Visually directed high-intensity focused ultrasound for organ-confined prostate cancer: a proposed standard for the conduct of therapy

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OBJECTIVE

To propose a standard for the conduct of visually directed transrectal high-intensity focused ultrasound (HIFU) and to offer a formal description of the changes observed on B-mode ultrasonography (US) during this procedure. We describe our early experience of using two different treatment methods; algorithm-based HIFU and visually directed HIFU for the treatment of organ-confined prostate cancer.

PATIENTS AND METHODS

Between November 2004 and October 2005, 34 men were treated using the Sonablate®-500 (Focus Surgery, Indianapolis, IN, USA) as primary therapy for T1 or T2 prostate cancer. None had had previous hormone therapy and all had ≥3-month PSA nadirs recorded at the follow-up. Nine men were treated using an algorithm-based protocol (group 1) and 25 using visually directed therapy (group 2). The conduct of visually directed treatment was described and changes seen using B-mode US were categorized using three 'Uchida' grades.

RESULTS

The mean PSA nadir achieved in group 2 was 0.15 ng/mL, vs 1.51 ng/mL in group 1 ($P < 0.005$). In group 2, 21 of 25 men achieved PSA nadirs of ≤0.2 ng/mL 3 months after treatment. Seven men achieved undetectable PSA values. The occurrence rate of treatment-related toxicity was similar in both groups.

CONCLUSION

Visually directed, transrectal HIFU enables clinically important and statistically significantly lower PSA nadirs to be achieved than algorithm-based HIFU. This is the first reported experience of visually directed HIFU for the treatment of organ-confined prostate cancer. We think that this is the first attempt to standardize the conduct of therapy; such standardization facilitates teaching it, and makes it possible to derive quality standards. The standardization of the conduct of therapy is a key step in the process of health technology assessment.

KEYWORDS

HIFU, ultrasound, prostate, ablation, visually directed

INTRODUCTION

Prostate cancer is the most common cancer in men and the second leading cause of death from malignancy in the UK [1]. The mainstay of treatment remains radical surgery or radiation therapy, but several minimally invasive treatments are now under evaluation that might prove to be of equivalent oncological effectiveness in the long term [2]. Transrectal high-intensity focused ultrasound (HIFU) is one such treatment that has been used on an experimental and clinical basis as noninvasive therapy for clinically localized prostate cancer since the 1990s [3].

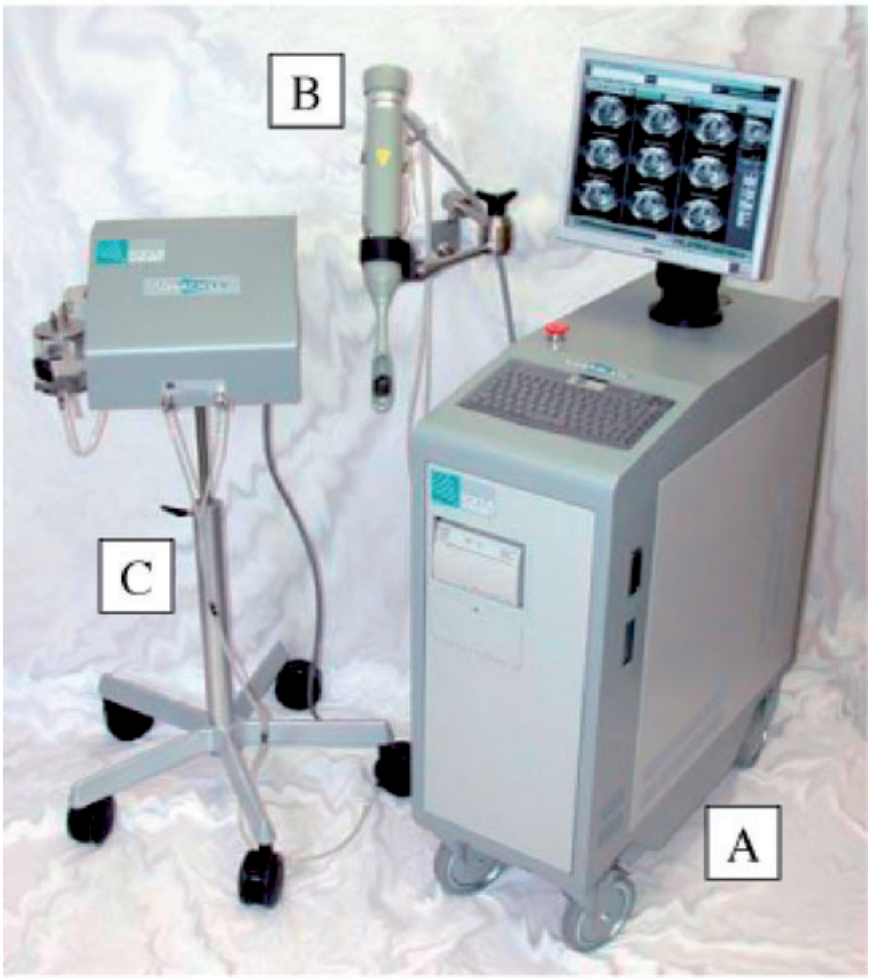
HIFU relies on the physical properties of ultrasound energy. For therapeutic purposes it is focused by either an acoustic lens, bowl-shaped transducer or electronic phased array. As ultrasound propagates through tissue, zones of high and low pressure are created. When the energy density (also known as focal intensity, measured in W/cm^2) at the focus is sufficiently high (during the high-pressure phase), tissue damage can occur as a result of thermal coagulation necrosis and/or acoustic cavitation. The volume of a HIFU-generated lesion at the focal point is small (typically 10 mm long by 1–2 mm wide, in a cigar shape orientated along the long axis of the beam). If the intention is to ablate a given volume of tissue, individual lesions are placed next to each other to provide a continuous zone of necrosis.

It was shown experimentally that when mammalian tissue at the focus of a HIFU beam is raised to >60 °C for 3 s, all of the cells in that volume are rendered nonviable [4]. The threshold for achieving this is thought to be relatively constant among subjects [5]. Accordingly, algorithms were developed assuming certain tissue-related properties, tissue homogeneity and fixed ultrasound absorption coefficients that aim to produce thermal ablation using predefined power/time combinations at given tissue depths. In reality, the HIFU beam propagates through tissue and tissue interfaces that are characterized by natural variability, e.g. prostates vary among persons in size and in the ratio of stroma to epithelium. This will effect absorption coefficients and attenuation. Moreover, the presence of disease (cancer or no cancer) and the androgenic status of a patient are likely to add to this variability. These facts make it unlikely that an algorithm-based method of treatment will be the most likely to achieve the desired effects in most patients.

It follows therefore that some method is required for adjusting the energy to suit the unique characteristics of the prostate being treated. It is generally accepted that real-time imaging is a desirable attribute for any new minimally invasive therapy [6], but there is debate about the best method to use. B-mode ultrasonography (US) is the only method in clinical use for monitoring HIFU therapy of the prostate, and this relies on detecting hyperechoic grey-scale changes within the treatment field. These changes are the result of both acoustic cavitation and tissue water vaporization, the latter occurring at boiling point. Grey-scale changes seen on B-mode US were correlated with histological changes within treated tissue during extracorporeal [7] and transrectal therapy [8], and their formation postulated for use in the control of prostate ablation [9], but they have not been formally categorized to aid the clinician in conducting the therapy.

We describe our early experience of HIFU therapy using two distinct approaches to treatment. The first regimen was based on an estimated energy exposure, the algorithm-based approach; the second actively sought to generate grey-scale changes and to use these to guide energy exposure to the prostate. We described this type of treatment as 'visually directed'. In addition to describing the outcomes of care associated with these two approaches, we propose a standardized nomenclature for the changes seen on B-mode US imaging during HIFU therapy for prostate cancer.

FIG. 1. The Sonablate-500 with (a) treatment console and ultrasound generator, (b) diagnostic/therapeutic probe and (c) water cooling unit (the 'Sonachill').



PATIENTS AND METHODS

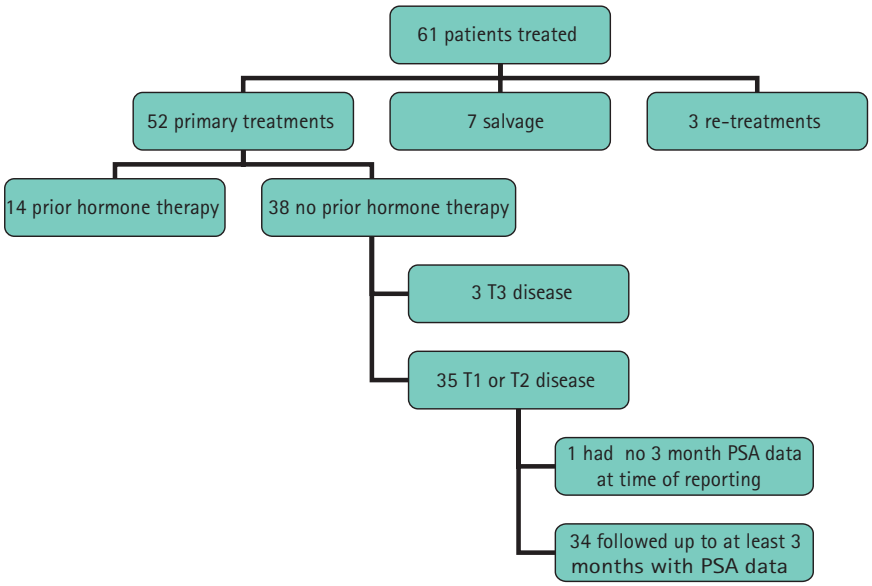
Between November 2004 and October 2005, 61 men were treated using the Sonablate-500® (Focus Surgery, IN, USA) which consists of a power generator, water-cooling system (the 'Sonachill®'), a treatment probe and a probe-positioning system (Fig. 1). The probe has two curved rectangular piezoceramic transducers with a driving frequency of 4 MHz and focal lengths of 30 and 40 mm, respectively. During treatment, these can be driven at low energy to provide real-time diagnostic US imaging or at high energy for therapeutic ablation (*in situ* intensity 1300–2200 W/cm^2). The probe is covered by a condom through which cold (17–18 °C) de-gassed water circulates pumped by the Sonachill.

Thirty-four of the 61 men treated were included in this report (Fig. 2). All had prostate cancer stage ≤T2 (N0,M0), a PSA level of <15 ng/mL and prostate gland volumes of <40 mL. Men who had had previous hormone therapy, chemotherapy, radiotherapy or surgery for prostate cancer were excluded, as were men with tight anal stenoses or prostatic calcification of >1 cm diameter, as visualized by a previous TRUS. Written informed consent was obtained before treatment in all cases, and all men were followed-up for ≥3 months. It was necessary to exclude from the analysis men who had previously had hormone therapy, as this would confound the PSA nadir recorded after therapy.

Men were prepared before the procedure with two phosphate enemas to empty the rectum; an oral bowel preparation was used in some cases. Treatment was under general anaesthesia in all cases to reduce patient movement and discomfort. Men were placed in the lithotomy position, and the anal sphincter gently dilated. The treatment probe was introduced with a covering of ultrasound gel to couple it to the rectal mucosa, and then held in position by an articulated arm attached to the theatre table. A 16 F Foley urethral catheter was inserted under sterile technique, and a 10 mL balloon inflated to allow accurate visualization of the bladder neck and median sagittal plane.

Axial and sagittal US images were taken through the prostate using the transducer in the diagnostic mode. Treatment planning used proprietary software, which allows the prostate to be divided into 'blocks': anterior,

FIG. 2. The characteristics of all patients treated between November 2004 and October 2005.



middle and posterior, on both right and left sides. The software directs the transducer to move automatically so that the acoustic focus is moved sequentially through each point in the block. Each acoustic pulse ablates a volume of 3 × 3 × 10 mm, by heating the tissue to 80–98 °C almost instantaneously [10], and individual lesions overlap slightly to 'paint out' the entire volume, using a combination of 3-s exposures ('on') time and 6-s pauses ('off') time, during which the gland was visualized with real-time US. The 4-cm focal length probe was used to treat anterior and middle blocks, and the 3-cm probe used to treat the posterior block.

The software is semi-automated, with the amount of energy applied to the prostate remaining under the control of the user. As a result, it is possible to treat the prostate in several ways. For instance, one approach uses pre-set energy exposure levels, the intensity of which depends on the part of the prostate that was being treated, and whether the treatment is a primary or salvage (after radiation) case. To a large extent, these energy exposure levels are derived from animal experiments [11] or as a result of outcome monitoring in case series [12]. This might be termed an algorithm-based approach. Clinical series using this technique showed that the mean PSA nadirs achievable after treatment were ≈1.4 ng/mL [13]. These results are similar to those achieved by other transrectal HIFU devices that rely on the upper power limit being set without user control [14].

An alternative method of managing energy exposure might involve abandoning any pre-set criteria to permit the maximum energy exposure deemed to be both effective and safe. This would only be possible if both therapeutic objectives of effectiveness and safety were under the control of the operator, but to a large extent they are. The site intensity at the focal point (the target zone) can be monitored using visual feedback, as evidenced by hyperechoic changes on B-mode US. It is possible to increase energy exposure to obtain these visual changes and to decrease the exposure if the changes become uncontrolled. Our hypothesis is that obtaining visual changes at the focal point can serve as a real-time feed-back to the operator that cytocidal levels of energy are being delivered to the part of the prostate being treated. Implicit in this approach are strong, and we think robust, safety considerations. By controlling the visual change at the threshold level at the focal point, the operator is as certain as possible that the energy is being deposited in the intended area. Moreover, other in-built safety features, such as the reflectivity index in the near field, place an upper boundary on energy absorption in the area abutting rectal mucosa. We termed this approach 'visually directed'. Using this, the grey-scale changes seen on diagnostic US are actively monitored, and the power adjusted accordingly. For consensus on the types of changes seen, a semiquantitative method of analysis was developed (Appendix), which allows comparison within and between treatments. These 'Uchida' changes were named after Toyoaki Uchida (Professor of Urology in Tokai University Hachioji Hospital, Tokyo, Japan) who performed the preliminary clinical work on the Sonablate device.

Using visually directed treatment, the operator aims to generate grey-scale changes throughout the target tissue. During treatment, the power level (energy exposure) is constantly adjusted to achieve Uchida Grade I or II changes (Fig. 3). By obtaining these changes, the operator can control the energy in the target zone that is either on or just below the cavitation threshold. This grey-scale US feedback is also used to provide a ceiling threshold. Grade III changes occur when uncontrolled cavitation occurs in the near field; this is corrected by reducing the energy exposure. Visually directed HIFU therefore takes into account both inter- and intraprostatic differences in acoustic and thermal properties, and allows the user to respond in real-time to the therapy.

Nine men were treated using the algorithm-based protocol (group 1) and 25 men using the visually directed protocol (group 2). All patients were discharged on the day of treatment. Demographic details are given in Table 1; all patients were followed up for ≥3 months. After therapy, patient status and treatment-related complications were assessed at fixed intervals by visits to the clinic and by telephone consultations with a specialist nurse practitioner. All men were discharged with an indwelling urethral catheter. The PSA level was measured at 3 months after treatment to give a nadir value. Statistical analysis was used to assess the correlation of variables between groups.

RESULTS

Table 1 shows details of the operative variables and results. The difference between the mean PSA nadirs of the groups was significant ($P < 0.005$). In group 2, 21 of 25 patients achieved PSA nadirs of ≤0.2 ng/mL at 3 months after treatment; seven patients achieved undetectable PSA values. The mean PSA nadir achieved in group 2 was 0.15 ng/mL, vs 1.51 ng/mL in group 1.

A trial without catheter was successful at the first attempt in eight of the nine patients in group 1, and 21 of 25 in group 2 (84%). In the

3 months after HIFU, a few patients in each group required flexible cystoscopic investigation. Some also had infective complications, which are listed in Table 1.

DISCUSSION

Visually directed HIFU for organ-confined prostate cancer can produce a low PSA nadir 3 months after the procedure. In the present patients, the mean PSA nadir was significantly lower than that using an algorithm-based protocol for treatment of similar patients, and compares favourably with both brachytherapy and cryotherapy for the treatment of organ-confined prostate cancer [15,16]. In the Seattle brachytherapy series [17] 72% of patients with no evidence of disease biochemically achieved PSA nadirs of <0.2 ng/mL, with the mean PSA nadir being 0.25 ng/mL. In the present study we achieved PSA nadirs of ≤0.2 ng/mL in 84% of patients using the visually directed method, and an undetectable PSA level in just under a third of those treated.

Clinicians familiar with TRUS will acknowledge that the characteristics of prostate glands differ between patients. Even men who have had no previous therapy can have glands of different density and with different patterns of micro- or macro-calcification. Just as the amount of pressure that is required to exert on the scalpel is based upon the real-time characteristics of the tissue it is passing through, so is the amount of energy required to cause ablation within the prostate gland.

We have given the first formal description of grey-scale US changes associated with transrectal HIFU treatment for prostate cancer (Appendix). These 'Uchida changes' allow a descriptive analysis of changes seen during therapy and permit a formal system of treatment to be developed, which is consistent between users but flexible according to the gland treated. Grey-scale changes seen on B-mode US have been identified in relation to ablative therapies; these have previously been termed 'pop-corning' in relation to HIFU treatment of the prostate, and 'gas cloud' formation in relation to radiofrequency ablation in the liver, but have not been quantified for use as a method of real-time feedback.

In the past, cavitation was avoided, as it was assumed to be uncontrollable, and that the

FIG. 3. TRUS image showing a sagittal plane through the mid-prostate. (a) Grade I Uchida changes: A, pretreatment image; B, intraoperative image showing discrete hyperechoic grey-scale changes within the treatment zone. (b) Grade II Uchida changes: A, pretreatment image; B, intraoperative image showing confluent grey-scale changes within the treatment zone. (c) Grade III Uchida changes: A, pretreatment image; B, intraoperative image showing hyperechoic grey-scale changes migrating outside the treatment zone, extending into the near-field.

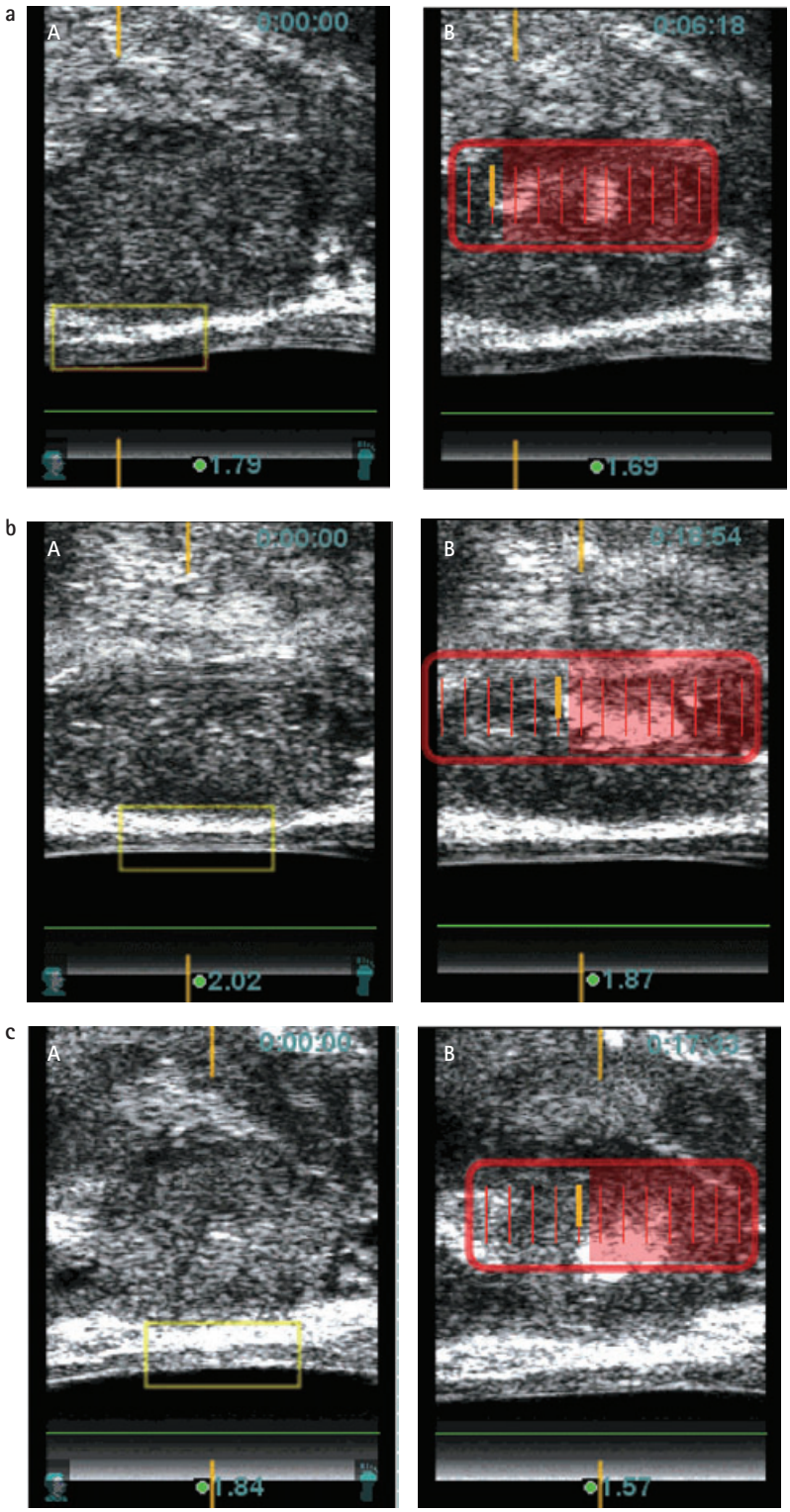


TABLE 1 The patients' demographics, outcome details and complications after prostate HIFU

Variable	Group 1	Group 2
Number of patients	9	25
Mean (range):		
age, years	64 (53–75)	61 (50–76)
prostate volume, mL	30 (24–38)	30 (17–54)
pretreatment PSA level, ng/mL	6.58 (4.12–10.60)	8.00 (3.00–14.80)
Gleason score	6 (6–7)	6 (5–7)
T stage, n		
1	5	15
2	4	10
Outcome details		
Mean (range):		
operative time, min	227 (125–350)	248 (200–345)
days to trial without catheter	12 (10–21)	14 (10–42)
PSA level at 3 months, ng/mL	1.51 (0.10–3.10)	0.15 (0–1.05)
Complications		
N (%):		
undergoing flexible cystoscopy	3	4 (16)
UTI	1	2 (8)
epididymo-orchitis	0	1 (4)

risk of cavitation outside the area of interest was too great. Extensive dosimetry studies [7,18] showed that not only are the grey-scale changes visualized on B-mode US associated with histological ablation, but that single pulses of high-intensity ultrasound can produce well circumscribed, predictable volumes of necrosis. It might be argued that, by producing cavitation, the tissue is being 'over-treated'; in the absence of other real-time methods of detecting thermal ablation, this remains the best method of treatment monitoring. Tissue elastography [19] and ultrasound thermometry [20] are under development but remain experimental; MRI [21] might accurately detect temperature changes, but MRI devices are costly, do not provide feedback as instantaneously as B-mode US, and have not been used clinically in the setting of transrectal prostate HIFU.

Although presently the diagnostic TRUS uses 7 MHz probes and the 4–6 MHz centre frequency band of the Sonablate-500 is not the standard frequency for diagnostic imaging of the prostate, we have had no difficulty in using it for planning and monitoring treatment. This 4–6 MHz frequency band allows excellent visualization of the prostatic margin and grey-scale changes within the gland. Higher frequency TRUS is used in all patients before treatment, and even with the highest ultrasonic resolution the differentiation between benign and malignant prostate is still inaccurate and therefore unnecessary for the purposes of treatment [22].

Despite the few patients in each group, the catheter-free rate appears equivalent between them (>80% at the first attempt) with infective complications in ≈10% of patients. This is consistent with other reports using combined prostatic resection and HIFU [23]. After treatment, most patients have short-term irritative voiding symptoms as a result of the sloughing of prostatic tissue via the urethra. In the visually directed group, more patients underwent flexible cystoscopy. In all cases this was done to investigate irritative and obstructive voiding symptoms, with the result that urethral debris was cleared. The threshold for undertaking a flexible cystoscopy is now considerably higher, as most patients are taught intermittent self-catheterization before treatment, which allows the dislodging of prostatic slough with no need for formal intervention.

We assumed a relationship between the PSA nadir at 3 months and treatment outcome. Data assessing this relationship indicate that this is a justifiable association [24], but in that study the outcome was likelihood of disease on prostate biopsy at 6 months after treatment. Although it is logical to assume that this affects the long-term outcome, there are no long-term data to verify it at present; certainly the PSA nadir was shown to correlate with longer term outcome in the context of radical surgery and external beam radiotherapy [25,26].

The present study represents the first reported experience of visually directed HIFU for treating organ-confined prostate cancer. We think that this is the first attempt to standardize the conduct of treatment. Standardization of therapy makes it easier to teach and makes it possible to derive quality standards. Most importantly, standardizing the intervention is the key step in health technology assessment. Once this is done it is possible to start to explore the next phase of investigation, defining the determinants of outcome. This is likely to lead to better case selection and improved conduct of therapy.

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CONFLICT OF INTEREST

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Abbreviations: **HIFU**, high-intensity focused ultrasound; **US**, ultrasonography.

APPENDIX

UCHIDA CHANGES

We devised a method of assessing grey-scale US changes seen during visually directed therapy to allow quantification and comparison in and between treatments. 'Uchida changes' were classified as Grades I, II and III depending on whether hyperechoic regions were identified within individual target treatment zones, became confluent between adjacent HIFU treatment exposures, or were seen migrating outside the target treatment zone, respectively. These were then subclassified into 'a', 'b' and 'c' depending upon whether <10%, 10–50% or >50% of the focal region was involved in the changes, respectively (Fig. 3). The aim was to see some form of Uchida change every second or third exposure, to confirm that treatment was taking place on or near the cavitation threshold.