Results of low threshold to biopsy following high-intensity focused ultrasound for localized prostate cancer

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INTRODUCTION

There is a general acceptance that treatment success is based on having reached a prostate specific antigen (PSA) nadir \( \leq 0.5 \text{ ng/mL} \) within 3–4 months of high-intensity focused ultrasound (HIFU) and this PSA level to remain at such.\(^{[1,2]}\) Using this definition, success is achieved somewhere between 60 and 80\% of patients with HIFU in the early post-procedure phase. In series which record treatment failure as any positive biopsy, the actuarial disease-free survival (DFS) is worse than when applying a PSA alone criteria and sits at between 50 and 75\%.\(^{[2]}\) This study aims to reveal the possibility of residual prostate cancer at post-HIFU biopsy, if a low PSA level is used to prompt biopsy.

MATERIALS AND METHODS

Eleven patients were offered HIFU between 2006 and 2008 by a single urologist (HHW). The Sonoblate device was used (Focus Surgery, Inc., Indianapolis, IN, USA) by an experienced team that had in total performed more than 100 cases. The Sonoblate technician was present for all procedures to assist with setup.

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and delivery. The single piezoelectric crystal alternatively delivers high-energy power for ablation and low energy for ultrasound imaging of the prostate. The device is programmed such that the transducer within the treatment probe delivers ablative pulses at a “focal point” within the gland. These “lesions” are consecutive and overlapping laterally and longitudinally.

The procedure was performed under general anesthesia, in the lithotomy position. The treatment probe was attached to an articulating arm which itself was attached to the operating table. A cooling liquid surrounding the treatment probe was used to protect the rectal mucosa from heat damage. A urethral catheter was inserted at the end of the procedure.

Patients with D’Amico low- or intermediate-risk localized prostate cancer were included between 2006 and 2008, with the primary intention as this being the primary treatment for their disease. Patients with non-organ confined or metastatic disease or those receiving either hormonal therapy or chemotherapy were excluded, as were those with stricturing ano-rectal pathology. All patients were evaluated by history, examination, digital rectal exam (DRE), PSA, transrectal ultrasound (TRUS) prostate biopsy (12 core, local anesthetic prostate block) and volume study, radionuclide bone scan and abdominal-pelvic computed tomography (CT) scan. Patient characteristics are listed in Table 1.

Post-HIFU follow-up included clinical review at 2 weeks for removal of urethral catheter and trial of void, and subsequently review and PSA at 1, 3, 6 and 9 months and 3 monthly PSA thereafter. Biochemical success was defined as a PSA nadir ≤0.5 ng/mL (at any time). Our definition of failure was PSA≥0.5 ng/mL (at any time) or two consecutive rises in PSA (at any time). Biochemical failure would lead to a repeat TRUS prostate biopsy (12 core), World Health Organization (WHO) International Prostate Symptom Score (IPSS) and the International Index of Erectile Function (IIEF) questionnaires were administered before and after HIFU.

RESULTS

Eleven patients underwent one HIFU session. Ten patients had HIFU as the primary treatment, while one had it as second-line treatment after failed external beam radiation therapy (EBRT). The median (mean±SD) PSA nadir levels at 3 and 6 months were 0.6 (1.3 ± 2.13) ng/mL and 0.61 (1.08 ± 1.22) ng/mL, respectively. Of the 11 patients, only 2 (18%) were biochemically disease free at a median follow-up of 16 months. Nine patients (82%) had biochemical failure during follow-up and required repeat TRUS prostate biopsy. The median time to post-HIFU biopsy (9 patients) was 11.6 months (range, 5–20 months), and all had biopsy-proven residual disease. Of the nine patients who had repeat biopsy, two biopsies occurred within 6 months post-procedure, while the other seven occurred beyond the 6-month mark. In terms of timing of biochemical failure, seven patients had failed (either by way of not reaching a PSA nadir or two consecutive rises) within 3 months, increasing to a total of eight failures by 6 months, and nine failures by 9 months. The actuarial DFS rate was 16% at median follow-up. Three patients went onto salvage radical retropubic prostatectomy (RRP). All three had negative surgical margins and had an undetectable PSA (<0.01 ng/mL). Two had more HIFU. Three elected to be managed by watchful waiting. One was lost to follow-up. Table 2 summarizes these results.

There was no mortality or major morbidity. Minor urinary complaints were common. Five patients had acute retention of urine after the urethral catheter was removed on day 10–14. One required a transurethral resection of the prostate (TURP) (which incidentally found residual adenocarcinoma of the prostate on pathological assessment of the prostate chips) and the other four patients were taught clean intermittent self-catheterization. One patient required solfenacin for urge symptoms. Three patients required drug treatment for erectile dysfunction. There was no objective decline in flow rate (Qmax, mL/sec) as measured by office uroflow. However, there was minor deterioration in urinary and erectile function as measured by IPSS and IIEF questionnaires [Table 2].

DISCUSSION

These results highlight that having a low threshold for re-biopsy post-HIFU reveals a high local failure rate. At 9 months post-HIFU, nine patients (82%) had failed by way of PSA
Table 2: Oncological and clinical outcomes of 11 patients who underwent HIFU

| Outcome                                    | Value n (%)     |
|--------------------------------------------|-----------------|
| Oncological                                |                 |
| Biochemical disease-free rate              | 2 (18)          |
| Biochemical failure rate                   | 9 (82)          |
| Biopsy-proven persistent disease rate      | 9 (82)          |
| Mean (range)                               |                 |
| Functional                                 |                 |
| Qmax (mL/sec)                              |                 |
| Pre-HIFU                                   | 20 (15–29)      |
| Post-HIFU, at 3 months                     | 19 (10–30)      |
| WHO IPSS (out of 35 points)                |                 |
| Pre-HIFU                                   | 2/35 (0–7/35)   |
| Post-HIFU, at 3 months                     | 6/35 (1–13/35)  |
| WHO quality of life score (out of 6 points)|                 |
| Pre-HIFU                                   | 1/6 (0–2/6)     |
| Post-HIFU, at 3 months                     | 1/6 (0–3/6)     |
| IIEF (out of 25 points)                    |                 |
| Pre-HIFU                                   | 25/25 (15–25/25)|
| Post-HIFU, at 3 months                     | 17/25 (5–25/25) |
| Acute urinary retention                     | 5 (45)          |
| Mild stress urinary incontinence           | 1 (9)           |
| Urinary infection                          | 1 (9)           |
| Erectile dysfunction                       | 3 (27)          |

HIFU: High-intensity focused ultrasound

nadir (or rising PSA) criteria. Despite having acceptably low morbidity, the oncological efficacy of HIFU is doubtful in this series. These are the results of a single surgeon with a sub-specialized, high-volume prostate cancer surgical practice. These patients would have otherwise been offered RRP or radiotherapy (in its various forms). Having only II patients makes it difficult to interpret anything more than trends; however, the follow-up is long enough within this group for these observations to be meaningful. Our results are not biased by the use of neoadjuvant or adjuvant hormonal therapy.

HIFU remains an emerging technique for localized prostate cancer. A rectal probe focuses the delivery of ultrasonic energy into a precisely demarcated “lesion”, the size of a grain of rice, which ablates the tissue via the process of coagulative necrosis. A computer program organizes the delivery of these “lesions” in a coordinated and thorough fashion such that the entire gland is treated, with minimal collateral tissue damage. Of the two available devices, Ablatherm (EDAP TMS S. A., Vaulx-en-Velin, France) and Sonoblate (Focus Surgery, Inc., Indianapolis, IN, USA), the published series predominately relate to the Ablatherm device. The differences between the two relate to treatment delivery techniques, both having undergone improvements such as the inclusion of degassed rectal cooling liquid to minimize rectal injury. Interest in HIFU by urologists and patients alike is linked in part to the stage migration in the diagnosis of prostate cancer to an earlier T-stage, low-grade, low-volume, organ-confined disease in younger men. This is most prevalent in the United States, Canada, the United Kingdom, and Australia where PSA testing is routinely applied. There is reluctance by some to subject such patients to the morbidity of RRP and a similar distrust in an active surveillance program where there exists patient anxiety regarding whether the cancer may progress and the chance for curative treatment being missed. Other reasons for interest in HIFU include familiarity with TRUS among urologists which curtails the learning curve, the ability to perform this as a day-stay procedure, and reaching a PSA nadir within 3–4 months exposes the failed cases much earlier than would be the case with primary EBRT.

Since its introduction for use in prostate cancer in 1995, there have evolved a vague set of patient and tumor suitability criteria for using HIFU as a primary modality for localized prostate cancer. These criteria include: PSA<15 ng/mL, Gleason score (GS)<7, clinically organ-confined disease (T1–T2, N0, M0), prostate volume <40 mL, absence of intra-prostatic calcification, as well as the patient being unsuitable for, or refusing, established treatments (mainly RRP). These criteria are reflected in the published series’ baseline patient characteristics being in keeping with most centers selecting patients with D’Amico low-risk (and to a lesser extent, intermediate-risk) disease or those who are unsuitable for RRP as the types of patients being offered HIFU as the primary treatment. Centers which increase their PSA nadir to ≥0.5 ng/mL find a corresponding decline in negative biopsy, and therefore DFS rates. More recently, the use of a definition of biochemical failure as being the PSA nadir plus 1.2 ng/mL has the potential to cast HIFU in a more favorable light in terms of treatment success. Controversy surrounding the efficacy of HIFU is due to the lack of long-term PSA and prostate biopsy follow-up data, and the lack of standardized, reproducible definitions of success or failure of the treatment.

The two largest single institutional series have a biochemical DFS rate of 67–78%, over a median follow-up of 5 years. However, both series had a rate of hormonal treatment of 33–50%. Having said this, their definition of biochemical failure was more strict – a negative post-HIFU biopsy plus a PSA nadir <0.1 ng/mL. The largest series (six European centers, 1995–2000, Ablatherm, n=402) based their oncological efficacy on sextant prostate biopsies post-HIFU. The overall negative biopsy rate was 87% (92% for low-risk, 86% for intermediate-risk, 82% for high-risk disease groups) with a mean follow-up of 13.6 months. In addition, 9% had prior EBRT, 26% had some form of hormonal manipulation, 28% required a second HIFU session and they found a larger gland was predictive of failure. The study with the longest follow-up (mean 6.4 years) in 140 patients produced an actuarial DFS rate of 59%. It is therefore reasonable to quote a DFS rate of between 60 and 70% at 5 years, based on negative prostate
biopsies and PSA nadir ≤0.5 ng/mL. In one center, 30 patients with D’Amico high-risk prostate cancer were treated with Ablatherm HIFU\textsuperscript{[9,16]} All patients had hormonal therapy for 3 years and TURP prior to HIFU. At 1 year, three patients had a PSA >0.3 ng/mL and 23% had a positive biopsy.

Several series have elucidated that lowering the PSA nadir threshold for post-HIFU re-biopsy improves the negative biopsy rate, and the reverse is true.\textsuperscript{[3,7]} Using a PSA nadir <0.2 ng/mL, the negative biopsy rate can be up to 89%. However, when the nadir cut-off is increased to >1.00 ng/mL, the negative biopsy rate is closer to 50%. In addition, negative biopsy rates are higher in low-risk (vs. intermediate- or high-risk) disease. There are no standard definitions of biochemical failure/success and equally no firm consensus guidelines regarding the timing of re-biopsy post-HIFU. The American Society for Therapeutic Radiation and Oncology (ASTRO) definition of biochemical failure should not be applied to HIFU, as it is designed for radiotherapy PSA surveillance specifically. Uchida et al. analyzed the association between PSA nadir and treatment failure (by biopsy-proven residual disease, at 6 months).\textsuperscript{[12]} They reported a statistically significant association between treatment failure and PSA nadir. When the PSA nadir was between 0 and 0.2 ng/mL, the treatment failure rate was 11%, whereas when the PSA nadir was between 0.21 and 1.00 ng/mL, the treatment failure rate rose to 46%. A key conclusion from this work was that lowering the PSA nadir to ≤0.2 ng/mL corresponds to an 89% disease-free rate at 6 months. These findings were reiterated in another series.\textsuperscript{[6]}

Much of the earlier efficacy data are based on sextant biopsies carrying the inherent risk of under staging and sampling error. Limited patient follow-up is of course another reason due to which we lack true oncological efficacy data. Longer follow-up times, a widespread use of 12-core biopsies, and standardization of definitions for failure will hopefully deliver more accurate efficacy values. There is no doubt that HIFU is appealing in terms of its excellent morbidity profile, short learning curve, precisely demarcated and controlled delivery of ablative lesions and familiarity with ultrasound imaging techniques for delivery. HIFU has emerged as a type of focal ablative, gland-sparing therapy in the context of accurate TRUS imaging of the prostate, pathological staging data obtained from needle biopsies, and PSA values to identify patients with low volume or unifocal disease.\textsuperscript{[17]} In this series, all urinary and erectile morbidity was easily managed. However, a trend toward erectile dysfunction was noted. The use of self-administered IPSS and IIEF questionnaires is a reliable method of comparing pre- and post-HIFU morbidity. In the PSA era, where more prostate cancer is screen detected, HIFU provides another option for the treatment of low- to intermediate-risk organ-confined disease, with appropriate tumor and gland volume factors. It should be emphasized in discussions with patients that HIFU is an option only if the established modalities (RRP, EBRT) are not appropriate.

Recently, there have been attempts to better define biochemical failure. In a study of 285 men followed for a median of 4.7 years, 71 were defined as having clinical failure on the basis of a positive biopsy or the need for additional therapy and this was used to establish the Stuttgart definition of biochemical failure following HIFU as being PSA nadir plus 1.2 ng/mL.\textsuperscript{[13]} In another recent paper, PSA nadir after HIFU correlated highly significantly with treatment failure and DFS rate when a PSA nadir cut-off of equal of below 0.2 ng/mL was used.\textsuperscript{[18]} In neither of these studies was there complete reliance on treatment failure being defined by positive prostate biopsy, which is a limitation on any attempt to define treatment failure. Disturbingly, the use of the recently described Stuttgart definition for failure is being popularized and will undoubtedly cast HIFU in a more favorable light when the success of treatment is considered in short- to intermediate-term studies.

A low threshold to re-biopsy patients post-HIFU reveals a high local failure rate. Previous high thresholds to re-biopsy and possibly inadequate gland sampling may have overestimated its oncological efficacy. The high prevalence of positive biopsies on a very low threshold to biopsy suggests that great caution needs to be applied to the use of definitions of treatment success that rely upon definitions of biochemical failure that have not been entirely based on positive biopsy results.

The major drawback of this study is the small numbers of men treated, but the impact of such a significant number of men failing as determined by histopathologic assessment justifies the reporting of these findings. Modern HIFU has been available for use in clinical practice in many areas of the world for over 5 years, but has failed to become a mainstream approach to managing early stage prostate cancer. There is certainly a mismatch between the uptake of this technology and the results that have been seen with HIFU to this point in time. This may be a reflection of users quickly becoming dissatisfied with the clinical outcomes with their personal experience and the cost of the technology. With the former, a failure to obtain similar results to major series published is a disincentive to continue with the technology. Furthermore, there is a difficulty in reporting or publishing the unfavorable results of small series experiences, particularly when the favorable results have already been published for larger series. Following our treatment of 11 men in this report, the poor results made it difficult to morally justify the treatment of more men with HIFU in its current form. It is our belief that this therapy should only be offered in the setting of an Institutional Review Board approved trial where routine follow-up biopsy forms part of the protocol.
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