

Visually directed HIFU for organ confined prostate cancer – a proposed standard for the conduct of therapy

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Summary

Objective

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

Patients and methods

Between November 2004 and October 2005, thirty four men were treated using the Sonablate™-500 (Focus Surgery, IN, USA) as primary therapy for T1 or T2 prostate cancer. None had received prior hormone therapy and all had at least 3 month PSA nadirs recorded at follow up. Nine men were treated using an algorithm based protocol and twenty five men were treated using visually directed therapy. The conduct of visually directed treatment was described and changes seen on B-mode ultrasound were categorized using three 'Uchida' grades.

Results

The mean PSA nadir achieved in the visually directed group was 0.15ng/mL versus 1.51ng/mL in the algorithm based group ($p < 0.005$). In the visually directed group, 21 of 25 patients achieved PSA nadirs of ≤ 0.2 ng/mL three

months after treatment. Seven patients achieved undetectable PSA values. The complication rates in both groups were similar.

Conclusion

Visually directed, high power trans-rectal HIFU enables lower PSA nadirs to be achieved than algorithm based HIFU. This work represents the first reported experience of visually directed HIFU for the treatment of organ confined prostate cancer. We believe that this is the first attempt to standardise the conduct of treatment. Standardisation of therapy makes it easier to teach and makes it possible to derive quality standards. The standardisation of the conduct of therapy is a key step in the process of health technology assessment.

Keywords

HIFU, ultrasound, prostate, ablation, visually directed

Text

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; however there are several minimally invasive treatments now under evaluation which may prove to be of equivalent oncological effectiveness in the long term(2). Trans-rectal high intensity focused ultrasound (HIFU) is one such treatment, which has been used on an experimental and clinical basis as non-invasive therapy for clinically localized prostate cancer since the 1990's(3).

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 & low pressure are created. When the energy density at the focus is

sufficiently high (during the high pressure phase), tissue damage may occur as a result of thermal coagulation necrosis and cavitation. The acoustic focal volume of a single exposure is small (typically 10mm long by 1-2mm 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 of time between exposures for cooling.

It has been demonstrated experimentally that when mammalian tissue at the focus of a HIFU beam is raised to over 60°C for 3 seconds, all of the cells in that volume are rendered non-viable(4). This thermal coagulation necrosis has been the traditional goal of HIFU, as the threshold for thermal damage within a tissue type has been thought to be relatively constant between subjects(5). As a consequence, algorithms have been developed which aim to produce thermal ablation using pre-defined power/time combinations at given tissue depths. In reality, mechanical ‘acoustic cavitation’ also occurs in tissue as a result of gas being drawn out of solution during the pressure nadirs, to create microbubbles within the tissue. These bubbles may then oscillate in a stable fashion (stable cavitation) or collapse (unstable cavitation) resulting in large forces being deposited in the micro-environment.

It is generally accepted that real time imaging is a desirable attribute for any new minimally invasive therapy(6), but there remains debate surrounding the best method to use. B-mode ultrasound is the only modality in clinical use for the monitoring of HIFU therapy of the prostate, and this relies on the detection of hyper-echoic 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 have previously been correlated with histological changes within treated tissue during extracorporeal therapy(7), but there has never been a formal method of description for these changes, nor has there been an assessment of how the types of changes seen may relate to outcome.

We describe our early experience of HIFU therapy using two distinct approaches to treatment. The first regimen of these was conducted with the intent of avoiding grey scale changes. We have called this an 'algorithm based' therapy. The second type of treatment actively sought to generate grey scale changes and use these changes to guide energy exposure to the prostate. We have 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 describing the changes seen on B-mode imaging during HIFU therapy for the treatment of prostate cancer.

Patients and methods

Between November 2004 and October 2005, sixty one men were treated using the Sonablate™-500 (Focus Surgery, IN, USA). The Sonablate-500 consists of a power generator, water cooling system (the 'Sonachill'™), a treatment probe and a probe positioning system. The probe contains two curved rectangular piezo-ceramic transducers with a driving frequency of 4MHz and focal lengths of 30 and 40mm respectively. During treatment these may be driven at low energy to provide real-time diagnostic imaging or at high energy for therapeutic ablation (in situ intensity 1300-2200Wcm⁻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 have been included in this report (see chart 1). All had prostate cancer stage T2 or less (N0,M0), PSA <15ng/mL and prostate gland volumes <40mL. Those who had received prior hormone therapy, chemotherapy, radiotherapy or surgery for prostate cancer were excluded, as were men with tight anal stenoses or prostatic calcification greater than 1cm diameter as visualized on prior trans-rectal ultrasound (TRUS) examination. Written informed consent was attained prior to treatment in all cases, and all were followed up to at least 3 months following the procedure. It was necessary

to exclude from the analysis those patients who had taken prior hormone therapy as this would confound the PSA nadir recorded following therapy.

Patients were prepared before the procedure with two phosphate enemas to empty the rectum. Oral bowel preparation was used in some patients. Treatment was performed under general anaesthesia in all cases to reduce patient movement and discomfort. Patients 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 16ch foley urethral catheter was inserted under sterile technique, and 10ml balloon inflated to allow accurate visualization of the bladder neck and median saggital plane.

Axial and saggital images were taken through the prostate using the transducer in the diagnostic mode. Planning was carried out using proprietary software which allows the prostate to be divided into 'blocks' - anterior, 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 3x3x10mm by heating the tissue to 80-98°C almost instantaneously(8), and individual lesions overlap slightly to 'paint out' the entire volume, using a combination of 3 second exposures ('on') time and 6 second pauses ('off') time, during which real time visualization of the gland took place. The 4cm focal length probe was used to treat anterior and middle blocks, and the 3cm probe used to treat the anterior block.

The software is semi-automated, so control of the power input remains in the hands of the user. As a result, different approaches to the performance of a treatment are possible. One method of performing therapy relied on the use of the preset maximum outputs of the transducer until any evidence of tissue cavitation occurred (hyperechoic changes on B-mode ultrasound). If this

occurred the power input was reduced to a level where changes were no longer seen, and maintained at that level for the duration of the block. Clinical series using this technique have shown that the mean PSA nadirs achievable following treatment were around 1.4ng/mL(9), similar to those achieved by other trans-rectal HIFU devices used for treating organ confined prostate cancer with treatment protocols based on algorithms(10). This is what we have termed the 'low power' or 'algorithm' based protocol.

An alternative method of treatment using the semi-automated software has been termed 'visually directed' or 'high power' therapy. Using this technique, the grey scale changes seen on diagnostic ultrasound are actively monitored, and the power adjusted accordingly. In order for there to be consensus on the types of grey scale changes seen, a semi-quantitative method of analysis has been developed (see Box 1) which allows comparison within and between treatments. These 'Uchida' changes have been named after Toyooki Uchida (Professor of Urology in Tokai University Hachioji Hospital, Tokyo, Japan) who performed the preliminary clinical work on the Sonablate device.

By using the 'visually directed' method of treatment, the operator aims to generate grey scale changes throughout the target tissue. During treatment power levels (energy exposure) are under constant adjustment by the operator in order to achieve Uchida Grade I or Grade II changes. By obtaining these Uchida changes the operator is able to control energy in the target zone that is either on or just below the cavitation threshold. This grey scale feedback is also used to provide a ceiling threshold. Uchida Grade III changes occur when uncontrolled cavitation occurs in the near field. This undesirable deposition of energy is corrected by reducing energy exposure. Visually directed HIFU therefore takes into account both inter- and intra-prostatic 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 and twenty five men were treated using the visually directed protocol. Demographic details are given in Table 1. All were followed up for at least 3 months.

Following 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 patients were discharged with an indwelling urethral catheter. The PSA was measured at three months after treatment to give a nadir value.

Analysis was performed using an SPSS statistical package to assess the correlation of variables between groups

Results

Details of the operating parameters and results are given in table 2. The difference between the mean PSA nadirs of the two groups was statistically significant ($p < 0.005$). In the visually directed group, 21 of 25 patients achieved PSA nadirs of ≤ 0.2 ng/mL three months after treatment. Seven patients achieved undetectable PSA values. The mean PSA nadir achieved in the visually directed group was 0.15 ng/mL versus 1.51 ng/mL in the algorithm based group.

All patients were discharged on the day of treatment. Trial without catheter was successful at the first attempt in 8/9 patients in group 1 (89%), and 21/25 in group 2 (84%). Operative intervention after the procedure was necessary in 3/9 in group 1 (33%) and 4/25 in group 2 (16%). One patient in the algorithm group experienced a urinary tract infection following treatment (11%), whereas two patients in the visually directed group experienced urinary tract infections (8%) and one an episode of epididymo-orchitis (4%).

Discussion

Visually directed HIFU for organ confined prostate cancer is able produce a low PSA nadir three months following the procedure. In this group of patients, the mean PSA nadir is significantly lower than that observed using an algorithm based protocol for treatment of a similar group of patients, and compares favourably with both brachytherapy and cryotherapy for the treatment of organ confined prostate cancer(11;12). We have been able to achieve PSA nadirs $\leq 0.2\text{ng/mL}$ in 84% of patients using the visually directed method, and an unrecordable PSA in just under a third of those treated.

Clinicians familiar with trans-rectal ultrasound will acknowledge that the characteristics of prostate glands differ between patients. Even men who have had no prior therapy may 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 changes associated with trans-rectal HIFU treatment. These 'Uchida changes' allow 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 ultrasound have been previously identified in relation to ablative therapies; these have previously been called '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 has been avoided, as it was assumed to be uncontrollable and that the risk of cavitation outside the area of interest was too great. Extensive dosimetry studies(7;13) have shown that not only are grey scale

changes visualised on B-mode ultrasound associated with histological ablation, but that single pulses of high intensity ultrasound may produce well circumscribed, predictable volumes of necrosis. It may be argued that by producing cavitation, the tissue is being essentially 'over treated', but in the absence of other real-time methods of detecting thermal ablation, this remains the best method of treatment monitoring. Tissue elastography(14) and ultrasound thermometry(15) are in development but remain experimental; magnetic resonance imaging(16) may accurately detect temperature changes however MR devices are costly, do not provide feedback as instantaneously as B-mode ultrasound and have not been used clinically in the setting of trans-rectal prostate HIFU.

Although 4MHz is not the standard frequency for diagnostic imaging of the prostate, we have not experienced difficulty it using it for planning and monitoring treatment. This frequency allows excellent visualisation of the prostatic margin and grey scale changes within the gland. Higher frequency trans-rectal ultrasound and biopsy is performed on all patients prior to treatment, and even with the highest ultrasonic resolution the differentiation between benign and malignant prostate is still inaccurate(17).

Despite the small numbers of patients in each group, the catheter-free rate appears equivalent between groups (over 80% at first attempt) with infective complications occurring in around one in ten patients. This is consistent with other reports using combined prostatic resection and HIFU(18). After treatment, the majority of patients experience short term irritative voiding symptoms as a result of the sloughing of prostatic tissue via the urethra. In group 1, the re-intervention rate was higher, however in all three cases intervention consisted of flexible cystoscopy which was done for diagnostic reasons. The threshold for undertaking a flexible cystoscopy is now considerably higher..

We have assumed a relationship between PSA nadir at 3 months and treatment outcome. Preliminary data assessing this relationship would indicate that this is a justifiable association(19), however in this publication the outcome is likelihood of disease on prostate biopsy at six months after treatment. Although it is logical to assume that this impacts on long term outcome, there is no long-term data to verify it at present; certainly PSA nadir has been shown to correlate with longer term outcome in the context of radical surgery and external beam radiotherapy (20;21).

This work represents the first reported experience of visually directed HIFU for the treatment of organ confined prostate cancer. We believe that this is the first attempt to standardise the conduct of treatment. Standardisation of therapy makes it easier to teach and makes it possible to derive quality standards. Most importantly, standardising 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.

Acknowledgements

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Illustrations

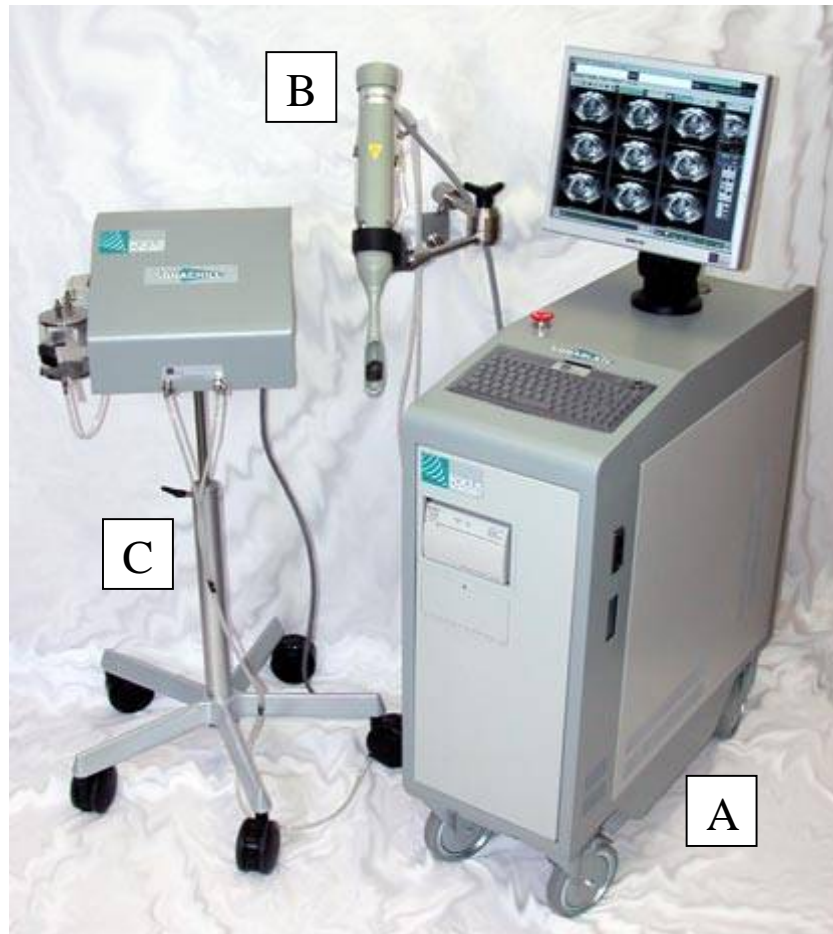


Figure 1. The Sonablate-500 (Focus Surgery, IN, USA) with (a) treatment console and ultrasound generator, (b) diagnostic/therapeutic probe and (c) water cooling unit (the 'Sonachill').

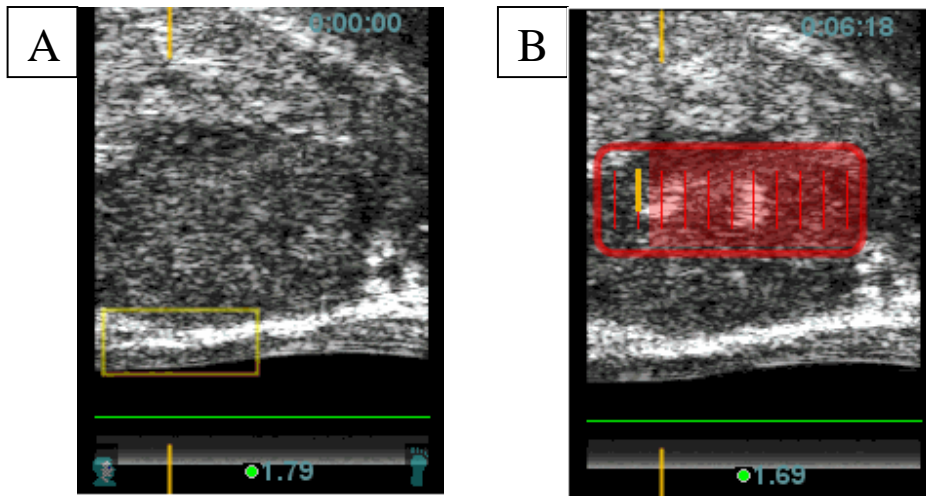


Figure 2a. Grade II Uchida changes. Trans-rectal ultrasound image showing saggital plane through mid-gland of prostate. A: pre-treatment image, B: intra-operative image showing discrete grey scale changes within the treatment zone

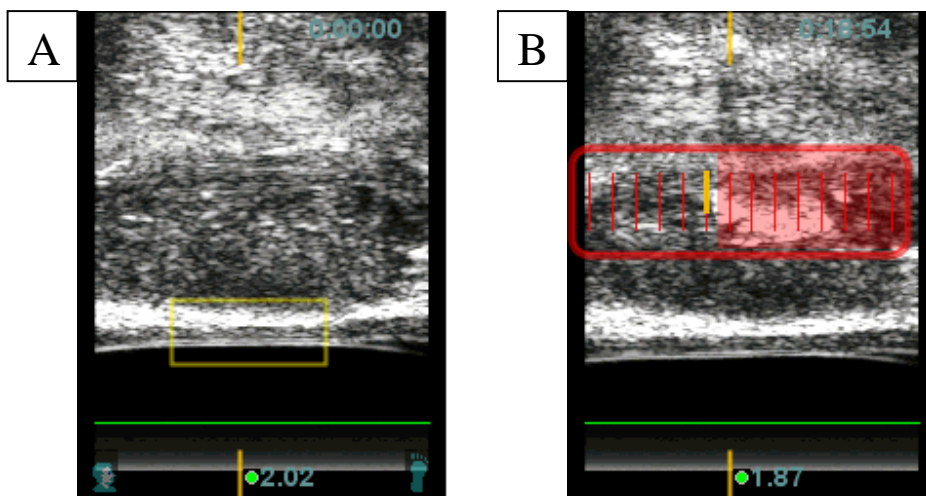


Figure 2b. Grade II Uchida changes. Trans-rectal ultrasound image showing saggital plane through mid-gland of prostate. A: pre-treatment image, B: intra-operative image showing conflent grey scale changes within the treatment zone

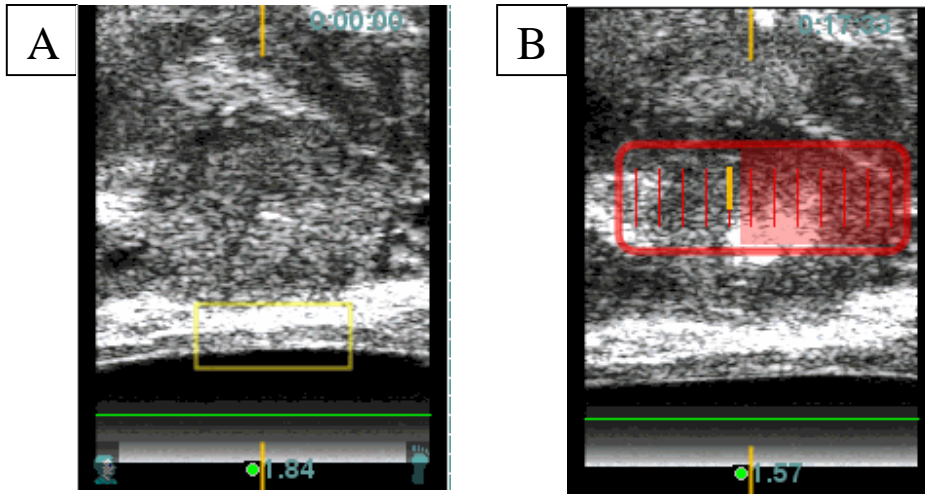


Figure 2c. Grade III Uchida changes. Trans-rectal ultrasound image showing saggital plane through mid-gland of prostate. A: pre-treatment image, B: intra-operative image showing grey scale changes outside the treatment zone, extending into the near-field.

Tables & their legends

Chart 1. Characteristics of all patients treated between November 2004 & October 2005.

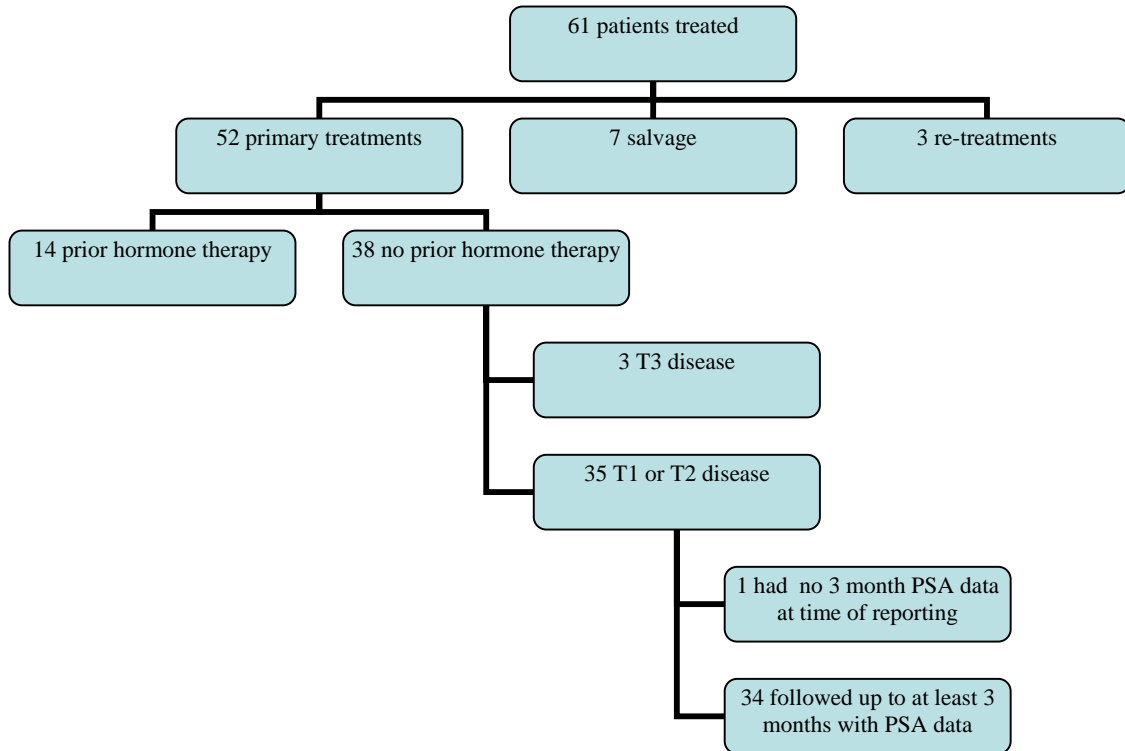


Table 1. Demographic of patients pre-treatment, by group.

	Group 1 (n=9)		Group 2 (n=25)	
	Mean	Range	Mean	Range
Age (years)	64	53 - 75	61	50 - 76
Prostate volume	30	24 - 38	30	17 - 54
Pre treatment PSA (ng/mL)	6.58	4.12 - 10.60	8.00	3.00 - 14.80
T stage	1 (5) / 2 (4)		1 (15) / 2 (10)	
Gleason score	6	6 - 7	6	5 - 7

Table 2 Outcome details

	Group 1 (n=9)		Group 2 (n=25)	
	Mean	Range	Mean	Range
Operative time (mins)	227	125 - 350	248	200 - 345
Days to Trial without catheter	12	10 - 21	14	10 - 42
PSA at 3 months (ng/mL)	1.51	0.10 - 3.10	0.15	0 - 1.05

Box 1 Uchida Changes

We devised a method of assessing grey scale changes seen during visually directed therapy to allow quantification and comparison in and between treatments. ‘Uchida changes’ were classified Grades I, II and III depending on whether hyperechoic regions were identified within individual target treatment zones, became confluent between adjacent treatment zones, or were seen outside the target treatment zone respectively. These were then sub-classified into ‘a’, ‘b’ and ‘c’ depending upon whether <10%, 10-50% or >50% of the focal region was involved in the changes respectively (see figure 2). 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.