Morbidity Associated with Primary High Intensity Focused Ultrasound and Redo High Intensity Focused Ultrasound for Localized Prostate Cancer

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Abbreviations and Acronyms

ADT = androgen deprivation treatment

BNI = bladder neck incision

GEE = generalized estimating equation

HIFU = high intensity focused ultrasound

IIEF-15 = International Index of Erectile Function-15

MRI = magnetic resonance imaging

PDE-5 = phosphodiesterase-5

PSA = prostate specific antigen

RT = radiation therapy

TRUS = transrectal ultrasound

UTI = urinary tract infection

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Purpose: High intensity focused ultrasound may have a role as an alternative to standard radical therapies for localized prostate cancer. An attribute of high intensity focused ultrasound is that it can be repeated. We determined morbidity after primary and redo high intensity focused ultrasound.

Materials and Methods: We performed an academic lead analysis of United Kingdom registry data on high intensity focused ultrasound treatments at 3 centers using patient reported continence and sexual function outcomes. Validated questionnaires were completed before and after each ultrasound treatment.

Results: A total of 359 patients received 1 whole gland high intensity focused ultrasound treatment for localized prostate cancer from October 2004 to June 2012, of whom 130 (36.2%) received re-treatment. Median followup was 27 months (range 3 to 81) after re-treatment. When analyzing adverse events, 10.8% of patients experienced urinary tract infection after the first treatment compared to 3.9% after re-treatment ($p = 0.009$). Urethral dilatation was required in 13.8% and 14.0% of patients after first and redo ultrasound treatments ($p = 0.7$), and bladder neck incision was required in 9.2% and 11.6%, respectively ($p = 0.2$). Before and after re-treatment 73.3% and 55.1% of patients had no leak, and 2.7% and 9.0% used daily pads ($p < 0.001$ and $p = 0.07$, respectively). Analysis of erectile function showed that 56.2% and 56.0% of patients were potent before and after re-treatment, respectively ($p = 0.9$).

Conclusions: Redo high intensity focused ultrasound is associated with an increase in urinary side effects but sexual side effects do not appear to be significantly increased. The number of adverse events seems to be equivalent after first and redo treatments. Meticulous patient selection is of paramount importance when selecting men for redo high intensity focused ultrasound.

Key Words: prostate, prostatic neoplasms, high-intensity focused ultrasound ablation, retreatment, adverse effects

THE optimal management strategy for newly diagnosed, clinically localized prostate cancer remains controversial and includes radical prostatectomy, radical radiotherapy and active surveillance. As an alternative, minimally invasive therapies such as cryotherapy and HIFU have been proposed as iso-effective cancer control with fewer complications and

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side effects.[1,2] Although HIFU still is considered experimental according to European Association of Urology guidelines,[3] several studies demonstrated oncologic efficacy comparable to that of radiation therapy with a biochemical failure-free survival rate of between 57% and 76% at 7 to 8-year followup.[2,4] The rate of erectile impotence after whole gland HIFU is greater than 50%[2,4] and the rate of stress urinary incontinence varies between 7% and 15%.[4,5]

An advantage of HIFU is that treatment can be repeated (redo HIFU) if the first treatment is not successful. We determine whether redo HIFU results in significant additional morbidity compared to primary HIFU.

PATIENTS AND METHODS

Since 2004, an academic led, independent, national United Kingdom HIFU registry has been maintained under the auspices of University College London. In this study we included all patients treated with HIFU using a Sonablate® 500 for localized prostate cancer at 3 United Kingdom institutions (Princess Grace Hospital, Basingstoke and North Hampshire Hospital, and University College London Hospital National Health Service Foundation Trust) from October 8, 2004 to June 26, 2012. We used standard power settings in the range of 20 to 45 W/cm^2 with a duty cycle of 3 seconds on and 3 seconds off or 3 seconds on and 6 seconds off as determined by the operator. Treatment was given on an individual basis with combinations of HIFU blocks derived from the 4 and 3 cm focal lengths to cover the area of recurrence.

Men who were unable or unwilling to undergo surgery, radiotherapy or active surveillance were offered HIFU. Contraindications to HIFU were previously reported.[6] Men received a single HIFU session or redo HIFU after failed first HIFU based on biochemical, histological or MRI evidence of localized residual disease. To achieve the size restrictions necessary for HIFU treatment cytoreduction with bicalutamide (50 mg once daily) and a 5α-reductase inhibitor (dutasteride or finasteride) for 3 months was done before HIFU. These treatments were stopped on the day of the first HIFU treatment.

At the outset all men were fitted with a urethral catheter for 7 to 10 days. After consultation in international user group meetings it was agreed that suprapubic catheters might result in earlier voiding, fewer urinary infections and a lower stricture rate. Since most patients were tertiary referrals and lived some distance away, all men were taught clean intermittent self-catheterization so that they could self-manage decreased flow due to debris passage and short-term prostatic inflammation. Followup after treatment mirrored the regimen used after standard radical therapies, including serum PSA measurement at 6 weeks and then every 3 months for the first year and every 6 months in subsequent followup years. Patients who did not achieve a PSA nadir of less than 0.5 ng/ml and those with PSA less than 0.5 ng/ml with 2 consecutive PSA increases were advised to undergo transrectal prostate biopsy. Of the 359 patients 175 (48.7%) underwent 1 post-HIFU TRUS biopsy and in 108 (30.1%) the TRUS biopsy was positive.

Post-HIFU adverse events included need for cystoscopy, BNI, urethral dilatation, UTI and epididymitis. These events were recorded from a review of clinical records on a continual basis by dedicated data management personnel. All patients at the 3 study centers were offered pretreatment and posttreatment validated questionnaires.[7] Incontinence data were collected from patient reported outcomes on leakage and pad use using the UCLA-EPIC urinary function question subset.[8]

From the IIEF-15 data we selected question 2 ("When you had erections with sexual stimulation, how often were your erections hard enough for penetration?") for analysis, which is accepted as a good indicator of erectile function.[9] We defined potency as scoring 2 or above on a scale of 0—no sexual activity, 1—almost never/never, 2—a few times (much less than half the time), 3—sometimes (about half the time), 4—most times (much more than half the time) and 5—almost always/always.

1) We compared perioperative outcomes and adverse events between single and redo HIFU. 2) We analyzed the change in urinary continence status from no leak to leak and any pad use. 3) We also evaluated sexual function before and after a single HIFU treatment and subsequently after redo HIFU as well as the differential rates of reported PDE-5 inhibitor use. For completeness so that these outcomes could be placed in context we also report disease control outcomes in the group as a whole. The criteria for HIFU failure was PSA nadir plus 2.0 ng/ml (Phoenix criteria) and/or additional salvage therapy.

The difference between single and redo HIFU cases was tested by the 2 independent samples t-test or the Pearson chi-square test, as appropriate. A GEE model with a logit link function was used for a binary dependent variable. Patient identity as a subject variable, time points as a within subject variable and an unstructured correlation structure were selected for the GEE model. The binary dependent variables tested were urinary leakage, pad use, intercourse and PDE-5 inhibitor use. Significance was considered at 0.05 and 2-sided p values are shown. Analysis was done with SPSS®, version 17.

RESULTS

Patient Characteristics

From October 2004 to June 2012 a total of 359 patients were treated with at least 1 whole gland HIFU session for localized prostate cancer. Of the 359 men 96 (26.7%) were pretreated with 3 months of cytoreduction, 130 (36.2%) underwent redo HIFU, 19 (5.3%) underwent 2 redo sessions and 1 (0.3%) underwent 3. The data presented on morbidity and oncologic outcomes were recorded after the first redo HIFU.

Preoperative characteristics were similar between men with only 1 HIFU and those with redo HIFU except Gleason score, which was higher in those with redo HIFU ($p = 0.004$, table 1). Median followup was 45 months (range 3 to 93) in the single