Results of high intensity focused ultrasound treatment of prostate cancer: early Canadian experience at a single center

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Introduction: *High intensity focused ultrasound (HIFU) is a non-invasive technique that uses focused ultrasound waves to ablate tissue. This retrospective study evaluates the early HIFU experience at a single Canadian center.*

Materials and methods: *Ninety-five patients were treated between March 2006 and December 2007 using the Sonablate 500 device (Focus Surgery, Indianapolis, IN, USA). Follow up occurred at 3 month intervals and included serial prostate-specific antigen (PSA) measurements, assessments of erectile function and continence rates with the international index of erectile function (IIEF) and expanded prostate cancer index composite (EPIC) questionnaires respectively. Early and late complications were also studied.*

Results: *There were 95 patients treated by five urologists. The mean age of patients was 64 years (range 46-91). The majority of men treated had Gleason 6 (n = 53) or Gleason 7 (n = 35) disease. The remainder had Gleason 8 (n = 5) and Gleason 9 (n = 2) prostate cancer. Prostate volume in the pre-treatment group was 30.5 cc (range 14.4 cc-73 cc). Cytoreductive androgen deprivation therapy prior to treatment was administered to 10 men. Post-HIFU with a minimum 6 months follow up (mean 10.62 months), 2% (1/59) of men had de novo moderate to severe erectile dysfunction (IIEF ≤ 11). With a minimum of 6 months follow up (mean 8.85 months), 17% (7/41) of the men had significant incontinence according to their EPIC scores. Early complications included catheter-related problems (n = 10), retention (n = 16), and urosepsis (n=1). Late complications included need for cystoscopy (n=25), TURP (n = 6), VIU/dilatation for stricture or bladder neck contracture (n = 13) and self-catheterization (n = 1). Prostatorectal fistula occurred in one patient who had prior radiotherapy. Salvage HIFU following radiation failure was performed in seven men. Recurrence of cancer following HIFU was diagnosed in seven men. Salvage treatment included radical prostatectomy (n = 3), radiation therapy (n = 2), repeat HIFU (n = 1), hormone therapy (n = 1).*

Conclusions: *In our early experience HIFU treatment for prostate cancer was associated with a moderate rate of complications and failure. Further studies are required to examine long term outcomes with HIFU.*

Key Words: HIFU, technique, treatment for prostate cancer

Introduction

As a result of prostate-specific antigen (PSA) screening programs and an increased public awareness of this disease, there has been an increase in the proportion of men diagnosed with early stage prostate cancer. This earlier diagnosis affords the clinician the opportunity to provide "cure" with the obligation to consider long term preservation of quality of life. Men diagnosed with localized prostate cancer face the choice between active surveillance or radical treatment with either radical prostatectomy (RP) or radiotherapy/brachytherapy.[1] Each modality confers an associated risk of morbidity. The potential for erectile dysfunction

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and urinary incontinence remains high, even in the era of minimally invasive radical prostatectomy. Patients undergoing radiotherapy/brachytherapy are at risk for bowel and bladder symptoms, as well as long term complications of erectile dysfunction and persistent lower urinary tract symptoms.[1,2] The choice of active surveillance carries the psychological burden of living with cancer and need for repeated check ups and biopsies.[3,4]

High intensity focused ultrasound (HIFU) has emerged as a new technique with which men are treated in a minimally invasive, out-patient manner that may lessen the risk of experiencing the more serious complications of radical therapy with the goal of providing equivalent cancer control.

Transrectal HIFU employs the principal of ultrasound energy focused through an acoustic lens to generate heat-induced coagulative tissue necrosis and cavitation.[5] The ultrasound probe is used to both image and sequentially ablate a targeted lesion without damaging the transmitted through or adjacent tissue. The dimensions of a single ablated zone are 3 mm x 3 mm x 12 mm high when using the Sonablate machine. HIFU is able to be performed on men most commonly using a spinal anesthetic and I.V. sedation. The treatment typically lasts between 2-3 hours (depending on the volume of the prostate) and all men are discharged home the same day. HIFU has been approved by Health Canada for the treatment of localized prostate cancer in both the primary and salvage setting.[6] Currently, HIFU remains investigational in the United States and is pending FDA approval. HIFU treatments at our center are performed using the Sonablate 500 device (Focus Surgery, Indianapolis, IN, USA). The Sonablate allows the physician to adjust the power based on tissue response, visualized in real time.[7] We report our early single center experience of HIFU for the treatment of localized prostate cancer in the primary and salvage setting.

Materials and methods

Men in this retrospective study elected to have HIFU for localized prostate cancer at our treatment facility, Can-Am HIFU (Toronto, Ontario, Canada). Men were counseled regarding their treatment options by their referring physician as well as the treating physicians. Exclusion criteria were prostate volume greater than 40 mL or maximum AP height greater than 40 mm, any calcification greater than 10 mm in maximum diameter, any condition with increased risk of fistulae or anorectal disease preventing probe insertion.[8-11]

All men were referred with baseline demographic information, most recent PSA and PSA at time of biopsy, prostate biopsy result. Men whose prostate volumes exceeded the upper limit of treatment criteria were initiated on a short course of anti-androgen therapy with either a 5-alpha reductase inhibitor or an LHRH-agonist to reduce gland volume. A pre-treatment follow up transrectal ultrasound (TRUS) was then necessary to ensure that the prostate responded sufficiently to meet the inclusion criteria. Prior to treatment, men were instructed on the follow up protocol, which included serial PSA measurements at 3 month intervals for the first 2 years. Men were requested to complete validated questionnaires before treatment and at each follow up appointment. All questionnaires were to be completed at 3, 6, 9, 12, 18 and 24 months post procedure. The questionnaires included the International Index of Erectile Function-5 (IIEF-5)[12] and the Expanded Prostate Cancer Index Composite – urinary domain (EPIC-Urinary).[13] The IIEF-5 classifies erectile dysfunction into five categories based on the scores: severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), and no ED (22-25). Moderate to severe ED is any score less than or equal to 11. The EPIC-Urinary questionnaire looks specifically at incontinence and voiding dysfunction. We looked specifically at Question 1 ("over the past 4 weeks how often have you leaked urine?") and Question 4 ("which of the following best describes your urinary control over the past 4 weeks?").[13] The definition of biochemical failure (BCF) specific to patients treated with HIFU therapy – the "Stuttgart definition" of PSA nadir plus 1.2 ng/mL was utilized.[14] The HIFU treatment was performed using the Sonablate 500 device after a spinal anesthetic and with I.V. sedation. The technique of HIFU using Sonoblate has been previously described.[5,7,8]

Results

A total of 95 men were treated with the Sonablate 500 device at our single center between March 2006 and December 2007. The mean age was 64 years (range 46-91). No men received a transurethral resection preoperatively as part of HIFU treatment. Risk stratification was as follows: 55.8% were low risk (Gleason 6, n = 53), 36.8% were intermediate risk (Gleason 7, n = 35), and 7.3% were high risk (Gleason 8 and 9, n = 7). Of the seven men who had high risk disease, three men (42.9%) had previous external beam radiation failure. All men required a TRUS and biopsy prior to their treatment. Prostate volumes were measured at the time of treatment as well. Mean prostate volume in the pre-treatment group was 30.5

cc (range=14.4 cc-73 cc). Prostate volumes between 40 cc-50 cc were measured in nine patients and one patient had a volume greater than 50 cc. The prostate volume at time of referral and at time of treatment may have been discrepant resulting in higher treatment volumes once patients arrived from out-of-province for treatment.

Cytoreductive hormones were used prior to HIFU in 10 men (10.5%) to achieve smaller gland sizes for treatment criteria. All hormones were discontinued following HIFU treatment. All men were discharged from our center the same day as their treatment. Our protocol has men begin clamping their suprapubic tubes on post-procedure day 10-14 to initiate trials of voiding. The SP tube is typically removed on post-procedure day 10-21. The nurses from our center conducted regularly scheduled phone follow ups to assess complications and remind men to complete the questionnaires. Complications were assessed by patient self-report, hospital records, and referring physicians' notes which were sent to our center. Complications were divided between early, late and serious. Sexual dysfunction and incontinence were assessed separately. Early complications included catheter-related issues, including catheters falling out or becoming blocked. Catheter-related issues occurred in 11% of men (n = 10/95). Urinary retention following the removal of the catheter occurred in 17% of men (n = 16/95). Urosepsis occurred in a single patient (n = 1/95). No cases of non-febrile urinary tract infection or epididymitis were seen in our series. Late complications occurred greater than 30 days following treatment. The need for cystoscopy to assess a change in urinary function occurred in 28% of men (n = 25/90). Retained necrotic tissue causing symptoms such as retention, which subsequently required transurethral resection, occurred in 6% of patients (n = 6/95). Urethral strictures requiring either dilatation with local anesthetic or visual internal urethrotomy (VIU) under general anesthetic occurred in 9% of men (n = 9/95). More significant bladder neck strictures/contractures requiring a combination of dilatation, incision, and/or transurethral resection occurred in 4% of men (n = 4/95). One patient required self-catheterization as a result of stricture and retention. One man developed a recto-urethral fistula. This man had previously had a transurethral resection of the prostate and external beam radiation therapy. He was managed conservatively with catheter drainage and did not require a bowel diversion.

As part of baseline assessment and postoperative follow up, men were requested to complete validated study questionnaires. Erectile dysfunction (ED) was assessed with the IIEF-5. Baseline data demonstrated a mean pre-HIFU IIEF score of 19.1/25 (n = 75, range 5-25). This would indicate a mild degree of ED before any treatment was carried out. The mean IIEF scores at each 3 month interval were 18.5 (n = 48), 18 (n = 52), 17.5 (n = 29), 17.4 (n = 24), 18 (n = 12), and 20.5 (n = 2), respectively. On further analysis of the data at 6 months, while the mean IIEF score was 18/25 (n = 52), the number of cases with moderate-severe ED (IIEF ≤ 11) was 19% (n = 10/52). However, 6 of those 10 men had pre-treatment IIEF score ≤ 11. An additional 3/10 men had pre-treatment IIEF scores ranging between 15-19, indicating pre-existing moderate ED. There was only a single patient who had a pre-treatment IIEF score of 25, who after 9 months of follow up had an IIEF score of 5. Only one patient had a significant decrease in erectile function following HIFU (n = 1/52, 2%). The remaining 81% (42/52) of men had a mean IIEF score of ≥ 21/25 (mild-no ED) at 6 months of follow up , Table 1.

Urinary function and continence rates were assessed with self-report and the EPIC-Urinary questionnaire. At baseline 51 men had an EPIC-Urinary questionnaire completed. The mean score of Questions 1 and 4 was

TABLE 1. **Baseline and follow up statistics for PSA, EPIC and IIEF**

Time	PSA (ng/mL)			EPIC (Q1&4) (score/9)			IIEF (score/25)		
(mo)	n	median	range	n	mean	range	n	mean	range
0	95	5.33	0.19-14.5	51	8.45	5-9	75	19.1	3-25
3	81	0.28	0.01-12	32	7.41	3-9	48	18.5	3-25
6	74	0.46	0.01-6.65	35	6.77	2-9	52	18.0	5-25
9	55	0.33	0.01-8.4	20	6.95	2-9	29	17.49	5-25
12	42	0.72	0.01-6.65	7	7.00	4-9	24	17.42	5-25
18	27	0.68	0.01-7.18	3	6.67	5-9	12	18.0	5-24
24	13	0.30	0.03-1.33	-	-	-	2	20.5	17-24

PSA = prostate-specific antigen; EPIC = expanded prostate cancer index composite; IIEF = international index of erectile function

8.45/9 (range 5-9). Of these men, 25% (13/51) had some leakage prior to treatment. At a minimum of 6 months, 41 men had filled out an EPIC questionnaire. At a minimum of 6 months follow up (mean 8.85 months) 20/41 (49%) had no leakage (scores of question 1 and 4 were 9/9) and 51% (21/41) reported any leakage after HIFU (scores of 8/9 or less). At a minimum of 6 months follow up (mean 8.85 months) 17% (7/41) had reported leakage at least once per day and/or frequent dribbling or worse. We would consider these patients as having clinically significant incontinence, Table 1.

The primary goal of HIFU for treatment of localized prostate cancer is oncologic control. Like other treatment modalities for prostate cancer, we follow PSA as a surrogate marker for cancer control. At baseline, the median PSA was 5.33 ng/mL (n = 95, range 0.19 ng/mL-14.5 ng/mL). At the follow up intervals of 3, 6, 9, 12, 18, and 24 months the median PSA levels were 0.28 ng/mL (n = 81, range 0.01 ng/mL-12 ng/mL), 0.46 (n = 74, range 0.01-6.65), 0.33 (n = 55, range 0.01-8.4), 0.72 (n = 42, range 0.01-6.65), 0.68 (n = 27, range 0.01-7.18), 0.30 (n = 13, range 0.03-1.33). Using the new definition of BCF that is specific to patients treated with HIFU therapy – the "Stuttgart definition" of PSA nadir plus 1.2 ng/mL, 15% (n = 14/95) of patients demonstrated BCF across all groups demonstrated BCF across all groups, Table 1.

The decision to biopsy was left to the physician involved in follow up. Seven men underwent a subsequent biopsy for cause and all demonstrated residual or recurrence of cancer following HIFU treatment. However, 2/7 men had previous failed external beam radiation treatment. For those men who had evidence of cancer following HIFU, salvage treatment was offered. The men received either radical prostatectomy (n = 3), external beam radiation therapy (n = 2), repeat HIFU (n = 1), or hormone therapy (n = 1). Salvage HIFU following external beam radiation therapy was performed in seven men. Five of the seven men had successful salvage therapy with HIFU.

Discussion

The intermediate term results of HIFU in the published literature demonstrate a lack of consensus on biochemical outcomes and acceptable side effect profiles.[9,15,16-19] Blana et al compared different definitions of biochemical failure in patients treated with HIFU.[14] They reviewed data from 285 patients treated over a 9 year period and applied various accepted surrogate markers of BCF. These included PSA threshold values, PSA nadir plus values, PSA velocity, PSA doubling time, ASTRO and Phoenix definitions. The clinical failure rate was 25%. The best predictor of clinical failure was PSA nadir plus 1.2 ng/mL. This established the new "Stuttgart definition" of BCF following HIFU. The most reliable measurement for estimation of biochemical failure was the 6 month PSA when the nadir was reached at 3 months. The median PSA nadir in our cohort was reached at 3 months. Eighty-one men showed no evidence of BCF, while 14 men (15%) met the Stuttgart definition of failure.

Overall, 92% (n = 88/95) of men had a successful treatment. HIFU successfully salvaged 5/7 men who failed primary radiation therapy, who would have otherwise undergone a salvage radical prostatectomy or been initiated on ADT. This information as well as another pilot study stimulated the ongoing "Salvage HIFU for Primary Radiation Failure" study described by Barkin.[7] Erectile dysfunction rates were acceptably low. At 6 months of follow up, rates of new cases of ED were 2% (n = 1/52). There appeared to be stability of IIEF scores over time demonstrating that those men with prior ED did not deteriorate. The majority of treated men (81%) had mild to no ED (IIEF scores between 21-25) at 6 months.

The incidence of post-prostatectomy incontinence (PPI) varies depending on the definition of incontinence, method of data collected and the time of assessment after surgery. A significant discrepancy exists in outcomes between independent questionnaires and retrospective chart reviews.[20,21] It appears that the incidence of PPI is higher after self-administered questionnaires as opposed to patient interviews. Litwin et al designed and validated the UCLA PCI QOL questionnaire and found that 40% of patients complained of persistent long term incontinence after radical prostatectomy.[4] Although most were mild, 4% complained of significant leakage affecting their lifestyle. A recent review out of the University of Chicago by Shikanov demonstrated that "objective" rate of the trifecta (biochemical control, continence and erectile function) at 9 months following robot-assisted radical prostatectomy was 44%. This was almost 50% lower than the "subjective " report rates.[22] Furthermore, Litwin et al, from the CaPSURE database noted that patient reported impairment in incontinence was 97% versus 21% reported by physician using their self-administered questionnaire.[23] In our series 20/41 (49%) of men followed up for at least 6 months were completely dry on EPIC scores. The remaining 21/41 reported some leakage and 7/41 (17%) of these men had significant leakage. These continence rates are acceptable compared to surgery considering that some men may have had pre-existing leakage (25% in our series on EPIC questionnaire) and the fact that continence rates may improve in this group with longer follow up.

Our ability to report on disease status following treatment remains challenging. There are no defined criteria such as a PSA velocity or PSA threshold, which are routinely employed to trigger a biopsy. The Stuttgart criterion (PSA nadir + 1.2 ng/mL) appears to predict clinical progression reliably. It has not become broadly accepted yet.

We have reported the short term results of a group of men treated early in the experience of our institution. Many of the early post-treatment side effects may over time change in nature. It has been reported that urinary symptoms, continence rates, and potency often improve with time. Our data examines a relatively short follow up. In our estimation many men who experience bothersome voiding symptoms or diminution in erectile function would, over time, see a gradual improvement.

A significant limitation of this study relates to collecting data from patients originating from disparate locations. Men were referred from across Canada and the United States. The difference we see in the prostate volumes at time of referral and time of treatment relate to differences in technique of measurement, passage of time, and the unpredictable nature of cytoreductive hormone therapy on gland size. At baseline, 75/95 men completed the IIEF questionnaire. There were several men who refused to fill out questionnaires at baseline and during the follow up. We relied on thorough follow up by the clinic nurses who contacted both the patients and their primary care physicians.

We acknowledge the fact that prostate cancer is a slow growing and chronic disease that requires long term follow up. In this particular report we intentionally looked at the minimum 6 month data only. The reason was that we wanted to compare to the gold standard of radical surgery, where one should achieve biochemical nadir by 3 months and where early rise at 6 months indicates failure or the need for salvage radiation. In this case we utilized the 3 month nadir and the 6 month definition of biochemical failure to predict for us the patients that would fail in the long term. We are still doing HIFU, now 4.0 years since this cohort was treated. It is still difficult for full follow up because patients do come from across North America. However, our data collection has improved significantly because of electronic reporting and a central registry. This cohort is still being followed with an additional six patients reporting late biochemical, biopsy proven failure and requiring some secondary treatment.

Approximately 18 months ago, new software was introduced to the Sonoblate machine called TCM or Tissue Change Monitoring.[7] This allows the physician immediate feedback on the achievement of the desired temperatures "at each 3 mm treatment lesion". If this has not been successful, then the surgeon has the option of re-treating that specific segment immediately.

In the last 12 months, with this new software and modified techniques, our 6 month nadir on Gleason 6 and 7 patients has been less than .02 ng/mL, in 92% of the patients.

Conclusion

Our initial HIFU experience in a cohort of 95 men resulted in a no evidence of disease (NED) rate of 85% at a median follow up of 8 months. De novo erectile dysfunction was documented in only 2% of treated men, with 81% having mild or no erectile dysfunction. Seventeen percent of patients had significant urinary incontinence at 6 months. Erectile dysfunction and incontinence rates with HIFU in our series with a minimum follow up of 6 months were acceptable. In the short term, patient adherence and limited duration of follow up prevented complete data ascertainment. This early encouraging data justifies continuing treatments, stimulates modifications in technique and software and warrants further prospective longitudinal trials and follow ups of this novel, minimally invasive technology. □

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