Original Article

Whole-Gland Salvage High-Intensity Focused Ultrasound Therapy for Localized Prostate Cancer Recurrence After External Beam Radiation Therapy

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BACKGROUND: Whole-gland high-intensity focused ultrasound (HIFU) has been used as salvage therapy for local recurrence following external beam radiation therapy for decades. This article describes the use of the Sonablate 500 HIFU system in the salvage setting. **METHODS:** An evaluation was performed of a consecutive group of men with biochemical failure after external beam radiation therapy with histologically proven local recurrence and bone-scan and pelvic magnetic resonance imaging to exclude macroscopic metastases, and who chose to have whole-gland salvage HIFU (Sonablate 500) at 2 centers (3 expert HIFU surgeons at each center). The modified Clavien system was used to categorize adverse events and validated questionnaires for functional outcomes. Progression following HIFU treatment was defined as ASTRO-Phoenix criteria (prostate serum antigen [PSA] >nadir+2 ng/mL) and/or a positive biopsy and/or start of hormone therapy. **RESULTS:** Eighty-four men underwent whole-gland salvage HIFU (2004-2009). Median age, pretreatment serum PSA, and biopsy Gleason score was 68 years (range, 64-72 years), 4.3 ng/mL (range, 1.9-7.9 ng/mL), and 7 (range, 6-7), respectively. Mean follow-up was 19.8 months (range, 3.0-35.1 months). After salvage HIFU, 62% of the men were pad-free and leak-free. Mean International Index of Erectile Function-5 point score fell from 8.8 to 4.7 ($P < .001$). International Prostate Symptoms Score and RAND-SF36 scores were not affected. Two men developed rectourethral fistulae after 1 salvage procedure. A further 2 fistulae occurred in the 6 men undergoing a second salvage HIFU. Intervention for bladder outlet obstruction was needed in 20% (17 of 84 patients). If PSA nonresponders were included, 1- and 2-year progression-free survival rates were 59% (50 of 84 patients) and 43% (36 of 84 patients), respectively. If PSA nonresponders were excluded, 1- and 2-year progression-free survival rates were 62% (48 of 77 patients) and 48% (37 of 77 patients), respectively. **CONCLUSIONS:** Salvage whole-gland HIFU is a high-risk procedure. Although its use in early cancer control is promising, strategies to better identify metastatic disease prior to salvage therapy and reduce local toxicity are needed to improve on this. ***Cancer*** **2012;118:3071-8.** © *2011 American Cancer Society.*

Men who have external beam radiation therapy (EBRT) for clinically localized prostate cancer have a 20% to 63% chance of experiencing biochemical failure.[1-4] Salvage prostatectomy, cryosurgery, brachytherapy, and high-intensity focused ultrasound (HIFU) have been applied for localized recurrence after EBRT, with varying rates of genitourinary and bowel complications and biochemical disease-free rates.[5-7] In fact, most men (up to 92%) actually receive systemic androgen deprivation therapy,[8,9] and this has well-reported adverse effects.[10] Table 1 provides a summary of the efficacy and toxicity that result from current standard salvage therapies.

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Table 1. Summary of Current Modalities Used in Salvage Therapy for Radiorecurrent Prostate Cancer

Modality	No. of Studies	Total No. of Patients	Mean Follow-Up, Months (Range)	Disease-Free Survival[a]	Incontinence	Stricture	Perineal Pain	Rectal Toxicity (Grade 3-4) or Rectal Injury	Rectourethral Fistula
Surgery	14	531	43 (2-92)	55% (50%-60%)	40% (0%-67%)	24% (0%-30%	NA	5% (0%-10%)	NA
Brachytherapy	10	255	42 (19-64)	62% (34%-89%)	7.9% (0%-31%)	NA	NA	6.3% (0%-24%)	3.4% (0%-12%)
Cryotherapy	8	473	24 (12-82)	45% (18%-77%)	36% (6.5%-95%)	17% (0%-55%)	36% (5.6%-44%)	NA	2.6% (0%-11%)
HIFU	2	102 (71,31)	10 (7, 14.8)	38%, 71%	7%, 6.5%	17%, 36%	NA	NA	6%, 3%-6%

Abbreviations: HIFU, high-intensity focused ultrasound; NA, not available.
[a] A variable number of definitions are used.

Although HIFU has demonstrated varying outcomes in the primary setting,[11-13] it is at an earlier phase of health technology assessment. We report on whole-gland salvage HIFU data from 2 centers.

MATERIALS AND METHODS

Institutional review board exemption was granted. Between 2004 and 2009, 84 men received salvage whole-gland HIFU treatment using the Sonablate 500 device (Focus Surgery, Inc., Indianapolis, Ind) following biochemical failure after EBRT (44 in London, Ontario, Canada; 40 at University College London, UK). A proportion of the UK group have previously been reported in 2008 as a feasibility study that had short follow-up of mean 7.4 months in 31 men.[14] Three HIFU surgeons per center, who are experts in delivering treatment for primary disease, carried out the treatments; those surgeons on learning curves for primary HIFU were excluded from conducting these treatments. There were a number of software updates to the Sonablate 500 during this period, and these were incorporated into this study in a pragmatic fashion with ongoing technological development.

Patient Selection

Very limited data was available from referring physicians regarding the pre-EBRT disease characteristics and the radiation dose used. All men underwent histological verification of locally recurrent disease as well as cross-sectional imaging (multiparametric magnetic resonance imaging [MRI; T_2-weighted, diffusion weighted, dynamic contrast-enhanced] or pelvis computed tomography scan) and radioisotope bone-scan to exclude macroscopic regional and distant metastases. All men had histologically proven localized cancer (radiological stage $\leq$ T3aNoMo, but excluding clinical T3a). Inclusion criteria were broad (Table 2), and no limits were placed on 1) characteristics of the original pre-EBRT disease, 2) absolute PSA level at time of HIFU treatment, 3) PSA kinetics of biochemical failure, or 4) grade of recurrent disease.

HIFU Treatment

All had a suprapubic catheter placed, which was planned to be removed 2 to 6 weeks after treatment, dependent on individual patient urethral voiding function. Men were given quinolone antibiotics after HIFU. The whole prostate was targeted, through use of a HIFU treatment protocol previously reported.[15]

Table 2. Baseline Data for Men Undergoing Whole-Gland Salvage HIFU for Localized Radiorecurrent Prostate Cancer

Characteristic	Value
Age, years (mean, interquartile range)	68.3 (65-72)
Pretreatment prostate volume, cc (mean, median, interquartile range)	25.1, 24 (19-30)
Pretreatment PSA, ng/mL (mean, median, interquartile range)	5.7, 3.8 (1.5-7.7)
Number of cores taken before HIFU (mean, median, interquartile range)	7.6, 7 (6-8)
Number of cores positive before HIFU (mean, median, interquartile range)	3.8, 3.5 (2-6)
Maximum cancer core length, mm (mean, median, interquartile range)	3, 4.2 (2-6)
Median Gleason score (range)	7 (6-7)
Receiving adjuvant hormones, % (N)	36 (30)
Receiving secondary HIFU treatment, % (N)	7 (6)

Abbreviations: HIFU, high-intensity focused ultrasound; PSA, prostate serum antigen.

Table 3. Perioperative Outcomes of Whole-Gland Salvage HIFU for Localized Radiorecurrent Prostate Cancer

Outcome	Value
Procedure time, min (mean, median)	158 (144)[a]
In-hospital stay, days (mean, median)	1.4 (1)[a]
Successful trial without catheter, %	97[a]
Dilatation of stricture (local anesthetic), %	14 (12/84)[b]
Cystoscopy and washout (general anesthetic), %	27 (23/84)[b]
Bladder neck incision/transurethral resection of necrotic tissue, %	20 (17/84)[b]
Postprocedure urinary tract infection/epididymitis, %	29 (24/84)[b]
Osteitis pubis, % (N)	1.2 (1/84)[b]
Rectourethral fistula after 1 treatment, % (N)	2.4 (2/84)[b]

Abbreviation: HIFU, high-intensity focused ultrasound.
[a] Data only available on 40 patients.
[b] Values in parentheses are no. of patients per total population.

Follow-Up Protocol

Suprapubic catheter was removed as soon as urethral voiding was adequate. Clinic visits were 3-monthly in the first year and 6-monthly thereafter with serum PSA measurements. Post-treatment biopsies were encouraged and offered to all men but many men in the UK center declined due to a stable PSA response. The UK center in addition carried out multiparametric MRI in all men in whom PSA started to rise. If the MRI results were suspicious, biopsy was carried out. Measures of functional status included validated questionnaires. These were the International Prostate Symptoms Score (IPSS), UCLA-EPIC Urinary domain to determine continence status (leak-free and pad-free, and only pad-free) and International Index of Erectile Function-5 point (IIEF-5).[16,17] Health-related quality-of-life outcomes were measured using the RAND SF36 only in Canada.[18]

Statistics

Chi-squared and Student *t* test were employed to test significance, with statistical significance determined by $P \leq .05$. Where appropriate, regression analysis was used to account for confounding. Hazard ratios were calculated for actuarial cancer control outcomes. Kaplan-Meier curves were derived for cancer control outcomes. For the purpose of this study, progression following HIFU treatment was primarily defined as a positive biopsy and/or last PSA >nadir+2 ng/mL and/or adjuvant hormone therapy (American Society for Therapeutic Radiology and Oncology [ASTRO] Phoenix criteria). Stata software (version 8) was used. PSA responders are patients in whom the serum PSA fell after treatment, ie, a PSA nonresponder is one in which the post-therapy PSA was higher than the pretreatment PSA level. If patient PSA level does not decrease following therapy, it is suggestive that the patient has metastatic rather than locally recurrent disease.

RESULTS

Baseline Demographics and Perioperative Outcomes

Data concerning hospital stay (Table 3) were incomplete (37% data returns available); 93% of men in whom length of stay was documented were found to have been discharged within 23 hours of treatment. Intervention for bladder outlet obstruction was needed in 20% (17 of 84 patients). A total of 17% had 1 additional procedure, 11% had 2 additional procedures, 5% had 3 procedures, 2% had 4 procedures, and 1% had 5 procedures. In addition, 2.4% (2 of 84 patients) developed rectourethral fistulae after 1 treatment. These occurred early in the learning curve in the first 20 cases. A further 2 men developed fistula in the group of 6 who had redo-salvage HIFU treatment. Mean prostate volume of those with a fistula was 21.3 cc (median, 18 cc; range, 12-34 cc). This value is not dissimilar to the overall cohort's mean/median prostate volume. Table 4 summarizes this data according to the modified Clavien classification.[19,20]

Functional Outcomes

Mean IIEF-5 demonstrated a statistically significantly decrease following salvage HIFU (Table 5), and although a clinically significant difference may be apparent in IPSS scores, this was not statistically significant. A total of 62% reported they were completely pad-free and leak-free. Health-related quality-of-life outcomes (RAND-SF36)

Table 4. Complications Classified According to the Modified Clavien System for Reporting Surgical Complications

Clavien Grade	Definition	Salvage Whole-Gland HIFU Rate, % (N)
1	Any deviation from the normal intraoperative or postoperative course, including the need for pharmacologic treatment other than antiemetics, antipyretics, analgesics, diuretics, electrolytes, or physiotherapy	32 (27/84)
2	Complications needing only the use of intravenous medications, total intravenous nutrition, or blood transfusion	12 (10/84)
3a	Complications needing surgical, endoscopic, or radiologic intervention under local anesthesia	14 (12/84)
3b	Complications needing surgical, endoscopic, or radiologic intervention under general anesthesia	48 (40/84)
4a	Life-threatening complications requiring intensive care unit management: single-organ dysfunction	3.6 (3/84)
4b	Life-threatening complications requiring intensive care unit management: multiorgan dysfunction	0
5	Death of the patient	0

Abbreviation: HIFU, high-intensity focused ultrasound.

Table 5. Functional Outcomes After Whole-Gland Salvage HIFU for Localized Radiorecurrent Prostate Cancer

Questionnaire	No. Men With Available Data	Pretreatment, Mean (median)	180 Days Post-Whole-Gland Salvage HIFU	*P*
IPSS	46	8.3 (7)	11.6 (9.5)	.06
IIEF-5	43	8.6 (6)	6.2 (3)	<.001
RAND SF36	39	102.7 (103)	100.4 (100)	.03

Abbreviations: HIFU, high-intensity focused ultrasound; IIEF-5, International Index of Erectile Function 5-Point; IPSS, International Prostate Symptoms Score; RAND SF36, RAND short form (36).

showed no statistically significant difference between baseline and day 180.

Cancer Control Outcomes

Mean follow-up was 19.8 months (range, 3.0-35.1 months) (Table 6). Overall, 25% (21 of 84 patients) of the whole cohort and 43% (21 of 49 patients) of those biopsied were identified to have residual cancer on biopsy after salvage HIFU. All patients having retreatment salvage HIFU had a positive biopsy following their initial therapy with negative bone-scan and negative MRI for lymph nodes. The number of PSA responders was 77 of 84 patients (92%). If PSA nonresponders were included, 1- and 2-year progression-free survival rates were 59% and 43%, respectively. If PSA nonresponders were excluded, 1- and 2-year progression-free survival rates increased to 62% and 48%, respectively. Neither pretreatment serum PSA nor biopsy Gleason score were found to predict failure from salvage therapy. PSA nadir $\geq$0.5 ng/mL was predictive of failure (hazard ratio, 0.16; 95% confidence interval, 0.08-0.34; $P < .001$) (Table 7). The 1- and 2-year progression-free survival for patients with a PSA nadir of <0.5 ng/mL was 82% and 68%, respectively, compared to 37% and 13% for those with a PSA nadir $\geq$0.5 ng/mL (Fig. 1 and Table 6). No failures had a second different type of local salvage therapy. Failures either underwent hormone therapy or watchful waiting.

Table 6. Cancer Control Outcomes After Whole-Gland Salvage HIFU for Localized Radiorecurrent Prostate Cancer (n = 84)

Outcome	Value
Mean follow-up, days	619
Median PSA nadir, ng/mL	0.2
Mean time to PSA nadir, months	3.1
PSA response to treatment, % (N)	92 (77)
Biopsy after salvage therapy	
Number having biopsy, % (N)	60 (49)
Positive biopsy, % (N)	25 (21)
Actuarial 1- and 2-year progression-free survival (including PSA nonresponders)[a]	59% (50/84) and 43% (36/84)
Actuarial 1- and 2-year progression-free survival (excluding PSA nonresponders)[a,b]	62% (48/77) and 48% (37/77)

Abbreviation: HIFU, high-intensity focused ultrasound; PSA, prostate serum antigen.
[a] PSA nadir plus 2 ng/mL or positive biopsy or initiating hormone therapy.
[b] n=77

We compared the PSA nonresponders to those that had a PSA response. The numbers in the former group were small (n = 7), so these comparisons are unlikely to have sufficient power to detect real differences (Table 8).

As expected, the recurrence rate at 1 year was significantly higher in the PSA nonresponders compared to those that had a PSA response after salvage HIFU. However, given that PSA is used to define recurrence together with a positive biopsy this is not surprising. There was a trend not to biopsy PSA nonresponders, likely due to clinicians thinking that such men had micrometastatic disease and unlikely to benefit from further local salvage therapy. There may be a trend toward higher volume cancer prior to therapy in those patients who are PSA nonresponders.

Table 7. Determinants of Outcome Following Whole-Gland Salvage HIFU Therapy for Localized Radiorecurrent Prostate Cancer

Characteristic	Hazard Ratio (95% Confidence Interval)	*P*
Pretreatment PSA, ng/mL		
<5.0	1.00	.87
5.0-10	1.24 (0.52-2.96)	
>10	1.02 (0.46-2.28)	
Gleason score		
6	1.00	.59
7	1.50 (0.65-3.49)	
>7	1.26 (0.38-4.14)	
PSA nadir, ng/mL		
>0.5	1.00	<.001
≤0.5	0.16 (0.08-0.34)	

Abbreviation: HIFU, high-intensity focused ultrasound; PSA, prostate serum antigen.

DISCUSSION

Summary of Results

Whole-gland salvage HIFU therapy for presumed localized recurrence after external beam radiotherapy prostate cancer appears to have encouraging short-term cancer control rates with up to 66% and 48% progression-free survival at 1 and 2 years of follow-up, respectively. In this high-risk population, 62% were leak-free pad-free continent, erectile function scores decreased significantly, but there was no impact on overall health-related quality-of-life outcomes. The rectourethral fistula rate after 1 treatment was 2.4%, but 33% after a redo-salvage procedure.

Limitations

Prior to discussing the clinical implications of these results, it is important to detail the limitations of our study. First, the series combines data from 2 centers. It is likely that there were unknown factors in patient selection, work-up and intervention between each center that may have affected the outcomes. However, we believe that

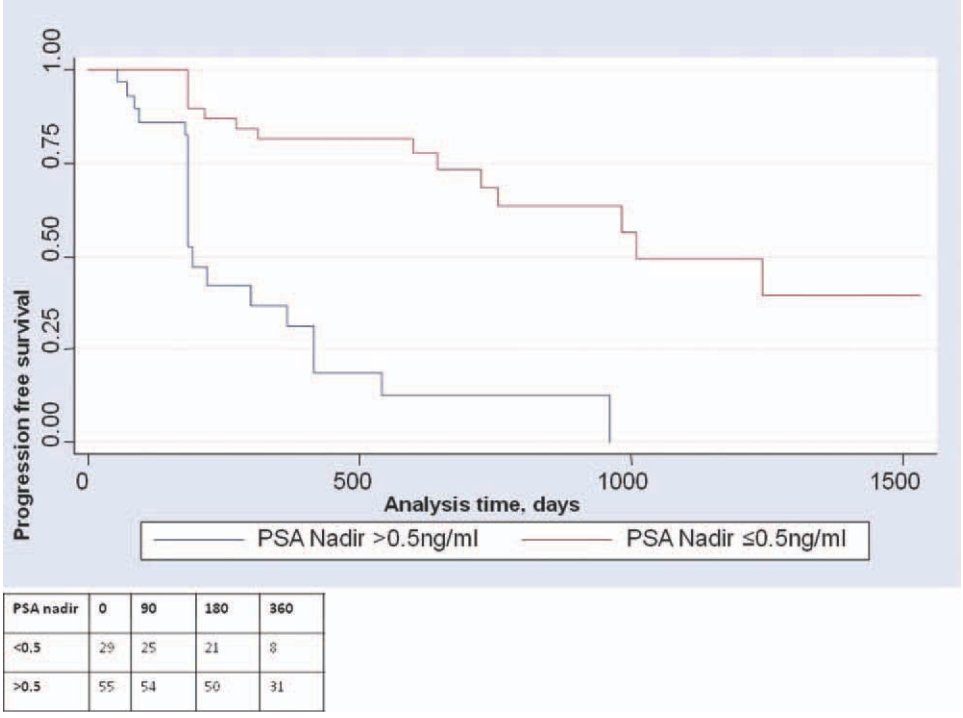

Figure 1. Kaplan-Meier curves are shown that compare the impact of PSA nadir on biochemical progression-free survival.

Table 8. Comparison of PSA Nonresponder Group With PSA Responders Following Whole-Gland Salvage HIFU Therapy

Characteristic	PSA Responder	PSA Nonresponder	*P*
N	77	7	–
Mean age	68.5	68.2	0.43
Mean pretreatment PSA, ng/mL	5.8	4.3	0.28
Biopsy Gleason score ≥7	49%	43%	0.74
Neoadjuvant hormone use	36%	29%	0.67
Mean number of positive biopsy cores	3.2	4.8	0.16
Post-treatment biopsy	62%	33%	0.17
Positive post-treatment biopsy	25%	29%	0.82
Radiological T3 stage	55%	50%	0.82
Recurrence at 1 year	70%	21%	<0.001

Abbreviation: HIFU, high-intensity focused ultrasound; PSA, prostate serum antigen.

the strength of our study is the improvement in external validity that is achieved.

Second, approximately one-third of men were started on androgen suppression at the time of referral to us. We required that men stop hormone therapy from the time of first being evaluated but accept this adds significant confounding to our cancer control outcomes. When the effect of hormones before salvage HIFU were evaluated, we found no statistical difference in the failure rates between those that did and those that did not receive androgen suppression pretreatment ($P = .85$). Failure rates at 1 and 2 years were 69% versus 64% and 35% versus 54%, respectively for those that did and those that did not receive hormones, respectively. In addition, there was no statistically significant difference in the pre-therapy biopsy positive rate or Gleason score in those receiving and those not receiving neoadjuvant hormone therapy ($P = .40$). The neoadjuvant hormone group had a slightly lower pretreatment PSA 3.9 ng/mL versus 6.7 ng/mL ($P = .04$). Patient receiving neoadjuvant hormone therapy had significantly larger pretreatment prostate volumes suggesting the reason for therapy may have been gland shrinkage rather than disease control although with the numerous referrers this was difficult to determine.

Third, perioperative outcome data were available in only a subset of patients. We accept that this may have underestimated the perioperative outcomes reported, but believe we have minimized this error by reporting the percentages of complications using the denominator as the number of men in which the data was available. We have attempted to look at this whether there were differences in those that had perioperative data versus those that did not. Perioperative outcomes (Clavien system) complications were generated from the UK cohort as data were only available on these patients. Obviously, the therapy was performed by 2 different units, and as such the rate of adverse events may have been different for those patients not included in the presented analysis. This could clearly be a confounder. Comparing the characteristics of patients undergoing therapy in the UK cohort with those of the Canadian cohort, the Canadian patient group had a slightly higher pretreatment Gleason grade, a lower pretreatment serum PSA. There was no statistical difference in retreatment rates (5% versus 10%), and PSA nadirs were similar if nonresponders were excluded. The Canadian group were much more likely to have a posttreatment biopsy, but this biopsy was done at 6 months, which falls outside the 90-day period in which complications of treatment according to the Clavien system are reported. Furthermore, there was no difference in pretreatment neoadjuvant hormone therapy (38% versus 34%). Data concerning energy use and conduct of therapy is not available.

Finally, the validity of using ASTRO-Phoenix criteria for failure may be questioned. Because there are no definitions of biochemical failure for this intervention in the salvage setting, we used ASTRO-Phoenix because men referred for salvage therapy will have failed by such criteria. Again, we have reported other cancer control outcomes in an open manner to mitigate this limitation. Furthermore, we were unable to collate precise preradiotherapy patient features, because these men were tertiary referrals with original disease diagnosed many years prior to referral, and referring physicians were unable to give details. This prevented us from evaluating the impact of the original disease on salvage outcomes.

Clinical Implications

Patients experiencing biochemical recurrence following radical EBRT may have either a local recurrence,

metastatic disease, or both. Patients thought to have localized recurrence after EBRT have historically been offered androgen ablation therapy, radical prostatectomy, or observation. These strategies can lead to significant local or systemic side effects, so other modalities such as cryotherapy and brachytherapy have recently been investigated as salvage modalities. These demonstrate varying degrees of success and toxicity. In summary, surgery, brachytherapy, and cryotherapy had cancer-control rates of 31% to 83%, 20% to 89%, and 18% to 74%, respectively (estimated 5-year biochemical disease-free status rate) (one series at 5-years, other series at 1-2 years). Incontinence rates varied with modality and were found to be 17% to 67%, 0% to 31%, and 4.3% to 96%, respectively. The rectal damage or fistula rates were 4.7%, 3.4%, and 2.5%, respectively. HIFU seems to compare favorably with these series, although the data is limited by numbers and follow-up.[21] In summary, cancer control rates of 17% to 57% have been reported from retrospective case series, with reported toxicity including rectal fistula in 0% to 16%, and incontinence in 10% to 50%.[22-26]

Our data show that a repeat salvage HIFU procedure carries a very high risk of rectal fistula and should not be recommended. These cases are difficult. Glands are stiff; ultrasound definitions of gland contour are poor due to lack of vascularity; and standard visual cues (hyperechogenicity) used in primary HIFU cases to calibrate the power levels are not seen, resulting in lower power levels applied uniformly across the whole small gland rather than a pulse-by-pulse titration as we normally carry out in primary cases.

One of the major challenges in selecting men suitable for salvage therapy is accurate locoregional staging, especially because the estimates of micrometastatic disease in this group is as much as 50%.[3] The proportion of men who fail within any published series of salvage therapy depends as much on case selection criteria as it does on ablative modality. Our entry criteria were fairly broad, but we required that men had clinically, radiologically (MRI/CT pelvis and/or positron emission tomography),[27,28] and pathologically confirmed localized recurrence with no strict restriction on PSA level, PSA kinetics, or pre-EBRT disease characteristics. Although this maximizes external validity of the study, it is likely to lead to higher rates of failure. Our hypothesis forming comparison of the low numbers of PSA nonresponders to the PSA responders may point to higher volume disease on biopsy predicting for failure, but this did not reach statistical significance. Future clinical trials with stricter inclusion criteria will need to determine the role of HIFU in an optimized setting (clinicaltrials.gov identifier NCT00772317).

In conclusion, in this high-risk group, we demonstrated that salvage whole-gland HIFU can achieve encouraging cancer control in the short term, although genitourinary and rectal toxicity is significant. Long-term follow-up, better imaging of local and distant disease prior to and after salvage HIFU, and strategies to reduce toxicity further in this high-risk group are necessary. Our data has a number of limitations, which will require a prospective multicenter medium- to long-term trial to overcome. The latter may involve avoiding transrectal biopsies, and instead using transperineal template biopsies, and a focal salvage approach[29,30] in order to limit periprostatic damage and energy deposition.

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CONFLICT OF INTEREST DISCLOSURE

Drs Emberton and Ahmed receive research funding for other clinical trials in imaging and therapy of prostate cancer from Steba Biotech (France), Advanced Medical Diagnostics SAS (Belgium), and USHIFU/Focus Surgery (USA). Dr Emberton is a paid medical consultant to Steba Biotech, Advanced Medical Diagnostics, USHIFU, and GlaxoSmithKline. Dr Ahmed is a paid medical consultant for Steba Biotech (paid into a university discretionary research account). Drs Ahmed and Emberton have both received payments to attend medical conferences from the above companies. Dr Emberton is a paid consultant to GlaxoSmithKline and holds stock rights options (unused) in Advanced Medical Diagnostics. Dr McCartan is a paid consultant for USHIFU. Drs Ahmed, Emberton, Kirkham, Freeman, and Allen have share options in Prostate Mapping, Ltd. Dr Chin has attended and has received payments for consulting services from AstraZeneca Canada, Sanofi Aventis, Paladin, Amgen, Novartis, and Johnson & Johnson. The other authors have no conflicts of interest.

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