Fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localized prostate cancer

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What's known on the subject? and What does the study add?

- High-intensity focused ultrasound (HIFU) is an alternative treatment option for localized prostate cancer (PCa), which is applied for over 15 years. There are conflicting recommendations for HIFU among urological societies, which can be explained by the lack of prospective controlled studies, reports on preselected patient populations and limited follow-up providing little information on overall and cancer-specific survival.
- We report on a large, unselected consecutive patient series of patients who have undergone primary HIFU for clinically localized PCa with the longest follow-up in current literature. Our results improve the understanding of the oncological efficacy, morbidity and side effects of primary HIFU.

Objective

- To assess the safety, functional and oncological long-term outcomes of high-intensity focused ultrasound (HIFU) as a primary treatment option for localized prostate cancer (PCa).

Patients and Methods

- We conducted a retrospective single-centre study on 538 consecutive patients who underwent primary HIFU for clinically localized PCa between November 1997 and September 2009.
- Factors assessed were: biochemical disease-free survival (BDFS) according to Phoenix criteria (prostate-specific antigen nadir + 2 ng/mL); metastatic-free, overall and PCa-specific survival; salvage treatment; side effects; potency; and continence status.

Results

- The mean (SD; range) follow-up was 8.1 (2.9; 2.1–14.0) years.
- The actuarial BDFS rates at 5 and 10 years were 81 and 61%, respectively. The 5-year BDFS rates for low-, intermediate- and high-risk patients were 88, 83 and 48%, while the 10-year BDFS rates were 71, 63 and 32%, respectively.
- Metastatic disease was reported in 0.4, 5.7 and 15.4% of low-, intermediate- and high-risk patients, respectively.
- The salvage treatment rate was 18%.
- Seventy-five (13.9%) patients died. PCa-specific death was registered in 18 (3.3%) patients (0, 3.8 and 11% in the low-, intermediate- and high-risk groups, respectively).
- Side effects included bladder outlet obstruction (28.3%), Grade I, II and III stress urinary incontinence (13.8, 2.4 and 0.7%, respectively) and recto-urethral fistula (0.7%). Preserved potency was 25.4% (in previously potent patients).

Conclusions

- The study demonstrates the efficacy and safety of HIFU for localized PCa.
- HIFU is a therapeutic option for patients of advanced age, in the low- or intermediate-risk groups, and with a life expectancy of ~10 years.

Keywords

HIFU, localized, long-term, outcome, prostate cancer

Introduction

High-intensity focused ultrasound (HIFU) is an alternative treatment option for localized prostate cancer (PCa). There are two HIFU systems currently marketed, the Ablatherm™ (EDAP-TMS, Vaulx-en-Velin, France) and the Sonablate™ (Focus Surgery Inc., Indianapolis, IN, USA). Over the last 15 years, >25 000 HIFU PCa treatments have been performed worldwide. Although there is a growing number of publications reporting on good cancer control and moderate side effects with primary HIFU [1–4], recommendations for HIFU are the subject of controversy among European urological societies [5]. This can be explained by the lack of prospective controlled studies as well as limited follow-up, providing little information on overall and cancer-specific survival [2]. In addition, most publications on HIFU are limited by the fact that they report on a preselected patient population, which inevitably leads to a bias in the reported results. In the USA, Federal Food and Drug Administration approval will be judged on the results of a prospective trial which is under way.

The aim of the present study was to provide oncological and functional follow-up on an unselected series of patients, who underwent HIFU treatment for localized PCa over a 14-year period. This is the longest follow-up of any HIFU series in the current literature.

Patients and Methods

Patient Selection

HIFU treatment was offered to patients with clinically localized PCa who were either assessed to be unsuitable for surgery (e.g. because of advanced age or comorbidity) or if they declined to undergo radical treatment after informed consent. HIFU was also offered as an option to patients with incidental PCa after TURP. Staging for distant metastasis was performed by means of abdominal/pelvic CT and bone scan in intermediate- and high-risk patients. Patients with a minimum gap of 2 years since their first HIFU treatment were considered for this analysis without any further pre-selection. Patients who had undergone short-term pre-treatment androgen deprivation therapy (ADT) were not excluded. Pre-treatment ADT was not part of a neoadjuvant HIFU therapy concept but was sometimes initiated by the referring urologists in order to offer the patient safety when the treatment decision was deferred. Patients were identified as low-, intermediate- and high-risk according to D'Amico's 2003 risk group categories [6].

Treatment and Follow-Up

Ablatherm® devices were used to perform HIFU. Where prostate volume was ≤30 mL, TURP was performed immediately before HIFU to reduce prostate size, remove calcification and reduce postoperative catheterization time. With larger prostate glands (>30 mL), TURP was performed 4–6 weeks before HIFU. This protocol was initiated in 2001. All patients were assessed at 3-month intervals using TRUS, DRE and PSA measurement. For this analysis, biochemical disease-free survival (BDFS) was defined according to the Phoenix criteria (PSA nadir + 2 ng/mL) [7]. A random control biopsy was recommended at 3–6 months after treatment or in cases of rising PSA level.

Erectile function was assessed according to the ability to perform intercourse with or without medical assistance. Continence was assessed as follows: grade 1 stress urinary incontinence (SUI): loss of urine under heavy exercise requiring 0 to 1 pad per day; grade 2 SUI: urine loss at light exercise requiring >1 pad per day and grade 3 SUI: urine loss at rest.

Patients who attended follow-up visits other than at our institution were periodically contacted so that they could complete a self-administered questionnaire. This included sections on PSA, post-treatment biopsy, additional lower urinary tract interventions, salvage PCa treatment, side effects, and results of imaging.

Of the patients who failed HIFU treatment, information regarding type and sequence of salvage treatment, last PSA and metastatic status was recorded. The registration offices, family doctors and referring urologists of those patients who had died provided information on cause-specific mortality, last PSA and metastatic status.

Statistical Analysis

Statistical analysis was performed using SPSS software version 19 (SPSS Inc., Chicago, Il, USA). The t-test was used for parametric quantitative variables, and the Mann–Whitney U-test for non–parametric variables. Categorical variables (e.g. success rates at the last evaluation) were compared using the chi–squared test. Actuarial estimates for survival were calculated using Life Table methods. The log rank test was used to compare the curves based on Kaplan–Meier models. A multivariate Cox proportional hazards regression analysis was used to estimate the prognostic relevance of different clinical variables on biochemical failure as defined by the Phoenix criteria. A P value <0.05 was considered to indicate statistical significance.

Results

Patients

Between November 1997 and September 2009, 538 patients were treated for localized PCa at one institution (University of Regensburg). Patient characteristics are shown in Table 1.

The majority of patients had T1c and T2 disease with a Gleason score ≤6. The majority of patients could be classified as low- or intermediate-risk. Pre-treatment ADT was administered to 196 (36.4%) patients; in 160 (29.7%) for <6 months and 36 (6.7%) for ≥6 months, and was not continued after treatment. The mean (SD) follow-up was 8.1 (2.9) years and the median (range) follow-up was 8.3 (2.1–14) years. Only 53 (9.9%) patients were lost to follow-up.

Treatment

Patients were treated between 1997 and 2000 with the 2nd Ablatherm® prototype device, between 2000 and 2005 with the Ablatherm-Maxis®, and thereafter with the Ablatherm Integrated Imaging® device. Treatment data are shown in Table 2. Most patients underwent HIFU with the Ablatherm® Maxis device and received one HIFU session. The percentage of patients receiving two or more HIFU sessions differed between risk groups with 13.1, 26.1 and 31.9% of patients within the low-, intermediate- and high-risk groups, respectively ($P < 0.001$). In 203 (37.7%) patients HIFU and TURP were performed on the same day and in 213 (39.6%) patients, the procedures were conducted sequentially with an interval of 4–6 weeks.

Table 1 Patient characteristics.

Characteristic	
No. of patients	538
Mean (SD) age, years	67.7 (7)
Mean (SD) PSA, ng/mL	11.2 (19.7)
Mean (SD) prostate volume, mL	20.9 (9.2)
Clinical stage, *n* (%)	
pT1a	37 (6.9)
pT1b	33 (6.1)
T1c	151 (28.1)
T2	296 (55.0)
T3	21 (3.9)
Gleason score, *n* (%)	
≤6	402 (74.7)
7	88 (16.4)
8–10	41 (7.6)
Undefined	7 (1.3)
D'Amico risk group, *n* (%)	
Low	229 (42.6)
Intermediate	211 (39.2)
High	91 (16.9)
Unknown	7 (1.3)

Table 2 Treatment data.

Variable	Value
Treatment device, *n* (%)	
Ablatherm® 2nd prototype	43 (8)
Ablatherm Maxis®	355 (66)
Ablatherm Integrated Imaging®	140 (26)
Median (range) treatment time, min	154 (40–375)
Mean (SD) no. of lesions per treatment	599.6 (177.6)
Mean (SD) treated volume, mL	34.6 (14.0)
Mean (SD) treated volume ratio: treated volume/prostate volume	1.9 (0.9)
HIFU sessions per patient, *n* (%)	
1	423 (78.6)
2	111 (20.6)
3	4 (0.8)

Oncological Outcome

The mean (SD) PSA nadir was 0.4 (1.6) ng/mL (median 0.07 ng/mL), which was achieved at a mean (SD) of 19.9 (11.4) weeks after HIFU. A PSA nadir ≤0.2 ng/mL, 0.21–1.0 ng/mL and >1 ng/mL was reached by 70.8, 18.4 and 10.8% of patients, respectively. A total of 297 (55.2%) patients underwent at least one follow-up biopsy. Of these patients, 76 (25.6%) had histological evidence of cancer; incidence in the low-risk group was 20/125 (16%), in the intermediate-risk group it was 35/122 (28.7%) and in the high-risk group it was 20/50 (40%). Progression to metastatic disease based on bone scan and CT data occurred in 1/229 (0.4%) patients in the low-risk group and in 12/211 (5.7%) and 14/91 (15.4%) patients in the intermediate- and high-risk groups, respectively ($P < 0.001$).

The actuarial BDFS rates at 5 and 10 years for the whole population were 81% and 61%. The 5-year BDFS rates for patients in the low-, intermediate- and high-risk groups were 88, 83 and 48%, respectively, and the 10-year BDFS rates were 71, 63 and 32%, respectively (Fig. 1). The 5-year BDFS rates for patients with a PSA nadir ≤0.2 ng/mL, 0.21–1 ng/mL and >1 ng/mL were 91, 67 and 27%, respectively ($P < 0.001$).

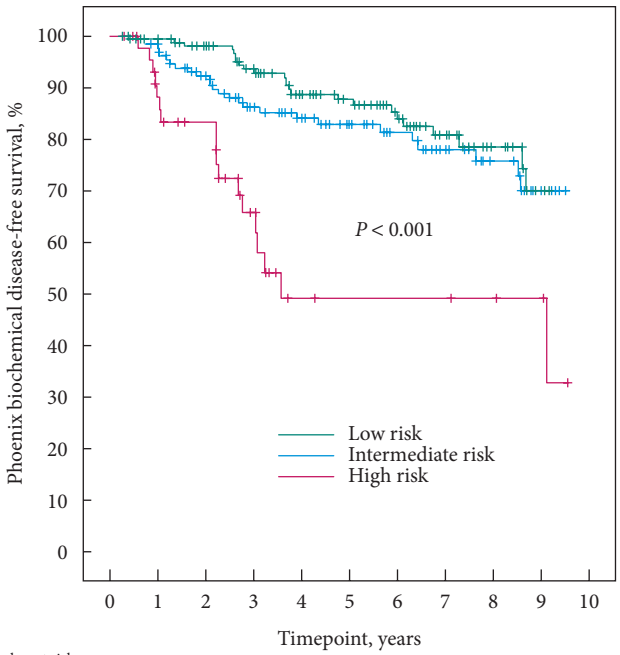
The 5-year BDFS rates were not significantly different for patients without and with pre-treatment ADT (83 vs 78%, respectively, $P = 0.236$). When patients with and without pre-treatment ADT were differentiated, the rates were 88, 45 and 19% vs 93, 77 and 30%, respectively.

In the univariate analysis, PSA nadir was found to be a significant predictor for BDFS. In the multivariate Cox regression analysis, age and a pre-treatment PSA value >20 ng/mL were significant variables for biochemical failure (Table 3).

Salvage Treatment

A total of 97 (18%) patients received salvage treatment during follow-up. Detailed description of the types of salvage treatment is given in Table 4. A significantly greater proportion of patients in the high-risk group received salvage treatment. In addition, the mean time between last HIFU and salvage treatment was significantly shorter in the high-risk group ($P = 0.003$).

Fig. 1 Kaplan–Meier estimates for 5- and 10-year BDFS for low-, intermediate- and high-risk patients.



Number at risk

Low risk	229	160	153	140	122	99	81	63	41	26	14
Int. risk	211	134	129	112	89	74	61	51	39	28	16
High risk	91	47	36	31	18	9	6	6	6	5	4

Thirteen (30.2%), 77 (21.7%) and seven (5.0%) patients who were treated with the Ablatherm® prototype, -Maxis and Integrated Imaging devices, respectively, received salvage treatment ($P < 0.001$).

The median (range) PSA at initiation of salvage treatment was 2.4 (0–277) ng/mL. At last follow-up, 20 (20.6%) patients who had received salvage treatment were diagnosed with metastatic disease compared with seven (1.6%) patients in the non-salvage treatment group.

Cause-Specific Mortality

During follow-up 75 (13.9%) patients died. PCa-specific death occurred in 18 (3.3%) patients which included none, eight (3.8%) and 10 (11%) patients within the low-, intermediate- and high-risk group, respectively ($P < 0.001$).

Safety

There was no case of peri-operative mortality. Recto-urethral fistula occurred in four (0.7%) patients, all of whom were undergoing repeat HIFU. UTIs were reported in 55 (10.2%) patients. The most frequent side effect was BOO, which was seen in 152 (28.3%) patients. The mean (SD) time between HIFU and first BOO was 1.4 (1.8) years. There was a statistically higher rate of BOO in patients after repeat HIFU compared with those undergoing one HIFU session (36.5 vs 26%; $P = 0.035$). The incidence of BOO did not decrease when TURP was conducted in conjunction with HIFU. By contrast, there was a significant difference according to HIFU device: 39.5, 30.1 and 20.0% in patients treated with the Ablatherm® prototype, -Maxis and Integrated Imaging devices, respectively ($P < 0.03$).

Six months after treatment, 93 (17.3%) patients had grade 1 SUI and 15 (2.8%) patients had grade 2 SUI. At last evaluation, 83.1% of patients were pad-free. Grades 1 and 2 SUI were reported by 74 (13.8%) and 13 (2.4%) of patients, respectively. Four (0.7%) patients had grade 3 SUI that required intervention. Of 202 patients with unimpaired pre-treatment potency outcome data were provided by 169 (83.7%) patients. Twelve months after HIFU, 43 (25.4%) were potent (intercourse without medical assistance), 67 (39.6%) were able to perform intercourse with medical assistance and 59 (35%) patients were impotent. For both continence and potency outcomes, there was no significant difference between patients treated with different HIFU devices.

Discussion

The recommendations for HIFU as an alternative treatment option for localized PCa differ among European urological societies. Although the recommendations are based on the same data, HIFU is recommended for a selected group of patients by the associations of Italy, France [8] and the UK, but it is not routinely recommended by the German and European Association of Urology guidelines [9]. Recently, Warmuth et al. [5] performed a systemic literature review to assess the efficacy and safety of HIFU in the primary and salvage setting. They considered only prospective studies with >50 patients and assessed their quality using the Recommendations Assessment, Development, and Evaluation (GRADE) approach. After identification of 20 uncontrolled studies they concluded that the available evidence on efficacy and safety of HIFU is of very low quality based on uncontrolled case series and limited follow-up. The ideal setting would be prospective randomized controlled trials with long follow-up comparing HIFU with other standard treatment options. But it is unlikely that such data will be available in the near future, therefore, it is important to get the best information possible from large patient series with long follow-up of good quality.

Most published HIFU series are limited by the fact that their follow-up is too short to provide sufficient information on oncological efficacy and cancer-specific survival. In addition, many authors perform patient selection in their retrospective publications and report only on a subgroup of their treated patients. Currently, a report

Table 3 Multivariate analysis of factors affecting biochemical failure.

Prognostic factor	Hazard ratio	95% CI	*P*
Age	1.03	0.99–1.08	0.103
Pre-HIFU PSA			
≤10 ng/mL	1	Reference	Reference
10–20 ng/mL	1.21	0.64–2.29	0.554
>20 ng/mL	3.63	1.63–8.08	**0.002**
Pre-HIFU Gleason score			
≤6	1	Reference	Reference
7	1.73	0.84–3.56	0.137
≥8	1.63	0.57–4.65	0.363
Stage			
T1	1	Reference	Reference
T2	1.25	0.65–2.41	0.510
T3	3.19	0.56–18.27	0.194
Pre-treatment ADT			
No	1	Reference	Reference
Short (≤6 months)	0.83	0.45–1.54	0.556
Long (>6 months)	1.67	0.61–4.53	0.319
Prostate volume	1.02	0.99–1.06	0.214
TURP			
No	1	Reference	Reference
Combined	0.64	0.33–1.26	0.200
Split	0.77	0.36–1.64	0.497
HIFU sessions			
1	1	Reference	Reference
≥2	0.74	0.37–1.47	0.392
HIFU device			
Ablatherm® 2nd prototype	1	Reference	Reference
Ablatherm®-Maxis	0.90	0.38–2.17	0.819
Ablatherm® Integrated imaging	2.95	1.01–8.59	**0.048**

Table 4 Salvage treatment conducted according to overall patient group and risk group sub-categories.

Variable	Total, *N* = 538–	Risk group		
		Low-risk, *N* = 229	Intermediate-risk, *N* = 211	High-risk, *N* = 91
Patients with salvage treatment, *n* (%)*	97 (18)	25 (10.9)	41 (19.4)	31 (34.0)
Mean (SD) time between HIFU and initiation of salvage treatment, years†	3.2 (2.4)	4.0 (2.7)	3.6 (2.5)	2.0 (1.5)
Type of salvage therapy, *n* (%)				
Hormone therapy	41 (7.6)	8 (3.5)	17 (8.1)	16 (17.6)
Radiation	44 (8.2)	14 (6.1)	19 (9.0)	11 (12.1)
Chemotherapy	5 (0.9)	0	1 (0.5)	4 (4.4)
Radical prostatectomy	7 (1.3)	3 (1.3)	4 (1.9)	0

*P = *0.012 low-risk vs intermediate-risk group;* P < *0.001 low-risk vs high-risk group;* P = *0.011 intermediate-risk vs. high-risk group.*
†P = *0.03 low- or intermediate-risk vs high-risk group.*

by Blana et al. [1] on 140 patients treated at two centres had a mean follow-up of 6.4 years; however, those patients with a PSA >15 ng/mL and a Gleason score >7 were excluded from that study.

Our publication has several special aspects: with a mean follow-up of 8.1 and a range of up to 14 years, the current study has the longest follow-up of any HIFU series to date. We would have been able to create a mean follow-up of 10 years by extending the minimum distance to HIFU treatment; however, we did not choose to do so, as this would have reduced our patient numbers and excluded the valid information on morbidity and early cancer control of those patients treated with the latest generation Ablatherm device.

Furthermore, the study includes all consecutive patients treated for primary PCa over a period of 14 years without pre-selection. In addition to providing follow-up data from 90.1% of all patients, we made an effort to obtain all valid information on life status, metastatic status and cause-specific mortality on those patients who failed HIFU

treatment. These aspects give us more insight into the oncological efficacy and the morbidity profile of primary HIFU.

The estimation of biochemical failure after HIFU remains controversial. In the first years of HIFU treatment the initiation of salvage treatment was done individually based on positive biopsy results and PSA kinetics. Nowadays, most authors use the Phoenix criteria to define biochemical failure [1,2,10]. With the 'Stuttgart criteria' (PSA nadir + 1.2 ng/mL) an attempt was made to propose a HIFU-specific definition of biochemical failure [11], but this definition is not yet broadly accepted owing to a lack of validation [12], and the authors consider the Phoenix to be a better definition, especially if one is to compare outcomes with other published series. Using the Phoenix definition in the current study, the BDFS rates were satisfactory at 88 and 83% at 5 years and 71 and 63% at 10 years for the low- and intermediate-risk groups, respectively. Our results are consistent with those of Crouzet et al. [2] who reported 5- and 7-year BDFS rates of 83 and 75% for low-risk, 72 and 63% for intermediate-risk and 68 and 62% for high-risk patients, respectively. Although we see HIFU mainly indicated in well-informed patients of higher age and low-to-intermediate risk, 91 (16.9%) patients in our series at high risk were selected for treatment based on patient preference or comorbidity. The BDFS rates in this group were acceptable at 48% at 5 years but were lower at 32% at 10 years. These numbers suggest that HIFU should not be recommended as a first-line option to high-risk patients with a life expectancy of 10 years. The fact that patients with high PSA values are not safely treated with HIFU is supported by our multivariate analysis. Among eight tested parameters, a PSA >20 ng/mL was an independent variable affecting biochemical recurrence. Neoadjuvant ADT did not affect biochemical recurrence, a finding recently confirmed by Fujisue et al. [13]. The fact that the Integrated Imaging device had an adverse effect on biochemical outcome in the multivariate analysis (Table 3) can be explained by the fact that the follow-up in this group was shorter; therefore, the rate of censored data is much higher in the Integrated Imaging group, leading to worse results.

Although follow-up biopsies were recommended to all patients in the early part of the study, later it was mostly performed for cause in patients with suspicious local or recurrent disease. In the current study, 55.2% of patients underwent follow-up biopsy with a resultant positive rate of 25.6%. This compares with a negative biopsy rate of between 51 and 96% based on a review by Rebillard et al. [8].

Without prospective comparative trials it cannot be known to what degree HIFU treatment affects metastasis-free and cancer-specific survival compared with watchful waiting or standard treatment methods. This is a limitation of most PCa treatment options as only radical prostatectomy has been prospectively investigated in this setting [14]; however, the present results underline the oncological efficacy for low- and intermediate-risk patients with a life expectancy of 10 years as cause-specific survival rates were 100 and 96.2% and metastasis-free survival rates were 99.6 and 94.3% for the low- and intermediate-risk groups, respectively. These results are very similar to a series of 1062 patients who underwent external beam radiotherapy reported by Zelefesky et al. [15] where metastasis-free survival at 8 years was 93% and PCa-specific death rates for low- and intermediate-risk patients were 0 and 4.5%, respectively. The lack of comparative studies does not allow a comparison of the outcomes of HIFU and cryotherapy of the prostate. Bahn et al. [16] presented a cryotherapy series of 590 patients with a mean follow-up of 5.4 years. According to ASTRO criteria, the actuarial 7-year BDFS rates were 92, 89 and 89% for low-, intermediate- and high-risk patients, respectively.

The salvage treatment rate of 18% in the present study was relatively low when indirectly compared with the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database, which reported recurrent disease in 587/935 (63%) patients after external beam radiotherapy at a mean time of 38 months [17]; the patient population is not directly comparable with that of the current study, as 45% of patients were classified as high risk in the CaPSURE database. In terms of the side effects of HIFU, a complete continence rate of 86.2% at last evaluation supports favourable continence results. By contrast, an impotence rate of 35% 12 months after HIFU with only 25.4% being fully potent does not support the assumption that full-gland HIFU will preserve potency to a high degree. It may be that preservation of erectile function in patients of advanced age is not of paramount importance, as illustrated by the fact that only 202 (37.5%) of our treated patients claimed to be potent prior to treatment. Higher potency rates have been reported when a nerve-sparing approach has been used. Shoji et al. [18] described potency rates of 52, 63 and 78% at 6, 12 and 24 months, but it is our opinion that attempts to spare the neurovascular bundle with HIFU may undertreat the peripheral zone and that such approaches should only be offered within well-conducted trials of focal therapy.

The most common complication after HIFU is the development of BOO [19,20]. There was a trend towards a lower BOO rate reported if TURP and HIFU were separated by an interval >3 months. Although this is contradicted by Netsch et al. [20] who reported rates of 34 and 18% when the interval was 0 or 2 days and >1 month, respectively. Notably, the BOO that occurs can be treated safely by transurethral incision.

The present study has several limitations. They include the fact that this is a single-arm study without comparison with another standard treatment option and that validated questionnaires for continence and potency were not included until 2007 (data not reported). A major limitation is the low number of 55.2% of patients that underwent a post-HIFU biopsy as well as the fact that we could not make a distinction between patients who underwent routine biopsy and those who were biopsied for a rising PSA level. In addition, three different generations of the Ablatherm® device were used, which might influence the results. Comorbidity was not assessed systematically with a scoring system such as the Charlson comorbidity index.

In conclusion, we report on a large consecutive patient series after primary HIFU for clinically localized PCa with the longest follow-up in current literature. Our results improve the understanding of the oncological efficacy, morbidity and side effects of primary HIFU. The study underlines that HIFU is a therapeutic option for patients of advanced age, at low-to-intermediate risk and with a life expectancy of ~10 years. The rate of serious side effects such as recto-urethral fistulae is low. Before treatment, patients need to be informed about the high rate of BOO. Although continence results are favourable, whole-gland HIFU does not seem to be associated with potency results superior to standard treatment options. The current follow-up is too short to provide evidence that primary HIFU is an oncologically safe treatment option for young patients.

Conflict of Interest

Andreas Blana is a paid consultant for EDAP-TMS.

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Abbreviations: HIFU, high-intensity focused ultrasonography; PCa, prostate cancer; BDFS, biochemical disease-free survival; ADT, androgen deprivation therapy; SUI, stress urinary incontinence; CaPSURE, Cancer of the Prostate Strategic Urological Research Endeavor.