# Focal Therapy for Localized Prostate Cancer: A Phase I/II Trial

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**Abbreviations and Acronyms**

EPIC = Expanded Prostate Cancer Index Composite
FACT-P = Functional Assessment of Cancer Therapy-Prostate
HIFU = high intensity focused ultrasound
IIEF-15 = International Index of Erectile Function-15
I-PSS = International Prostate Symptom Score
mp-MRI = multiparametric magnetic resonance imaging
MRI = magnetic resonance imaging
PSA = prostate specific antigen
SPC = suprapubic catheter
TPM = template prostate mapping
TRUS = transrectal ultrasound

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Endorsed by the Cancer Research United Kingdom Clinical Trials Awards and Advisory Committee/Feasibility Studies Committee, and approved by the National Cancer Research Network.

**For another article on a related topic see page 1484.**

**Purpose:** Men with localized prostate cancer currently face a number of treatment options that treat the entire prostate. These can cause significant sexual and urinary side effects. Focal therapy offers a novel strategy that targets the cancer rather than the prostate in an attempt to preserve tissue and function.
**Materials and Methods:** A prospective, ethics committee approved trial was conducted to determine the side effects of focal therapy using high intensity focused ultrasound. Multiparametric magnetic resonance imaging (T2-weighted, dynamic contrast enhanced, diffusion-weighted) and template transperineal prostate mapping biopsies were used to identify unilateral disease. Genitourinary side effects and quality of life outcomes were assessed using validated questionnaires. Posttreatment biopsies were performed at 6 months and followup was completed to 12 months.
**Results:** A total of 20 men underwent high intensity focused ultrasound hemiablation. Mean age was 60.4 years (SD 5.4, range 50 to 70) with mean prostate specific antigen 7.3 ng/ml (SD 2.8, range 3.4 to 11.8). Of the men 25% had low risk and 75% had intermediate risk cancer. Return of erections sufficient for penetrative sex occurred in 95% of men (19 of 20). In addition, 90% of men (18 of 20) were pad-free, leak-free continent while 95% were pad-free. Mean prostate specific antigen decreased 80% to 1.5 ng/ml (SD 1.3) at 12 months. Of the men 89% (17 of 19, 1 refused biopsy) had no histological evidence of any cancer, and none had histological evidence of high volume or Gleason 7 or greater cancer in the treated lobe. In addition, 89% of men achieved the trifecta status of pad-free, leak-free continence, erections sufficient for intercourse and cancer control at 12 months.
**Conclusions:** Our results appear sufficiently promising to support the further evaluation of focal therapy as a strategy to decrease some of the harms and costs associated with standard whole gland treatments.

**Key Words:** high-intensity focused ultrasound ablation, magnetic resonance imaging, biopsy, prostatic neoplasms

PROSTATE cancer is associated with treatment options that remain controversial.[1] Whole gland therapy using surgery or radiotherapy is associated with well documented morbidity including urinary incontinence (5% to 20%), erectile dysfunction (30% to 60%) and bowel toxicity (5% to 10%). Active surveillance provides a rational choice for some individuals with



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clinically insignificant disease as a strategy to reduce the burden of over treatment. However, active surveillance is infrequently used and approximately a third of patients on active surveillance require treatment.[2–4]

Focal therapy may offer another, complementary strategy that addresses the problem of over treatment. Focal therapy in prostate cancer incorporates the principles of organ preservation used in other solid organ cancers.[5–7] Using this approach damage to the bladder neck, rectum, external urinary sphincter and neurovascular bundles is minimized by targeting the cancer with a margin of normal tissue. In the prostate up to a third of men with localized prostate cancer have unilateral disease that may be suitable for hemiablation of 1 lobe.[8–10]

To test the principle that focal therapy using HIFU might confer fewer side effects we conducted a prospective phase I/II trial. This trial standardized the performance of focal therapy in a carefully characterized cohort using outcomes assessed with validated patient reported measures. As such, our report conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[11] In addition, it is a therapeutic exploratory trial that represents stage 3 in the Medical Research Council (United Kingdom) guidelines for evaluating a complex intervention.[12]

## METHODS

### Design, Setting and Patients

Our phase I/II trial received research ethics committee approval (University College London Hospitals Local Research Ethics Committee A, United Kingdom). In addition, the study was independently audited by hospital research officials. The protocol was independently peer reviewed and endorsed by Cancer Research United Kingdom's Clinical Trials Awards and Advisory Committee/Feasibility Study Committee, and was approved by the National Cancer Research Network. The National Cancer Research Network is a national United Kingdom government agency of independent experts which monitors and prioritizes key cancer trials.

Men could enter into the study through 1 of 2 routes between July 2006 and October 2008 (fig. 1). Those men with low to intermediate risk unilateral disease (Gleason 4 + 3 or less, PSA 15 ng/ml or less, cT2bN0M0 or less) diagnosed by TRUS guided biopsies who had received no prior treatment could enter stage 1. These men underwent mp-MRI and template transperineal mapping biopsies (TPM) within the trial. Of the 25 men entering via this route 16 (64%) had bilateral disease and were excluded from study. For the other study entry option those men who had mp-MRI and TPM to protocol standards outside of the trial were eligible to enter the therapy stage. Of the 119 men who underwent TPM during the recruitment period 34% (40 of 119) had unilateral disease but only a minority (9%, 11 of 119) were recruited. In either scenario men who had no evidence of disease in 1 lobe of the prostate were deemed eligible for hemiablation. Histological outcome was the primary factor in determining laterality.

### Intervention

***Cancer localization.*** MRI was performed at 1.5 Tesla using pelvic phased array coils. Sequences included T2-weighting, dynamic gadolinium (Dotarem®) contrast enhancement and diffusion weighting. TPM biopsies were performed with the patient under general/spinal anesthesia with the prostate sampled at 5 mm intervals[13] and reported by a single uropathologist (fig. 2).

***Treatment.*** Men underwent hemiablation using a transrectal HIFU device (Sonablate® 500). All had sterile urine

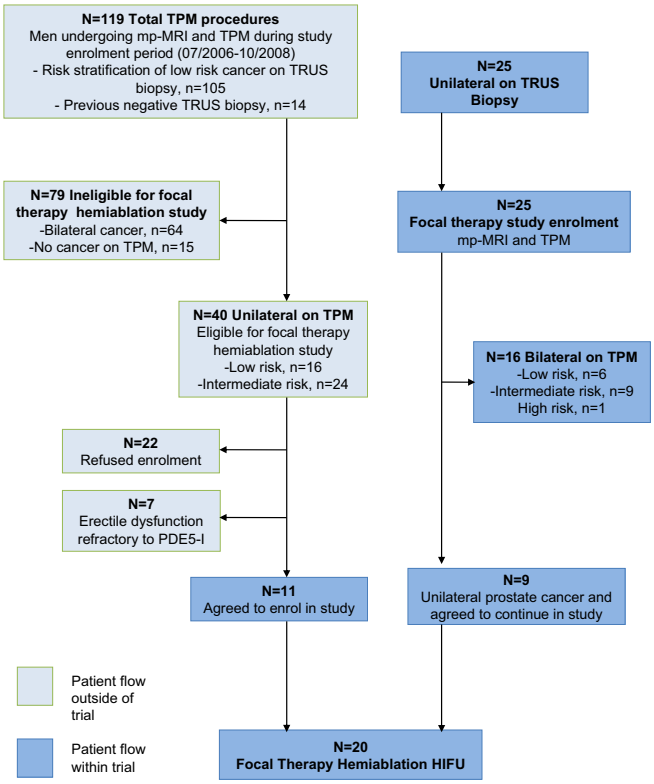


**Figure 1.** Flow chart demonstrating patient flow within focal therapy study. *PDE5-I*, phosphodiesterase type 5 inhibitor.

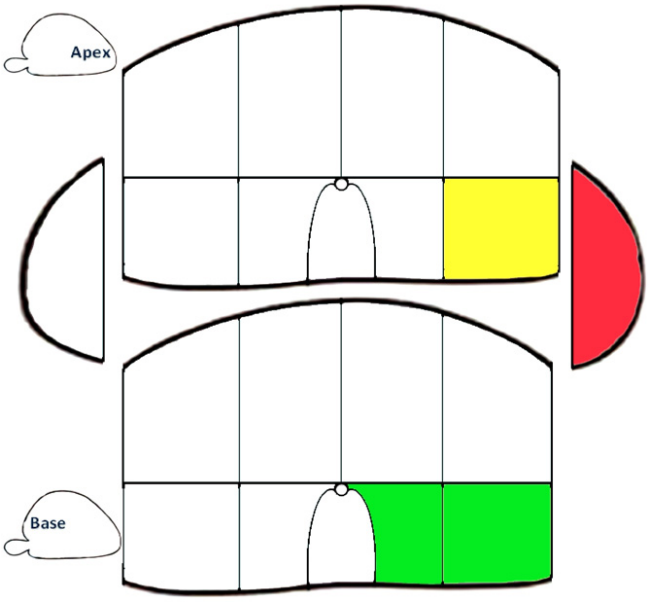


**Figure 2.** Template transperineal biopsies use 5 mm sampling frame to biopsy entire gland. Biopsies are plotted into 20 zones (modified Barzell system) and diagram depicts 2 positive zones. Red zones represent areas with Gleason 4 + 3 and/or maximum cancer core length involvement 6 mm or greater. Yellow zones represent areas with Gleason 3 + 4 and/or maximum cancer core length involvement 4 to 5 mm. Green zones represent areas of Gleason 3 + 3 with maximum cancer core length involvement 3 mm or less.

culture within 6 weeks of treatment and all had intravenous gentamicin at the time of anesthetic. A SPC was placed before HIFU. The whole of the positive prostate lobe was treated up to the midline as defined by the urethra. Where disease was identified in the midline in 4 men, the zone of ablation was extended 5 mm over midline. The SPC was placed on free drainage for 2 days and urethral voiding was encouraged thereafter. All men were given ciprofloxacin and oral analgesia (co-dydramol) for 7 days.

***Assessment.*** Contrast enhanced MRI was performed within 1 month to confirm the area of ablation, demonstrated by confluent poor enhancement. As many men traveled a long distance, the timing of SPC removal was delayed to coincide with this MRI even if urethral voiding was restored earlier. Followup consisted of clinic visits at 1 month and every 3 months thereafter for PSA measurement, adverse event reporting and validated questionnaires. Questionnaires included the I-PSS, IIEF-15, UCLA-EPIC urinary incontinence scale and FACT-P. At 6 months another mp-MRI followed by TRUS guided biopsies of the treated side were scheduled with a minimum requirement for sampling every 1 ml residual tissue with 1 core. Biopsies of the contralateral side were permitted if a new lesion, suspicious of cancer, was seen on mp-MRI.

***Statistical considerations.*** As the primary objective of the study was to determine the side effect profile of HIFU hemiablation, the sample size was powered on a common event rate, namely erectile dysfunction. We estimated that focal therapy would lead to a 5% rate of erectile dysfunction (insufficient for penetrative sex) at 12 months. The sample size calculation was based on a comparison to a known rate[14] of 40% erectile dysfunction (achieved with whole gland HIFU treatment at our center).[15] Therefore, with an alpha of 0.01 and power of 90% (1-$\beta$), the sample size required was deemed to be 20.

The paired 2-sided Student t test was used to evaluate differences between continuous variables (PSA and questionnaire scores) measured at baseline and at each followup visit. Categorical patient reported functional outcomes were dichotomized into none to moderate or severe. McNemar's test was applied to assess whether marginal proportions were significantly different from each other between baseline and at each followup. Statistical signif-

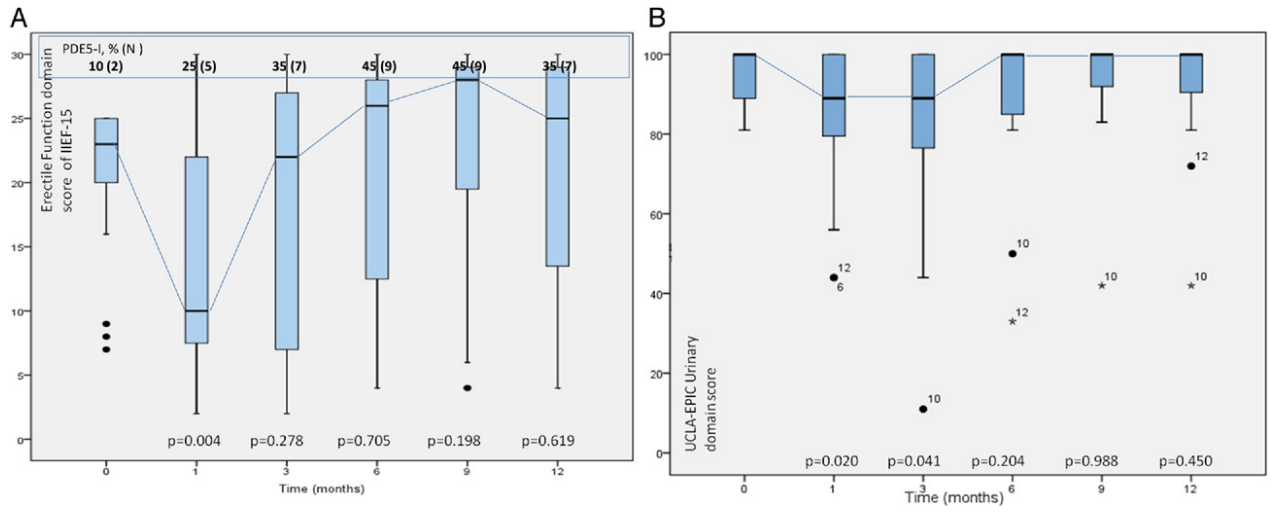


**Figure 3.** IIEF-15 erectile function domain scores (*A*) and UCLA-EPIC urinary domain scores (*B*) before and after focal therapy using HIFU hemiablation. *PDE5-I*, phosphodiesterase type 5 inhibitor.

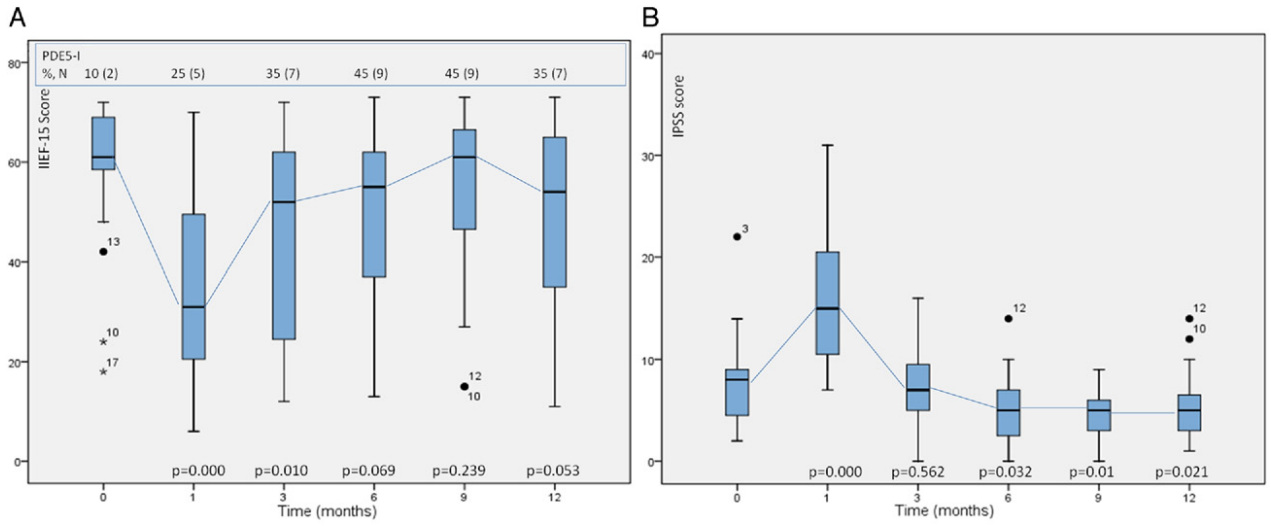


**Figure 4.** IIEF-15 questionnaire scores (*A*) and I-PSS (*B*) before and after focal therapy using HIFU hemiablation. *PDE5-I*, phosphodiesterase type 5 inhibitor.

icance was set at p ≤0.05 and all statistical tests were performed using SPSS® v.16.0.

## RESULTS

### Baseline Characteristics

Of the patients 40% had intermediate risk disease on TRUS guided biopsy (D'Amico risk categories).[16] The proportion with intermediate risk disease increased to 75% after TPM. Furthermore, 15% of patients (3 of 20) had biopsy characteristics which demonstrated the absence of Gleason pattern 4 and 5 with maximum cancer core length involvement 3 mm or less.

### Perioperative Outcomes

Mean procedure time was 2 hours with 18 patients discharged home within 24 hours. All men were able to void on postoperative day 2 with the SPC clamped. Of these men 30% experienced self-resolving, mild to moderate intermittent dysuria lasting a mean of 6.5 days. Intermittent hematuria with passage of debris occurred in 65% of patients for a mean of 15 days. A presphincteric stricture requiring dilation developed in 1 man.

### Patient Reported Outcomes

Figures 3 to 5, *A* summarize the functional status after hemiablation as assessed by validated questionnaire scores analyzed using standard methods.[17–20] The table provides greater detail of the subscores obtained.

***Erectile function (primary outcome).*** Erectile function domain and total IIEF-15 scores showed no

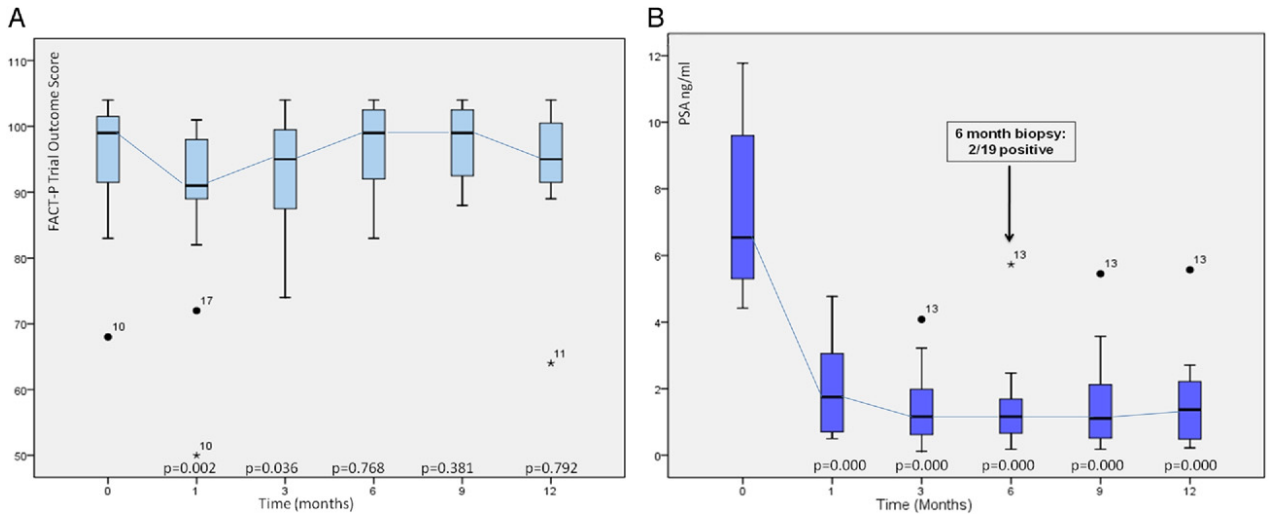


**Figure 5.** FACT-P trial outcome scores (*A*) and PSA (*B*) before and after focal therapy using HIFU hemiablation

*Detailed quality of life scores from IIEF-15 and FACT-P individual domain scores and I-PSS-QoL*

| | Baseline | 1 Mo Followup | 3 Mos Followup | 6 Mos Followup | 9 Mos Followup | 12 Mos Followup |
|---|---|---|---|---|---|---|
| % Lower urinary tract symptoms (No):* | | | | | | |
| Mild | 45 (9) | 5 (1) | 60 (12) | 80 (16) | 95 (19) | 80 (16) |
| Moderate | 50 (10) | 65 (13) | 40 (8) | 20 (4) | 5 (1) | 20 (4) |
| Severe | 5 (1) | 30 (6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| p Value | | 0.039 | 0.453 | 0.031 | 0.004 | 0.031 |
| Quality of life due to urinary symptoms score† | 1.1 | 2.3 | 1.5 | 1.0 | 0.9 | 1.0 |
| p Value | | 0.150 | 0.421 | 0.878 | 0.578 | 0.889 |
| Mean sexual function domain scores (range): | | | | | | |
| Erectile function‡ | 20.9 (7–25) | 14.3 (2–30) | 17.9 (2–30) | 21.7 (4–20) | 23.3 (4–30) | 21.8 (4–30) |
| p Value | | 0.004 | 0.278 | 0.705 | 0.198 | 0.619 |
| Orgasmic function§ | 8.7 (0–10) | 6.1 (0–10) | 6.4 (0–10) | 7.1 (1–10) | 7.4 (0–10) | 7.1 (1–10) |
| p Value | | 0.004 | 0.032 | 0.021 | 0.118 | 0.072 |
| Sexual desire‖ | 8.7 (0–10) | 5.9 (2–10) | 6.5 (4–10) | 6.9 (2–10) | 7.0 (2–10) | 7.0 (2–10) |
| p Value | | 0.001 | 0.015 | 0.002 | 0.004 | 0.028 |
| Intercourse satisfaction¶ | 9.8 (0–14) | 4.4 (0–12) | 7.1 (0–14) | 8.5 (0–15) | 9.6 (0–15) | 7.6 (0–15) |
| p Value | | 0.000 | 0.059 | 0.242 | 0.825 | 0.095 |
| Overall satisfaction** | 8.2 (3–10) | 5.8 (2–10) | 5.8 (2–10) | 7.4 (2–10) | 7.6 (2–10) | 7.0 (2–10) |
| p Value | | 0.001 | 0.003 | 0.114 | 0.290 | 0.030 |
| % IIEF-15 erectile dysfunction domain score (No.): | | | | | | |
| None | 40 (8) | 15 (3) | 35 (7) | 60 (12) | 65 (13) | 55 (11) |
| Mild | 40 (8) | 20 (4) | 20 (4) | 10 (2) | 10 (2) | 5 (1) |
| Mild-moderate | 5 (1) | 10 (2) | 5 (1) | 5 (1) | 5 (1) | 10 (2) |
| Moderate | 15 (3) | 35 (7) | 10 (2) | 20 (4) | 10 (2) | 15 (3) |
| Severe | 0 (0) | 20 (4) | 25 (5) | 5 (1) | 10 (2) | 5 (1) |
| Missing | 0 (0) | 0 (0) | 5 (1) | 0 (0) | 0 (0) | 10 (2) |
| None-moderate | 100 (20) | 80 (16) | 70 (14) | 95 (19) | 90 (18) | 95 (19) |
| Severe | 0 (0) | 20 (4) | 25 (5) | 5 (1) | 10 (2) | 5 (1) |
| p Value | | 0.125 | 0.063 | 1.000 | 0.500 | 1.000 |
| % IIEF-15 orgasmic dysfunction domain score (No.): | | | | | | |
| None | 80 (16) | 40 (8) | 30 (6) | 45 (9) | 55 (11) | 35 (7) |
| Mild | 10 (2) | 20 (4) | 25 (5) | 10 (2) | 0 (0) | 20 (4) |
| Mild-moderate | 5 (1) | 10 (2) | 10 (2) | 25 (5) | 30 (6) | 30 (6) |
| Moderate | 0 (0) | 0 (0) | 10 (2) | 10 (2) | 5 (1) | 5 (1) |
| Severe | 5 (1) | 30 (6) | 20 (4) | 10 (2) | 10 (2) | 10 (2) |
| Missing | 0 (0) | 0 (0) | 5 (1) | 0 (0) | 0 (0) | 0 (0) |
| None-mild | 95 (19) | 80 (14) | 75 (15) | 90 (18) | 90 (18) | 90 (18) |
| Mild-moderate-severe | 5 (1) | 20 (6) | 20 (4) | 10 (2) | 10 (2) | 20 (2) |
| p Value | | 0.125 | 0.625 | 1.000 | 1.000 | 1.000 |
| % IIEF-15 sexual desire (dysfunction) domain score (No): | | | | | | |
| None | 80 (16) | 15 (3) | 10 (2) | 30 (6) | 20 (4) | 30 (6) |
| Mild | 10 (2) | 25 (5) | 45 (9) | 30 (6) | 50 (10) | 25 (5) |
| Mild-moderate | 5 (1) | 30 (6) | 20 (4) | 25 (5) | 20 (4) | 25 (5) |
| Moderate | 0 (0) | 20 (4) | 20 (4) | 10 (2) | 5 (1) | 15 (3) |
| Severe | 5 (1) | 10 (2) | 0 (0) | 5 (1) | 5 (1) | 5 (1) |
| Missing | 0 (0) | 0 (0) | 5 (1) | 0 (0) | 0 (0) | 0 (0) |
| None-mild | 95 (19) | 90 (18) | 95 (19) | 95 (19) | 95 (19) | 95 (19) |
| Mild-moderate-severe | 5 (1) | 10 (2) | 0 (0) | 5 (1) | 5 (1) | 5 (1) |
| p Value | | 1.000 | 0.500 | 1.000 | 1.000 | 1.000 |

*Continued*

| | Baseline | | 1 Mo Followup | | 3 Mos Followup | | 6 Mos Followup | | 9 Mos Followup | | 12 Mos Followup | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| % IIEF-15 intercourse satisfaction (dysfunction) domain score (No.): | | | | | | | | | | | | |
| None | 20 | (4) | 0 | (0) | 10 | (2) | 25 | (5) | 25 | (5) | 10 | (2) |
| Mild | 55 | (11) | 30 | (6) | 25 | (5) | 25 | (5) | 40 | (8) | 35 | (7) |
| Mild-moderate | 10 | (2) | 10 | (2) | 25 | (5) | 20 | (4) | 15 | (3) | 20 | (4) |
| Moderate | 0 | (0) | 5 | (1) | 10 | (2) | 5 | (1) | 10 | (2) | 5 | (1) |
| Severe | 15 | (3) | 55 | (11) | 25 | (5) | 25 | (5) | 10 | (2) | 30 | (6) |
| Missing | 0 | (0) | 0 | (0) | 5 | (1) | 0 | (0) | 0 | (0) | 0 | (0) |
| None-mild | 85 | (17) | 45 | (9) | 70 | (14) | 75 | (15) | 90 | (18) | 70 | (14) |
| Mild-moderate-severe | 15 | (3) | 55 | (11) | 25 | (5) | 25 | (5) | 10 | (2) | 30 | (6) |
| p Value | | | 0.008 | | 0.687 | | 0.625 | | 1.000 | | 0.375 | |
| % IIEF-15 overall satisfaction (dysfunction) domain score (No.): | | | | | | | | | | | | |
| None | 45 | (9) | 15 | (3) | 20 | (4) | 25 | (5) | 35 | (7) | 30 | (6) |
| Mild | 40 | (8) | 25 | (5) | 20 | (4) | 50 | (10) | 45 | (9) | 25 | (5) |
| Mild-moderate | 10 | (2) | 30 | (6) | 20 | (4) | 10 | (2) | 5 | (1) | 25 | (5) |
| Moderate | 5 | (1) | 10 | (2) | 15 | (3) | 5 | (1) | 5 | (1) | 15 | (3) |
| Severe | 0 | (0) | 20 | (4) | 20 | (4) | 10 | (2) | 10 | (2) | 5 | (1) |
| Missing | 0 | (0) | 0 | (0) | 5 | (1) | 0 | (0) | 0 | (0) | 0 | (0) |
| None-mild | 100 | (20) | 80 | (16) | 75 | (15) | 90 | (18) | 90 | (18) | 95 | (19) |
| Mild-moderate-severe | 0 | (0) | 20 | (4) | 20 | (4) | 10 | (2) | 10 | (2) | 5 | (1) |
| p Value | | | 0.125 | | 0.125 | | 0.500 | | 0.500 | | 1.000 | |
| Mean FACT-P score (SD, range): | | | | | | | | | | | | |
| Physical well-being | 26.0 | (2.0, 22–28) | 23.8 | (5.3, 6–28) | 25.6 | (2.6, 18–28) | 25.9 | (2.7, 18–28) | 26.5 | (2.2, 21–28) | 27.2 | (1.4, 23–28) |
| p Value | | | 0.053 | | 0.466 | | 0.884 | | 0.481 | | 0.058 | |
| Social/family well-being | 25.4 | (3.4, 16–28) | 24.5 | (2.3, 21–28) | 22.9 | (6.1, 2–28) | 25.0 | (2.7, 19–28) | 24.5 | (3.7, 17–28) | 26.2 | (1.9, 22–28) |
| p Value | | | 0.230 | | 0.105 | | 0.531 | | 0.302 | | 0.297 | |
| Emotional well-being | 20.2 | (3.4, 12–24) | 21.1 | (3.3, 12–24) | 19.6 | (3.5, 11–24) | 21.3 | (1.9, 18–24) | 22.0 | (2.4, 15–24) | 22.6 | (2.4, 15–24) |
| p Value | | | 0.350 | | 0.691 | | 0.260 | | 0.043 | | 0.015 | |
| Functional well-being | 25.7 | (3.4, 15–28) | 24.7 | (4.0, 16–28) | 24.5 | (3.7, 14–28) | 26.0 | (3.4, 14–28) | 25.7 | (3.7, 13–28) | 25.5 | (6.5, 0–28) |
| p Value | | | 0.305 | | 0.243 | | 0.816 | | 1.000 | | 0.811 | |
| Prostate ca subscale | 42.5 | (5.8, 31–48) | 38.7 | (7.3, 16–46) | 40.2 | (6.9, 21–48) | 43.1 | (5.2, 31–48) | 43.7 | (5.4, 30–48) | 43.2 | (4.4, 35–48) |
| p Value | | | 0.004 | | 0.013 | | 0.346 | | 0.181 | | 0.964 | |
| FACT-General (composite)†† | 97.3 | (8.2, 73–108) | 94.0 | (8.6, 79–105) | 92.8 | (11.9, 62–107) | 98.0 | (9.4, 69–108) | 98.6 | (8.9, 75–108) | 101.3 | (7.5, 80–108) |
| p Value | | | 0.055 | | 0.105 | | 0.881 | | 0.596 | | 0.172 | |
| FACT-P (composite)‡‡ | 139.8 | (12.5, 104–155) | 132.7 | (14.6, 98–151) | 133.0 | (17.1, 87–154) | 141.1 | (13.5, 100–105) | 142.2 | (13.1, 105–156) | 144.2 | (10.9, 116–156) |
| p Value | | | 0.004 | | 0.036 | | 0.739 | | 0.361 | | 0.310 | |

Comparison between continuous variables was evaluated using unpaired *t* test (2-sided) with scores compared to baseline to derive individual *p* values at each point. Comparison between dichotomous outcomes was evaluated using McNeMar's test with proportions compared to baseline to derive individual *p* values at each point.

* I-PSS ordinal sum. 0–7 Mildly symptomatic; 8–19 moderately symptomatic; 20–35 severely symptomatic.

† I-PSS urinary quality of life score (0–5), with low scores demonstrating good quality of life.

‡ Ordinal sum of questions 1,2,3,4,5 and 15 on IIEF-15. Maximum score possible 30. Erectile dysfunction classified into 5 categories of no dysfunction (25–30), mild (19–24), mild to moderate (13–18), moderate (7–12) and severe (0–6).

§ Ordinal sum of questions 9 and 10 on IIEF-15. Maximum score possible 10. No dysfunction (9–10), mild (7–8), mild-moderate (5–6), moderate (3–4), severe (0–2).

‖ Ordinal sum of questions 11 and 12 on IIEF-15. Maximum score possible 10. No dysfunction (9–10), mild (7–8), mild-moderate (5–6), moderate (3–4), severe (0–2).

¶ Ordinal sum of questions 6, 7 and 8 on IIEF-15. Maximum score possible 15. No dysfunction (13–15), mild (10–12), mild-moderate (7–9), moderate (4–6), severe (0–3).

** Ordinal sum of questions 13 and 14 on IIEF-15. Maximum score possible 10. No dysfunction (9–10), mild (7–8), mild-moderate (5–6), moderate (3–4), severe (0–2).

†† Ordinal sum of physical well-being, social well-being, emotional well-being and functional well-being subscales.

‡‡ Ordinal sum of FACT-General and Prostate Cancer subscale.

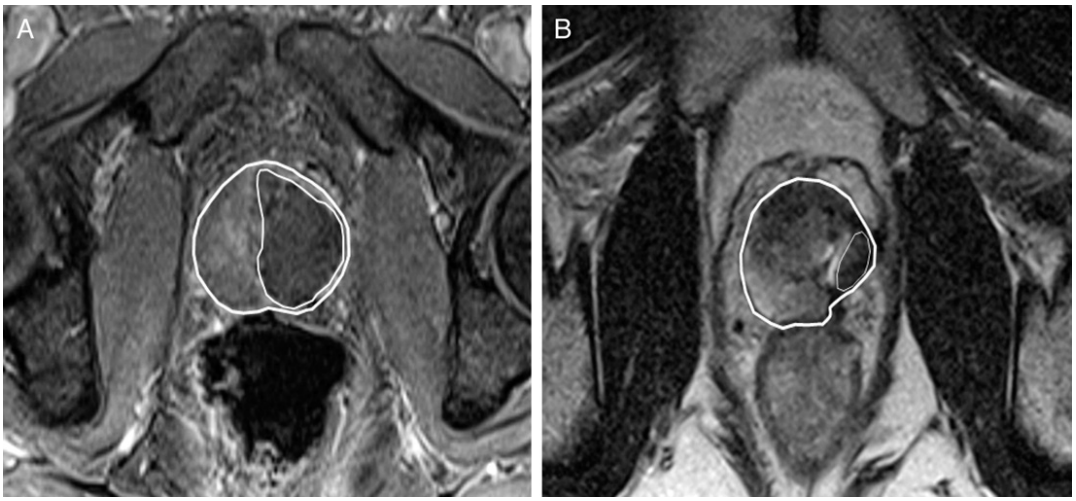


**Figure 6.** Axial contrast enhanced MRI demonstrating area of poor perfusion in left hemi-prostate 2 weeks after left HIFU hemiablation (*A*), and axial T2-weighted MRI demonstrating treated area on left has reduced in size at 6 months leaving 0.9 ml residual tissue (*B*).

statistically significant difference from baseline at 6 and 3 months, respectively (figs. 3, *A* and 4, *A*). For the 95% of men with none or mild to moderate erectile dysfunction at 12 months the response to question 2 on the ability to have an erection sufficient for penetrative sex demonstrated that all had erections sufficient for penetrative sex at 12 months.

***Urinary function.*** UCLA-EPIC urinary incontinence scores demonstrated no statistically significant difference between baseline and 6 months (fig. 3, *B*). Of 20 men 18 (90%) were pad-free and leak-free by 6 months, and 19 (95%) were pad-free by 3 months. The subject who was not pad-free used 1 pad daily and was treated for stricture formation. I-PSS increased initially. However, by 6 months scores were significantly lower than at baseline (see table and fig. 4, *B*). I-PSS was compared between those cases with treatment across the midline vs up to the midline. There was no statistically significant difference between scores at 1 ($p = 0.08$), 3 ($p = 0.56$), 6 ($p = 0.32$), 9 ($p = 0.10$) and 12 ($p = 0.79$) months. However, at 1 month there may be a clinically important difference with a mean I-PSS of 22 and 14, respectively.

***Rectal toxicity and health related quality of life scores.*** There were no recto-urethral fistulas. In addition, the FACT-P Trial Outcomes Index and other aggregate scores initially demonstrated a statistically significant deterioration between 1 and 3 months,[21] but there was no difference between baseline and 6 months (see table and fig. 5, *A*).

### Biochemical, Imaging and Histological Outcomes

***Biochemical.*** An 80% decrease in mean PSA was seen at 3 months. This reduction persisted to 12 months (7.3 vs 1.5 ng/ml, fig. 5, *B*).

***Imaging.*** A mean of 2.4 ml residual tissue was seen in the treated side (fig. 6). mp-MRI at 6 months demonstrated residual cancer in the treated lobe in 2 men, but no suspicious lesions in the untreated lobe in any.

***Histology.*** One man refused to undergo biopsy due to concern over impact on sexual function. mp-MRI of this patient at 6 months demonstrated no suspicious lesion in the treated and untreated lobe. Small amounts of prostatic acini were seen in 7 cases. Extensive fibrosis was seen in 18 cases with necrosis in 10. The sampling density of biopsy cores per ml residual tissue was significantly higher at 6 months compared to pretreatment TPM biopsies (2.6 vs 1.1 cores per ml, $p = 0.003$). The 2 men with positive 6-month mp-MRI had low volume disease with 1 mm Gleason 3 + 3 in 1 of 4 and 1 of 5 biopsies, respectively. Pretreatment TPM biopsies showed Gleason 3 + 3 cancer in 3 of 32 and 6 of 35 cores, and maximum cancer core length of 1 and 12 mm, respectively. The first patient decided on a period of active surveillance. The other patient underwent further HIFU to the treated side with a resultant decrease in PSA from 3.6 to 1.4 ng/ml during 3 months. He refused further biopsies but PSA remained stable with a further negative mp-MRI.

## DISCUSSION

### Summary of Results

Our results demonstrate that hemiablation is feasible and safe when delivered in an ambulatory care setting. It appeared to be well tolerated in terms of genitourinary function. Specifically we were able to refute the study null hypothesis that there would be

no difference between erectile dysfunction rates after focal therapy compared to a known rate for whole gland therapy. After focal therapy 89% of patients (17 of 19) achieved the trifecta status of pad-free, leak-free continence, erections sufficient for intercourse, and early cancer control with absence of high volume and Gleason 7 or greater cancer on biopsy.

### Limitations

The number of men treated was small with short followup. In starting our program of research into focal therapy we followed the Medical Research Council guidance on evaluating complex interventions.[12] This study represents stage 3 of those guidelines, designed to evaluate safety and side effects before a phase II efficacy trial. The men described in this report will be monitored in the long term as part of a registry.

In addition, our sample was not representative of all men with prostate cancer as the precision estimates required good baseline sexual function. The proportion of men able to maintain good genitourinary function after focal therapy may be lower in a more representative group. These study requirements meant that patients who gave consent to this study represented a small proportion, 14% (20 of 144), of the total number initially evaluated with TPM who were eligible from a pathological perspective and willing to participate.

Characterization using TPM biopsies before focal therapy was different from the 6- month verification biopsy. Our original design stipulated TPM at both points. However, our ethics committee and independent protocol review believed that 3 general anesthetic procedures within 1 year would pose a large burden on the men, especially as histological outcomes were not primary objectives. Although the likelihood that small lesions missed at baseline TPM would have progressed or de novo cancer emerged within 6 months is low, we accept that this is a significant limitation which future studies will need to address.

Finally, we used a definition of clinically insignificant cancer to describe histological outcomes. This definition incorporates an upper limit on cancer burden (3 mm or less) and grade (absence of Gleason pattern 4/5), and reflects the current opinion that not all men with prostate cancer need to be treated.[22,23]

### Comparison With Other Studies

Several case series report the outcomes of men treated in a focal manner.[24–27] In nontrial conditions it appears that treating in a tissue preserving manner has low rates of side effects. However, these studies are limited as a result of their retrospective nature, nonstandardized techniques for cancer localization and treatment verification, and in many the reporting of functional outcomes took place without validated instruments.

Another legitimate criticism of focal therapy is that it has been applied to men who might be better suited to active surveillance. The population of men recruited to our study did not conform to a low risk group since a quarter would be classified as low risk. We accept that insisting upon cancer being confined to 1 lobe may have led to an unknown selection bias.

### Clinical Implications

Our results appear sufficiently promising to support the further evaluation of focal therapy as a strategy to decrease the harm associated with standard whole gland treatment. Indeed a phase II study is currently planned using TPM before focal therapy followed by 12-month biopsies of the treated side and further TPM at 36 months (clinicaltrials.gov identifier http://clinicaltrials.gov/ct2/show/NCT01194648).

The opportunity afforded to us by focal therapy to reduce treatment related side effects may be considerable. The results achieved in this study suggest that the strategy of tissue preservation may avoid some of the adverse consequences of prostate cancer treatment. Focal therapy might also provide the means, through day case ambulatory treatment and avoidance of complications, by which the escalating costs associated with increased specification to deliver whole gland treatment, might be tempered.[28,29]

HIFU is only one technology that can deliver focal therapy. The small amount of residual tissue seen with viable prostatic acini at 6 months may show signs of progression with greater followup. This ablative heterogeneity is likely related to the prostatic heterogeneity resulting from differences in cellular density, microvascular density, and periprostatic fat and vessels. Cryotherapy, photodynamic therapy and interstitial photothermal therapy, and modern radiotherapeutic platforms all have the potential to deliver focal therapy.

## CONCLUSIONS

Hemiablation is just one form of focal therapy, one that may also be subject to the accusation of over treatment. Although we have demonstrated good functional returns in several aspects, this particular intervention is not without significant side effects such as debris/sloughing, stricture and urinary tract infection. These side effects may be related to the strategy of hemiablation in which there is urethral damage, prostatic swelling and necrotic tissue. With precise characterization it should be possible to

treat the cancer in a truly focal manner, either with the aim of cancer eradication, or possibly with the aim of treating only clinically important disease and tolerating indolent lesions in the knowledge that they pose little or no long-term harm.[30] Before this can happen comparative studies are needed to demonstrate that the process of characterization and treatment can be taught and quality controlled, that functional outcomes are reproducible and that rates of cancer control can stand the test of time.

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## EDITORIAL COMMENT

While the future of focal therapy for prostate cancer is uncertain, the quality of recent and ongoing trials has dramatically improved. Many, if not most, of the published experiences are rendered uninterpretable due to methodological limitations.[1] This prospectively planned and registered study with prespecified end points provides meaningful data using validated instruments. For that reason, along with the tempered and reasonable interpretation of the data, the authors should be commended. I question the

inclusion of intermediate risk patients (clinical stage T2b ± PSA 10 to 15 ng/ml ± primary Gleason pattern 4), am concerned about residual untreated tissue on some post-ablation biopsies and maintain significant obstacles remain (eg completely characterizing the cancer, appropriately selecting patients, defining recurrence and progression, establishing rates and success of salvage therapy). However, only through clinical trials such as this and more than 10 others on www.clinicaltrials.gov[2] will we effectively determine whether focal therapy is appropriate or should be relegated to historical obscurity.

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