

# Short-term outcome after high-intensity focused ultrasound in the treatment of patients with high-risk prostate cancer

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## OBJECTIVE

To assess the short-term outcome in patients with high-risk prostate cancer treated by transrectal high-intensity focused ultrasound (HIFU).

## PATIENTS AND METHODS

From April 2003 to November 2004, 30 patients with high-risk prostate cancer were enrolled in this prospective study; all had transurethral resection of the prostate before transrectal HIFU treatment, using the Ablatherm device (EDAP, Lyon, France) during the same session, associated with hormonal therapy with luteinizing hormone-releasing hormone analogues. After the procedure, all the patients were evaluated every 3 months by physical examination, prostate-specific antigen (PSA) assay and a continence questionnaire. The follow-up schedule also

included a transperineal prostate biopsy 6 months after the treatment. All the patients had a minimum follow-up of 12 months.

## RESULTS

The HIFU treatment took a median (interquartile range, IQR) of 140 (100–160) min. No complications were reported during treatment. The mean (IQR) hospitalization was 2.2 (1–4) days, and the suprapubic drainage tube was removed after 12 (7–18) days. The complications after treatment were: urinary tract infections in five patients (16%), stenosis of the intraprostatic and membranous urethra in three (10%), and secondary infravesical obstruction in four (13%). At 12 months after the procedure, 28 patients (93%) were continent. Seven of the 30 men (23%) had a positive prostate biopsy. At the 1-year follow-up only three of the 30

patients with high-risk prostate cancer had a PSA level of >0.3 ng/mL.

## CONCLUSIONS

HIFU is a modern, minimally invasive therapy for prostate cancer, often used in selected patients with localized disease. The present results show that HIFU was also feasible in patients with high-risk prostate cancer. The low complication rates and favourable functional outcome support the planning of further larger studies in such patients. The oncological efficacy of HIFU should be assessed in further studies with a longer follow-up.

## KEYWORDS

high-intensity focused ultrasound, HIFU, prostatic neoplasm, complications, urinary continence

## INTRODUCTION

The use of intense focused ultrasound for local tissue destruction was established in 1944 [1]. However, the technology had no clinical application in its early stages because of the lack of a suitable imaging system to monitor the procedure. In recent decades, ultrasonography (US) has made real-time control of the technique possible, and high-intensity focused ultrasound (HIFU) is currently being developed for many surgical applications as an approach requiring no skin incision [2].

HIFU induces coagulative necrosis in biological tissues [3] and was reported to destroy the cells of Dunning R3327 prostate cancer implanted in rats [4].

Experimental studies on dogs showed that HIFU produced by a piezoelectric transducer placed transrectally could destroy prostatic tissue without damaging the rectal wall [5]. The transrectal approach made HIFU treatment simple and minimally invasive.

Such treatment might be indicated for patients with localized prostate cancer who are either unwilling or unfit for radical prostatectomy [6–9], and in cases of salvage therapy for local recurrence after external beam radiotherapy (EBRT) [10]. To date, few studies have analysed the application of HIFU in patients with locally advanced and/or high-risk prostate cancer. Moreover, despite the increasing interest in this procedure most of the available clinical data are from the centres

that pioneered the clinical experimentation of the technique [2].

The aim of the present study was to report the short-term outcome in patients with high-risk prostate cancer treated by HIFU and concomitant hormonal therapy in one centre during the initial experience with the procedure.

## PATIENTS AND METHODS

In March 2003 the Ethics Committee of the University of Verona approved this clinical experimentation. Specifically, the committee allowed the enrolment and treatment with HIFU in association with LHRH analogue hormonal therapy of patients with locally advanced or high-risk prostate cancer. The

LHRH analogue therapy was scheduled for 3 years. The enrolment began in April 2003 and was completed by December 2004. All the patients provided written informed consent to the treatment, and to the use of the clinical data.

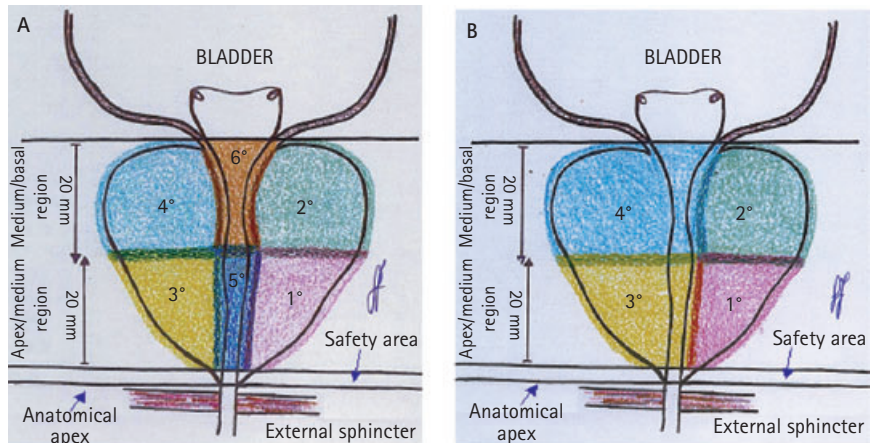
In all patients prostate cancer had been diagnosed by at least a six-core prostate biopsy. In patients with a PSA level of >20 ng/mL and/or a Gleason score of >6, abdominal CT and bone scans were used to exclude the presence of lymph node or bone metastases. Further exclusion criteria were: a life-expectancy of <5 years, high anaesthesiological risk (American Society of Anesthesiologists class >3), Eastern Cooperative Oncology Group (ECOG) performance status of >2, presence or history of treatments for colorectal cancer, or for inflammatory bowel disease, previous rectal amputation, previous prostate brachytherapy, history of rectal fistula, and presence of prostheses either for urinary incontinence or erectile dysfunction. No patient had radiation or hormonal therapy before HIFU.

The patients' risk of progression was assessed according to the criteria of D'Amico *et al.* [11], i.e. preoperative total PSA level, clinical stage and Gleason score. Specifically, patients with a clinical stage of  $\geq T3a$  or Gleason score of 8–10, or total PSA level >20 ng/mL were identified as the high-risk group.

The database also included patient age, ECOG performance status, prostate volume as estimated using the ellipse method ( $\text{length} \times \text{depth} \times \text{width} \times \pi/6$ ) during TRUS, and urinary continence status, as assessed by a patient-reported institutional questionnaire.

The HIFU treatment was administered with the patient under general anaesthesia, and always after TURP. At the end of TURP, a suprapubic tube and urethral catheter were placed. The HIFU treatment was carried out during the same session, using the Ablatherm device (EDAP, Lyon, France). This system has a treatment module that includes the patient's bed, probe-positioning system, ultrasound power generator, cooling system for preserving the rectal wall, and the ultrasound scanner used during the treatment localization phase. There is also a treatment and imaging endorectal probe that incorporates both a biplanar imaging probe working at 7.5 MHz and a treatment

FIG. 1. (A) The six-block treatment strategy was based on the identification of six areas of treatment: apex/medium region (1°) and medium/basal region (2°) of left lobe, right lobe (3°,4°), and prostatic urethra (5°,6°). (B) The four-block treatment strategy was based on the identification of four areas of treatment including prostatic urethral areas within the apex/medium region (3°) and medium/basal (4°) of the right lobe blocks, respectively.



transducer focused at 40 mm and working at 3 MHz. In all cases the size of the primary lesion was 19–24 mm long and 1.7 mm in diameter. The shot duration was 5 s, with each shot followed by a 5-s interval.

All HIFU treatments were applied by one surgeon (V.F.), who had been trained at the Department of Urology, Academic Teaching, München-Harlaching, Germany, where he had performed 10 procedures under the tutelage of a urologist with significant expertise in the field (Stefan Thuroff).

For HIFU treatment, the patient was placed in the lateral decubitus position, fixed on his right side, with legs bent. After anal divulsion, the probe was inserted within the rectum. The strategy of treatment was based on the identification of six blocks of treatment: the apex/medium region and medium/basal region of left lobe and right lobe, and prostatic urethra. In prostates of <40 mL, the treatment was in four blocks, including the prostatic urethra within the right lobe blocks (Fig. 1A,B).

The treatment of the apex/medium region required marking of the anatomical prostatic apex on transverse and longitudinal TRUS. The treatments started 4–6 mm proximally to the anatomical apex, identifying a 'safety area' where no ultrasound was delivered, to prevent external urinary sphincter lesions. The superior limit of the first block was fixed 20 mm from the caudal one. The area of

treatment was visualized stratum-by-stratum on transverse US. In each stratum, the surgeon planned the lesions to cover the whole lobe. Specifically, in those patients with locally advanced or high-risk prostate cancer, the lateral limits of the treatment were widened, including one or two HIFU lesions for each stratum beyond the prostatic capsule (1.7 × 2 mm).

The primary lesion had a focal length of 18–24 mm and a distance from the rectal wall of 3–6 mm (Fig. 2A–B). Having completed the planning of the lesions, the application of the lesions began in the marked area. After ending the treatment of the apex/medium region, the next block (medium/basal region of the same lobe) was marked. The inferior limit of the new block overlapped the superior limit of the first block by 1–1.5 mm. The superior boundary of the medium/basal region block was 20 mm from the lower one, usually sufficient to treat the bladder neck and the proximal part of seminal vesicle (Fig. 3). The same procedures were repeated in the right lobe and prostatic urethra, which was treated after catheter removal. Nerve-sparing procedures were not used, considering the age and risk group of the patients.

At the end of the procedure the rectal probe was removed and a three-way catheter placed within the urethra to allow continuous bladder irrigation. The suprapubic tube was kept closed. All the patients were given ciprofloxacin 200 mg i.v. during surgery and

FIG. 2. (A) Longitudinal view: the treatments started 4 mm proximally to the anatomical apex, identifying a 'safety area'. The superior limit of the first block was fixed 20 mm from the caudal one. (B) The area of treatment was visualized stratum-by-stratum on transverse US. In each stratum, the surgeon planned the lesions to cover the whole lobe. The primary lesion had a distance from the rectal wall of 3–6 mm.

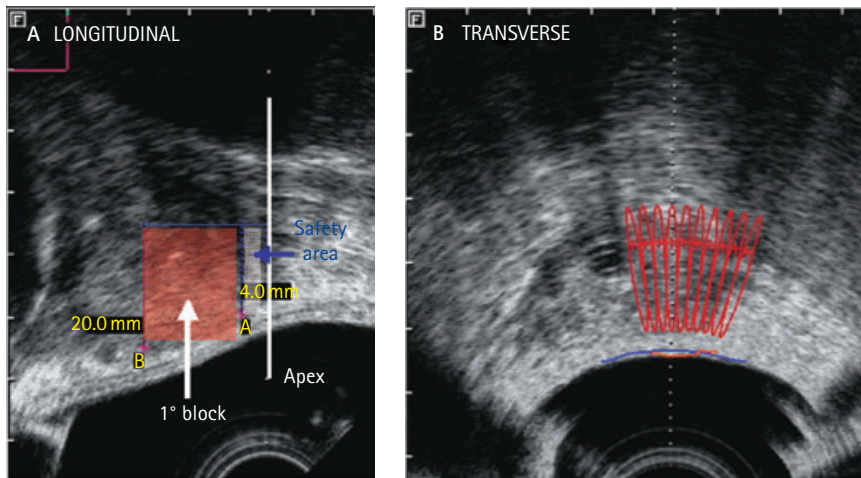


FIG. 3. The inferior limit of the new block overlapped the superior limit of the first block by 1–1.5 mm. The superior boundary of the medium/basal region block was 20 mm from the lower one, usually sufficient to treat the bladder neck and the proximal part of seminal vesicle.

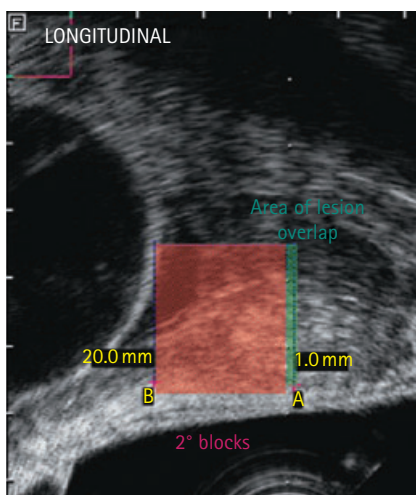


FIG. 4. Cysto-urethrogram of a patient with an infravesical obstruction due to necrotic prostatic tissue within the prostate.



surgery and thereafter every month. PSA levels were measured at 3, 6, 9 and 12 months after treatment. Disease recurrence was defined by a total PSA level of  $>0.3$  ng/mL. The transperineal sextant biopsy of the prostate was repeated 6 months after the procedure [12]. The recovery of continence was evaluated at 3, 6, 9 and 12 months after treatment by a patient-reported institutional questionnaire. All patients who used no pads, or those using a single pad that was dry at the end of the day, were considered continent.

Frequencies are presented as the median and interquartile range (IQR). The Wilcoxon test was used to compare the median data before and after treatment. In all statistical analyses,

a two-sided  $P < 0.05$  was considered to indicate statistical significance.

## RESULTS

Thirty patients were enrolled and treated with HIFU and concomitant hormonal therapy (median age 73.5 years, IQR 69.75–77). The ECOG performance status was '0' in 25 (83%) patients and '1' in five (17%). The median total PSA level before HIFU was 18 (9–35) ng/mL. At the DRE the clinical stage was T2b in nine (30%) patients and T3 in 21 (70%). The Gleason score on prostate biopsy was 7 in five (17%) patients, 8 in 10 (33%), 9 in 11 (37%), and 10 in four (13%). At biopsy, the median number of positive cores was 4 (3–6). The median prostate volume was 35 (29.4–43.4) mL, and the median weight of resected prostate at TURP was 15 (10–20) g. Prostate adenocarcinoma was found in 20 patients (67%) in the TURP specimen.

After TURP, HIFU treatment required a median overall duration of 140 (100–160) min; the median number of lesion produced was 750 (600–815). The volume of treatment was  $>100\%$  in all cases. No complications were reported during HIFU. The urethral catheter was removed during the first day after HIFU in all patients; the mean duration of hospitalization was 2.2 (1–4) days. No patients received blood transfusions during the peri-operative course. The suprapubic tube was removed after a median of 12 (7–18) days from HIFU. At the 1-year follow-up, symptomatic lower UTIs were reported in five patients (16%), while urethral stenosis in the prostatic or membranous tracts was diagnosed in three (10%). These stenoses were treated by cold-knife incision and subsequent urethral calibration. In four patients (13%) an endoscopic resection of the necrotic prostatic tissue was necessary because of infravesical urinary tract obstruction (Fig. 4). There were no major complications, e.g. recto-urethral fistula.

All the patients were continent before surgery; there was complete urinary continence in 15 (50%) at 3 months after HIFU, in 25 (83%) after 6 months, in 27 (90%) after 9 months, and in 28 (93%) after 12 months. All patients who were incontinent within 3 months after HIFU had mixed urinary incontinence with a predominant urgency component. The two patients incontinent at 1 year after HIFU were 78 and 79 years old, and used two pads/day.

antibiotic treatment was continued for 7 days with ciprofloxacin tablets 250 mg twice daily. The urethral catheter was removed during the first day after surgery and the patients were discharged with the suprapubic tube, which was removed in the outpatient clinic after the recovery of spontaneous voiding.

To assess any surgical complications all patients were evaluated at 1 month after

At 6 months after HIFU the median prostate volume was 4.1 (1.3–6.6) mL, significantly lower than the basal value ( $P < 0.001$ ). The 6-month sextant prostate biopsy was positive in seven of the 30 patients (23%), in four of whom the prostate cancer was present in one core, with two cores positive in the other three patients.

At the 1-year follow-up, only three of the 30 patients (10%) had a total PSA level of  $>0.3$  ng/mL, but all were  $<1.0$  ng/mL. These three patients had two positive cores at the 6-month sextant prostate biopsy.

## DISCUSSION

The treatments recommended for patients with high-risk prostate cancer include hormonal therapy plus EBRT, EBRT with or without concurrent short-term androgen ablation for selected patients with one adverse high-risk factor, or radical prostatectomy with extended pelvic lymph node dissection in selected cases with low tumour volume and no fixation to adjacent organs [13]. The strongest evidence is in favour of hormonal therapy plus EBRT, using the data from a few randomized controlled trials. Specifically, the European Organisation for the Research and Treatment of Cancer trial 22863 and Radiation Therapy Oncology Group trials 86–10, 88–31, and 92–02 showed that long-term hormonal therapy (24–36 months, according to the different trial designs) provided significant survival advantages compared to radiation therapy alone or when combined with short-term hormonal therapy in patients with high-risk prostate cancer [14–17]. The use of HIFU associated with concomitant hormonal therapy with adjuvant LHRH analogues is an investigational treatment in patients with high-risk prostate cancer (clinical stage  $\geq T3a$  or Gleason score 8–10, or total PSA level  $>20$  ng/mL) [11]. Androgen blockade was achieved using a 3-monthly depot preparation of LHRH analogue, because currently this protocol has the strongest evidence for androgen deprivation in favour of such a scheme [16]. Recently, data from the Early Prostate Cancer Trial showed that adjuvant bicalutamide after EBRT provides a significant increase in both clinical progression-free survival and cancer-specific survival probabilities in patients with locally advanced prostate cancer [18].

In the previous reports, prostate HIFU was used in patients with clinically localized

prostate cancer either unwilling or unfit for radical prostatectomy [2], or with biochemical and/or clinical recurrence after EBRT [10]. The present study suggests the possible application of HIFU in patients with locally advanced or high-risk prostate cancer. The present oncological data are promising, although they must be regarded as preliminary and needing reassessment over a longer follow-up. The oncological endpoints selected were a positive prostate biopsy 6 months after the procedure and/or a total PSA level of  $>0.3$  ng/mL.

HIFU induces coagulative necrosis and tissue destruction; histologically, a prostate biopsy taken 48 h after HIFU showed severe inflammation, which hampers the identification of vital prostate cancer cells. Indeed, a prostate biopsy at 3 months after HIFU showed the presence of an intense fibrotic reaction, which allows easy identification of the residual vital cancer cells [2]. In our opinion, 6 months after HIFU is the optimum time to repeat the prostate biopsy. Due to the presence of a low-volume residual prostate (a mean of  $<6$  mL), we chose to use only a sextant biopsy. Moreover, with the intention of reducing the risk of infection, we used a transperineal prostate biopsy technique, rather than the common transrectal approach [19]. In the present study, the use of follow-up prostate biopsies was intended to assess the local efficacy of HIFU in the short term. We identified only fibrosis in 77% of the treated patients, while there were small areas of vital cancer within one biopsy core in 13% of patients, suggesting good efficacy for HIFU in destroying prostate cancer cells. Moreover, the rates of positive prostate biopsy overlapped those reported in the other published series in patients with better risk profiles [6,8–10]. The concomitant use of hormonal manipulation did not affect the identification of vital cancer cells, although the Gleason score was not applicable in this setting [20]. The comparison of such biopsy data to those deriving from series of EBRT plus hormonal therapy is difficult, because prostate biopsies after radiotherapy are usually indicated at  $\geq 18$  months after treatment, in selected cases with local cancer recurrence when salvage radical prostatectomy is considered [21]. Indeed, data from patients undergoing brachytherapy showed that the percentage of positive biopsies at 2 years after implantation was 70–90% [22,23].

In patients treated by HIFU there are rapid increases in serum PSA level within 48 h of treatment, followed by a rapid decline, reaching a PSA nadir after 1–3 months [24]. This trend allows follow-up strategies and definitions of biochemical recurrence similar to those after radical prostatectomy, and different from the American Society for Therapeutic Radiology and Oncology criteria used in all studies on radiotherapy.

In the present study, the follow-up PSA levels were influenced by the concomitant androgen-deprivation therapy. Only three patients had PSA levels of  $>0.3$  ng/mL (but  $<1$  ng/mL). At the 1-year follow-up, 90% of the patients treated by HIFU and 3-monthly depot preparations of LHRH analogues had undetectable PSA levels, and none had clinical disease progression. These values are promising but preliminary, and do not allow clear comparisons with the results from the randomized controlled trials using LHRH analogues and EBRT [14–17]. A further potential advantage of HIFU treatment in high-risk patients might be the possibility of a second treatment if there is clinical local recurrence, with morbidity rates lower than those of other salvage therapies.

As in patients with localized prostate cancer, HIFU was a safe treatment, with low complication rates even in those with locally advanced or high-risk prostate cancer. Specifically, there were no adverse events associated with the bladder or rectum. The development of a recto-urethral fistula is the most severe complication of HIFU treatment, and reported to be as frequent as 3% in the initial studies where the Ablatherm device v1.0 was used. Currently, with the use of the most advanced device, available since 2000, the occurrence of such fistulae is a rare event. Specifically, the use of a cooling device for the rectal mucosa, and the security systems which stop the ultrasound generator if the patient moves or there is an inappropriate distance between the generator and the rectal wall, lowered the risk of fistula to  $<0.5\%$  [7–9,25]. However, such concerns are more relevant in patients who had had previous EBRT and were treated with HIFU because of a local recurrence [10].

The most common complications are currently UTIs, reportedly in 4–10% of patients, and stenosis of the prostatic-membranous urethra, in 5–20%. With the advent of the combined treatment with TURP

and HIFU, the incidence of such stenoses is 5–7% [7]. In our clinical practice, urethral stenosis was the most relevant complication; in all cases we used cold-knife urethrotomy and subsequent urethral calibrations. Stenoses might be due to the overlap of the treatment blocks, which occurs at the level of the prostatic urethra. In the present three cases of urethral stenosis we used a six-block strategy, which exposed the urethra to significantly many primary lesions. By contrast, there was no urethral stenosis in the patient treated with a four-block strategy. Consequently, the four-block strategy can be considered an appropriate treatment even for patients with locally advanced or high-risk cancers, where, in the present series, we elected to widen the lateral limits of the treatment, with the aim of treating patients with extracapsular extension.

Identifying the anatomical apex of the prostate by US and the presence of a safety area of 4–6 mm was intended to give optimum preservation of the external urethral sphincter. Considering only those patients treated with the new Ablatherm device (available since 2000), the rates of urinary incontinence were <5% [6–9]. The present study provides further data on the time to recover continence during the first year after HIFU. At the 3-month follow-up, most patients who were incontinent had mixed urinary incontinence, with a significant 'urgency' component. Further studies are needed to investigate the potential role of anticholinergic drugs in such patients.

The effect of HIFU treatment on erectile function was not a relevant outcome in the present study, because 80% of the patients had erectile dysfunction before HIFU; moreover, all patients were aged >65 years and the need to treat these high-risk patients with combined HIFU and hormonal deprivation therapy did not justify the choice of a nerve-sparing approach.

In conclusion, HIFU is a minimally invasive therapy for prostate cancer often used in selected patients with localized disease. The present results showed that HIFU combined with adjuvant pharmacological castration was feasible also in patients with high-risk prostate cancer. The low complication rates, favourable functional outcome and particularly the promising preliminary oncological data support the planning of further larger studies in such patients. The

oncological efficacy of the present protocol should be assessed in further studies with more patients and a longer follow-up.

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#### CONFLICT OF INTEREST

None declared.

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Abbreviations: **HIFU**, high-intensity focused ultrasound; **US**, ultrasonography; **EBRT**, external beam radiotherapy; **ECOG**, Eastern Cooperative Oncology Group; **IQR**, interquartile range.