Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study

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Summary

Background Radical whole-gland therapy can lead to significant genitourinary and rectal side-effects for men with localised prostate cancer. We report on whether selective focal ablation of unifocal and multifocal cancer lesions can reduce this treatment burden.

Methods Men aged 45–80 years were eligible for this prospective development study if they had low-risk to high-risk localised prostate cancer (prostate specific antigen [PSA] ≤15 ng/mL, Gleason score ≤4+3, stage ≤T2), with no previous androgen deprivation or treatment for prostate cancer, and who could safely undergo multiparametric MRI and have a general anaesthetic. Patients received focal therapy using high-intensity focused ultrasound, delivered to all known cancer lesions, with a margin of normal tissue, identified on multiparametric MRI, template prostate-mapping biopsies, or both. Primary endpoints were adverse events (serious and otherwise) and urinary symptoms and erectile function assessed using patient questionnaires. Analyses were done on a per-protocol basis. This study is registered with ClinicalTrials.gov, number NCT00561314.

Findings 42 men were recruited between June 27, 2007, and June 30, 2010; one man died from an unrelated cause (pneumonia) 3 months after treatment and was excluded from analyses. After treatment, one man was admitted to hospital for acute urinary retention, and another had stricture interventions requiring hospital admission. Nine men (22%, 95% CI 11–38) had self-resolving, mild to moderate, intermittent dysuria (median duration 5·0 days [IQR 2·5–18·5]). Urinary debris occurred in 14 men (34%, 95% CI 20–51), with a median duration of 14·5 days (IQR 6·0–16·5). Urinary tract infection was noted in seven men (17%, 95% CI 7–32). Median overall International Index of Erectile Function-15 (IIEF-15) scores were similar at baseline and at 12 months (p=0·060), as were median IIEF-15 scores for intercourse satisfaction (p=0·454), sexual desire (p=0·644), and overall satisfaction (p=0·257). Significant deteriorations between baseline and 12 months were noted for IIEF-15 erectile (p=0·042) and orgasmic function (p=0·003). Of 35 men with good baseline function, 31 (89%, 95% CI 73–97) had erections sufficient for penetration 12 months after focal therapy. Median UCLA Expanded Prostate Cancer Index Composite (EPIC) urinary incontinence scores were similar at baseline as and 12 months (p=0·045). There was an improvement in lower urinary tract symptoms, assessed by International Prostate Symptom Score (IPSS), between baseline and 12 months (p=0·026), but the IPSS-quality of life score showed no difference between baseline and 12 months (p=0·655). All 38 men with no baseline urinary incontinence were leak-free and pad-free by 9 months. All 40 men pad-free at baseline were pad-free by 3 months and maintained pad-free continence at 12 months. No significant difference was reported in median Trial Outcomes Index scores between baseline and 12 months (p=0·113) but significant improvement was shown in median Functional Assessment of Cancer Therapy (FACT)-Prostate (p=0·045) and median FACT-General scores (p=0·041). No histological evidence of cancer was identified in 30 of 39 men biopsied at 6 months (77%, 95% CI 61–89); 36 (92%, 79–98) were free of clinically significant cancer. After retreatment in four men, 39 of 41 (95%, 95% CI 83–99) had no evidence of disease on multiparametric MRI at 12 months.

Interpretation Focal therapy of individual prostate cancer lesions, whether multifocal or unifocal, leads to a low rate of genitourinary side-effects and an encouraging rate of early absence of clinically significant prostate cancer.

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Introduction

The management of localised prostate cancer remains controversial because the systematic over-diagnosis that accompanies the current diagnostic pathway results in over-treatment.[1] At present, radical whole-gland surgery or radiotherapy can result in substantial side-effects that are a consequence of damage to surrounding structures. These include urinary incontinence (5–20%), erectile dysfunction (30–70%), and bowel toxicity (5–10%).[2,3] Technological refinements do not seem to have reduced the burden of harm.[4,5]

Apart from active surveillance for low-risk disease, few strategies are available to address the burden of treatment-related side-effects in other risk categories. One strategy that has shown promise relates to managing prostate cancer in the same manner as most other solid organ malignancies—by focusing the therapy to the cancer lesion, injury to the

bladder, rectum, and neurovascular bundles could be reduced.[6,7]

We have previously assessed hemi-ablation of patients with localised unilateral prostate cancer,[8] which included treatment of the entire half of the prostate associated with cancer. Regardless of the grade, volume, or location of cancer that affected half of the prostate, the entire side was ablated. This strategy is the most straightforward to undertake, standardise, and train others to do, but is limited because only one in five men have true unilateral disease on template biopsies. Furthermore, hemi-ablation might represent overtreatment since a low-volume, low-grade lesion would be treated in the same manner as a high-volume, high-grade cancer. In this study, we postulated that selective focal ablation of unifocal and multifocal cancer lesions with a margin of normal tissue could reduce genitourinary and rectal side-effects for men with localised prostate cancer.

Methods

Study design and patients

We undertook a two-centre, prospective development study, as defined by the IDEAL (Idea, Development, Exploration, Assessment, and Long-term) guidelines for assessing innovation in surgery.[9] Men could enter into the study if they had localised prostate cancer on multiparametric MRI and transperineal template-prostate-mapping biopsies.[10]

We included men with low-risk to high-risk disease (prostate-specific antigen [PSA] ≤15 ng/mL, Gleason score ≤4+3, stage ≤T2), aged 45–80 years with a life expectancy of 5 years or more, a prostate volume of 40 mL or less or maximum anterior–posterior length of 40 mm or less who had undergone multiparametric MRI and transperineal template (5 mm spaced) biopsies in the 6 months before recruitment. We excluded men who had androgen suppression within the previous 6 months, previous radiation therapy or chemotherapy for prostate cancer, latex allergies, previous rectal surgery preventing insertion of transrectal probe, intraprostatic calcifications making high-intensity focused ultrasound (HIFU) of focal areas of cancer difficult, previous transurethral resection of the prostate or laser prostatectomy in 5 years before recruitment, previous HIFU, cryosurgery, or thermal or microwave therapy to the prostate at any point before recruitment. Men who were not fit for general anaesthesia or regional anaesthesia as assessed by a consultant anaesthetist, or were unable to have MRI scanning (eg, severe claustrophobia, permanent cardiac pacemaker, metallic implant likely to contribute significant artifact to images) were also excluded. All men gave written informed consent.

Our trial was approved by the University College London Hospitals Local Research Ethics Committee A, UK, which is under the auspices of the National Research Ethics Service. The study was independently audited by hospital research and development officials. Additionally, the protocol was anonymously peer-reviewed by the National Cancer Research Network (NCRN), UK, and the Medical Research Council, UK.

For the **study protocol** see https://www.ucl.ac.uk/focal/therapy/hifu/focal/Focal-HIFU-Protocol

Procedures

To locate areas of cancer, multiparametric MRI was done at 1·5 T magnetic field strength with pelvic phased-array coils. Sequences included T2-weighting, dynamic gadolinium contrast-enhancement and diffusion-weighting. Template-prostate-mapping biopsies were done under general or spinal anaesthesia with the prostate sampled at 5 mm intervals. Two biopsies were taken at the same grid coordinate if the prostate was longer than the standard length of a biopsy core. All biopsies were reported by a single uropathologist.

Men underwent focal ablation with a transrectal HIFU device (Sonablate 500; Focus Surgery, Indianapolis, IN, USA). Ultrasonic waves were generated with a cylindrical piezoelectric ceramic transducer and then focused with a spherical plate onto a target area determined by the focal length of the transducer. The sound waves were transmitted to the tissues by a coupling mechanism from a transducer placed either extracorporeally or transrectally. Transmission of sound waves transrectally was achieved by placing the probe in a condom filled with chilled circulating degassed water. The dimensions of the target area were determined by the focal length of the transducer, the applied frequency, the intensity of the applied power (W/cm^2), and the duration of the pulse. The lesion produced was pseudoellipsoid in shape and referred to as the focal zone. Its long axis lies at right angles to the transducer and is greatest in length towards the transducer.

Tissue destruction is produced by thermal, mechanical, and cavitation effects to produce a clearly demarcated region of coagulative necrosis surrounded by normal tissue on microscopic examination. Thermal energy comes from absorption of mechanical energy. Adequate cell destruction can be produced by short exposure (1 s) to temperatures of 60°C or more, which has therefore been adopted as the minimum target temperature. In practice, this temperature is easily attained with temperatures of 80°C or more recorded during HIFU therapy. Cooling due to tissue perfusion in the focal zone is not a problem because the rate of heating is greater than that of cooling when the exposure time is within a window of 3 s. The mechanical effects of HIFU are more complex and involve shear forces, torque, and streaming. These forces result in destruction by both physical and thermal means. Cavitation results from gas (bubble) formation within cells due to heat and mechanical energy deposition causing bubbles to oscillate.

All patients had sterile urine on culture before treatment. If culture was positive for infection, men were treated with antibiotics and their treatment rescheduled; prophylactic intravenous gentamicin was given to all men at the time of general anaesthetic. A suprapubic

catheter was inserted before HIFU under the same anaesthetic.

We standardised the process of focal therapy by setting three broad guidelines. First, a maximum of 60% of the prostate could be ablated. Second, the edge of the ablation zone had to be at least 10 mm from a neurovascular bundle. The ablation zone had to be at least 5 mm from both neurovascular bundles if disease was bilateral. Third, untreated areas could not have any histological evidence of prostate cancer; high-grade prostate intraepithelial neoplasia and atypical small acinar proliferation were permitted. The operator made judgments as to the location and boundaries of the cancer lesions for treatment planning on the basis of the information from both multiparametric MRI (when a lesion was visible) and template-prostate-mapping biopsies. The areas positive for cancer were treated with at least a 3–5 mm margin around the lesion (2–4 HIFU pulses). In areas where a discrepancy between multiparametric MRI and template-prostate-mapping biopsies was identified, histopathological findings took precedence. Some cancer lesions were quite close and were therefore included in the same area of treatment. As a result, more than two lesions could be treated as long as there were only two areas of treatment. Designation of individual lesions was usually straightforward but when positive biopsies were close together, lesions were labelled separately if there was at least one intervening normal biopsy.

After ablation, the suprapubic catheter was placed on free drainage into a urinary leg-bag for 1–2 days and urethral voiding was encouraged thereafter by closure of a valve attached to the catheter. Because many men travelled a long distance, the timing of catheter removal was delayed to coincide with the first trial visit after the operation at 10–14 days (for an early MRI) even if urethral voiding was restored earlier. All men were given ciprofloxacin and oral analgesia (co-dydramol) for 7 days. A contrast-enhanced MRI was done 10–14 days after focal HIFU to confirm the area of ablation, as shown by a confluent perfusion deficit.

Follow-up consisted of clinic visits at 1 month, 3 months, 6 months, 9 months, and 12 months for PSA measurement and adverse event reporting. Men filled in validated questionnaires at each clinic visit. Questionnaires included the International Prostate Symptom Score (IPSS), International Index of Erectile Function-15 (IIEF-15), UCLA-Expanded Prostate Cancer Index Composite (EPIC) urinary incontinence scale, and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) score, which includes FACT-General (FACT-G) scores and the Trials Outcome Index.[11–15] Phosphodiesterase-5 inhibitors were permitted at any timepoint during follow-up. At 6 months, another multiparametric MRI followed by targeted biopsies of the treated areas were scheduled with a minimum requirement for sampling every 1 mL of residual tissue with one core. Our justification for one biopsy for every mL of residual tissue reflects the biopsy density of the original template biopsies before focal HIFU (which was about 1 mL for every biopsy). Retreatment with a further focal HIFU was permitted if biopsies were positive. A further multiparametic MRI scan was done at 12 months. As the purpose of the 6-month biopsies was to determine whether the ablation was successful, our ethics committee did not permit sampling of untreated tissue due to the requirement for another general anaesthetic. However, biopsies of the untreated tissue were permitted if a new, potentially malignant lesion was seen on multiparametric MRI.

The primary outcomes were feasibility, patient acceptability, and side-effect profile of focal HIFU. Feasibility and acceptability were reported with rates and description of adverse events, serious and otherwise. Urinary symptoms and erectile function were assessed with patient questionnaires. The IIEF-15 was used to report the proportion of men capable of having erectile function sufficient for penetration at 12 months as well as total IIEF-15 score and domain scores on erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction. Urinary function was assessed with IPSS, the IPSS quality-of-life questionnaire, and the UCLA EPIC continence questionnaire. The continence questionnaire included total scores as well as the proportion of patients who were pad-free, or leak-free and pad-free at 12 months. Quality of life was measured with FACT-P with summary measures of the Trial Outcome Index score, FACT-P score, and FACT-G score.

Secondary outcomes were histological and imaging measures of cancer control. A composite outcome in the form of trifecta status was assessed at 12 months. For this status to be met, we defined trifecta as leak-free and pad-free continence, erections sufficient for penetration, and no evidence of clinically significant disease at 12 months multiparametric MRI[16,17] in those men with normal baseline genitourinary function.

Statistical analysis

Since the primary objective of the study was to determine the side-effect profile of focal ablation, the sample size was powered on a common event, namely erectile dysfunction. We estimated that focal ablation therapy would lead to an absolute rate of 15% erectile dysfunction (insufficient for penetrative sex) at 12 months. The sample size calculation was based on a comparison with a known rate of 40% erectile dysfunction,[18] which usually occurs when HIFU is applied to the whole prostate.[19] Therefore, with an α level of 0·05 and power of 90% (1–β), the sample size required was at least 33 men with good baseline function. We adjusted the sample size to allow for the estimated rate of 25% of men having poor baseline erectile function in the general population, and therefore aimed to recruit 42 men in total.

Validated questionnaires were analysed with standard methods. Missing values for patient-reported outcome

variables (between 2% and 10% missing values for individual questions) were imputed with a fully conditional specification method and logistic regression model (categorical data). The imputation was based on the observation of values missing completely at random. We classed the variables for which missing values were to be imputed (questionnaires) as categorical. Therefore, logistic regression was used with available values of the same variables at different timepoints either side of the imputed value as predictors. Imputed values were rounded up to next integer values. Maximum and minimum values were set according to extremes of questionnaire item scales.

Categorical outcomes were reported as point estimates with binomial 95% CIs to demonstrate level of precision. Wilcoxon signed rank test (two-tailed) was used to assess differences between continuous variables that were not normally distributed (PSA and questionnaire scores) measured at baseline and at the 12-month follow-up visit. Changes over time were reported with box-and-whisker plots. Subgroup analyses were hypothesis-generating and with small numbers in each subgroup, it was deemed inappropriate to run statistical tests of significance in such comparisons. p values of 0·05 or less were deemed significant. All statistical tests were done with SPSS (version 17.0). This study is registered with ClinicalTrials.gov, number NCT00561314.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. HUA, LD, RS, JvdM, and ME had access to the raw data. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

42 men were recruited between June 27, 2007, and June 30, 2010. One man had an unrelated death 3 months after focal therapy. He had baseline retroperitoneal fibrosis, hypertension, and a single kidney. He had an uneventful recovery after HIFU and had no respiratory symptoms immediately before treatment, or at 2 weeks and 6 weeks after treatment during the formal trial visits. The cause was independently verified by local physicians as respiratory failure following pneumonia. As a result, 41 men were included in analyses; 30 (73%) had intermediate and high-risk disease (table 1).[20] Three men had baseline mild stress urinary incontinence but required no pads; 35 had good baseline sexual function with erections sufficient for penetration. Of 41 men, 20 (49%) had unilateral, one-area ablation, 15 (37%) had bilateral, two-area ablation, and six (15%) had midline, one-area treatment (figure 1). Baseline characteristics of these three groups are shown in the appendix.

30 (73%, 95% CI 57–86) men had a hospital stay of less than 24 h. All 41 were able to void urine through the

	Patients (N=41)
Age (years)	63 (58·0–66·0)
Serum PSA (ng/mL)	6·6 (5·4–7·7)
Reason for PSA test and biopsy	
PSA screening (patient request)	31 (76%)
Lower urinary tract symptoms*	10 (24%)
Prostate volume (mL)	35 (29·0–45·5)
PSA density (ng/mL per mL prostate)	0·18 (0·14–0·22)
Initial biopsy	
TRUS biopsy	35 (85%)
TPM biopsy	6 (15%)
Gleason (TRUS-guided biopsy)	
3+3	24 (59%)
3+4	7 (17%)
4+3	5 (12%)
No TRUS biopsy	5 (12%)
Gleason (TPM biopsies)	
3+3	13 (32%)
3+4	24 (59%)
4+3	4 (10%)
Clinical stage	
T1c	37 (90%)
T2a	4 (10%)
TRUS guided biopsies	
Total cores	10·0 (8·0–12·0)
Total positive cores	2·0 (1·0–3·0)
Percent positive cores	11·0 (6·3–33·8)
TPM biopsies	
Total cores	46 (35·5–65·5)
Total positive cores†	5 (3·0–9·0)
Positive cores (%)	9·4% (4·6–18·5)
Core density (biopsies/mL)	1·4 (0·9–1·9)
Number of lesions on TPM	
One	21
Two	17
Three	3
Disease distribution	
Unifocal	
Unilateral	15 (37%)
Bilateral (midline lesion)	6 (15%)
Multifocal	
Unilateral	5 (12%)
Bilateral	15 (37%)
NCCN risk category[20]	
Low	11 (27%)
Intermediate	26 (63%)
High	4 (10%)

Data are median (IQR), number, or number (%). PSA=prostate-specific antigen. TRUS=transrectal ultrasound. TPM=template prostate mapping. NCCN=National Comprehensive Cancer Network. *These men were opportunistically screened with a PSA test when they presented with symptoms of lower urinary tract infection, rather than part of a formal request (by their physician or by the men themselves) for a PSA test. †A high number of positive cores were retrieved, despite only a maximum of three lesions, because large dominant lesions were sampled several times.

Table 1: **Baseline characteristics**

See Online for appendix

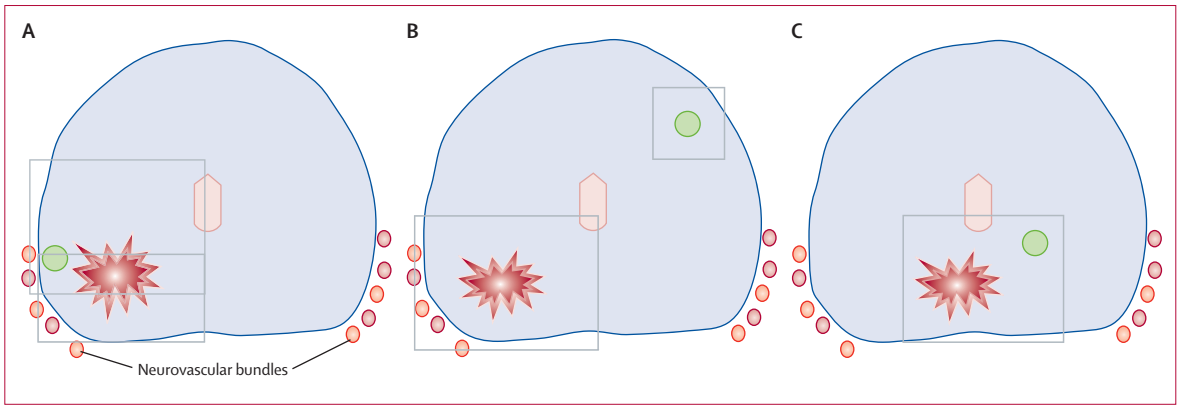


Figure 1: **Schematic diagrams of the types of focal therapy**
Unilateral one-area ablation (A). Bilateral two-area ablation with preservation of one neurovascular bundle (B). Midline one-area ablation allows preservation of both neurovascular bundles (C). Large red areas represent dominant cancers (index lesions) whereas small green areas represent small low-grade secondary lesions. Grey transparent boxes represent ablation zones on the high-intensity focused ultrasound device.

	Value
Total anaesthetic time (min)	135·0 (115·0–150·0)
Procedure time (Suprapubic catheter+focal HIFU; min)	105·0 (87·0–125·0)
Total hospitalisation time (admission to discharge; h)	12·0 (10·0–27·0)
Discharge time (end procedure to discharge; h)	6·0 (5·0–18·0)
Time with suprapubic catheter (days)*†	8·5 (8·0–15·0)
Dysuria (negative urine culture)	9/41 (22%, 11–38)
Duration of dysuria (days)	5 (2·5–18·5)
Intermittent haematuria (start of stream only)	16/41 (39%, 24–56)
Duration of intermittent haematuria (days)	15 (10·3–15·0)
Urinary debris	14/41 (34%, 20–51)
Duration of urinary debris (days)	14·5 (6·0–16·5)
Urinary tract infection (positive urine culture)	7/41 (17%, 7–32)
Acute retention of urine	1/41 (2%, 0–13)

Data are median (IQR) or number of patients affected/N (%, 95% CI). HIFU=high-intensity focused ultrasound. *Suprapubic catheter was usually removed at the same time as the postoperative early contrast MRI for convenience to reduce visits for men who travelled far to the study centre. †The man who had diarrhoea and mucus discharge and had a suprapubic catheter for 6 months was excluded from these descriptive values.

Table 2: **Perioperative outcomes in men undergoing focal high-intensity focused ultrasound for unifocal and multifocal localised prostate cancer**

urethra on the first day after the operation with the suprapubic catheter clamped. About a fifth had self-resolving, mild to moderate, intermittent dysuria (table 2). One man had acute retention of urine 3 days after removal of the suprapubic catheter, which required a urethral catheter for 5 days. In terms of rectal adverse events, one man had diarrhoea and mucus discharge 2 weeks after focal HIFU while the suprapubic catheter was still in situ. He had multiparametric MRI and urethrogram within 4 weeks, which showed extravasation of urine outside the prostate; although the serosal layer of the rectum was affected by treatment no definitive rectourethral fistula was seen. However, as a precautionary measure, he was managed conservatively with a suprapubic catheter and quinolone antibiotics, serial 2 monthly multiparametric MRI, and a further repeat urethrogram until the extravasation had resolved by 6 months. At that point, he developed a stricture requiring endoscopic dilatation; a further two limited endoscopic prostate-tissue resections to a prostate that had a total volume of 80 mL were done when voiding did not return to normal.

Overall IIEF-15 scores initially decreased, indicating diminished erectile function but showed a gradual return to baseline by 12 months (p=0·060; figure 2A). IIEF-15 domain scores in intercourse satisfaction (p=0·454), sexual desire (p=0·644), and overall satisfaction (p=0·257) all showed decreased scores at 1 month and 3 months, but there was no significant difference between baseline and 12 months (figure 2 C, F). IIEF-15 erectile and orgasmic domains showed significant deteriorations from baseline to 12 months (p=0·042 and p=0·003, respectively; figure 2 B, D). Of 35 men with erectile function satisfactory for penetration before treatment, 31 (89%, 95% CI 73–97) described erections sufficient for penetration at 12 months. No formal programme of penile rehabilitation was available, but all men were offered phosphodiesterase-5 inhibitors (eg, sildenafil, tadalafil) if needed; 14 of the 31 men required phosphodiesterase-5 inhibitors.

In a post-hoc analysis to explore whether type of ablation made any difference to erectile dysfunction, we assessed the following factors. Of those men who had erections sufficient for penetration at baseline, 28 of 31 (90%, 95% CI 74–98) of those who had unilateral nerve-sparing ablation and four of four (100%, 40–100) who had bilateral nerve-sparing ablation had erections sufficient for penetration at 12 months. Although only six patients received midline nerve-sparing ablation, we assessed the hypothesis that bilateral ablation might result in higher erectile dysfunction rates than unilateral ablation. Of those men who had erections sufficient for penetration at baseline, 17 of 18 (94%, 95% CI 73–100) who had unilateral

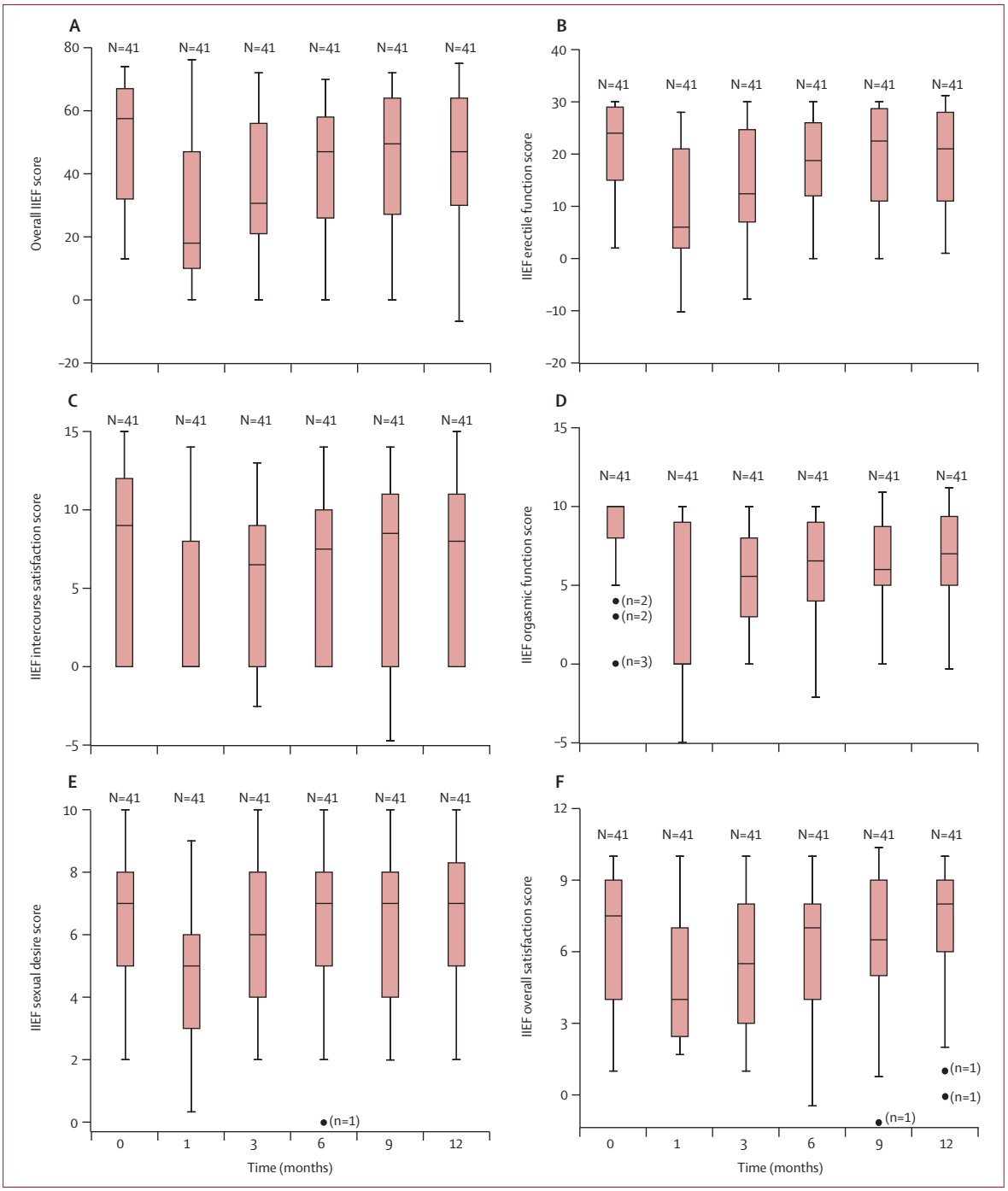


Figure 2: **Sexual function after focal high-intensity focused ultrasound for unifocal and multifocal localised prostate cancer, measured with the International Index of Erectile Function-15 (IIEF-15) questionnaire**

Two-tailed p values were reported for Wilcoxon signed ranks test comparing baseline and 12-month median scores. Box and whiskers plots indicate median with IQR (boxes), and range (whiskers). Dots are outliers. Median baseline versus 12-month scores: total IIEF-15 (57·5 [IQR 30·0–67·0] *vs* 47·0 [29·5–63·3], p=0·060; A); IIEF-15 erectile-function domain (24·0 [13·0–29·0] *vs* 21·0 [10·3–27·3], p=0·042; B); IIEF-15 intercourse-satisfaction domain (9·0 [0·0–12·0] *vs* 8·0 [0·0–11·0], p=0·454; C); IIEF-15 orgasmic-function domain (10·0 [6·5–10·0] *vs* 7·0 [5·0–8·5], p=0·003; D); IIEF-15 sexual-desire domain (7·0 [5·0–8·5] *vs* 7·0 [5·0–8·0], p=0·644; E); IIEF-15 overall-satisfaction domain (7·5 [4·0–9·0] *vs* 8·0 [6·0–9·0], p=0·257; F).

ablation and 15 of 17 (88%, 95% CI 64–99) who had bilateral or midline ablation had erections sufficient for penetration at 12 months.

UCLA EPIC urinary incontinence scores showed an initial deterioration in continence function but had returned to a similar value as at baseline by 12 months

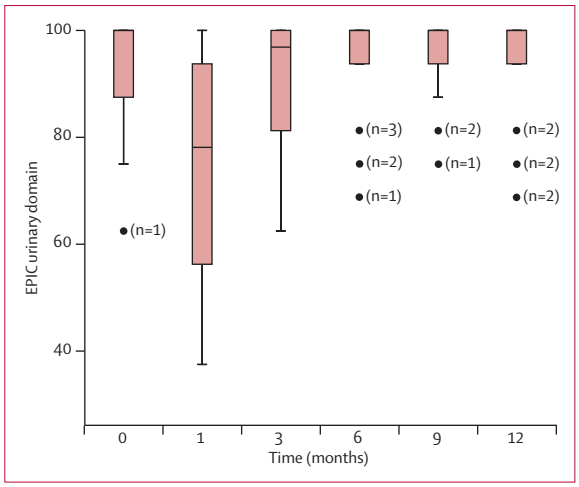


***Figure 3*: Continence function after focal high-intensity focused ultrasound for unifocal and multifocal localised prostate cancer, measured with UCLA Expanded Prostate Cancer Index Composite (EPIC) incontinence questionnaire**
Two-tailed p values were reported for Wilcoxon signed ranks test comparing baseline and 12-month median scores. Median baseline *vs* 12 month scores: 100 (IQR 86·0–100·0) *vs* 100 (92·5–100·0, p=0·045). Box and whiskers plots show median with IQR (boxes) and range (whiskers). Dots are outliers.

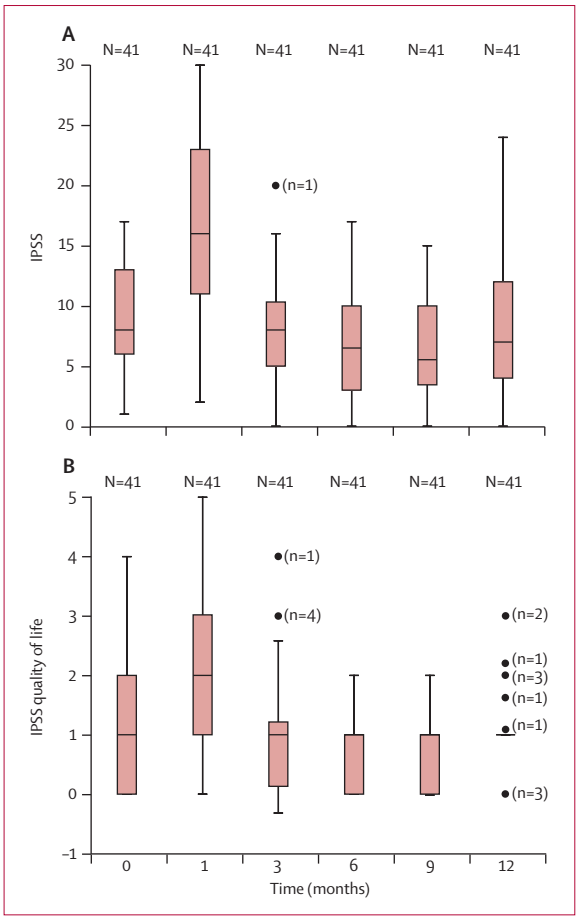


***Figure 4*: Urinary function after focal high-intensity focused ultrasound for unifocal and multifocal localised prostate cancer, measured with International Prostate Symptom Score (IPSS) questionnaire**
Two-tailed p values were reported for Wilcoxon signed ranks test comparing baseline and 12-month median scores. Box and whiskers plots show median with IQR (boxes) and range (whiskers). Dots are outliers. Median baseline versus 12-month International Prostate Symptom Score (IPSS): 8·0 (IQR 5·5–13·0) *vs* 7·0 (3·0–12·0, p=0·026; A). Median baseline versus 12-month IPSS-quality of life: 1·0 (0·0–2·0) *vs* 1·0 (1·0–1·0, p=0·655; B).

(p=0·045; figure 3). IPSS values increased initially although by 12 months showed significantly lower values, suggesting improvement in lower urinary-tract symptoms from baseline (p=0·026; figure 4). No significant difference was seen in IPSS-quality-of-life score between baseline and 12 months (p=0·655; figure 4). Of 38 men with no urinary leak at baseline all (100%, 95% CI 91–100) were leak-free and pad-free by 9 months; 40 men pad-free at baseline were pad-free again by 3 months and maintained pad-free continence at 12 month (100%, 91–100; one man did not report on this parameter at 12 months and was excluded).

Significant deterioration of health-related quality of life was shown between baseline and 12 months on the total FACT-P and total FACT-G scores (p=0·045 and p=0·041, respectively; figure 5). No significant difference was seen between baseline and 12 months in the Trial Outcomes Index between baseline and 12 months (p=0·113; figure 5).

Compared with baseline, a significant decrease in PSA levels was reported at 12 months (p<0·0001; figure 6). The time to nadir was not calculated because the PSA changes showed a pattern of ongoing small decreases in PSA up to trial end at 12 months.

One man refused to undergo biopsy at 6 months because of his concern over the effect of further biopsies on sexual function. The man with diarrhoea and rectal mucus discharge was excluded from biopsy because of risk of infection and promotion of fistula formation. Both had multiparametric MRI at 6 months, which showed no evidence of disease. The second man had transurethral resection of obstructing prostate tissue at 7 months, which was histologically confirmed as benign. Of the 39 men biopsied, nine (23%, 95% CI 11–39) had evidence of cancer while three (8%, 2–21) had evidence of clinically significant cancer (Epstein criteria[21,22]—Gleason >3+3, >2 cores positive, >2 mm cancer involvement; table 3). All biopsies done after focal HIFU had one or more of the following features: necrosis, fibrosis, or giant-cell reaction. Presence of these features showed that treated areas were accurately targeted. Multiparametric MRI at 6 months showed signs of residual cancer in the treated areas in nine men; seven of whom had cancer confirmed on biopsy. Two men with negative multiparametric MRI but positive biopsies both had clinically insignificant disease. No areas of residual cancer were identified in untreated areas on multiparametric MRI so untreated areas were not biopsied.

Of those men with positive biopsies at 6 months, five chose to undergo active surveillance and four had

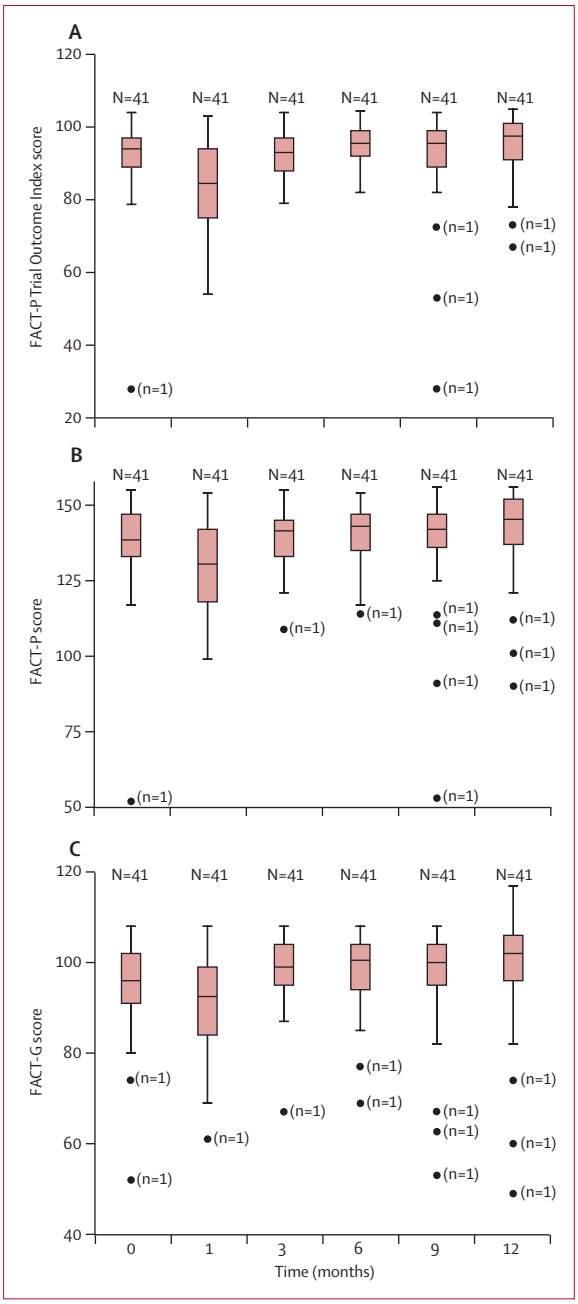


Figure 5: **Quality-of-life outcomes after focal high-intensity focused ultrasound for unifocal and multifocal localised prostate cancer, measured with the Functional Assessment of Cancer Therapy (FACT) questionnaire**
Two-tailed p values were reported for Wilcoxon signed ranks test comparing baseline and 12-month median scores. Box and whiskers plots show median with IQR (boxes) and range (whiskers). Dots are outliers. Median baseline versus 12-month Trials Outcome Index score: 94·0 (IQR 89·0–97·3) *vs* 97·5 (91·0–101·0, p=0·113; A). Median baseline versus 12-month Functional Assessment of Cancer Therapy (FACT)-Prostate score: 138·5 (133·0–147·0) *vs* 145·3 (137·0–152·0, p=0·045; B). FACT-general score: 96·0 (91·0–102·3) *vs* 102·0 (96·0–105·0, p=0·041; C).

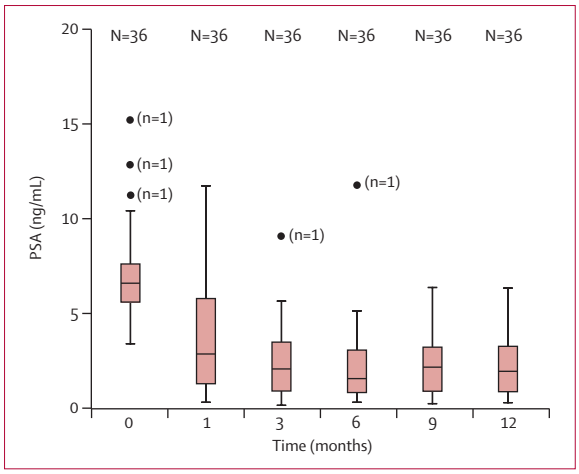


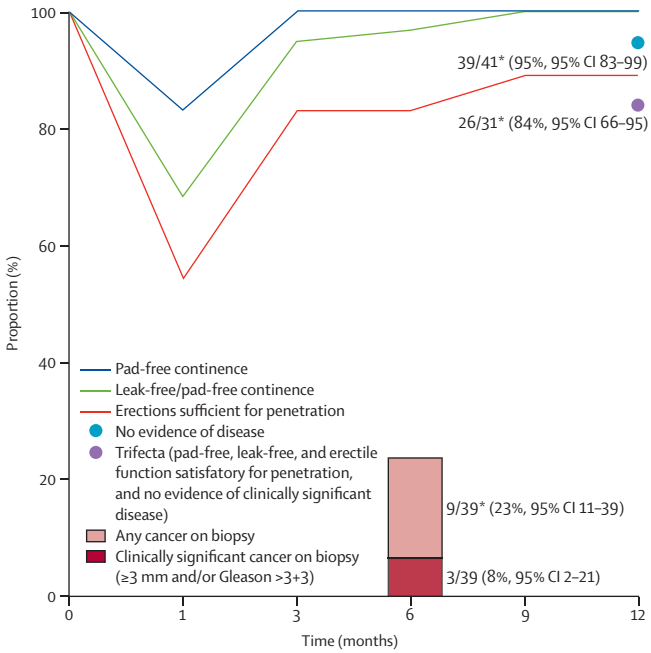
Figure 6: **PSA levels after focal high-intensity focused ultrasound for unifocal and multifocal localised prostate cancer**
Wilcoxon signed ranks test comparing median prostate-specific antigen levels at baseline (6·6 [IQR 5·4–7·7] ng/mL) and at 12 months (1·9 [0·8–3·3] ng/mL; two-tailed p<0·0001). Box and whiskers plots show median with IQR (boxes) and range (whiskers). Dots are outliers.

	Value
Number of cores taken	6·0 (5·0–7·0)
Absence of any cancer	30/39 (77%, 61–89)
Positive biopsy outcomes*	
Positive biopsies†	9/39 (23%, 11–39)
Maximum cancer core length (in positive cores), mm	1·0 (1·0–3·5)
Gleason (N)	
3+3	6
3+4	3
Absence of clinically significant disease‡	36/39 (92%, 79–98)
Other histological findings	
Prostatic acini	21/39 (54%, 37–70)
Atrophy	25/39 (64%, 47–79)
Fibrosis	35/39 (90%, 76–97)
Giant-cell reaction	4/39 (10%, 3–24)
Necrosis	15/39 (38%, 23–55)

Data are median (IQR) or number of patients/N (%, 95% CI). *Two men were not biopsied because of suprapubic catheter in situ in one patient and refusal by another. †Five men opted for surveillance. Of these, four had 1 mm of Gleason 3+3 and one had 2 mm of Gleason 3+4. Four men opted for retreatment. Of these, two had clinically significant cancer (5 mm and 6 mm of Gleason 3+4) and two had no more than 1 mm of Gleason 3+3. ‡As defined by Epstein criteria: Gleason >3+3, >2 cores positive, ≥3 mm cancer involvement.

Table 3: **Histological outcomes at 6 months in men undergoing focal high-intensity focused ultrasound for unifocal and multifocal localised prostate cancer**

retreatment. PSA levels in the retreatment group changed from a median of 3·9 ng/mL (IQR 3·7–4·5) at 6 months (before retreatment) to 3·9 ng/mL (3·7–4·1) at 9 months and 2·9 ng/mL (1·8–3·6) at 12 months. None of the four men undergoing repeat focal therapy consented to further biopsies but all had multiparametric MRI at trial exit showing no evidence of clinically significant disease at 12 months. No man required adjuvant radiotherapy, prostate cancer surgery, or androgen deprivation therapy during the trial duration.



Functional outcome						
Continence*						
Pad-free and leak free	38	26 (68%, 51–83)	36 (95%,82–99)	37 (97%, 86–100)	38 (100%, 91–100)	38 (100%, 91–100)†
Pad-free	40	33 (83%, 67–93)	40 (100%, 91–100)	40 (100%, 91–100)	40 (100%, 91–100)	40 (100%, 91–100)‡
Erections satisfactory for penetration§	35	19 (54%, 37–71)	29 (83%, 66–93)	29 (83%, 66–93)	31 (89%, 73–97)	31 (89%, 73–97)¶
Use of phosphodiesterase-5 inhibitors‖	3/35 (9%)	4/19 (21%, 6–46)	14/29 (48%, 29–67)	17/29 (59%, 39–76)	17/31 (55%, 36–73)	14/31 (45%, 27–64)

Figure 7: **Trifecta rate after focal high-intensity focused ultrasound for unifocal and multifocal localised prostate cancer**

Patient-reported trifecta outcomes were reported with validated questionnaires. Data are number of patients (%, 95% CI). *Derived using UCLA EPIC urinary domain questions: "over the past 4 weeks how often do you leak urine?" and "over the past 4 weeks how many pads or adult diapers per day did you usually use to control leakage?". †Before imputation of data, 36 of 36 men were leak-free and pad-free. ‡Before imputation of data, 38 of 38 men were pad-free. §Proportion of men scoring ≥2 on question 2 of IIEF-15: "over the past 4 weeks when you had erections with sexual stimulation, how often were your erections hard enough for penetration?". ¶Before imputation of data, 29 (88%) of 33 men had erections sufficient for penetration. ||Phosphodiesterase-5 inhibitors (tadalafil, sildenafil, or vardenafil; percentage calculated with denominator as those achieving erections sufficient for intercourse).

Of the 31 men with good baseline function, 26 (84%, 95% CI 66–95) achieved the trifecta status of having leak-free and pad-free continence, erections sufficient for intercourse, and no evidence of clinically significant disease on multiparametric MRI at 12 months (figure 7).

Discussion

To our knowledge, our study is the first to assess targeting of individual known cancer areas, with a margin of normal tissue, in men with multifocal as well as unifocal prostate cancer across all cancer-risk categories. Focal therapy of discrete areas of cancer, whether unifocal or multifocal, is feasible, safe, and can be delivered in an ambulatory care setting. Early self-resolving lower urinary-tract symptoms were common. However, the strategy was well tolerated in the genitourinary functional domains. Almost 90% of men reported having erections satisfactory for intercourse at 12 months, and all were continent.

There was a significant decrease in PSA levels from baseline to 12 months, with concentrations of serum PSA continuing to decline months after the initial treatment. This prevents an estimate of time to PSA nadir. Conclusions from this finding should not be made, although if this decline in serum PSA were to be reproduced, one possible reason for it might be the presentation of antigens to the immune response leading to a secondary immune response against the remaining prostate tissue.[23]

There are several limitations to our study. First, the number of participants included in the study was small. As a prospective development study representing stage 2b of the IDEAL guidelines for evaluating novel surgical strategies,[24] we designed our trial to primarily assess side-effects. Second, characterisation of disease with template-prostate-mapping biopsies before focal therapy was different to the 6-month verification biopsy, because of research ethics committee stipulations to limit patient burden. We have recently started recruiting patients to a multicentre, phase 2 trial that will address some of the legitimate concerns regarding the natural history of untreated prostate tissue. The trial will assess focal HIFU applied to clinically significant areas of prostate cancer identified on entry by multiparametric MRI and template prostate-mapping biopsies[25,26] followed by further multi-parametric MRI and template prostate-mapping biopsies applied to treated and untreated tissue at 3 years (NCT01194648). Third, our focal therapeutic strategy included ablation of normal surrounding tissue, which might contribute to the adverse events reported in our study. Destruction of some normal tissue is necessary to incorporate an adequate margin but because of the nature of the HIFU therapy, our margins are likely to be larger than they need to be. Other ablative modalities could serve to reduce the margins of ablated normal tissue. Furthermore, image-registration of preoperative MRI to treatment delivery could further help to reduce destruction of normal tissue by allowing the clinician to more accurately define the boundaries of the target lesion.

Many retrospective case series have reported encouraging short-term functional and cancer-control outcomes of men treated in a focal manner with HIFU and cryotherapy.[27–32] A prospective feasibility trial has reported on the use of focal interstitial laser therapy in a small cohort of 12 men with very low-risk unifocal disease.[33] We have previously reported[8] the outcomes from a prospective development study of 20 men with unilateral disease undergoing ablation of an entire prostate lobe using HIFU. 18 (90%) were leak-free and pad-free continent while 19 (95%) were pad-free after

Panel: Research in context

Systematic review

In 2007, we did a systematic review[7] of reports on Medline and PubMed databases using the terms "focal therapy" and "prostate cancer" and/or "high intensity focused ultrasound" and/or "cryotherapy/cryoablation/cryosurgery". We also searched for all prostate cancer clinical trials in the UK National Cancer Research Network portfolio, ClinicalTrials.gov, and ISRCTN trial registries. We only identified one prospective, commercially funded, phase 1 trial assessing photodynamic therapy in progress at the time. All other data were from two retrospective case series that were poorly reported. Subsequent to this review, we started a health technology assessment of focal therapy, following the phased approach described by the Medical Research Council complex interventions guidelines and subsequently formalised in the IDEAL guidelines for assessing surgical procedures.[9]

Interpretation

Our study showed that the rate of genitourinary side-effects associated with focal therapy is low, coupled with an encouraging rate of early absence of clinically significant prostate cancer. These findings reaffirm two other prospective development studies[8,33] in which focal using high-intensity focused ultrasound and photothermal therapy was used.

Focal therapy could hold promise in mitigating the harms that result from current therapeutic strategies. Prioritisation and support of a pragmatic, randomised, clinical trial comparing focal therapy with whole-gland treatments is urgently needed. Such a trial should be done before informal diffusion and dissemination of focal therapy. Any randomised controlled trial should be pragmatic in nature and adaptive in execution, so that actual clinical practice is reflected and new technological developments can be incorporated as they occur. Furthermore, since the natural history of prostate cancer is long, timelines based on metastases and mortality, which would require a trial at least 15 years in duration, might not be feasible or warranted. Therefore, endpoints that are clinically meaningful in the medium term are needed so that findings are delivered efficiently and in a timely fashion to change practice. Subsequent linkage to national electronic registries will ensure that robust cancer-control outcomes are still reported at a later date.

hemi-ablation; 17 (89%) of 19 achieved trifecta status at 12 months.[8]

The current study allowed user or operator determination of ablative zones within the prostate on an individual basis provided our standardised method of focal therapy was followed. However, the treatments invariably followed one of three patterns of ablation (figure 1), by contrast with our previous study,[8] whereby the treatment method was fixed and standardised by mandating therapy to the entire half of the prostate associated with cancer (hemi-ablation) regardless of individual lesion grade, volume, or location and proximity to a neurovascular bundle.

While our current study is not directly comparable to previous studies of focal therapy (panel), it continues to support the proposition that tissue preservation leads to functional preservation. The histological outcomes in this study were slightly worse than those reported for hemi-ablation, perhaps because of the requirements for increased precision of focal ablation—individual areas of cancer were targeted as opposed to a standardised hemi-ablation—with a resulting reduction in margin around the cancer. Image-registration software to accurately fuse, in real-time, pretreatment location data to intraoperative ultrasound images could improve histological outcomes.[34] Another reasonable explanation might relate to physical limitations of the ablative technology. Other ablative therapies as well as brachytherapy[35] and image-guided radiosurgery platforms are able to treat discrete volumes of tissue and might have differing outcomes. New platforms such as irreversible electroporation and photodynamic therapy are theoretically more tissue-specific and could allow neurovascular bundle preservation even if the ablative zone is close to the prostate capsule; tissue specificity of these techniques has not yet been assessed.

In conclusion, focal therapy of individual prostate-cancer lesions, regardless of whether they are multifocal or unifocal, leads to a low rate of genitourinary side-effects and an encouraging rate of early freedom from clinically significant prostate cancer. If the functional outcomes that we report are reproduced in larger studies and coupled with acceptable rates of cancer control in the medium to long term, focal therapy could offer a strategy by which the burden of treatment-related side-effects are addressed for a substantial proportion of men with localised prostate cancer. The design and execution of comparative-effectiveness research assessing long-term cancer control needs to be prioritised, especially at a pace than can match the potential for informal diffusion.

Contributors

ME and HUA conceived the study. ME supervised the project and is guarantor of the data. HUA, LD, RGH, RS, and MS recruited, treated, and followed up patients. HUA and JVdM analysed the data. HUA wrote the first draft of the paper. AF provided histological expertise for the project and reported all biopsies. APK and CA undertook MRIs and provided imaging expertise. All authors contributed to the drafting and editing of the manuscript and approved the final version.

Conflicts of interest

ME and HUA received funding from USHIFU, GlaxoSmithKline, and Advanced Medical Diagnostics for clinical trials. ME and HUA are paid consultants to Steba Biotech and have received funding from USHIFU, Focused Surgery, Misonix (manufacturers and distributors of the Sonablate 500 high-intensity focused ultrasound device), and Oncura and GE Healthcare for medical consultancy and travel to conferences. All other authors declared no conflicts of interest.

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