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ORIGINAL ARTICLE

Morbidity associated with repeated transrectal high-intensity focused ultrasound treatment of localized prostate cancer

Andreas Blana · Sebastian Rogenhofer · Roman Ganzer · Peter J. Wild · Wolf F. Wieland · Bernhard Walter

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Abstract The aim of this cross-sectional study was to compare single with repeated high-intensity focused ultrasound (HIFU) treatment in patients with localized prostate cancer, regarding treatment-related morbidity. A number of 223 consecutive patients with localized prostate cancer were treated with HIFU. Among them, 174 (78%) patients had one treatment, while 49 (22%) needed a second treatment. The patients' status and treatment-related side effects were followed up. The complications rates after one HIFU in 223 patients were: urinary tract infection 0.4%, chronic pelvic pain 0.9%, infravesical obstruction 19.7%, stressincontinence 7.6%, impotence 49.8%. Among the 49 patients who received a second HIFU therapy, the cumulative incontinence rate (12.2%; $P = 0.024$) and cumulative impotence rate (55%; $P < 0.001$) were significantly increased. Although there is an increase in morbidity if transrectal HIFU is repeated, the risk of side effects related to additional HIFU sessions in the case of primary treatment failure is still low.

Keywords High-intensity focused ultrasound (HIFU) · Prostate cancer · Therapeutic ultrasound · Side effects

A. Blana (✉) · S. Rogenhofer · R. Ganzer · W. F. Wieland · B. Walter
Department of Urology, University of Regensburg, St. Josef Hospital, Landshuterstraße 65, 93053 Regensburg, Germany
e-mail: blana@caritasstjosef.de

P. J. Wild
Institute of Pathology, University of Regensburg, Franz-Josef-Strauß Allee 11, 93053 Regensburg, Germany

Introduction

Appropriate treatment for localized prostate cancer is currently debated. Although radical prostatectomy is still regarded as the standard treatment for patients with organ-confined disease and a life expectancy exceeding 10 years, other treatment options may be an alternative. For patients whose life expectancy is less than 10 years or who are not in the appropriate physical condition for surgery, three-dimensional radiotherapy, brachytherapy and cryosurgical ablation of the prostate are alternative treatment options. However, in the case of treatment failure, these treatments cannot be repeated except for cryotherapy. And salvage radical prostatectomy is associated with a high morbidity rate [12]. High-intensity focused ultrasound (HIFU) treats the prostate by inducing mechanical effects, cavitation and thermal effects without damage to the tissue in the path of the ultrasound beam [11]. In contrast to radiotherapy, there is no maximal dose for ultrasound. One advantage of HIFU is that it can be repeated in case of primary treatment failure. For patients with localized prostate cancer, up to five HIFU sessions administered to one single patient have been reported (3), with an average of 1.17–1.8 sessions per patient [2, 3, 8, 9, 15, 16]. So far, no study has investigated the cumulative impact of multiple HIFU sessions on morbidity.

We report on the results of single and multiple HIFU treatments of patients with localized prostate cancer, with emphasis on side effects. The aim of our study is to find out whether it is a safe choice for the patient to repeat HIFU after a primary treatment failure.

Patients and methods

Equipment

Ablatherm-prototypes and the Ablatherm® device (EDAP, Lyon, France) were used. The three-dimensional movable treatment head of the HIFU device integrates a piezoelectric therapeutic applicator (3.0 MHz) and a 7.5 MHz ultrasound scanner for treatment planning. The burst of ultrasound waves emitted by the tablespoon-shaped applicator produces an almost instant coagulation necrosis. The size of each created lesion is 1.7 mm in diameter and its length can be set anywhere between 19 and 24 mm.

Furthermore, a cooling device with a degassed coupling liquid in a balloon surrounding the treatment head protects the rectal mucosa. By removing the thermal energy released at the balloon–rectum interface, the temperature at the rectum is kept at a maximum of 15°C.

Procedure

The treatment is performed under spinal anaesthesia with a suprapubic tube in place, the patient lying fixated in a right-sided position. Therapy planning starts by marking the apex in transversal and longitudinal transrectal ultrasound (TRUS). For repetition –treatments, it can be difficult to define the borders of the prostate. In these cases, the apex is marked by passing a flexible cystoscop right of the external sphincter. The tip of the cystoscop is perfectly visualized as a hyperechoic reflex on TRUS. To protect the external sphincter the treatment starts 6 mm cranial from the apex. According to the size of the gland, one to four overlapping target areas are defined and treated from the apex to the bladder neck, including the base of the seminal vesicles. The distance between the rectal mucosa and the dorsal prostate capsule can be defined to be from 3 to 6 mm. One of the piezoceramic elements of the applicator works as a continuous rectal wall-distance control unit to prevent accidental injury of the rectum. The shot duration for standard treatments is 5 s followed by a 5 s pause. When HIFU has to be repeated, the shot duration is lowered to 4.5 s because of the reduced blood flow in a pretreated prostate, which is associated with less heat conduction and thus higher temperatures in the tissue caused by the energy of the focused ultrasound. Up to 1,000 lesions are applied during each treatment, depending on the size of the gland.

Patients

In this cross-sectional study, we have included all 223 patients with clinical stages T1–T3, N0, M0 biopsy-proven localized prostate cancer, that were treated with HIFU at our department from November 1997 to June 2003. Among them, 87 patients (39%) were not suitable for radical prostatectomy (life expectancy less than 10 years and/or high risk because of comorbidity) while 136 patients (61%) chose HIFU because they were not willing to take the potential risks of the operation. The study has been approved by the local ethics committee, and written informed consent was obtained from the patients before they were admitted to the study. Preoperative assessment included transrectal ultrasonography (TRUS), digital rectal examination, pelvic CT scan or MRI and bone scan were performed for all patients.

Two hundred and twenty-three patients with a mean age of 68.2 ± 6.8 years, mean PSA 11.3 ± 10 ng/ml (range 0.5–81.2), mean Gleason score 5.3 ± 1.5 and a prostate volume of 23.5 ± 10.7 cm^3 (range 3–62.5) were treated. Of them, 46% had already been treated with neoadjuvant hormonal therapy before their visit to our hospital and 15 (31%) had a TUR-P prior to HIFU. None of them had received post-procedure irradiation, androgen ablation or any other anticancer therapy.

Follow-up

All 223 patients had a minimum follow-up of 3 months including TRUS, digital rectal examination and PSA assay at day 1 and every 3 months. A random control sextant biopsy was performed at 3, 12 and 24 months or when any biochemical failure was evidenced (increase of PSA superior to 0.2 ng/ml after the last control). Patients' status and treatment-related complications were followed-up by periodic patients' visits and by self-administered questionnaires (every 3 months in the first 2 years, every 6 months in the third year, then annually). During their visits the patients were enquired for any adverse effects associated with HIFU which may have occurred during the last follow-up period. Questions on stress incontinence included the number of pads the patients used and whether the loss of urine was under heavy exercises (Grade 1), under light exercises (Grade 2) or at rest/during sleep (Grade 3). Erectile function was rated normal if the patient was able to penetrate his partner without mechanical or pharmacological support. For the evaluation of obstructive and irritative symptoms, we used the International Prostate Symptom Score

(IPSS), which is equivalent to the translated version of the American Urological Association (AUA)—7 Symptomscore by Barry et al. [1]. The IPSS is completed by one question regarding the direct influence of micturation on quality of life (QL). All singular adverse events and answers of the patients at the last assessment were used to present the results of this investigation.

Statistical analysis

Statistical analyses were performed using the two-sided, non-parametric McNemar test for two dichotomized dependent variables and the Cochran test for multiple dichotomized variables. Furthermore, the non-parametric Friedman test was used to globally compare multiple ordinal variables simultaneously. The differences between two dependent ordinal variables were tested using the two-sided non-parametric marginal homogeneity test. The SPSS software version 10.0 (SPSS Inc., Chicago, IL, USA) was used. P values < 0.05 were considered statistically significant. Data are presented as mean ± SD. For multiple testing, the closed test principle was used.

Results

One hundred and seventy-four (78%) patients had one HIFU treatment with a median follow-up of 13 months (range 3–54), and 49 (22%) needed a second HIFU session due to primary treatment failure proven by positive biopsies (46 patients, 94%) or due to incomplete primary treatment, i.e. technical failure (3 patients, 6%). The median period between the first and second HIFU was 7 months (range 1–49) and the follow-up after the last HIFU was 13 months (range 3–50). Only two of these patients had to be treated a third time.

For the first HIFU ($n = 223$) 643 ± 179 lesions per session were needed resulting in a mean treated volume of 33 ± 16 cm^3. Compared with the mean volume of the prostate, 142% of the gland was treated by overlapping the treatment areas. The mean operating time for all initial HIFU sessions was 164 ± 42 min.

The mean time for the second treatments ($n = 49$) was only 107 ± 41 min. This shorter operating time compared to the primary treatments is due to a decreased mean volume of the prostate after the first session of 12.8 ± 6.6 cm^3 (range 1.4–27.4; 54% of the initial size). Consequently, the mean number of shots for second treatments was reduced to 400 and the mean treated volume was only 19 ± 8 cm^3.

Adverse events caused by HIFU treatment in 223 patients are summarized in Table 1. For the treatment of symptomatic urinary tract infections (UTI), antibiotics had to be administered. Chronic pelvic pain syndrome (CPP) was defined as a constant pain in the perineal area that lasts for more than 3 months after HIFU, according to the National Institutes of Health (NIH) definition [18]. Patients with infravesical obstruction required a TUR-P or urethrotomy for persistent urinary retention. Stress incontinence was graduated according to Stamey [13] into three grades. Grade 1 was defined as loss of urine during heavy exercises, using not more than one pad per day, and Grade 2 as loss of urine during light exercises but not at rest or during sleep. Finally Grade 3 as total loss of urine. Patients that were able to penetrate their partner without mechanical or pharmacological support were rated potent.

In order to assess the rate of side effects after a second HIFU treatment versus that after an initial treatment, the group of 49 patients with a history of two or more HIFU sessions was investigated (Table 2; Figs. 1, 2, 3). Patient status was assessed three times: before HIFU (moment 0), after the first HIFU (moment I) and after the second HIFU (moment II). The frequency of UTI, CPP, and infravesical obstruction and rectourethral fistula at moment II compared to moment I was not significantly altered. Two cases of CPP and one rectourethral fistula occurred after a second HIFU treatment while these complications were not observed after a first HIFU. However, the impotence rate caused by HIFU ranged from 38.8% after one HIFU treatment to 55.1% after two treatments ($P = 0.039$). Incontinence caused by HIFU was 6.1% after one treatment and cumulated to 12.2% after the second treatment. The global Friedman test for the occurrence of incontinence was statistically significant ($P = 0.024$) and the incontinence rate after the second HIFU was significantly higher compared to

Table 1 Adverse effects caused by one high-intensity focused ultrasound (HIFU) treatment $n = 223$

	Patients	
	No. of patients (n)	Percentage
Urinary tract infection	9	0.4
Chronic pelvic pain	2	0.9
Infravesical obstruction	44	19.7
Stress incontinence I	16	7.2
Stress incontinence II	1	0.4
Stress incontinence III	0	0
Rectourethral fistula	0	0
Rate of impotence		49.8

Table 2 Adverse effects after two HIFU treatments $n = 49$

	Before HIFU (moment 0)	After one HIFU (moment I)	After two HIFU (moment II)	*P* value
Urinary tract infection	–	2 (4.1%)	2 (4.1%)	1.0[a]
Chronic pelvic pain	–	0	2 (4.1%)	0.5[a]
Infravesical obstruction	–	11 (22.4%)	7 (14.3%)	0.5[a]
Rectourethral fistula	–	0	1 (2%)	1.0[a]
Rate of impotence	13 (26.5%)	32 (65.3%)	40 (81.6%)	< 0.001[b] 0.039[a]
Stress incontinence	2 (4.1%)	5 (8.2%)	8 (16.3%)	0.024[c] 0.266[d]

[a]Comparing moment I and moment II; McNemar test

[b]Comparing moments 0, I and II; Cochran test

[c]Comparing moments I and II; Friedman test

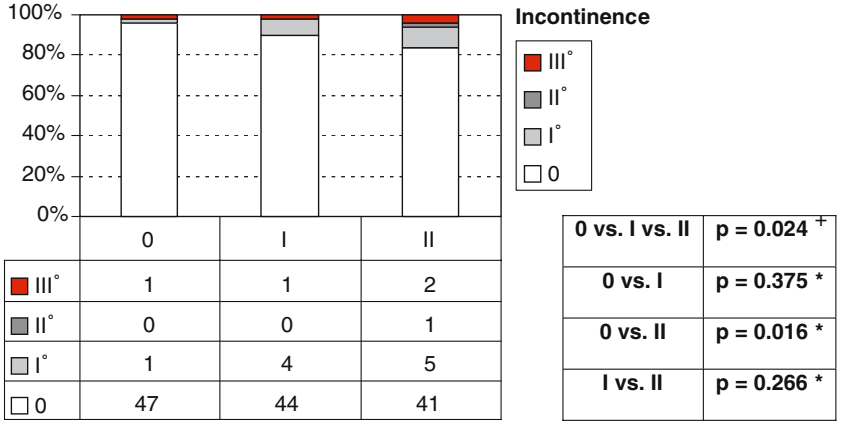
[d]Comparing moments 0, I and II; marginal homogeneity test

the baseline (moment 0) incontinence rate ($P = 0.016$; Fig. 1). However, the test comparing the incontinence rate at moment II with moment I showed no significant differences ($P = 0.266$; Fig. 1). Boxplots for the comparison of the IPSS are given in Fig 2. IPS scores based on patients' answers showed no significant difference before and after the HIFU treatments ($P = 0.145$). In Fig. 3 boxplots for the patients' answers concerning the QL, being the last question of the IPSS, show no global significant difference due to repetition of HIFU ($P = 0.102$).

Discussion

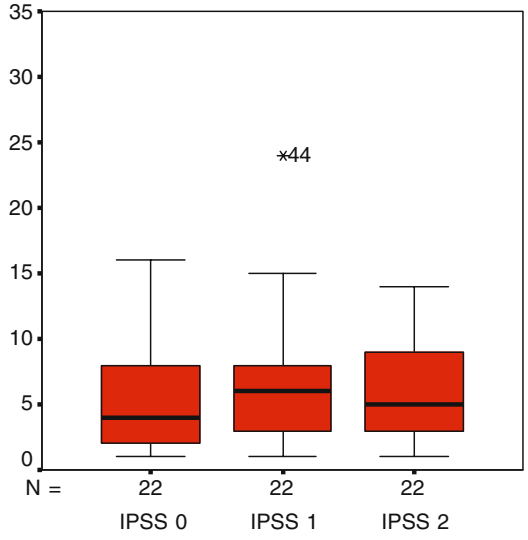
The increasing number of studies on HIFU therapy indicates the broad distribution of this promising technique. Several studies show good local control of the prostate cancer while the treatment-related morbidity is low [2, 4, 7–10, 15, 16]. Due to incomplete treatment or treatment failure, HIFU has to be repeated for some patients. In the largest existing study, the European Multicentric Study reporting on 402 patients treated with the Ablatherm device (EDAP, Lyon, France), the rate of HIFU sessions per patient was 1.47 [15]. About the same repetition rate was reported by Uchida et al. [16] using the Sonablate-200 device (Focus Surgery, Indianapolis, USA) in order to treat 20 patients. The choice of the treatment device seems to be of no importance regarding the repetition rate. In our study, the HIFU rate per patient was 1.23. Because it was not the goal of the present study to investigate the efficiency of HIFU, we also included five patients (2.2%) that had been treated with a clinical T3 tumor. This is the first study reflecting the aspect of side effects after repetitive HIFU treatments.

The focus of our short-time analysis was on 49 patients (out of 223) who had needed extra HIFU treatments. In this group, incontinence and impotence were significantly increased after two HIFU applications. After two HIFU sessions the overall incontinence rate was 12.2%, primarily Grade 1. Looking at patients with one or more HIFU treatments Uchida et al. [16] reported no incontinence at all while other series observed incontinence rates up to 12.7% [9]. Definition



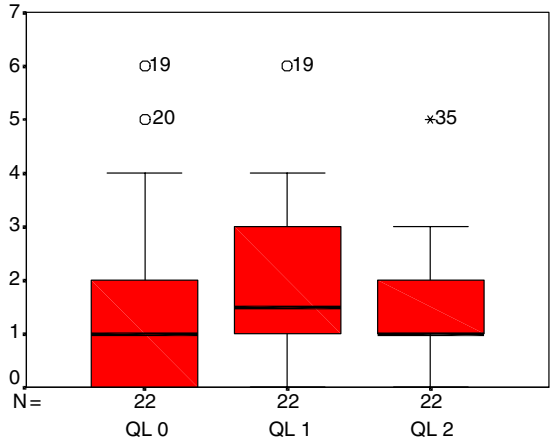
	0	I	II
III°	1	1	2
II°	0	0	1
I°	1	4	5
0	47	44	41

Fig. 1 Cumulative incontinence before HIFU (moment 0), after one HIFU (moment I) and after two HIFU (moment II), $n = 49$. *III°* stress incontinence III; *II°* stress incontinence II; *I°* stress incontinence I; continent: *0* before HIFU, *I* after one HIFU, *II* after two HIFU; + Friedman test; * marginal homogeneity test



0 vs. I vs. II	p = 0.145 +
0 vs. I	p = 0.814 *
0 vs. II	p = 0.623 *
I vs. II	p = 0.057 *

Fig. 2 Boxplots for International Prostate Symptom Score (IPSS). *IPSS 0* before HIFU, *IPSS 1* after one HIFU, *IPSS 2* after two HIFU; + Friedman test; * marginal homogeneity test



0 vs. I vs. II	p = 0.102 +
0 vs. I	p = 0.674 *
0 vs. II	p = 0.744 *
I vs. II	p = 0.003 *†

Fig. 3 Boxplots for Quality of life (QL). *QL 0* before HIFU, *QL 1* after one HIFU, *QL 2* after two HIFU; + Friedman test; * marginal homogeneity test; † not significant according to the applied closed test principle

and evaluation of incontinence is different in most of the series, making it difficult to compare data. In our unfavourable group with repetitive treatments, the amount of incontinence was still in the same range as that given for radical prostatectomy in the literature [14, 17]. Fifty-five percent of our patients who were potent preoperatively had become impotent after a second HIFU. Our study is limited by the fact that no validated questionnaire has been administered to assess impotence. So far, there is no report on a prospective series using validated questionnaires in HIFU. In the literature impotence rates are reported ranging from 30 to 61% after HIFU [9, 16]. All other observed side effects statistically occur as often after a single HIFU treatment as after a repetitive treatment. The overall risk for additional HIFU sessions in case of primary treatment failure seems to be acceptable for patients with localized prostate cancer, although our data suggest that the patient should be specifically informed about the risk of impotence and incontinence if a second HIFU is planned.

The shape of a single HIFU lesion in vivo depends on the perfusion of the gland and the specific heat capacity of the tissue [5, 6, 11]. These parameters are most likely to be different in prostates after HIFU therapy. This aspect could lead to a different efficiency and to a varying rate of side effects after multiple HIFU treatments. Another reason for a higher incontinence and impotence rate after two HIFU sessions could be due to the difficulty in defining the borders of the prostate because of the sometimes diffuse picture of the scar tissue in the transrectal ultrasound.

Conclusion

This is the first report on the cumulative adverse effects after repetitive HIFU treatments. Additional HIFU

treatments in case of primary treatment failure for patients with localized prostate cancer are associated with only a minor increase in morbidity. However, the forthcoming aim will be to lower the rate of patients with residual cancer after initial HIFU treatment by refined patient selection and more effective treatment modalities.

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