at 5 and 7 yr were 77% and 69%, respectively. The actuarial disease–free SR at 5 and 7 yr were 66% and 59%, respectively.
***Conclusions:*** This study demonstrates the effective long-term cancer control achieved with HIFU in patients with low- or intermediate-risk localised prostate cancer.


* Corresponding author. Department of Urology, University of Regensburg, St Josef Hospital, Landshuterstr 65, 93049 Regensburg, Germany. Tel. +49 941 7823502; Fax: +49 941 7823515.
E-mail address: blana@caritasstjosef.de (A. Blana).
[1]Both authors contributed equally to this work.

## 1. Introduction

The incidence of prostate cancer is increasing and, currently, 70% of cases at the time of diagnosis are still organ-confined [1]. The two primary therapeutic options for patients with localised prostate cancer are surgery or radiation therapy, and both are associated with significant complications. Moreover, certain patients are unsuitable for such surgical procedures, and others cannot tolerate radiation therapy because of existing comorbidities [2]. Transrectal high-intensity focused ultrasound (HIFU), a minimally invasive therapeutic option, has been shown to provide good outcome with limited morbidity [3–6]. HIFU acts through coagulative necrosis of the tissue to destroy prostate cells without damaging the intervening structures and without any increased risk of metastasis formation [7,8]. HIFU can be used as primary therapy as well as salvage treatment after a first HIFU treatment or after failure of external beam radiation therapy (EBRT), which is one of the advantages of the procedure [9].

Ablatherm™ (EDAP, Lyon, France) prototypes have been in use since 1993; the Ablatherm Maxis™ was the first-generation HIFU device to be EC validated and commercialised in 2000 [10]. The second and latest version with integrated imaging has been available since 2005. The current procedure is based on progressive optimisation of controllable technical parameters (ultrasound frequency, shot duration, and intershot latency) to ensure optimal efficacy of treatment. In many centres, a transurethral resection of the prostate or a bladder-neck incision is performed during the same operation directly before the HIFU treatment or a few weeks prior to HIFU. This approach is to reduce the risk of prolonged urinary retention and to permit the treatment of larger prostate glands [1,11,12]. To date, there is experience of more than 10 yr with HIFU in patients with localised prostate cancer. A number of publications have confirmed its safety and short-term efficacy, but, until now, the question of long-term efficacy of HIFU for a substantial number of treated patients remained unanswered [2]. This is the first report on long-term outcome of up to 8 yr with transrectal HIFU in patients with localised prostate cancer.

## 2. Methods

### 2.1. Patients

The study enrolled patients from the Regensburg University Hospital, Regensburg, Germany, and the Edouard Herriot Hospital, Lyon, France. Patients treated with a prototype or first-generation Ablatherm Maxis HIFU device were included. Selection criteria comprised patients with clinical T1–T2 NxM0 prostate cancer with a prostate-specific antigen (PSA) level $< 15$ ng/ml and a Gleason score (GS) $\leq 7$ [13]. Some patients were considered not suitable for a radical prostatectomy (life expectancy $< 10$ yr and/or significant comorbidity that excluded major surgery), whereas others declined to undergo surgery or EBRT. All patients gave written informed consent before entering the study, which was approved by the local ethics committee. Patients with a previous history of any curative treatment for prostate cancer or hormonal therapy for more than 3 mo were excluded. In some cases, a short course of hormonal therapy ($\leq$3 mo) was used to downsize the prostate volume or to offer patients therapy until they underwent HIFU. Hormonal therapy was stopped prior to HIFU treatment. Patients were stratified according to the 1992 American Joint Committee on Cancer (AJCC) risk factors as low risk on the basis of clinical stage $\leq$ T2A, GS $\leq 6$, and pretreatment PSA $\leq 10$ ng/ml, or intermediate risk on the basis of clinical stage $\leq$ T2B, GS = 7, and pretreatment PSA of 10.01–20 ng/ml.

### 2.2. Follow-up

PSA measurements were performed in all patients at 3 mo and every 6 mo thereafter. At least six prostate biopsies were taken as controls between 3 and 6 mo after HIFU and additionally in case of a rising PSA. Treatment failure included any patients with biochemical failure, positive biopsies, or salvage therapy requirement. Patient records were updated during May and August 2006. The follow-up period was defined as the interval between the last HIFU session and the last available data for each patient. Adverse events, deaths, and causes of death were recorded.

### 2.3. End points

Four end points were used in this analysis. Overall survival was calculated by the time of death, regardless of cause. Prostate cancer–specific survival was calculated by the time of death from prostate cancer, with deaths from other causes treated as censoring events. The Phoenix definition of biochemical failure (PSA nadir + 2) was used [14]. Disease-free survival was defined as the time of HIFU treatment failure (time to PSA nadir + 2 ng/ml, time of first positive biopsy, or time point for salvage therapy). Treatment-related morbidity was also recorded.

### 2.4. Statistical analysis

Actuarial estimates for survival were calculated by means of life table methods. The Wilcoxon test was used to find treatment differences in the overall survival distributions. Results were analysed at time points at which at least 10% of the population were available for the following variables: overall, cancer-specific, biochemical-free, and disease-free survival rates. A multivariate Cox proportional hazards regression model was used to estimate the prognostic relevance of age, PSA, GS, clinical stage, and nadir PSA

**Table 1 – Baseline characteristics of 140 patients treated with high-intensity focused ultrasound**

| Parameter | |
|---|---|
| Median (range) age (yr) | 70 (45–87) |
| Mean (SD) PSA (ng/ml) | 7.0 (3.5) |
| No. of patients with PSA (ng/ml) | |
| ≤10 | 113 |
| >10 | 27 |
| Mean (SD) prostate volume (ml) | 25.9 (11.2) |
| No. of patients with clinical stage | |
| T1 A | 8 |
| T1 B | 14 |
| T1 C | 33 |
| T2 A | 51 |
| T2 B | 27 |
| T2 C | 7 |
| Mean (SD) Gleason score | 5.2 (1.4) |
| No. of patients with Gleason score | |
| 2–6 | 118 |
| 7 | 22 |

SD, standard deviation; PSA, prostate-specific antigen.

on overall survival and biochemical failure–free survival. Statistical analyses were performed with SPSS, version 15 (SPSS Inc, Chicago, IL, USA).

## 3. Results

A total of 140 patients (77 Lyon; 63 Regensburg) met the selection criteria and responded to the requested update. Pre-HIFU patient characteristics are shown in Table 1. Overall, 72 (51.4%) and 68 (48.6%) patients were classified as low- and intermediate-risk patients, respectively. A total of 76 (54.3%) and 64 patients (45.7%) were treated with a prototype or the Ablatherm Maxis™ HIFU device, respectively. The mean (standard deviation [SD]) follow-up was 6.4 yr (1.1) (range, 5.0–8.8). The mean (SD) number of HIFU sessions was 1.3 yr (0.49) with 1, 2, and 3 sessions for 99, 39, and 2 patients, respectively. The mean (SD) period between the first and second HIFU session was 9.9 mo (8.2); the second and third sessions were 17.0 mo (10.4) apart. Hormonal therapy was given to 23 (16.4%) patients for a mean (SD) duration of 51 d (25). No statistical differences were observed between patients receiving or not receiving hormonal therapy for any of the five study end points (Table 2). Consequently, outcome from both groups of patients was pooled for the remaining analysis.

The mean (SD) time to obtain the PSA nadir was 4.9 mo (5.2) with a mean (SD) PSA nadir value of 0.62 ng/ml (1.15) and a median value of 0.16 ng/ml (range, 0.0–9.1). The mean (SD) last PSA measurement recorded was 1.9 ng/ml (3.3) with a median of 0.88 ng/ml (range, 0.0–21.6), and 0.9 ng/ml (range, 0.0–19.7) for low- and intermediate-risk patients, respectively. Of the 140 patients included in the study, 132 had control biopsy in the follow-up period. Of these patients, post-HIFU biopsies were negative in 114 patients (86.4%) with no statistical differences between low- (61 [89.7%]) and intermediate-risk patients (53 [82.8%]) ($p = 0.31$). Of the 114 patients with a negative biopsy, 14 patients subsequently met the definition of biochemical failure, 2 patients required additional treatment, and 8 patients showed biochemical failure and received an additional treatment during follow-up.

The procedure was well tolerated and no intraoperative or perioperative deaths occurred. During the subsequent follow-up 16 (11.4%) patients died. The actuarial overall survival rate at 5 and 8 yr were 90% and 83%, respectively (Fig. 1). Prostate cancer–specific survival rate at 5 and 8 yr were 100% and 98%, respectively. Only 1 patient (0.7%) died as a result of metastatic prostate cancer. In the Cox regression analysis, age was the only statistically significant variable for overall survival ($p = 0.017$).

A total of 21 (15%) patients received salvage treatment consisting of hormonal therapy, radiotherapy, or both in 12, 7, and 2 patients, respectively. The choice of salvage treatment was made by the

**Table 2 – Comparative outcome in patients receiving hormonal therapy prior to high-intensity focused ultrasound and those not pretreated**

| Outcome | Hormonal therapy ($n = 23$) | No hormonal therapy ($n = 117$) | Significance |
|---|---|---|---|
| PSA nadir (ng/ml) | 0.36 | 0.67 | $p = 0.247$ |
| Last PSA value (ng/ml) | 1.2 | 2.1 | $p = 0.250$ |
| Mean (SD) time to PSA nadir (mo) | 8.6 (12.3) | 4.9 (5.2) | $p = 0.166$ |
| Biochemical failure–free survival rate at 5 yr | 72% | 73% | $p = 0.460$ |
| Salvage treatment–free survival rate at 5 yr | 87% | 86% | $p = 0.973$ |
| Disease-free survival rate at 5 yr | 58% | 63% | $p = 0.745$ |

PSA, prostate-specific antigen; SD, standard deviation.

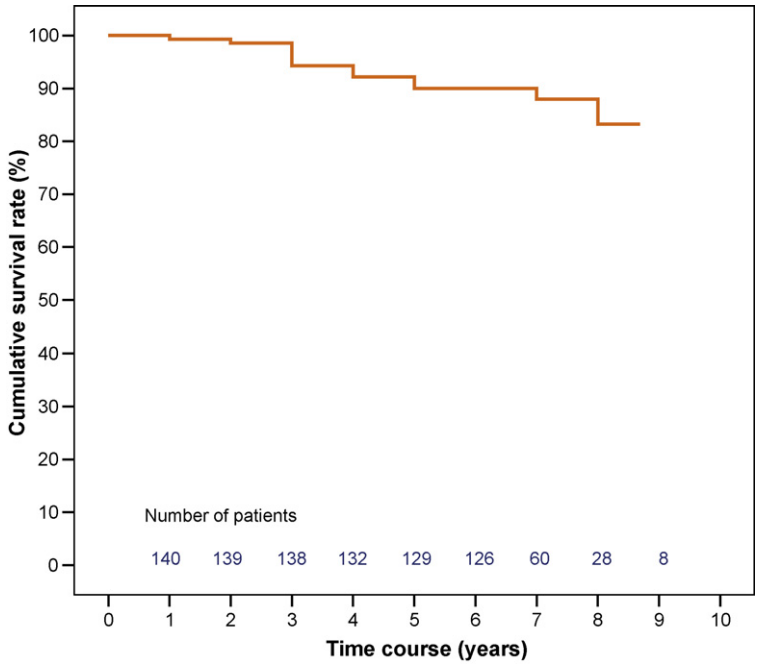


**Fig. 1 – Overall survival rates in 140 patients with localised prostate cancer following treatment with high-intensity focused ultrasound.**

patients according to their medical status and their preference after being informed of all options. Significantly more intermediate-risk than low-risk patients received salvage therapy: 6.9% and 23.5% for low- and intermediate-risk patients, respectively ($p = 0.008$). The actuarial biochemical failure–free survival rates at 5 and 7 yr were 77 and 69%, with no statistical difference between low- and intermediate-risk patients ($p = 0.086$; Fig. 2). A total of 30 patients (21.4%) were considered biochemical failures after HIFU treatment: 13 (18.1%) of the low-risk patients and 17 (25%) of the intermediate-risk patients. In the Cox regression analysis of independent predictors of biochemical failure–free survival, prostate volume ($p = 0.008$) and PSA nadir ($p < 0.001$) were statistically significant.

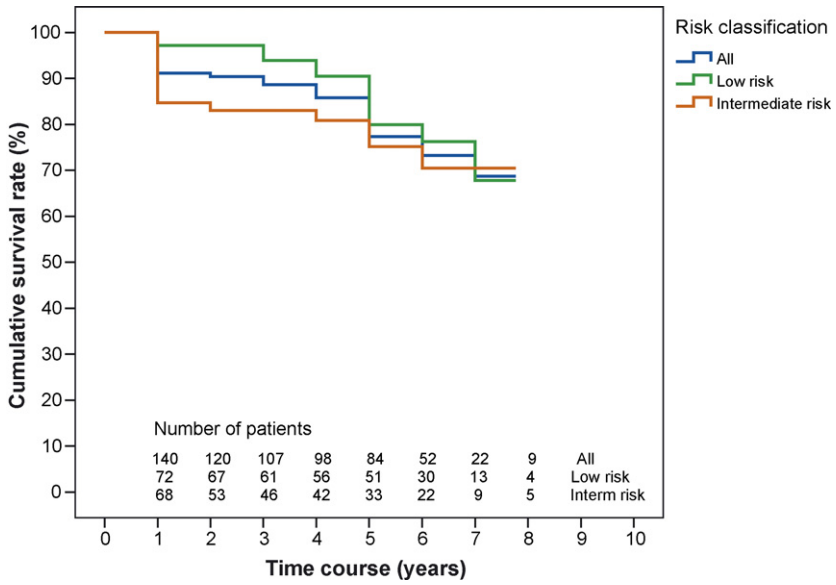


**Fig. 2 – Biochemical failure–free survival rates in 140 patients with localised prostate cancer following treatment with high-intensity focused ultrasound.**

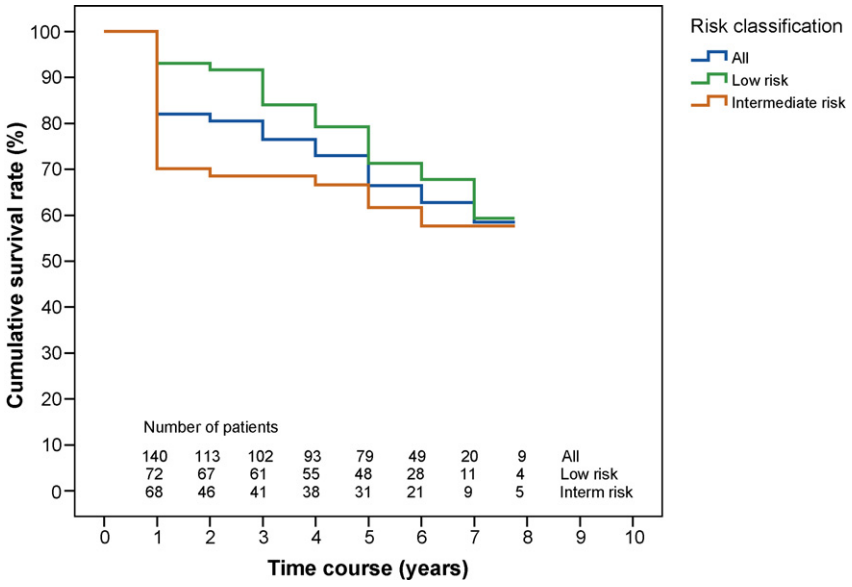


**Fig. 3 – Disease-free survival rates in 140 patients with localised prostate cancer following treatment with high-intensity focused ultrasound.**

The actuarial disease-free survival rates for the total population at 5 and 7 yr were 66 and 59%, respectively, with a significant difference between low- and intermediate-risk patients ($p = 0.021$; Fig. 3). A total of 47 patients (33.6%) were considered as HIFU treatment failures: 20 (27.8%) of the low-risk patients and 27 (39.7%) of the intermediate-risk patients failed HIFU. Biochemical failure, positive biopsies, biochemical failure plus positive biopsies, and introduction of salvage therapy occurred in 25, 13, 5, and 4 patients, respectively. Twenty-one of these patients received hormonal therapy, whereas, for the remaining 26 patients, hormonal therapy was being considered on the basis of PSA evolution.

The prognostic value of the PSA nadir level was evaluated. Patients who received a pre-HIFU short-term hormone deprivation were excluded from this analysis to avoid any influence on PSA evolution. Two subgroups were defined according to PSA nadir value, $\leq$ 0.5 ng/ml and $>$ 0.5 ng/ml; they represented 80 (68.4%) and 37 (31.6%) patients, respectively. There was a significant inverse relationship between the actuarial disease-free survival rate and PSA nadir: 83% vs. 34% at 5 yr for the low and high PSA nadir, respectively ($p < 0.001$). Differences between the two subgroups were analysed: No differences were found for GS, tumour stage, or risk group. The only differences were in the pre-HIFU PSA (6.1 vs. 8.1 ng/ml; $p = 0.001$) and prostate volume (23.6 vs. 34 ml; $p < 0.001$).

In the 3-mo postoperative period, 48 patients (34.3%) presented with at least one episode of incontinence. At the last evaluation, 132 patients (94.3%) were continent, 7 patients (5%) presented with incontinence grade I (loss of urine under heavy exercises requiring 0 to 1 pad per day), and 1 patient (0.7%) presented with incontinence grade II (loss of urine under light exercises using more than 1 pad per day). Urinary infection was recorded in 10 patients (7.1%), urinary obstruction in 19 patients (13.6%), and pelvic pain in 8 patients (5.7%). The maximum duration of pelvic pain was 6 mo. No unexpected late complications were described, as well as no cases of observed rectourethral fistula or requirement for blood transfusion. Erectile function was evaluated in 100 previously potent patients. Data were not available for 19 patients (19%), and no information on the use of phosphodiesterase (type 5) inhibitors or other aids was available for the analysis. At the last evaluation, 46 patients (56.8%) claimed sexual potency (intercourse possible), 14 patients (17.3%) were partially impotent (a degree of erectile function but intercourse not possible), and 21 patients (25.9%) were totally impotent (no erections).

## 4. Discussion

The first cases of prostate cancer treated successfully with HIFU were reported by Madersbacher in 1995 [15]. Ablatherm prototypes for use in clinical trials were available in 1993, thus resulting in the initial series reported in 1996 by Gelet and collea-

gues [16]. Since then a growing number of studies have been published showing great promise for HIFU as a minimally invasive strategy for localised prostate cancer [10]. Previously reported survival data following HIFU has been based on a short follow-up. However, long-term follow-up was required before HIFU would be considered as a standard of care. Long-term outcome at a mean of 6.4 yr has been made available in the current study, and indicates an overall survival rate of 83% and a prostate cancer–specific survival rate of 98%. In addition, 69% of the patients were biochemically disease free at 7 yr. When summarizing the present clinical outcome according to the Phoenix definition [14], the actuarial disease-free survival rate at 7 yr was 59%. As with other treatment options, the outcome was in favour of patients with lower risk factors, such as GS, PSA level, and clinical stage. The results have to be interpreted with the knowledge that only 16% of the patients showed GS 7 tumours and 19.3% of the patients had a PSA $>$ 10 ng/ml.

In the present study, 23 (16.4%) patients received a short course of androgen-deprivation therapy (ADT) to reduce prostate gland volume and make it more amenable to HIFU treatment. This strategy has been applied by radio-oncologists for a number of years and has been reported to shrink prostate volume by up to 30% [17]. In the present study, the maximum duration of ADT in those patients who received it was 3 mo. Results show that this neoadjuvant use of ADT did not adversely affect the long-term oncological outcome of HIFU therapy and that none of the four end points studied were influenced by its use. Moreover, neither the PSA nadir nor the time to achieve it differed between patients who did or did not receive ADT. These findings confirm those previously reported in the literature [18].

The current results have been obtained with patients treated with prototypes or first-generation commercialised HIFU device at the beginning of our experience with this technology. Since then, many technical improvements have been made, including the ability to define more accurately the anatomical apex, resulting in better treatment planning and optimisation of the gland coverage. These improvements might result in better outcome results, which has to be proven in the future. The PSA nadir has been shown to be an independent and major predictive factor for HIFU success [10,19,20]. A total of 68.4% of the patients in the current series had a nadir of 0.5 ng/ml or less, and a significant inverse relationship was noted between the actuarial disease-free survival rate and PSA nadir, with higher rates being observed in patients achieving a PSA nadir of 0.5 ng/ml or less.

The present study population included mostly patients with a life expectancy of 10 yr or less and/or patients with major medical comorbidities precluding surgery. The management of early prostate cancer in this particular population of elderly or debilitated population remains under debate. Treatment options usually include watchful waiting, radiotherapy, and, to a lesser degree, hormonal therapy for patients with poorer outcomes who need symptom palliation [21]. Recently, Wong [22] showed that men aged 65–80 yr with low- and intermediate-risk prostate cancer who underwent active treatment (radical prostatectomy or radiotherapy) were 30% less likely to die during the subsequent 12 yr of follow-up than men who underwent observational management. In contrast, Albertsen et al [23] showed a very low cancer-specific death rate within the first 15 yr, even with a watchful-waiting strategy in low- and intermediate-risk groups. It is noted that the follow-up in the present study was too short to state that HIFU will improve survival compared with a watchful-waiting strategy. Radiotherapy as a primary treatment modality for localised prostate cancer in the elderly appears to be the preferred treatment option because radical prostatectomy is not recommended in patients with a life expectancy less than 10 yr [21]. With dose escalation above 72 Gy, Kupelian et al [24] reported a biochemical failure–free rate at 5 yr of 69%. Recently the same group reported on patients treated with hypofractionated intensity-modulated radiotherapy with a biochemical failure–free rate at 5 yr of 94% and 83% for the low- and intermediate-risk groups, respectively [25]. If Kupelian et al's failure criterion (PSA nadir + 2 ng/ml) were applied in the present study, the disease-free rate at 5 yr would be 77%. Low-dose brachytherapy (BT) has emerged as a popular treatment option in localised prostate cancer. Zefelsky et al [26] have reported a multi-institutional study involving patients with a minimum follow-up of 5 yr after BT. Distribution of PSA levels, GS, and clinical stage were equivalent to the present study. The 8-yr PSA relapse–free survival (nadir + 2 ng/ml) was 74% and 61% for the low- and intermediate-risk groups, respectively. A comparable 7-yr PSA relapse–free survival rate of 69% for all patients in the current study has been achieved. However, only prospective studies or matched-pair analysis would allow a direct comparison of the two treatment modalities.

A potential advantage of HIFU versus radiotherapy is that it can be repeated if there is a proven local recurrence. Because prostate biopsies remain

the only definitive means of assessing local response after any local therapy, the present study involved control prostate biopsies 3 to 6 mo after HIFU and also cases in whom PSA increased thereafter. This approach allowed early retreatment as soon as required in patients who may have had a local proven recurrence. The importance of control biopsies as a single outcome measure is questioned by the fact that 24 of the 114 patients with a negative biopsy failed during follow-up owing to biochemical failure or administration of a salvage treatment. Recent research suggests that the accuracy of biopsy in pinpointing cancer foci after HIFU might be improved with the use of transrectal colour Doppler, although the findings related only to men pretreated with hormonal therapy [27].

A total of 85% of patients did not require salvage treatment; this result was comparable to data reported in the literature [6,10,28]. Up to five HIFU sessions on a single patient have been reported [5], and Blana and colleagues [29] have reported on morbidity associated with multiple HIFU sessions. They found that stress incontinence and impotence were the only two complications that significantly increased after a second procedure. In their experience, although an overall cumulative increase in morbidity after repetitive HIFU procedure was observed, the risk of side-effects was still low.

Comparative morbidity following curative treatments for prostate cancer is open to debate. Radiation therapy has proven to result in lower rates of urinary incontinence compared with radical prostatectomy, whereas urinary irritation and bowel dysfunction were significantly higher with radiation therapy [30]. In the present study, the incontinence rate of 5.7% (5% grade 1) is only slightly higher than the reports in the literature on radiation therapy, whereas no bowel symptoms were reported. It is a limitation of the study that no validated questionnaire was used to assess erectile function, although the rates reported are comparable to previous studies using similar methods of assessment [29]. Urinary obstruction is a common complication after HIFU due to the scarring and necrosis that occurs and the findings in the current study are comparable to the published literature [29].

The study reported here has a number of limitations. First, it was a retrospective cohort with a relatively small sample size rather than a large prospective trial. Consequently, the findings have to be interpreted within the context of any observational data limitations. Another drawback is the lack of validated questionnaires to evaluate functional outcome. In addition, although comparisons are being made with radiotherapy, this information has to be interpreted with caution because of a number of biases, including different definitions of end points being reported. A randomized clinical trial comparing both techniques would be of major interest to clarify the role of HIFU therapy in the armamentarium for localised prostate cancer in the elderly.

## 5. Conclusion

This study demonstrates the effective long-term cancer control achieved using HIFU in patients with low- or intermediate-risk localised prostate cancer. We believe that HIFU provides a potential treatment option for localised prostate cancer in patients who are not eligible for surgery. The additional benefit of a favourable morbidity profile should persuade clinicians to consider more patients for this curative option, which is, in our opinion, a valid alternative to radiotherapy.

## Conflicts of interest

The authors have nothing to disclose.

## References

[1] Azzouz H, de la Rosette JJMCH. HIFU: local treatment of prostate cancer. EAU-EBU Update series 2006;4:62–70.
[2] Aus G. Current status of HIFU and cryotherapy in prostate cancer – a review. Eur Urol 2006;50:927–34.
[3] Rebillard X, Gelet A, Davin JL, et al. Transrectal high-intensity focused ultrasound in the treatment of localized prostate cancer. J Endourol 2005;19:693–701.
[4] Blana A, Walter B, Rogenhofer S, Wieland WF. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. Urology 2004;63:297–300.
[5] Chaussy C, Thuroff S, Rebillard X, Gelet A. Technology insight: high-intensity focused ultrasound for urologic cancers. Nat Clin Pract Urol 2005;2:191–8.
[6] Thuroff S, Chaussy C, Vallancien G, et al. High-intensity focused ultrasound and localized prostate cancer: efficacy results from the European multicentric study. J Endourol 2003;17:673–7.
[7] Chapelon JY, Margonari J, Vernier F, Gorry F, Ecochard R, Gelet A. In vivo effects of high-intensity ultrasound on prostatic adenocarcinoma Dunning R3327. Cancer Res 1992;52:6353–7.
[8] Oosterhof GO, Cornel EB, Smits GA, Debruyne FM, Schalken JA. Influence of high-intensity focused ultrasound on the development of metastases. Eur Urol 1997;32:91–5.
[9] Gelet A, Chapelon JY, Poissonnier L, et al. Local recurrence of prostate cancer after external beam radiotherapy: early

experience of salvage therapy using high-intensity focused ultrasonography. Urology 2004;63:625–9.
[10] Poissonnier L, Chapelon J-Y, Rouvière O, et al. Control of prostate cancer by transrectal HIFU in 227 patients. Eur Urol 2007;51:381–7.
[11] Chaussy C, Thuroff S. The status of high-intensity focused ultrasound in the treatment of localized prostate cancer and the impact of a combined resection. Curr Urol Rep 2003;4:248–52.
[12] Vallancien G, Prapotnich D, Cathelineau X, Baumert H, Rozet F. Transrectal focused ultrasound combined with transurethral resection of the prostate for the treatment of localized prostate cancer: feasibility study. J Urol 2004;171:2265–7.
[13] Soulié M, Barré C, Beuzeboc P, et al. Cancer de la prostate. Prog Urol 2004;1402:913–56.
[14] Roach III M, Hanks G, Thames Jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO phoenix consensus conference. Int J Radiation Oncology Biol Phys 2006;65:965–74.
[15] Madersbacher S, Pedevilla M, Vingers L, Susani M, Marberger M. Effect of high-intensity focused ultrasound on human prostate cancer in vivo. Cancer Res 1995;55: 3346–51.
[16] Gelet A, Chapelon JY, Bouvier R, et al. Treatment of prostate cancer with transrectal focused ultrasound: early clinical experience. Eur Urol 1996;29:174–83.
[17] Ash D, Al-Qaisieh B, Bottomley D, Carey B, Joseph J. The impact of hormone therapy on post-implant dosimetry and outcome following iodine-125 implant monotherapy for localized prostate cancer. Radiother Oncol 2005;75: 303–6.
[18] Uchida T, Illing RO, Cathcart PJ, Emberton M. The effect of neoadjuvant androgen suppression on prostate cancer-related outcomes after high-intensity focused ultrasound therapy. BJU Int 2006;98:770–2.
[19] Lee HM, Hong JH, Choi HY. High intensity focused ultrasound therapy for clinically localized prostate cancer. Prostate Cancer Prostatic Dis 2006;9:439–43.
[20] Uchida T, Illing RO, Cathcart PJ, Emberton M. To what extent does the prostate-specific antigen nadir predict subsequent treatment failure after transrectal high-intensity focused ultrasound therapy for presumed localized prostate cancer. BJU Int 2006;98:537–9.
[21] Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2008;53:68–80.
[22] Wong YN, Mitra N, Hudes G, et al. Survival associated with treatment vs. observation of localized prostate cancer in elderly men. JAMA 2006;296:2683–93.
[23] Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095–101.
[24] Kupelian P, Kuban D, Thames H, et al. Improved biochemical relapse-free survival with increased external radiation doses in patients with localized prostate cancer: the combined experience of nine institutions in patients treated in 1994 and 1995. Int J Radiat Oncol Biol Phys 2005;61:415–9.
[25] Kupelian PA, Willoughby TR, Reddy CA, Klein EA, Mahadevan A. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. Int J Radiat Oncol Biol Phys 2007;68:1424–30.
[26] Zelefsky MJ, Kuban DA, Levy LB, et al. Multi-institutional analysis of long-term outcome for stages T1–T2 prostate cancer treated with permanent seed implantation. Int J Radiation Oncology Biol Phys 2007;67:327–33.
[27] Rouvière O, Mège-Lechevallier F, Chapelon J-Y, et al. Evaluation of color Doppler in guiding prostate biopsy after HIFU ablation. Eur Urol 2006;50:490–7.
[28] Uchida T, Ohkusa H, Yamashita H, et al. Five years experience of transrectal high-intensity focused ultrasound using the sonablate device in the treatment of localized prostate cancer. Int J Urol 2006;13:228–33.
[29] Blana A, Rogenhofer S, Ganzer R, Wild PJ, Wieland WF, Walter B. Morbidity associated with repeated transrectal high-intensity focused ultrasound treatment of localized prostate cancer. World J Urol 2006;24:585–90.
[30] Frank SJ, Pisters LL, Davis J, Lee AK, Bassett R, Kuban DA. An assessment of quality of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer. J Urol 2007;177: 2151–6.

## Editorial Comment on: First Analysis of the Long-Term Results with Transrectal HIFU in Patients with Localized Prostate Cancer

Vincenzo Ficarra, Giacomo Novara
*Department of Oncological and Surgical Sciences, Urology Clinic, University of Padua, Padua, Italy*
vincenzo.ficarra@unipd.it

Transrectal high-intensity focused ultrasound (HIFU) is an interesting and modern minimally invasive alternative therapy for prostate cancer. In recent years, literature data showed safety and promising oncologic results in patients with clinically localized prostate cancer who are either unwilling or unfit for radical prostatectomy or radiation therapy [1] as well as in those men with high-risk localized or locally advanced prostate cancer [2]. Considering the available short-term results, the last version of the European Association of Urology guidelines on prostate cancer still considered HIFU as an investigational treatment, a longer follow-up being needed to

assess its true role in the management of prostate cancer [3].

In this scenario, the manuscript by Blana et al deserves particular attention, considering that it represents the first contribution evaluating the long-term oncologic outcomes after HIFU treatment in a series of patients with low- or intermediate-risk prostate cancer [4]. Specifically, the authors reported 8-yr biochemical disease-free survival as high as 83% and 8-yr cancer-specific survival probability of 98%. At follow-up, most of the patients died from causes other than prostate cancer and the reported 8-yr overall survival was 83%. These data confirm the efficacy of HIFU in patients with localized prostate cancer also at long-term follow-up. These oncologic results can be considered competitive with those reported after radical prostatectomy or external-beam radiation therapy.

Relevant information coming from the study by Blana et al was represented by the independent prognostic role of prostate volume and value of prostate-specific antigen (PSA) nadir to predict biochemical failure, defined by the Phoenix criteria. According to these data, it is possible to hypothesize that patients with larger prostates were not completely treated and that this issue could influence also the value of PSA nadir. In our own experience, a limiting factor to performing a radical HIFU treatment was the height (ie, the anteroposterior diameter) of the prostate. To date, the available technology allows us to plan treatment for lesions 24 mm in length; however, after compressing the gland by use of a transrectal balloon, treating prostates significantly higher than this measurement can be a challenge. With the aim of selecting those patients suitable for HIFU treatment without preliminary transurethral resection of the prostate or androgen deprivation, the height of the gland should be probably considered a parameter more appropriate than the overall prostate volume.

Beyond the oncologic outcomes, the article by Blana et al confirmed the very promising functional data of HIFU treatments, in terms of both urinary continence and recovery of erectile function. Specifically, at a mean follow-up as long as 6.4 yr, 94% of the patients were continent and 57% potent (mean age, 70 yr). However, 34% of patients presented at least one episode of urinary incontinence during the first 3 mo after surgery. Also in our previous experience, only 50% of patients were completely continent 3 mo after the treatment, but this condition can be related mainly to transitory urgency-predominant mixed urinary incontinence [3]. I do believe that further studies are needed to investigate the potential role of anticholinergic drugs in such patients.

I believe that the investigational stage of HIFU treatment will be completed and urologists should increasingly consider this new minimally invasive therapy in their armamentarium.

## References

[1] Aus G. Current status of HIFU and cryotherapy in prostate cancer – a review. Eur Urol 2006;50:927–34.
[2] Ficarra V, Zecchini S, Novara G, et al. Short-term outcome after high-intensity focused ultrasound in the treatment of patients with high-risk prostate cancer. BJU Int 2006;98:1193–8.
[3] Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2008;53:68–80.
[4] Blana A, Murat FJ, Walter B, et al. First analysis of the long-term results with transrectal HIFU in patients with localized prostate cancer. Eur Urol 2008;53:1194–203.

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## Editorial Comment on: First Analysis of the Long-Term Results with Transrectal HIFU in Patients with Localized Prostate Cancer

James A. Eastham
*Division of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*
easthamj@mskcc.org

Although dramatic improvements have occurred in all treatment modalities over the past decade, no single treatment is accepted universally as the preferred therapeutic option for clinically localized prostate cancer. As such, a variety of alternative treatment strategies are being evaluated to determine their role in patient management. Many of these new options are considered ''less invasive'' such that treatment is more convenient or has a quicker recovery than traditional therapies such as radical prostatectomy, external-beam radiation therapy, or brachytherapy. Treatment considerations for prostate cancer, however, require a balance of oncologic outcomes (curing the cancer)

while at the same time minimizing the impact of treatment on both short-term and long-term quality of life. Improvement in one area often comes at the expense of other areas. Therefore, any new technology or procedure must be evaluated in terms of multiple treatment outcomes to determine its role in the management of men with prostate cancer.

Blana et al present oncologic efficacy and quality-of-life outcomes for men with low- or intermediate-risk prostate cancer treated with high-intensity focused ultrasound (HIFU) [1]. The investigators conclude that their results demonstrate that HIFU provides ''effective long-term cancer control'' and is ''a valid alternative to radiotherapy.'' Do the data support such conclusions?

## 1. Oncologic outcomes

The authors, in part, define efficacy based on the Phoenix definition of biochemical failure [2]. Is this appropriate? The authors of the consensus panel outlining the appropriate use of the Phoenix definition specifically state that ''these definitions are *not* recommended for use in patients treated with other modalities, such as cryosurgery or radical prostatectomy.'' In addition, it would seem appropriate to consider patients requiring more than one HIFU session (almost 30% of those treated) as having failed their initial therapy as well. In light of these considerations the oncologic efficacy of HIFU in this series is questionable at best.

## 2. Quality of life

Certainly the treatment can be delivered safely with fairly rapid return to normal physical activities. However, is HIFU a ''valid alternative to radiotherapy'' in terms of urinary and sexual function? The investigators report an approximately 6% risk of urinary incontinence, 7% incidence of urinary tract infection, 14% likelihood of urinary obstruction, and 6% of pelvic pain. Approximately 57% of patients potent prior to HIFU experienced significant erectile dysfunction following treatment. These outcomes certainly temper the enthusiasm for HIFU as a minimally invasive treatment alternative.

## 3. Moving forward

The challenge to any new treatment method is to demonstrate that it can safely eradicate prostate cancer with minimal short- and long-term morbidity to the patient. Investigators of any new technology are encouraged to define appropriate oncologic end points. The Phoenix definition is meant for external-beam radiotherapy, a non-ablative treatment for prostate cancer. Using such a definition for HIFU, cryotherapy and so forth are inappropriate. Use of biopsy data, including an appropriate number of cores, seems reasonable as an initial assessment of efficacy. Baseline and longer-term quality-of-life assessments are crucial for assessing this aspect of treatment. Although these assessments have been underused in reporting patient outcomes for all treatment options for prostate cancer, this should not serve as a rationale for not appropriately evaluating outcomes in future studies.

The results presented for the prototype and first-generation HIFU systems do not seem to support the authors' enthusiasm that HIFU is a valid alternative to radiotherapy. However, this certainly does not suggest that HIFU should be abandoned. Improvements in technology and imaging have already resulted in equipment modifications that will likely improve treatment outcomes. Only through appropriately planned and conducted trials will we develop an understanding of how to include any new treatment as an option for prostate cancer.

## References

[1] Blana A, Murat FJ, Walter B, et al. First analysis of the long-term results with transrectal HIFU in patients with localized prostate cancer. Eur Urol 2008;53:1194–203.

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

DOI: 10.1016/j.eururo.2007.10.064

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