Original Article

Focal Salvage Therapy for Localized Prostate Cancer Recurrence After External Beam Radiotherapy

A Pilot Study

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BACKGROUND: The objective of this study was to evaluate the safety, feasibility, side-effect profile, and proof of concept for focal salvage therapy using high-intensity focused ultrasound (HIFU). **METHODS:** A registry-based analysis was conducted between 2004 and 2009 of 430 patients who underwent HIFU. Thirty-nine patients received focal salvage therapy for localized recurrence after external beam radiotherapy. Multiparametric magnetic resonance imaging studies combined with transperineal template prostate mapping biopsies or transrectal biopsies were used to localize disease. Validated questionnaires were used to assess functional outcomes. Biochemical failure was defined by using both Phoenix criteria (prostate-specific antigen [PSA] nadir plus 2 ng/mL) and Stuttgart criteria (PSA nadir plus 1.2 ng/mL). **RESULTS:** The mean pre-HIFU PSA level was 4.6 ng/mL. The median follow-up was 17 months (interquartile range, 10-29 months). International Index of Erectile Function-5 scores decreased from a median ± standard deviation (SD) of 18 ± 16 to 13 ± 21 at 6 months, demonstrating worsening function. Scores on the University of California Los Angeles-Expanded Prostate Cancer Index Composite Urinary domain indicate that pad-free, leak-free continence status was 64%, and the pad-free rate was 87.2% at last follow-up. One rectourethral fistula occurred and spontaneously resolved with urinary and bowel diversion. The actuarial progression-free survival rate (including PSA nonresponders) was 69% at 1 year and 49% at 2 years according to Phoenix criteria. Excluding PSA nonresponders, these rates were 74% and 58%, respectively (Phoenix criteria). **CONCLUSIONS:** The results from this study indicated that focal salvage therapy is a potential strategy for localized recurrence after radiotherapy that may reduce the harms resulting from whole-gland salvage therapies. ***Cancer*** **2012;118:4148-55.** © *2012 American Cancer Society.*

KEYWORDS: focal, salvage, high-intensity focused ultrasound, prostate cancer, external beam radiotherapy.

INTRODUCTION

Biochemical failure in men who have undergone external beam radiation therapy (EBRT) for localized prostate cancer can occur in approximately 10% to 30%.[1-3] The biochemical control rates observed are significantly better with high-dose radiation compared with conventional doses. However, most men who fail EBRT receive androgen-deprivation therapy, which can have an impact on quality of life and cardiac, metabolic, and bone health.[4,5] However, many patients have localized disease that may be suitable for local salvage therapy using surgery, brachytherapy, cryotherapy, or high-intensity focused ultrasound (HIFU). Those who undergo whole-gland salvage therapy have a significant risk of genitourinary and bowel complications, because the viability of surrounding tissues may have been compromised by previous radiation. The biochemical cancer control rates that result from these salvage therapies are on the order of 40% to 60% over 2 to 5 years follow-up.[6-8]

We previously reported our early results using focal therapy in men with primary disease.[9] Focal salvage therapy has been proposed as an alternative that may provide treatment for localized, radiorecurrent disease while reducing the impact on functional status.[10,11] Approximately 66% of men who have localized failure after EBRT can develop recurrent unifocal or

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M.E. conceived the study. H.U.A. and N.M. were responsible for data collection and were involved in data analysis. H.U.A. was responsible for production of the first draft. C.A., A.K., and A.F. were involved in providing specific radiologic and histologic expertise to the study. P.C. was responsible for data analysis. All authors were involved in article preparation and approval of the final article. M.E., P.C., and H.U.A. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. M.E. is guarantor of the study.

The first 2 authors contributed equally to this article.

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unilateral cancer, and the main site of recurrence is usually the site of the index lesion before EBRT.[12-16] By targeting this lesion with a margin of normal tissue, side effects may be reduced by minimizing collateral tissue damage with acceptable cancer control.[17-19] To test this hypothesis, we evaluated the safety, feasibility, side-effect profile, and early cancer control rates of focal salvage therapy using HIFU.

MATERIALS AND METHODS

Institutional review board exemption was granted by the local ethics committee (National Research Ethics Service [United Kingdom] approved; University College London Hospital Committee A). All patients who underwent HIFU were placed in a registry subject to our local institution governance procedures. Between 2004 and 2009, 430 patients underwent HIFU treatment using the Sonablate 500 device (Focus Surgery Inc, Indianapolis, Ind). Of these, 40 patients underwent whole-gland salvage therapy, and 39 patients underwent focal salvage therapy when they developed a biochemical recurrence after EBRT. The whole-gland cohort has been reported elsewhere.[20]

Patient Selection

All 39 men underwent histologic verification of locally recurrent disease after multiparametric (mp)-magnetic resonance imaging (MRI) studies of the prostate (T2-weighted, diffusion-weighted, dynamic contrast-enhanced, 1.5-Tesla, pelvic-phased array; Siemens, Munich, Germany). Pelvic MRI, radioisotope bone-scan, and fluorodeoxyglucose-positron emission tomography (FDG-PET) studies were used to exclude macroscopic metastases. All men had histologically proven, localized cancer (radiologic stage $\leq$T3aN0M0 but excluding clinical stage T3a). Inclusion criteria were broad with no limits placed on characteristics of the pre-EBRT cancer, PSA levels, kinetics of recurrence, or grade of recurrent disease.

Disease Localization

Disease was localized using prostate mp-MRI studies in combination with either transperineal template prostate mapping (TPM) biopsies using a 5-mm sampling frame or transrectal ultrasound (TRUS) biopsies (only if the positive cores matched the side of the MRI lesion). The latter group underwent hemiablation salvage HIFU.

Focal Salvage High-Intensity Focused Ultrasound Protocol

The principles of HIFU are described as follows: By using a cylindrical piezoelectric ceramic transducer, ultrasonic waves are generated and then focused (using either a spherical plate or a flat plate with an appropriate lens) to a target area determined by the focal length of the lens. The sound waves are transmitted to the tissues by a coupling mechanism from a transducer placed either extracorporeally or transrectally. Transrectally, this is achieved by placing the probe within a condom filled with chilled, circulating, degassed water. The dimensions of the target area are determined by the focal length of the transducer, the applied frequency, the intensity of the applied power (W/cm^2), and the duration of the shot. The lesion produced is pseudoellipsoid in shape and is referred to as the *focal zone*. Its long axis lies at right angles to the transducer and is greatest in length toward the transducer. Tissue destruction is produced by thermal, mechanical, and cavitation effects to produce a clearly demarcated region of coagulative necrosis surrounded by "normal" tissue on microscopic examination. Thermal energy comes from absorption of mechanical energy. Adequate cell kill can be produced by even short exposure (1 second) to temperatures of $\geq$60°C, which has been adopted as the minimum target temperature. In practice, this temperature is easily attained with temperatures of $\geq$80°C recorded during HIFU therapy. Cooling because of tissue perfusion in the focal zone is not a problem, because the rate of heating is greater than that of cooling when the exposure time is within a window of 3 seconds. The mechanical effects of HIFU are more complex and involve shear forces, torque, and streaming. They result in destruction through both physical and thermal means. Cavitation results from gas (bubble) formation within cells. It is caused by heat and mechanical energy deposition, causing bubbles to oscillate.

All men had a suprapubic catheter placed that was removed 2 to 6 weeks after treatment, depending on individual patient voiding. Men received ciprofloxacillin antibiotics for 7 days postoperatively. Focal salvage therapy was either hemiablation (ablation of the lobe up to urethra) or quadrant ablation (ablation of 1 half of the lobe anterior or posterior). If there was multifocal cancer, then the patient underwent index lesion ablation if the untreated areas had $\leq$1 core with $\leq$3 mm 3 + 3 disease (on TPM) and/or no lesion on mp-MRI.

Follow-Up

Clinic visits occurred every 3 months to record adverse events and serum PSA level. Validated questionnaires included the International Prostate Symptoms Score (IPSS), the University of California Los Angeles-Expanded Prostate Cancer Index Composite (UCLA-EPIC) Urinary domain, and the International Index of Erectile Function-5 point scale (IIEF-5).[21,22] A higher IPSS indicates worsening symptoms, a lower UCL-EPIC score indicates worsening symptoms, and a lower IIEF-5 indicates worsening erectile function.

Table 1. Baseline Data for Men Undergoing Focal Salvage High-Intensity Focused Ultrasound for Radiorecurrent Prostate Cancer

Characteristic	Value
Preoperative characteristics	
No. of patients	39
Age: Mean±SD, y	70.5±6.8
PSA: Mean/median [range], ng/mL	4.6/3.3. [0.02-27.9]
Pre-EBRT characteristics	
PSA: Mean/median [range], ng/mL (n=29)	24/19 [0.2-129]
Gleason score: No. of patients	
≤6	18
3+4	6
4+3	2
4+4	2
Not known	11
D'Amico risk group[a]	
Low	6
Intermediate	13
High	15
Not known	5
EBRT characteristics	
Total dose: Mean/median [range], Gy	63/64 [50-74]
No. of fractions: Mean/median [range]	29/32 [16-37]
Time from EBRT to salvage focal HIFU: Mean/median [range], y	7.2/6.5 [4-15]
Post-EBRT biopsy characteristics	
No. of patients: Mean/median	26/20
No. positive: Mean/median	4.4/4
No. with cancer (%)	40 (48.3)
Gleason score: No. of patients (%)	
6	2 (5.3)
7	32 (84.2)
≥8	4 (10.5)
Overall Gleason score [range]	7 [6-9]
Tumor classification: No. of patients (%)	
T1c-T2	25 (64.1)
T3	33.3 (20)
Unknown	2.6 (1)
Prostate volume: Mean/median, mL	26/31
Prior hormone therapy: No. of patients (%)	29 (74.4)

Abbreviations: EBRT, external beam radiotherapy; PSA, prostate-specific antigen; SD, standard deviation.
[a] Patients who were referred to the authors' center usually had data available on PSA, Gleason grade, and overall risk category but had no staging information available on pre-EBRT disease.

Our protocol required that any 2 consecutive rises in PSA were investigated using mp-MRI and further TPM. In men who had a rising PSA level and the absence of cancer in the prostate, a bone scan was obtained to determine the presence of macroscopic metastatic disease. For the purpose of this study, oncologic failure was defined according to 4 sets of criteria. The first 2 used post-therapy PSA kinetics alone (Phoenix criteria, PSA nadir plus 2.0 ng/mL; Stuttgart criteria, PSA nadir plus 1.2 ng/mL), and the third and fourth used a combination of Phoenix or Stuttgart PSA kinetics with post-therapy biopsy status and need for androgen-deprivation therapy.

Table 2. Perioperative Outcomes After Focal Salvage High-Intensity Focused Ultrasound for Radiorecurrent Prostate Cancer

Perioperative Outcome	Focal Salvage
Type of focal therapy: No. of patients	
Hemiablation	16
Focal ablation	23
In-hospital stay: Mean/median, d	1.5/1
Average no. of treatments	1.1
Procedure time: Mean/median, min	77/80
Suprapubic catheter: No. of patients (%)	32 (86)
Successful trial of void at first attempt, %	83
Postfocal salvage HIFU endoscopic procedures	
No. of procedures per patient	0.31
Local anesthetic dilatation: No. of patients (%)	1 (3)
Washout of debris: No. of patients (%)	5 (18)
BNI/resection of necrotic tissue: No. of patients (%)	3 (8)
Epididymitis/urinary tract infection: No. of patients (%)	3 (8)
Osteitis pubis: No. of patients (%)	0 (0)
Rectourethral fistula: No. of patients (%)	
After 1 salvage treatment	1 (2.6)
After redo salvage treatment	0 (0)

Abbreviations: BNI, bladder neck incision; HIFU, high-intensity focused ultrasound.

Statistics

Actuarial recurrence-free survival rates were used to report failure for all 4 criteria. All patients were censored on the date of their last follow-up appointment or at the time of death. All statistical analyses were performed using Stata software (version 8; Stata Corp., College Station, Tex).

RESULTS

Baseline Demographics and Perioperative Outcomes

Baseline demographics are summarized in Table 1, and perioperative outcomes are summarized in Table 2. Patients originally received a mean of 63 grays (Gy) in a mean of 29 fractions, and all men received conformal beam radiation therapy a mean of 7.2 years before referral for biochemical failure. Twenty men underwent mp-MRI and TPM biopsies, and 19 men underwent mp-MRI and TRUS-guided biopsies. The 1 man who developed a rectourethral fistula was managed conservatively, and the fistula resolved spontaneously after 6 months of suprapubic catheter drainage and colostomy, as confirmed on repeat serial MRI studies, urethrograms, and clinical symptoms. This man had disease with a higher risk of recurrence in a very small, 17-mL prostate, 75%

Table 3. Complications Classified According to the Modified Clavien System for Reporting Surgical Complications

Clavien Grade	Definition	No. of Patients (%)
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	3 (8)
2	Complications needing only the use of intravenous medications, total intravenous nutrition, or blood transfusion	0 (0)
3a	Complications needing surgical, endoscopic, or radiologic intervention under local anesthesia	1 (3)
3b	Complications needing surgical, endoscopic, or radiologic intervention under general anesthesia	9 (23)
4a	Life-threatening complications requiring intensive care unit management: Single-organ dysfunction	0 (0)
4b	Life-threatening complications requiring intensive care unit management: Multiorgan dysfunction	0 (0)
5	Death of the patient	0 (0)

Table 4. Functional Outcomes After Whole-Gland and Focal Salvage High-Intensity Focused Ultrasound for Radiorecurrent Prostate Cancer

Functional Outcome	Focal Salvage
Pretreatment IPSS: Mean [median]	10.1 [11]
IPSS at last follow-up: Mean [median]	13 [12]
Postsalvage change in IPSS: Mean±SD	−2.4±7.8
Preprocedure pad status: No. of patients (%)	0 (0)
Incontinence requiring pad at last follow-up: No. of patients/total (%)	5/39 (12.8)
Preprocedure incontinence: No. of patients (%)	5 (12.8)
Continence: Pad-free, leak-free at last follow-up: No. of patients/total (%)	25/39 (64.1)
Presalvage IIEF-15 score: Median±SD	18±16
Postprocedure IIEF-15 at 6 mo: Median±SD	13±21

Abbreviations: IIEF-15, International Index of Erectile Function 15-point scale; IPSS, International Prostate Symptoms Score; SD, standard deviation.

Table 5. Cancer Control Outcomes After Focal Salvage High-Intensity Focused Ultrasound for Radiorecurrent Prostate Cancer

Outcome	Median [IQR] or No. of Patients (%)
Follow-up, mo	17 [10-29]
PSA nadir, ng/mL	0.57 [0.1-2.3]
Mean time to PSA nadir, mo	4.3
Hormone therapy after salvage HIFU	16 (41)
Biopsy after salvage therapy	9 (23)
Positive biopsy	4 (44)

Abbreviations: HIFU, high-intensity focused ultrasound; IQR, interquartile range; PSA, prostate-specific antigen.

ungradeable prostate cancer on biopsy pre-HIFU with 11 of 16 cores positive, and T3b disease on MRI staging. He had received hormones pre-HIFU once biochemical failure was diagnosed. His original radiation therapy was 74 Gy 4 years before salvage HIFU for very-high-risk prostate cancer with a diagnostic PSA level of 81 ng/mL and a Gleason score of 3 + 5 on original diagnostic TRUS-guided biopsies. It is probable that very high energy levels were delivered, as needed; however, these, combined with a small gland with extensive disease that required seminal vesicle treatment, were all contributory factors. Table 3 summarizes these data according to the modified Clavien classification.[23,24]

Functional Outcomes

Functional outcomes are summarized in Table 4. Pad-free, leak-free continence status after treatment was 64%, and the pad-free rate was 87% as measured at last follow-up (UCLA Urinary Continence domain). IIEF-5 scores decreased from a median of 18 to 13 at 6 months.

Cancer Control Outcomes

The cancer control outcomes are summarized in Tables 5 and 6 and in Figures 1 and 2. A PSA response to treatment was observed in 87% of patients. Furthermore, to identify a group with poorer outcomes, we divided the cohort into those who achieved a PSA nadir <0.5 ng/mL (44%) and those who did not (56%). Of those who achieved this nadir, the 1-year, 2-year, and 3-year biochemical-free survival rates were 86%, 75% and 63%, respectively (Phoenix criteria), and 86%, 76%, and 42%, respectively (Stuttgart criteria). When a positive biopsy and the need for androgen-deprivation therapy were included in the calculation, these rates decreased to 79%, 67%, and 45%, respectively (Phoenix criteria), and 79%, 67%, and 30%, respectively (Stuttgart criteria) (Fig. 3). For those in whom the nadir was not achieved, the 1-year, 2-year, and 3-year biochemical-free survival rates were 55%, 24%, and 0%, respectively (Phoenix criteria), and 43%, 12%, and 0%, respectively (Stuttgart criteria). When a positive biopsy and the need for androgen-deprivation therapy were included, these rates decreased to 55%, 24%, and 0%, respectively (Phoenix criteria), and 43%, 12%, and 0%, respectively (Stuttgart criteria).

Two patients (5%) developed metastases, which were observed on bone scans during follow-up. The first patient received neoadjuvant hormone therapy for Gleason 7, 5-mm cancer core length, 40% core involvement, and T3 disease before HIFU. His PSA nadir was 0.61 ng/mL. The second patient had a PSA nadir of only 5.3 ng/mL after HIFU with

Table 6. Progression-Free Survival After Focal Salvage High-Intensity Focused Ultrasound for Radiorecurrent Prostate Cancer

Criteria	Progression-Free Survival Rate, %	
	1 Year	2 Years
Biochemical only: Phoenix criteria[a]		
Including PSA nonresponders	69	49
Excluding PSA nonresponders	74	58
PSA nadir <0.5 ng/mL[b]	86	75
Phoenix criteria with or without positive post-treatment biopsy, with or without initiation of hormone therapy[a,c]		
Including PSA nonresponders	62	43
Excluding PSA nonresponders	66	50
PSA nadir <0.5 ng/mL[b]	79	67
Biochemical only: Stuttgart criteria[d]		
Including PSA nonresponders	63	42
Excluding PSA nonresponders	67	49
PSA nadir <0.5 ng/mL[b]	86	76
Stuttgart criteria with or without positive post-treatment biopsy, with or without initiation of hormone therapy[c,d]		
Including PSA nonresponders	56	37
Excluding PSA nonresponders	58	43
PSA nadir <0.5 ng/mL[b]	79	67

Abbreviations: HIFU, high-intensity focused ultrasound; PSA, prostate-specific antigen.
[a] PSA nadir plus 2 ng/m/L.
[b] Forty-four percent of the entire cohort achieved a PSA nadir <0.5ng.mL.
[c] Failure was regarded as any 1 or more of these criteria.
[d] PSA nadir plus 1.2 ng/mL.

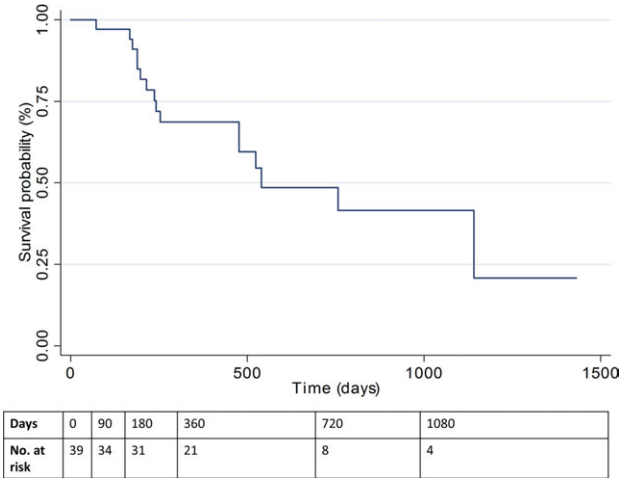

Figure 1. This Kaplan-Meier curve demonstrates biochemical progression-free survival after focal salvage high-intensity focused ultrasound therapy according to Phoenix criteria (prostate-specific antigen [PSA] nadir plus 2.0 ng/mL, including PSA nonresponders).

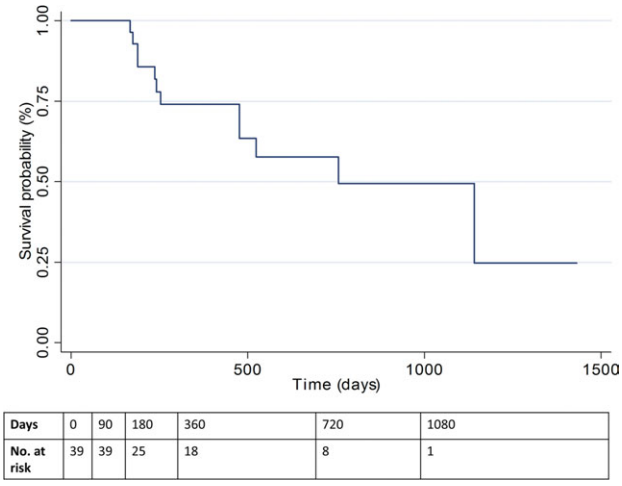

Figure 2. This Kaplan-Meier curve demonstrates biochemical progression-free survival after focal salvage high-intensity focused ultrasound therapy according to Phoenix criteria (prostate-specific antigen [PSA] nadir plus 2.0 ng/mL; excluding PSA nonresponders).

presalvage Gleason 7, 8-mm cancer, and T1c disease. He also received neoadjuvant therapy. Both patients probably had micrometastatic disease at the time of salvage treatment.

DISCUSSION

Summary of Results

Focal salvage therapy using HIFU for radiorecurrent prostate cancer is feasible and appears to exhibit a favorable balance of harms and benefits. It can be carried out as a short-stay procedure with encouraging genitourinary and bowel toxicity in the high-risk group that we studied. In the short follow-up of this study, the cancer control rates appear to be encouraging.

Limitations

Before discussing the clinical implications of these results, it is important to detail the limitations of our study. First, the series had a short follow-up. Although our primary objective was to evaluate side effects and adverse events of focal salvage therapy, we believed it was important to report the limited cancer control outcomes.

Second, approximately 50% of men underwent mp-MRI after a 10 to 12 core TRUS biopsy that was performed before referral to our center, provided these matched in terms of the positive side of salvage hemiablation. Although we accept that this may have lead to missing clinically significant disease in untreated areas, we believe that this error was very low as a result of the 95% negative predictive value of mp-MRI for clinically significant disease after EBRT indicated from our own results using mp-MRI versus TPM biopsies[25] and from the results reported by others who used mp-MRI versus wholemount pathology from salvage prostatectomy.[26] In addition, having criteria that are less restrictive may

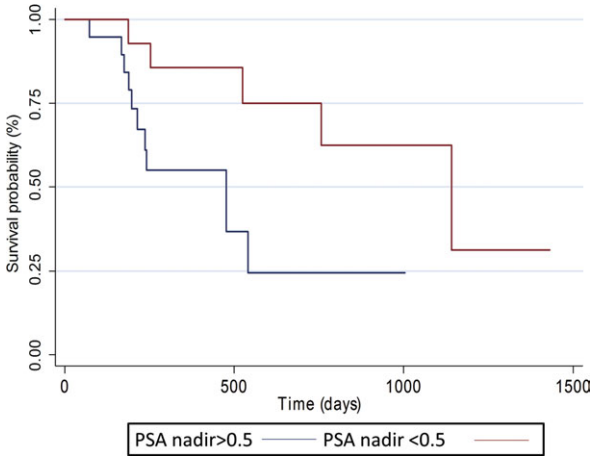

Figure 3. These Kaplan-Meier curves of biochemical progression-free survival after focal salvage high-intensity focused ultrasound therapy illustrate the effect of prostate-specific (PSA) nadir.

improve the external validity of our results, because many do not accept that TPM biopsies are needed before focal therapy.

Third, approximately 33% of men were placed on androgen suppression by referring physicians. Although we insisted that men completely stop hormone therapy from the time they were first evaluated at our unit, we accept that this is an important confounder in the cancer control rates. In fact, the use of hormones in this group may result in spurious progression, because, as men come off hormones, the testosterone and PSA levels are likely to rise, independent of the presence of cancer. This effect may be more evident in the focal setting rather than the whole-gland setting, because there is significantly more untreated tissue.

Fourth, applying Stuttgart and Phoenix criteria for failure may not be valid in a focal strategy. We decided to use these definitions in a pragmatic fashion in the absence of other validated definitions.[27] Indeed, with untreated tissue potentially secreting PSA, the opportunities for focal therapy to fail by traditional biochemical criteria are likely to be greater. Furthermore, the 3-year Stuttgart failure rates are considerably worse than the Phoenix-defined failure rates. This may have been caused by a PSA bounce after the withdrawal of androgen-deprivation therapy, although this probably is unlikely for the following reason: The failure rates with Stuttgart criteria simply may have been because Stuttgart criteria are stricter. Essentially, patients fail earlier according to Stuttgart criteria versus Phoenix criteria, but a similar number of patients fail overall. For instance, there were 16 failures according to Phoenix criteria and 18 according to Stuttgart criteria overall. Furthermore, the time to Stuttgart failure is shorter than the time to Phoenix failure (median, 225.5 days vs 239 days). It is likely that, with longer follow-up, the 2 Stuttgart failures probably also would have been failures according to Phoenix criteria.

Finally, the median radiation dose in this series was 64 Gy, which is lower than the standard doses delivered in the current era. Therefore, our toxicity data may underestimate those obtained from men who were treated on dose-escalation protocols.

Clinical Implications

The toxicity from focal salvage therapy seems to be lower that the toxicity from whole-gland salvage therapy using the same ablative modality. We reported on toxicity profiles in our whole-gland salvage series[20] using this approach. Toxicity can be evaluated by reporting Clavien complications, all of which suggest that focal salvage is a less toxic therapy than whole-gland salvage. In summary, Clavien 1 rates were 32% versus 8%, Clavien 2 rates were 12% versus 0%, Clavien 3a rates were 14% versus 3%, Clavien 3b rates were 48% versus 23% and Clavien 4 rates were 3.6% versus 0%, respectively. The rectal fistula rate was higher for whole-gland salvage at 2.6% compared with 3.6% for focal salvage.

PSA response rates appeared to be similar between whole-gland and focal salvage HIFU, although follow-up periods were different. For focal salvage, the 1-year and 2-year progression-free survival rates (Phoenix criteria) were 69% and 49%, respectively; and, for whole-gland salvage, the 2-year and 3-year progression-free survival rates were 66% and 48%, respectively.

To our knowledge, only 1 other case series has evaluated the role of focal (hemiablation) salvage cryotherapy in 19 men.[5] Of 19 men in that series, 1 developed incontinence, and stricture formation occurred in another. Those authors reported that 1 man developed a urethral ulcer, which was managed conservatively and may have been a subclinical rectourethral fistula. The cancer control rates in that focal salvage cryotherapy series used American Society for Therapeutic Radiation and Oncology criteria (3 consecutive rises in PSA above nadir); thus, it is difficult to directly compare our outcomes, which were based on Stuttgart and Phoenix criteria. However, our results do reinforce these data in demonstrating that a focal salvage approach is feasible and safe. Furthermore, the rates of genitourinary and pelvic complications appear to be encouragingly low.[8]

One of the major challenges in selecting men who are suitable for salvage therapy is accurate staging. It is estimated that up to 50% of men who fail EBRT may have distant metastatic disease.[3] The proportion of men who fail within any salvage therapy series that has been

published depends as much on case-selection criteria as it does on technique.[28] Our principal qualification, men with clinically, radiologically (MRI, bone-scan, and computed tomography/FDG-PET), and pathologically proven, localized cancer, still may miss metastatic disease.

Localization of disease within the gland is the key to facilitating focal salvage therapy. TPM appears to be the gold standard for intraprostatic detection and localization[29]; it has the added advantage that the needle does not traverse rectal mucosa, thus minimizing injury to an area that has poor tissue viability from previous radiation exposure.[30] Although, in the interim, TPM ideally should be used to histologically verify localized recurrence, mp-MRI is likely to be used increasingly for this purpose followed by targeted biopsies.[20,21]

In conclusion, focal salvage therapy using HIFU for localized recurrence after radiotherapy may have potential as a treatment option in a select group of men. This strategy may lead to less harm, although the extent to which cancer control outcomes are affected has yet to be determined. The challenges in staging remain to rule out metastatic disease and localization of cancer and to identify disease that is amenable to tissue preservation.

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CONFLICT OF INTEREST DISCLOSURES

M.E. and H.U.A. receive research funding for other clinical trials in imaging and therapy of prostate from Steba Biotech (France), Advanced Medical Diagnostics SAS (Belgium), and USHIFU/Focus Surgery (United States). M.E. is a paid medical consultant to Steba Biotech, Advanced Medical Diagnostics, USHIFU, and GlaxoSmithKline. H.U.A. is a paid medical consultant for Steba Biotech (these funds are paid into a university discretionary research account). H.U.A. and M.E. have both received payments to attend medical conferences from the above companies. M.E. is a paid consultant to GlaxoSmithKline and holds stock rights/options in Advanced Medical Diagnostics. N.M. is a paid consultant for USHIFU.

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