

The feasibility and safety of high-intensity focused ultrasound as salvage therapy for recurrent prostate cancer following external beam radiotherapy

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OBJECTIVES

To investigate the use of minimally invasive high-intensity focused ultrasound (HIFU) as a salvage therapy in men with localized prostate cancer recurrence following external beam radiotherapy (EBRT).

PATIENTS AND METHODS

A review of 31 cases treated using the Sonablate® 500 HIFU device, between 1 February 2005 and 15 May 2007, was carried out. All men had presumed organ-confined, histologically confirmed recurrent prostate adenocarcinoma following EBRT.

RESULTS

The mean (range) age was 65 (57–80) years with a mean preoperative PSA level of 7.73 (0.20–20) ng/mL. The patients were followed for a mean (range) of 7.4 (3–24) months. Side-effects included stricture or intervention for necrotic tissue in 11 of the 31 patients (36%), urinary tract infection or dysuria syndrome in eight (26%), and urinary incontinence in two (7%). Recto-urethral fistula occurred in two men, although one was due to patient movement due to inadequate anaesthesia, so the 'true' rate is 3%. Half of the patients had PSA levels of <0.2 ng/mL at the last follow-up. Three patients had metastatic disease whilst another two had only local, histologically confirmed, failure. A further four patients had evidence of biochemical failure only.

Overall, 71% had no evidence of disease following salvage HIFU.

CONCLUSIONS

Salvage HIFU is a minimally invasive daycase procedure that can achieve low PSA nadirs and good cancer control in the short term, with comparable morbidity to other forms of salvage treatment. The issue of accurate staging at the time of recurrence is still problematic, as a proportion of these men will harbour microscopic metastases undetected by conventional staging investigations.

KEYWORDS

HIFU, transrectal, prostate cancer, Sonablate 500, recurrent, radiotherapy

INTRODUCTION

Men who have external beam radiation therapy (EBRT) or interstitial brachytherapy for clinically localized prostate cancer have a 20–30% chance of having prostate-specific antigen (PSA) failure [1–3]. Salvage therapy is indicated when men treated with radiotherapy, brachytherapy, or a combination of these for presumed localized prostate cancer have a recurrence. Prostatectomy, cryosurgery, brachytherapy and high-intensity focused ultrasound (HIFU) have been used in the salvage setting [4]. The success rates after salvage procedures are considerably lower than those that have been reported after primary treatments [5]. The use of salvage HIFU has been reported using the

Ablatherm® HIFU device (Edap-Technomed, Lyon, France). That particular series reported good early results, with negative biopsy rates as high as 80%, and 61% achieving a PSA nadir of <0.5 µg/L ($n = 71$); 44% were reported as free of biochemical relapse at last review, at a mean (range) follow-up of 14.8 (6–86) months [6]. In the same series, the rate of recto-urethral fistula was 6%, with 7% having urinary incontinence (UI) requiring pads, and 17% developing a bladder neck stenosis.

HIFU relies on the physical properties of ultrasound, which allow it to be brought into a tight focus either using an acoustic lens, bowl-shaped transducer or electronic phased array. As ultrasound propagates through a

tissue, zones of high and low pressure are created. When the energy density at the focus is sufficiently high (during the high pressure phase), tissue damage occurs. The acoustic focal volume of a single exposure is small (typically 10 mm long by 1–2 mm wide, in a cigar shape orientated along the long axis of the beam), so larger volumes of ablation are created by placing numerous overlapping lesions next to each other, allowing a short period between exposures for cooling. 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. Adequate tissue necrosis can be produced by short exposure (1 s) to temperatures of ≥60 °C, so this

Variable	Value	TABLE 1
<i>Baseline demographic data for the men treated with salvage HIFU following failed EBRT</i>		
Number of patients	31	
Median (range) age, years	68 (57–80)	
Receiving hormone therapy, n (%)	18 (58)	
Recurrent disease:		
Mean (range) PSA level, ng/mL	5.7 (0.2–20)	
Gleason score, n		
≤6	5	
7	17	
≥8	5	
Unknown	4	
Stage, n		
T1c	2	
T2a	4	
T2b	3	
T2c	7	
T3a, T3b	9	
Unknown	6	

temperature has therefore been adopted as the minimum target temperature [7]. In practice, this temperature is easily attained, as levels of >80 °C have been recorded during HIFU therapy. Cooling due to tissue perfusion in the focal zone is not a problem, as the rate of heating is greater than that of cooling when the exposure time is within a window of 3 s [8].

Currently, there are two commercially available transrectal devices. The Ablatherm® device (Edap-Technomed) and the Sonablate®500 (Focus Surgery, Indianapolis, IN, USA). The Ablatherm device until very recently had separate imaging (7 MHz) and therapy transducers (3 MHz) which had a fixed focal length of 4 cm. Prostate imaging during treatment was not possible but performed between treatment zones by inserting the imaging transducer through the therapeutic transducer. The latest modification to the Ablatherm combines treatment and planning probes, so that visual feedback is possible during treatment. However, because the Ablatherm uses algorithm-driven treatment protocols with preset energy levels, individual pulse energy levels cannot be modified by the operator. Other features include the incorporation of the probe into a table, which holds the pump and cooling mechanism and upon which the patient is placed in the right lateral position. Treatment is to each lobe in turn and performed anterior to posterior. Many centres that use the Ablatherm combine TURP or

bladder neck incision to reduce gland size and urinary morbidity [9].

The Sonablate system consists of a rectal probe (containing the transducer) with an operating frequency of 4 MHz to optimize the combined imaging and therapy roles of the transducer. This has the advantage of allowing visualization of treatment effect after each pulse of the treatment cycle. Degassed water is pumped through the system and is chilled to temperatures of 17–20 °C to prevent rectal wall injury by heat build-up. Treatment planning, execution and monitoring are controlled using a user interface that allows the surgeon to precisely target the area of treatment, adjust the focal length of the transducer (currently 3 cm, 4 cm or 4.5 cm) and alter the power intensity delivered to each focal zone individually. After adequate bowel preparation, treatment is usually performed under general anaesthesia, although epidural or spinal with heavy sedation is also possible, with the patient in the lithotomy position. The anterior portion of the prostate is treated initially, followed by midzone and posterior gland. Within each zone, multiple overlapping lesions are created to enhance ablation. Using the Sonablate 500, our own group has shown that by changing power levels in a real-time fashion, so as to visualize grey-scale changes (so called 'visually directed HIFU') within each focal treatment zone, leads to significantly lower PSA levels postoperatively in the primary setting [10]. This was the first attempt at

standardizing HIFU treatment. We now report our results using the Sonablate 500 HIFU device in a salvage setting for recurrent disease that is presumed localized to the prostate.

PATIENTS AND METHODS

A review of all cases treated in two centres (University College Hospital and Princess Grace Hospital) between 1 February 2005 and 15 May 2007 was carried out. All men with presumed, organ-confined, recurrent disease following EBRT monotherapy treated with salvage HIFU were included. An analysis of the demographic characteristics as well as side-effect profiles, PSA kinetics and early oncological outcomes was carried out.

RESULTS

In all, 31 men treated with salvage HIFU using the Sonablate 500 device were included. All men referred for salvage HIFU therapy were evaluated and counselled as to possible side-effects and lack of clear data on long-term outcome. Our criteria for inclusion was that all patients had histologically confirmed recurrent disease, and confirmation of localized cancer in the gland (≤T3bN0M0) from negative bone-scans and T2-weighted, T1-weighted and dynamic contrast-enhanced MRI showing local T-stage and absence of suspicious lymph nodes. As the patients were tertiary referrals, we did not have information on radiotherapy dosage used. However, all men received EBRT in the conventional or lower dose era, which usually included fractionated doses of 66–70 Gy. In all, 18 of the 31 patients (58%) were on hormone therapy at the time of HIFU treatment, with all of these men commencing hormonal treatment (goserelin [Zoladex®] depot s.c. implants) before referral to our centre.

All men were taught clean intermittent self-catheterization before treatment, so that they were able to self-manage poor flow or pending retention of urine due to passage of debris. Table 1 summarizes the preoperative demographic data. Treatment was carried out under general anaesthesia in one session and all the patients were discharged on ciprofloxacin 500 mg twice daily for 7 days and analgesia (either diclofenac or codeine phosphate-paracetamol preparations). Bladder drainage was by means of a suprapubic catheter in most of the men and this is now our standard practice.

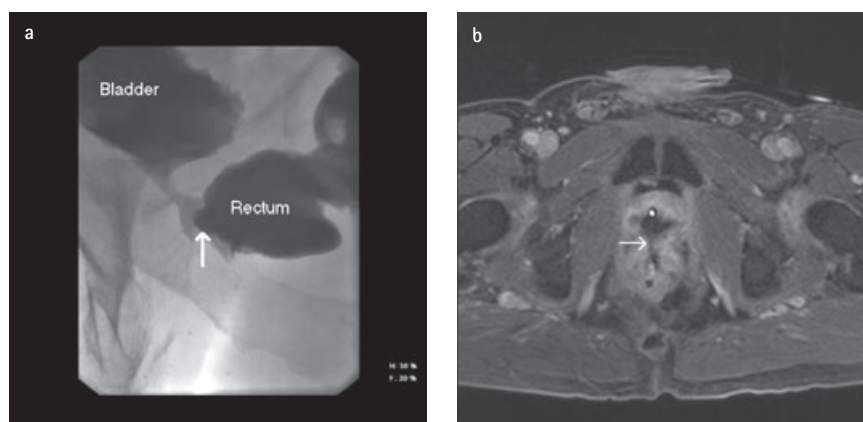
Table 2 summarizes the operative data and adverse events that occurred in the series. All cases were admitted on the morning of the procedure and mean (range) hospital stay after HIFU was 3.6 (3–6.6) h. Urethral strictures or the requirement for resection of necrotic debris occurred in 11 of the 31 patients (36%). In many of these cases, intervention for stricture such as dilatation or bladder neck incision was carried out at the same time as resection of necrotic debris, so these two adverse effects have been grouped together. UTI/dysuria syndrome and epididymitis occurred in eight (26%) and one patient (3.1%), respectively. Two patients had UI, with one having total UI requiring a sheath catheter. He is currently undergoing evaluation for artificial urinary sphincter insertion. Two men had prostatic-rectal fistulae and have been immediately defunctioned with laparoscopic colostomy and suprapubic catheterization (Fig. 1a,b). One fistula occurred in a patient who started to move during the procedure because the general anaesthetic was inadequate and although proctoscopy showed no overt damage, the HIFU procedure was continued. This fistula developed within 6 months. At last follow-up, he was undergoing evaluation for reconstructive surgery, but his PSA level remains unrecordable at 18 months of follow-up. The second patient developed a fistula within 6 months of salvage HIFU and is currently conservatively managed with a long-term suprapubic catheter and colostomy after having refused reconstructive surgery.

Table 3 summarizes the PSA kinetics and cancer control rates achieved in the present series. Overall, ≈65% achieved a PSA nadir of ≤0.2 ng/mL at 3 months and this proportion dropped to about half for those men reaching 6 and 9 months follow-up (Fig. 2a–c). If a PSA level of ≤0.5 ng/mL is used as the target level, 74% achieved this at 3 months, although all those men who had PSA levels at 3 months of 0.21–0.5 ng/mL (three of 31) had evidence of biochemical failure at 6 months and 9 months. In other words, the proportion remaining at a PSA level of <0.5 ng/mL was the same group who had PSA levels below 0.2 ng/mL. A rising PSA occurred in 10 patients (32%) and these men were further evaluated for local and metastatic failure. Biopsy was carried out in six of them and revealed local recurrence in two (7%) (Fig. 3a,b). Bone-scan revealed definitive metastatic disease in two (7%) and MRI (1.5 T, T2-weighted and dynamic gadolinium-

TABLE 2 Operative factors and complications in men treated with salvage HIFU following failed EBRT

Variable	Value
Mean (range):	
Discharge time after HIFU, h	3.6 (3–6.6)
Follow-up, months	7.4 (3–24)
Catheterization time, days	13 (7–30)
N (%):	
Catheter:	
Urethral	4 (13)
Suprapubic	27 (87)
Dilatation for stricture:	
Local anaesthesia	4 (13)
General anaesthesia	2 (7), requiring two procedures
Bladder neck incision for stricture	2
Dilatation and bladder neck incision	1 requiring two procedures
Dilatation and bladder neck incision	5 (16)
Requiring intervention for stricture/necrotic tissue:	11 (36)
1 intervention	4 (13)
2 interventions	4 (13)
3 interventions	2 (7)
4 interventions	1 (3)
UTI/dysuria syndrome	8 (26)
Epididymitis	1 (3)
UI:	2 (7)
Stress (no pads)	1 (3)
Total (sheath catheter)	1 (3)
Fistulae	2 (7)

FIG. 1. **a**, Urethrogram showing contrast entering the rectum through a prostate-rectal fistula in a man following salvage HIFU treatment for failed EBRT. **b**, Axial dynamic gadolinium-enhanced MRI at 1 month showing the fistula. There is an obvious connection between the prostatic cavity and the rectum. The prostate itself shows complete necrosis with surrounding secondary inflammatory enhancing the reaction.



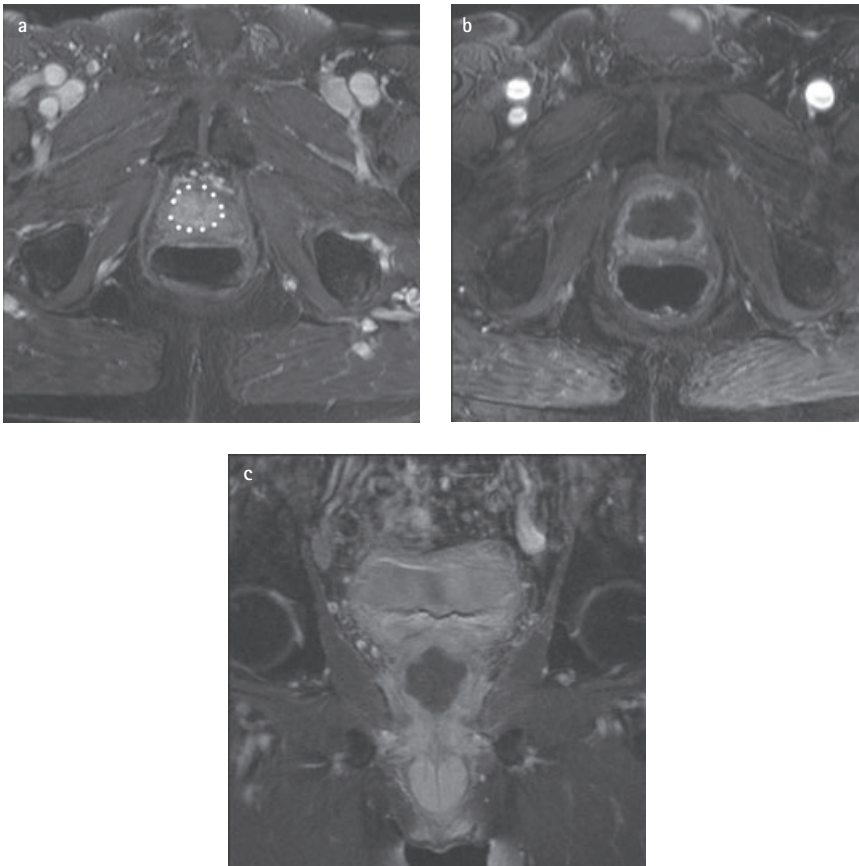
enhanced) revealed positive lymph nodes in another patient (3%). One of these patients had unrecordable PSA levels until 18 months follow-up. In summary, 7% of patients had evidence of local failure with a further 10% showing evidence of metastatic disease after

salvage HIFU. Two of these failures were in the group of patients who did not achieve a PSA nadir of <0.2 ng/mL. In addition, a further five patients had a PSA level of >10 ng/mL with four showing evidence of biochemical failure consistent with metastatic disease (13%).

TABLE 3 Early cancer control in men treated with salvage HIFU following failed EBRT

Variable	Number (%) of patients at follow-up at			Total number of men (%)
	3 months n = 31 (100)	6 months n = 22 (71)	9 months n = 12 (38)	
PSA level, ng/mL				
<0.05	14 (45)	10 (46)	6	
≤0.2	20 (65)	10 (46)	6	
0.21–0.5	5 (16)	0	0	
≤0.5	23 (74)	10 (46)	6	
>0.5	8 (26)	12 (55)	6	
Local recurrence (positive biopsy)				2 (7)
Metastatic disease on follow-up:				
Bone scan +ve				2
MRI lymph node +ve				1
Total				3 (10)
Rising PSA consistent with metastatic disease (negative biopsy, but negative bone scan)				6 (19)

FIG. 2. **a**, Axial dynamic gadolinium-enhanced MRI showing localized recurrent prostate cancer in the anterior apical area (enhancing area outlined) following EBRT before salvage HIFU. **b**, Axial dynamic gadolinium-enhanced MRI showing complete necrosis (no enhancement) of the prostate at 2 weeks after HIFU with some treatment outside the gland on the left and an enhancing ring typically seen after HIFU treatment. The PSA level dropped to 0.05 ng/mL with no hormonal ablation. **c**, Coronal dynamic gadolinium-enhanced MRI showing complete necrosis of the prostate at 2 weeks after HIFU in the same man.



Therefore, in this salvage HIFU cohort series there was 'no evidence of disease' in 71% (22/31) at last follow-up.

DISCUSSION

Patients with biochemical recurrence following radical EBRT may have either a local recurrence, metastatic disease, or both. Patients thought to have a localized recurrence after EBRT have historically been offered radical prostatectomy, androgen ablation therapy, or observation. These therapies are not without significant side-effects, so other methods such as cryotherapy and brachytherapy have recently been investigated in this setting. These methods show varying degrees of success and toxicity that are aptly summarized in a recent systematic review by Nguyen *et al.* [5]. They reported that surgery, brachytherapy and cryotherapy had a cancer-control (estimated 5-years biochemical disease-free status rate) rate of 31–83%, 20–89%, 18–74% (one series at 5-years, other series at 1–2 years), respectively. However, the average fistula rates were 4.7%, 3.4% and 2.5%, respectively. UI rates varied with the method used and were 17–67%, 0–31%, 4.3–96%, respectively. Our own series and data from one other published series using the Ablatherm device seems to compare favourably with these other modalities, although clearly the lack of 5-year follow-up data is a key limitation.

The use of salvage HIFU has been reported previously using another device (Ablatherm®, Edap) in 71 patients with a mean (range) follow-up of 14.8 (6–86) months. That series reported good early results. The toxicity rate was good with recto-urethral fistula in 6%, 7% had UI requiring pads, and 17% developing a bladder neck stenosis. In that report, negative biopsy rates were as high as 80%, with 61% achieving a PSA nadir of <0.5 µg/L; 44% were reported as free of biochemical relapse at last review (defined using the old ASTRO criteria for failure of three consecutive rises in PSA level) [6]. Reflecting upon what we found in our series, nine of 71 patients (13%) had metastatic disease within the follow-up period and four patients died of metastatic disease. This demonstrates the problem regarding the accurate staging of men who present with recurrent disease after primary treatment.

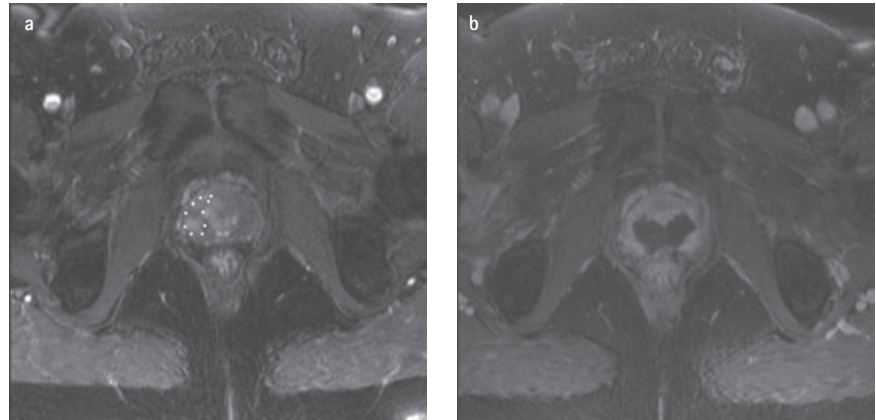
The morbidity in the present series is comparable; two of the 31 patients (7%)

developed fistulae within 6 months indicating the high risk of this catastrophic event in this group of men who have poor tissue viability and poor peri-prostatic blood supply affecting effective tissue repair. However, one of these cases was probably not directly related to the HIFU treatment with a reasonable assumption that inadequate anaesthetic lead to rectal mucosal damage. So, the true rate of prostate-rectal fistula is probably $\approx 3\%$. In addition, 36% required intervention for stricture or necrotic tissue or as in many cases, both of these adverse effects were present in the same patient. It was indeed difficult to differentiate from case notes whether a man had intervention for a stricture or necrotic tissue and these were therefore combined. Nonetheless, this rate is clearly higher than in our primary HIFU series in which only 20% of men with suprapubic catheters required intervention for stricture or necrotic tissue [11]. The cause of strictures after HIFU is unknown. Usually, after primary HIFU treatment, almost all men pass debris. In salvage cases, the poor blood supply may affect the inflammatory response causing poor debridement of necrotic tissue and the formation of strictures. Additionally, the infection rate of $\approx 26\%$ in the present series seems high. We recognize that several of these men had symptoms of dysuria commonly seen after HIFU therapy that were empirically started on antibiotics without evidence of bacteriuria on urine culture.

We have shown that $\approx 71\%$ of men treated using the Sonablate 500 HIFU device had no evidence of disease after a mean follow-up of 7 months. Of those reaching 6 and 9 months follow-up, half achieved and maintained a PSA nadir of <0.2 ng/mL. Although 74% at 3 months achieved a PSA level of <0.5 ng/mL, those men who did not achieve a level of <0.2 ng/mL had biochemical failure at subsequent follow-up. This may indicate that 0.2 ng/mL, as with other modalities such as prostatectomy in the primary setting, may be used as a standard for indicating successful outcome after salvage HIFU therapy. Such a finding is hypothesis generating and will clearly need verification in larger, long term outcome studies.

There are several limitations in the present data. First, as most of our patients were tertiary referrals, many (58%) were referred on hormonal ablation therapy. Hormonal therapy was stopped on the day of treatment, but we accept that the effect may still affect

FIG. 3. **a**, Axial dynamic gadolinium-enhanced MRI showing localized recurrent prostate cancer in the right side (enhancing area outlined) following EBRT before salvage HIFU. **b**, Axial dynamic gadolinium-enhanced MRI showing incomplete necrosis with residual enhancing tissue in the anterior and lateral edges of the prostate at 2 weeks after HIFU. Following salvage HIFU this man's PSA level increased to 20 ng/mL and was shown to have local recurrence on biopsies at 9 months.



PSA kinetics several months after salvage HIFU. Interestingly, half of the men who had biochemical failure after salvage HIFU (five of 10 men) were on hormonal therapy. The evidence for use of neoadjuvant hormonal therapy is far from conclusive in the salvage setting. Some have shown no reduction in positive surgical margins if men are placed on hormonal ablation before salvage surgery, whilst others have shown some benefit in reducing this adverse outcome, as well as having a greater biochemical disease-free survival with the addition of androgen blockade [12–15]. Clearly, the lack of a positive effect from neoadjuvant hormones may simply indicate their use in higher risk men who are prone to higher rates of failure. The evidence is limited due to the nature of retrospective analyses and lack of randomised trials.

Second, due to the nature of our referrals, the disease characteristics before EBRT were not available for most of the men and we were therefore unable to ascertain whether there was a relationship between those that failed and disease characteristics such as Gleason grade, PSA level and stage before EBRT. It has been shown that men with an initial presenting Gleason score of ≥ 8 , a clinical category of $\geq T2c$, or a PSA level of >20 ng/mL have a shorter time to PSA failure, have a higher rate of developing distant metastases, and have a 14-fold increase in prostate cancer-specific mortality compared with patients who present initially with low risk clinical features after salvage therapy [16–18].

In the present series, six of the 31 men had a PSA level of >10 ng/mL and five of these failed. This represents half of the failures in the series. This tentatively supports data that demonstrate PSA level at the time of salvage therapy predicts failure. For example, in patients who have a pre-salvage cryotherapy PSA level of <10 ng/mL vs >10 ng/mL, Izawa *et al.* [19] reported a 5-year disease-free survival of 57% vs 23%, respectively ($P = 0.004$). Further, de la Taille *et al.* [20] reported a 9-month PSA failure-free survival rate of 86% vs 42% ($P < 0.001$) in the same PSA groups, respectively. In some salvage prostatectomy series, a PSA level of >10 ng/mL has been associated with a worse pathological stage and a significantly higher rate of subsequent PSA failure, which makes patients who have PSA levels of >10 ng/mL suboptimal candidates for local salvage therapy [21,22].

Patient selection is clearly problematic. In our centre, we treated any man who had presumed, histologically confirmed, localized recurrence on the basis of a bone-scan and pelvic MRI (1.5 T T2-weighted, T1-weighted and gadolinium-enhanced MRI) provided they fully accepted that there was a tangible risk of under-staging due to undetectable microscopic deposits. Therefore, by doing so, we almost certainly treated some men who had micrometastatic disease at the time of treatment or earlier at time of biochemical failure. This is somewhat verified by three men who had evidence of metastatic disease on bone scan or MRI after salvage HIFU and

nine men who had evidence of biochemical failure but negative biopsies and no objective evidence of bone or lymph node metastases. The present series therefore shows that salvage HIFU is able to confer good local control in the short term in a significant proportion of men who have failed EBRT.

In conclusion, transrectal HIFU using the Sonablate 500 HIFU device in the salvage setting is a safe, well tolerated, daycase procedure. The morbidity shows low UI rates, although the endoscopic intervention remains high. The fistula rate of 3–6% is within the range expected from any other method of treatment in this high-risk patient population, although we need to learn more about why some develop such a catastrophic complication. Salvage HIFU is able to significantly lower the PSA level in men who have previously undergone EBRT for organ-confined prostate cancer. In the present cohort, about half of the men were able to achieve an early post-treatment PSA level of <0.2 ng/mL with over two-thirds showing no evidence of disease. Clearly, longer-term follow-up and prospective multicentre randomised controlled trials are required to assess whether these encouraging results are truly equivalent to other salvage treatments such as surgery, brachytherapy and cryosurgery. The difficulty in accurately staging recurrent disease to exclude metastatic disease is still problematic and such large trials will require strict inclusion criteria to minimize this difficulty.

CONFLICT OF INTERESTS

Hashim Uddin Ahmed and Mark Emberton receive funding from The Prostate Research Campaign UK (charity), Pelican Cancer Foundation, and Prostate Cancer Research Centre UK (charity) for work in focal therapy of prostate cancer. In addition, Mark Emberton receives funding and is a Consultant for Negma Lerads, France (manufacturers of TOOKAD, a photodynamic agent used in prostate cancer therapy) and Misonix/Focus Surgery/UKHIFU (manufacturers and distributors of the Sonablate 500 HIFU device). Rowland Illing receives funding from Pelican Cancer Foundation charity. Rowland Illing and Hashim Ahmed have received funding from Misonix/Focus Surgery/UKHIFU (manufacturers and distributors of the Sonablate 500 HIFU device) for conference

attendance and travel grants. In addition, Rowland Illing has received consultancy fees from these companies.

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Abbreviations: EBRT, external beam radiotherapy; HIFU, high-intensity focused ultrasound; UI, urinary incontinence.