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Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate Cancer: a Prospective Development Study

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Abstract

Background: Although localised prostate cancer is multifocal in most instances, the index lesion might be responsible for disease progression.
Objective: To determine the early genitourinary functional and cancer control outcomes of index lesion ablation.
Design, setting, and participants: This was a single-centre prospective development study in which 56 men were treated (July 2009–January 2011). The mean age was 63.9 yr (standard deviation 5.8) and median prostate-specific antigen (PSA) was 7.4 ng/ml (interquartile range [IQR] 5.6–9.5). There were seven (12.5%) low-risk, 47 (83.9%) intermediate-risk, and two (3.6%) high-risk cancers.
Intervention: Multiparametric magnetic resonance imaging (mpMRI) and prostate biopsies to localise disease, followed by index lesion ablation using high-intensity focused ultrasound.
Outcome measurements and statistical analysis: Primary outcomes were genitourinary side effects measured using validated questionnaires. Secondary outcomes included absence of clinically significant disease at 12 mo.
Results and limitations: The composite of leak-free, pad-free continence, and erections sufficient for penetration decreased from a baseline frequency of 40/56 (71.4%) to 33/56 (58.9%) at 12 mo. Pad-free and leak-free, pad-free continence was preserved in 48/52 (92.3%) and 46/50 (92.0%) patients, respectively. Erections sufficient for intercourse were preserved in 30/39 (76.9%) patients. The median PSA nadir decreased to 2.4 ng/ml (IQR 1.6–4.1). At 12 mo, 42/52 (80.8%) patients had histological absence of clinically significant cancer and 85.7% (48/56) had no measurable prostate cancer (biopsy and/or mpMRI). Two (3.6%) patients had clinically significant disease in untreated areas not detected at baseline. The main study limitation is the short follow-up duration.
Conclusions: Index lesion ablation had low rates of genitourinary side effects and acceptable short-term absence of clinically significant cancer. Comparative effectiveness trials are required to assess cancer control outcomes against radical therapy.

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Patient summary: In this study we looked at whether it is possible to treat the largest and highest-grade tumour in men who have more than one known prostate tumour. We show that the side effects of targeted ablation were low, with acceptable rates of early cancer control. Larger studies with longer follow-up are needed.
Trial registration: NCT00988130

1. Introduction

For the last 100 yr, treatments for localised prostate cancer have had the whole prostate as their therapeutic target. The utility of a whole-organ approach to prostate cancer treatment has recently been brought into question. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) failed to demonstrate an overall statistically significant survival benefit associated with radical prostatectomy when compared to a conservative strategy [1], although survival benefits were seen in the intermediate- and high-risk subgroups. This confirmed the findings from the Scandinavian Prostate Cancer Group SPCG-4 trial of watchful waiting versus radical prostatectomy in men with high-risk prostate cancer [2]. However, the risk of incontinence and erectile dysfunction associated with radical whole-gland therapy is 15–20% and 30–60%, respectively [3], with significant other complications [4].

Focal therapy involves targeting individual areas of cancer while preserving the majority of the prostate tissue and therefore minimising the collateral damage to surrounding structures such as the external urinary sphincter, bladder neck, neurovascular bundles, and rectum [5,6]. Support comes from studies in which tissue preservation was applied but all known cancer was targeted [7–9]. These studies had very low side-effect profiles and cancer-free rates consistently between 80% and 90%.

Concern regarding focal therapy has centred on the knowledge that prostate cancer is multifocal in origin. In prostate cancer, a larger dominant lesion is often accompanied by two or three smaller low-grade lesions. A hypothesis has emerged that the largest lesion in the prostate—the index lesion—drives disease progression [10]. The index lesion tends to be associated with the highest Gleason grade, harbours other pathological determinants of progression, and has been associated with lymph node metastases on genetic profiling [11,12]. If the index lesion could be isolated with reasonable precision and treatment directed to it alone, then the oncological efficacy of whole-gland treatment might be matched while minimising the risk of side effects. To the best of our knowledge, this is the first prospective study testing this hypothesis.

2. Patients and methods

2.1. Study design and conduct

Our single-centre study was a prospective development study according to the IDEAL (Idea, Development, Exploration, Assessment, and Long-term) guidelines for evaluating innovation in surgery [13]. The trial was approved by Local Research Ethics Committee A of the University College London Hospitals.

2.2. Patient population

Treatment-naïve men recently diagnosed with low-, intermediate-, or high-risk nonmetastatic prostate cancer (prostate-specific antigen [PSA] $\leq$20 ng/ml, Gleason $\leq$ 4 + 3, stage $\leq$T3aN0M0) were eligible (Fig. 1).

2.3. Study interventions

2.3.1. Cancer localisation

Prostate cancer was localised using multiparametric magnetic resonance imaging (mpMRI) and transperineal template prostate mapping (TPM) biopsies [14] (n = 24) and/or transrectal ultrasound (TRUS)-guided biopsies (n = 22). TPM biopsies were carried out under general or spinal anaesthesia, with the prostate sampled at 5-mm intervals.

The index lesion was identified according to the following criteria. First, if an mpMRI lesion was visible on at least two sequences (equivalent to Prostate Imaging Reporting and Data System score of 4 or 5), the dominant biopsy findings had to be concordant with that lesion location. Second, the dominant histological lesion was assigned in the following manner whether an mpMRI lesion was present or not (TPM biopsies were required if an mpMRI lesion was not present):

(1) If the prostate only harboured Gleason 6 disease, then the index lesion was the lesion with the maximum cancer core length (CCL_{max}) provided all other lesions on biopsy located in another quadrant of the prostate had CCL_{max} $\leq$5 mm.
(2) If there was grade heterogeneity between individual lesions, then the lesion with the highest Gleason grade was regarded as the index lesion provided it had no more than Gleason 4 + 3 and the other lesions had no more than Gleason 3 + 3 AND CCL_{max} $\leq$5 mm.

2.3.2. Treatment

Focal ablation of the index lesion was performed using transrectal high-intensity focused ultrasound (HIFU; Sonablate 500, Focus Surgery, Indianapolis, IN, USA) (Supplementary materials). Untreated areas could contain secondary small-volume (CCL $\leq$5 mm) Gleason 3 + 3 disease [14], high-grade prostate intraepithelial neoplasia, and/or atypical small acinar proliferation (Fig. 2).

2.3.3. Follow-up

Contrast-enhanced MRI was carried out at 10–14 d to evaluate the area of ablation, demonstrated by a confluent perfusion deficit (Fig. 3). Clinical review at 1, 3, 6, 9, and 12 mo assessed adverse events, serum PSA, and responses to validated questionnaires. Phosphodiesterase-5 inhibitor (PDE5-I) use was permitted at any time point before treatment and during follow-up to aid erectile function. At 6 mo, mpMRI followed by biopsies targeted to the treated area was scheduled, with a minimum sampling requirement of one core for every 1 ml of residual tissue. Repeat treatment using focal HIFU for treated or untreated areas that

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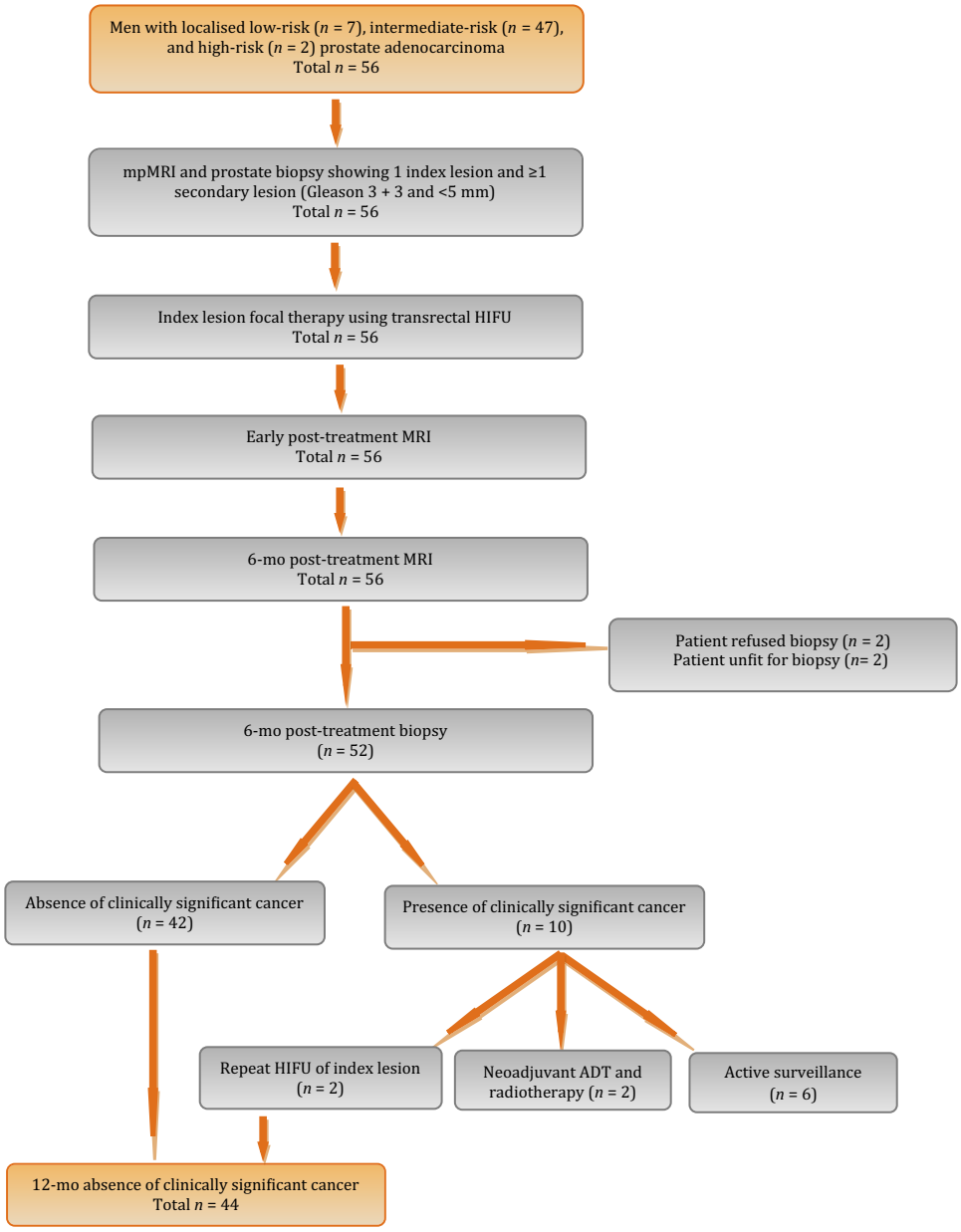

Fig. 1 – Trial flow chart. mpMRI = multiparametric magnetic resonance imaging; HIFU = high-intensity focused ultrasound; ADT = androgen deprivation therapy.

showed signs of progression was permitted if biopsies were positive. Further mpMRI was carried out at 12 mo in such cases. As the purpose of the 6-mo biopsies was to determine whether the ablation was successful, our ethics committee did not permit transperineal TPM biopsies of untreated tissue because of the requirement for another general anaesthetic. However, biopsies of untreated tissue were permitted if a new lesion suspicious for cancer was seen on mpMRI or if existing untreated tissue showed signs of progression.

2.4. *Study endpoints*

The primary outcome was the composite rate of genitourinary side effects measured using validated patient questionnaires [15–17]. Incontinence was defined using a score of 1–3 for question 1 (any leak) and of 1–3 for question 5 (any pad use) of the University of California, Los Angeles (UCLA) Expanded Prostate Cancer Index Composite (EPIC) continence questionnaire. Erectile dysfunction was defined as a score of 0 or 1 for question 2 of the 15-item International Index of Erectile Function (IIEF-15) questionnaire. Urinary function was evaluated using the International Prostate Symptom Score (IPSS), the IPSS-quality of life questionnaire, and the UCLA-EPIC continence questionnaire. Health-related quality of life was measured using the Functional Assessment of Cancer Therapy-Prostate (FACT-P). Responses to the validated questionnaires were collated using standard methods.

Secondary outcomes were histological parameters of cancer control on 6-mo biopsy, absence of clinically significant disease on mpMRI at 6 and 12 mo, description of PSA kinetics following index lesion ablation, and the proportion of men requiring salvage local radical therapy and systemic therapy for progressive prostate cancer.

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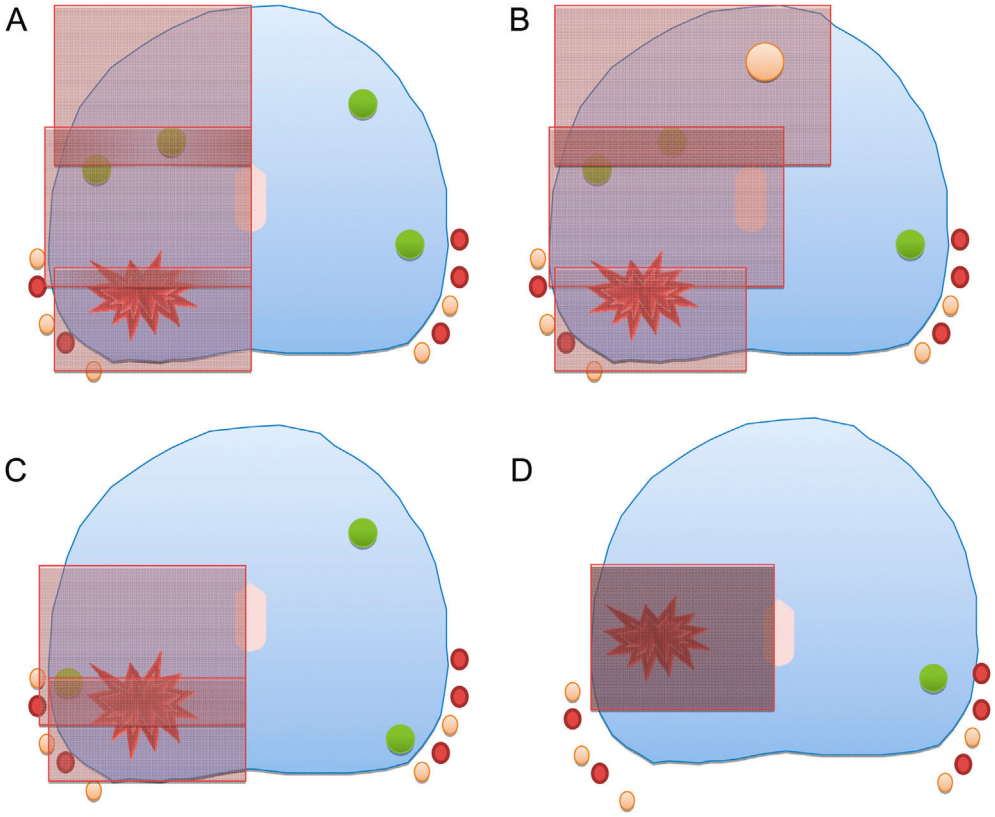

Fig. 2 – Schematic diagrams demonstrating the types of focal therapy conducted in this trial. Large red areas represent dominant cancers (so-called index lesions) whilst small green areas represent small, low-grade, secondary lesions. Red transparent boxes represent ablation zones on the high-intensity focused ultrasound device: (A) hemiablation, (B) extended (dogleg) ablation; (C) quadrant ablation; (D) focal ablation.

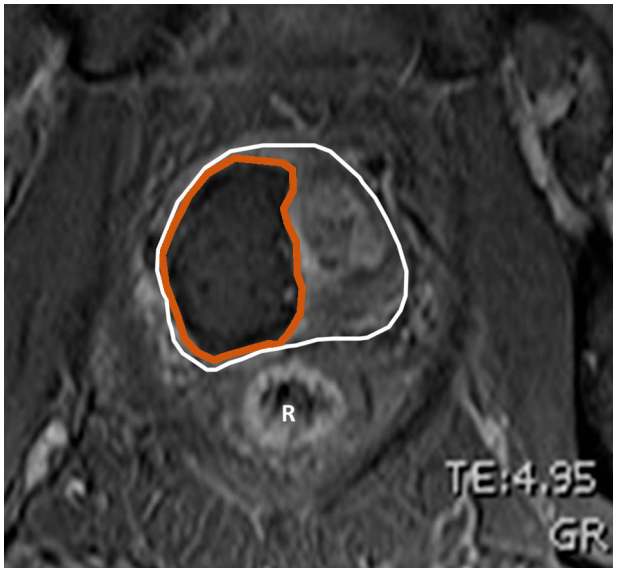

Fig. 3 – Contrast-enhanced axial scan of the prostate at mid-gland at 1 wk after high-intensity focused ultrasound ablation of an index lesion in the right prostate lobe. Example of right-sided index lesion treatment with confluent hemiablation necrosis demonstrated on early (1-wk) multiparametric magnetic resonance imaging. The orange line indicates the area of ablation with confluent necrosis, in this case hemiablation. The white line indicates the outline of whole prostate. R = rectum.

2.5. Statistical analysis

The sample size was calculated on a composite endpoint defined as the total proportion of men with erectile dysfunction and/or incontinence. It was estimated that baseline incontinence was about 10% and baseline impotence about 40% in men older than 60 yr [18,19]. Overall, we estimated that baseline genitourinary dysfunction would be approximately 50%. Were these men to undergo whole-gland therapy, 50% of those with good baseline function would also suffer some form of genitourinary dysfunction [20], so total genitourinary dysfunction would be approximately 75% at 12 mo if men were to undergo whole-gland therapy. It was hypothesised that focal therapy would give rise to genitourinary dysfunction in only 5% of those with good baseline function. Therefore, we estimated a total genitourinary dysfunction level of approximately 55% at 12 mo after focal index lesion ablation. Using sample size calculations comparing an estimate proportion (0.55) to a known proportion (0.75), with $\alpha = 0.05$ and power of 90%, the total number of patients required was 56 [21].

A Wilcoxon signed rank test (two-tailed) was used to evaluate differences between continuous variables (PSA, questionnaire scores) measured at baseline and at the 12-mo follow-up visit. Statistical significance was set at $p \leq 0.05$. Changes over time were described using 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 for such comparisons. Statistical analysis was performed using Stata version 11.2 (Stata Corp, College Station, TX, USA). This analysis was carried out on the available data. However, some functional measures were missing at baseline or at 12-mo follow-up for five men, so we conducted two sensitivity analyses

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to assess if this was likely to impact our results. We repeated the analysis described above for a "best" outcome scenario and a "worst" outcome scenario by setting missing baseline values to the maximum or minimum possible, respectively.

3. Results

3.1. Study patients

Fifty-six men were recruited (July 27, 2009–January 26, 2011) with a mean age of 64 yr. According to National Comprehensive Cancer Network criteria [22], seven men (12.5%) had low-risk, 47 (83.9%) had intermediate-risk, and two (3.6%) had high-risk nonmetastatic prostate cancer (Fig. 1, Table 1).

3.2. Primary outcome

Overall, 40 patients (71.4%; 95% confidence interval [CI] 59.6–83.2%) were leak-free, pad-free continent and had erections sufficient for penetration at baseline. This composite measure decreased to 33 patients (58.9%; 95% CI 46.0–71.8%) at 12 mo.

3.3. Secondary outcomes

3.3.1. Urinary function

In terms of absolute continence, the proportion of patients with pad-free continence fell from 54/54 (100%) at baseline to 50/54 (92.6%) at 12 mo, and the proportion of men with leak-free pad-free continence fell from 53/54 (98.1%) at baseline to 48/52 (92.6%) at 12 mo.

In terms of relative continence, of the 52 patients with pad-free continence at baseline, 48 (92.3%; 95% CI 81.5–97.9%) remained so at 12 mo. Of 50 patients with a leak-free, pad-free status at baseline, 46 (92.0%; 95% CI 80.8–97.8%) remained so at 12 mo (Supplementary Figs. 1–3).

3.3.2. Erectile function

In terms of absolute erectile function, the proportion of patients with erections sufficient for penetration decreased from 41/54 (75.9%) to 36/54 (66.7%) at 12 mo. PDE5-I use increased from 7/55 (12.7%) to 23/54 (42.6%).

In terms of relative erectile function, of 39 men with erections sufficient for penetration at baseline, 30 (76.9%; 95% CI 60.7–88.9%) remained so at 12 mo (Supplementary Figs. 4 and 5).

3.3.3. Health-related quality-of-life scores

Treatment appeared to have very little impact on generic health-related quality of life, both within the early postoperative period and at final follow-up ($p = 0.52$; Supplementary Fig. 7).

3.3.4. Adverse events

There were no patient deaths and no serious adverse events. Nine men (16.1%) had transient, self-resolving dysuria (with a negative urine culture), 36/56 (64.3%) had intermittent self-resolving haematuria, and 24/56 (42.9%) had urinary passage of debris. Ten patients (17.9%) had a postoperative urinary tract infection (confirmed by positive urine culture). One man (1.8%) underwent resection of an area at the bladder neck that was suspicious on 6-mo mpMRI, which was subsequently diagnosed as Gleason 4 + 4 prostate cancer. Two men (3.6%) underwent a bladder neck incision. One further man (1.8%) underwent rigid cystoscopic resection of retained necrotic prostatic tissue causing recurrent urinary tract infections (Table 2).

Table 1 – Baseline data for 56 men with multifocal prostate cancer in which the index lesion alone was targeted

Parameter	Result
Mean age, yr (SD; range)	63.9 (5.8; 51–76)
Serum PSA (ng/ml)	7.4 (5.6–9.5)
Reason for PSA test and biopsy	
PSA screening (patient request)	49 (87.5%)
Lower urinary tract symptoms	7 (12.5)
Prostate volume (ml)	38.0 (26.0–50.0)
PSA density (ng/ml per ml prostate)	0.20 (0.12–0.29)
Initial biopsy	
TRUS biopsy	22 (39.3)
TPM biopsy	34 (60.7)
Gleason (on initial TRUS-guided biopsy)	
3 + 3	17/46 (37.0)
3 + 4	25/46 (54.3)
4 + 3	4/46 (8.7)
4 + 4	0 (0)
No TRUS biopsy (including before TPM)	10/56 (17.9)
Gleason (TPM biopsy)	
3 + 3	12/34 (35.3)
3 + 4	19/34 (55.9)
4 + 3	3/34 (8.8)
4 + 4	0 (0)
No TPM biopsy	22/56 (39.3)
Clinical stage	
T1c	16 (28.6)
T2a	9 (16.1)
T2b	18 (32.1%)
T2c	11 (19.6%)
T3a	2 (3.6%)
TRUS-guided biopsies	
Total cores	12.0 (10.0–13.0)
Total positive cores	3.0 (2.0–4.0)
Percent positive cores	40.0 (21.3–65.0)
TPM biopsies	
Total cores	61.0 (41.5–71.3)
Total positive cores	11.5 (8.0–14.3)
Percent positive cores	60.0 (30.0–80.0)
Core density (biopsies/ml)	1.4 (1.1–1.8)
Number of lesions	
1	15 (26.8)
2	19 (33.9)
3	16 (28.6)
4	3 (5.4)
5	2 (3.6)
6	1 (1.8)
Disease distribution	
Unilateral	17 (30.4)
Bilateral	39 (69.6)
NCCN risk category	
Low	7 (12.5)
Intermediate	47 (83.9)
High	2 (3.6)

PSA = prostate-specific antigen; SD = standard deviation; IQR = interquartile range; TRUS = transrectal ultrasound; TPM = transperineal template mapping; NCCN = National Comprehensive Cancer Network.
Continuous data are presented as median (interquartile range) and categorical data as *n* (%) unless stated otherwise.

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3.3.5. Biochemical, imaging, and histological outcomes

A significant decrease in serum PSA from a median baseline value of 7.4 ng/ml (IQR 5.6–9.5) to 2.4 ng/ml (IQR 1.6–4.1) was observed at 12 mo ($p < 0.0001$; Fig. 3).

At 6 mo, two men refused a post-treatment biopsy, and another two had clinical reasons for omitting biopsies (chemotherapy for newly diagnosed lung cancer in one, and a persistent HIFU cavity connecting with the vas deferens on mpMRI in another). For these four men, mpMRI at 6 mo showed no evidence of measurable residual disease. There was no histological evidence of clinically significant disease (Gleason $\leq$ 3 + 3, CCL $\leq$3 mm) in the treated area in 44/52 patients (84.6%; 95% CI 70–92%), or of any cancer in the treated area in 34/52 patients (65.4%; 95% CI 52.5–78.3%). Two had clinically significant disease on biopsies from suspicious areas in the untreated side on mpMRI not present at baseline. Overall, histopathological absence of clinically significant cancer (treated and untreated sides) was observed in 42/52 men (80.8%, 95% CI 67.5–90.4%). The overall rate of absence of measurable disease was 86% (48/56) at the study end following repeat treatment in two patients. However, 43% of men had persistent cancer of any threshold at the study end. Two other men underwent salvage treatment with neoadjuvant hormone ablation therapy and external beam radiotherapy for residual Gleason 4 + 3 and Gleason 4 + 4 disease (Table 3).

Of 41 patients with good baseline status, 22 (53.7%, 95% CI 37.4–69.3%) achieved the trifecta outcome (absence of clinically significant disease, pad-free, leak-free continence, and erections sufficient for intercourse) at 12 mo (Fig. 4). The results for sensitivity analyses (data not shown) were very similar and did not affect our overall conclusion.

4. Discussion

In this first attempt to limit prostate cancer treatment to the index lesion, the majority of men returned to baseline genitourinary function and 86% of men were free of clinically significant prostate cancer at the study end.

Our study has some limitations. First, the study size was relatively small. It was powered to give reasonable precision for the key endpoints so that a comparative effectiveness study could be planned [15]. A pilot randomised controlled trial (RCT) of focal therapy versus radical therapy to

Table 2 – Perioperative outcomes in 56 men undergoing index lesion ablation

Parameter	Result
Median total anaesthetic time, min (IQR)	144.5 (115.5–162.25)
Median procedure time (SPC + focal HIFU), min (IQR)	114.5 (90–130)
Laterality of treatment, *n* (%)	
Unilateral	43 (76.8)
Bilateral (extending across the midline)	13 (23.2)
Median total hospitalisation time (admission to discharge), h (IQR)	16.0 (9.0–28.8)
Median discharge time (end of procedure to discharge), h (IQR)	9.5 (5.0–21.8)
Median catheterisation time, d (IQR)	9.0 (7.0–14.0)
Dysuria (negative urine culture), *n* (%; 95% CI)	9/56 (16.1; 7.6–28.3)
Median dysuria duration, d (IQR)	31.5 (23.8–52.8)
Intermittent haematuria (start of stream only), *n* (%; 95% CI)	36/56 (64.3; 50.4–76.6)
Median duration of intermittent haematuria, d (IQR)	32.0 (14.0–42.0)
Urinary debris, *n* (%; 95% CI)	24/56 (42.9; 29.7–55.8)
Median duration of urinary debris, d (IQR)	14.0 (7.0–27.0)
Urinary tract infection (positive urine culture), *n* (%; 95% CI)	10/56 (17.9; 8.9–30.4)
Number of urinary tract infections, *n* (%)	
0	46/56 (82.1)
1	7/56 (12.5)
2	1/56 (1.8)
3	2/56 (3.6)
Patients requiring cystoscopic intervention (general anaesthetic) for symptomatic reasons post-HIFU, *n* (%)	3/56 (5.4)
Bladder neck incision (for poor urinary flow)	2 (3.6)
Resection of necrotic prostatic tissue (for recurrent urinary tract infections)	1 (1.8)

IQR = interquartile range; SPC = suprapubic catheter; HIFU = high-intensity focal ultrasound; CI = confidence interval.

Table 3 – Histology outcomes at 6 mo after focal index lesion ablation in 52 men who underwent post-treatment prostate biopsy

Parameter	Value
Positive biopsy outcomes on the treated side	
Median number of biopsies taken, *n* (IQR)	5.0 (4.0–6.0)
Positive biopsies (any disease), *n* (%)	18/52 (34.6)
Positive biopsies (clinically significant disease), *n* (%)	8/52 (15.4) [a]
Median CCL_{max} in positive cores, mm (IQR)	2.0 (1.0–4.0)
Gleason score, *n* (%)	
3 + 3	12/18 (66.7)
3 + 4	5/18 (27.8)
4 + 3	1/18 (5.6)
Positive biopsy outcomes on the untreated side (targeted to suspicious areas on 6-mo MRI)	
Positive biopsies (any disease), *n* (%)	4/52 (7.7)
Positive biopsies (clinically significant disease), *n* (%)	2/52 (3.8) [b]
Gleason score (*n*)	
3 + 3	3 [c]
3 + 4	0
4 + 3	0
4 + 4	1
Absence of any cancer on both sides, *n* (%; 95% CI)	30/52 (57.7; 43.2–71.3)
Overall absence of clinically significant disease on both sides, *n* (%; 95% CI)	42/52 (80.8; 67.5–90.4)
Other histological findings, *n* (%; 95% CI) [d]	
Prostatic acini	2/51 (3.9; 0.5–13.5)
Atrophy	20/51 (39.2; 25.8–53.9)
Fibrosis	39/51 (76.5; 62.5–87.2)
Giant-cell reaction	4/51 (7.8; 2.2–18.9)
Necrosis	11/51 (21.6; 11.3–35.3)

IQR = interquartile range; CCL_{max} = maximum cancer core length; MRI = magnetic resonance imaging; CI = confidence interval.

[a] These men were counted within the "any disease" category. In other words, eight of the 18 men with positive biopsies on the treated side had clinically significant cancer.

[b] These men were counted within the "any disease" category. In other words, two of the four men with positive biopsies on the untreated side had clinically significant cancer.

[c] CCL_{max} in these three cases was <1 mm, 1 mm, and 4 mm.

[d] Data only available for 51/52 patients.

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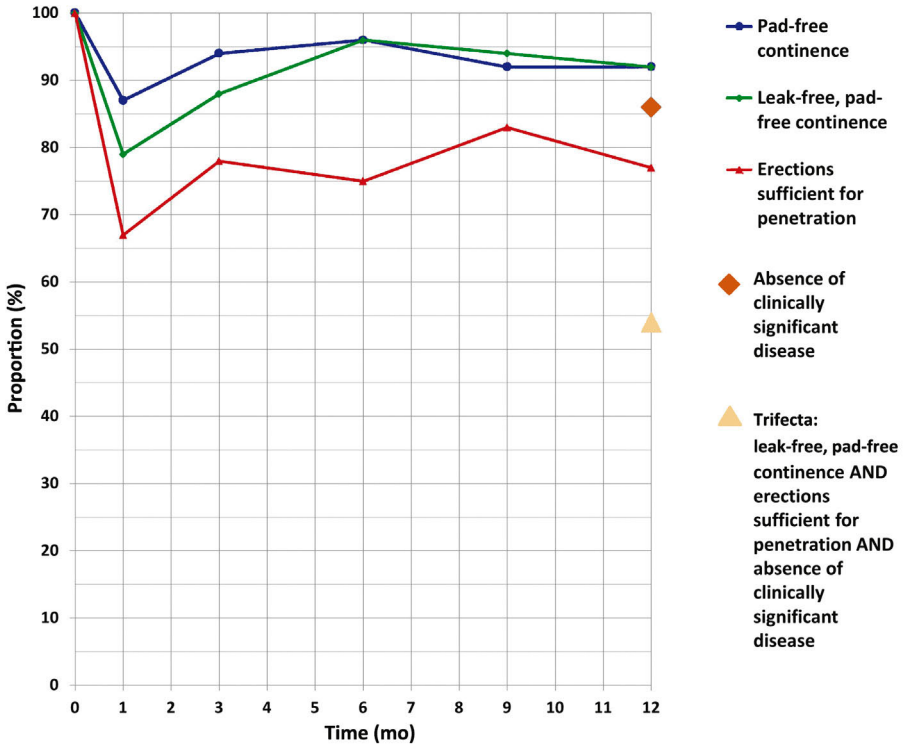

Functional outcome	Patients, *n* (%; 95% confidence level)					
	0 mo	1 mo	3 mo	6 mo	9 mo	12 mo
Pad-free continence	54 (100)	45/52 (87; 74–94)	51/54 (94; 85–99)	51/53 (96; 87–100)	49/53 (92; 82–98)	48/52 (92; 81–98)
Leak-free, pad-free continence	53 (100)	38/48 (79; 65–90)	45/51 (88; 76–96)	48/50 (96; 86–100)	48/51 (94; 84–99)	46/50 (92; 81–98)
Erections sufficient for penetration	41 (100)	26/39 (67; 50–81)	32/41 (78; 62–89)	30/40 (75; 59–87)	33/40 (83; 67–93)	30/39 (77; 61–89)
PDE5-I use	7/55 (13; 5–24)	6/55 (11; 4–22)	14/55 (25; 15–39)	25/54 (46; 33–60)	26/54 (48; 34–62)	23/54 (43; 29–57)

Fig. 4 – Summary of continence, erectile function, and cancer control outcomes and the trifecta rate following high-intensity focused ultrasound ablation of the index lesion. Patient-reported trifecta outcomes were collected using validated questionnaires. (1) Percentage continence data were derived using the questions "Over the past 4 weeks how often did you leak urine?" and "Over the past 4 weeks how many pads or adult diapers per day did you usually use to control leakage?" from the urinary domain of the University of California, Los Angeles Expanded Prostate Cancer Index Composite questionnaire. (2) The percentage of men with erections sufficient for penetration was calculated for men scoring ≥2 for the question "Over the past 4 weeks when you had erections with sexual stimulation, how often were your erections hard enough for penetration?" from the 15-item International Index of Erectile Function. (3) The percentage phosphodiesterase-5 inhibitor (PDE5-I) use (tadalafil, sildenafil, or vardenafil) was calculated using the number of men achieving erections sufficient for penetration from part (2) as the denominator.

determine whether recruitment is possible has recently been funded in the UK [23]. Second, compared to most other studies of focal therapies, we relaxed the risk stratification methods to reflect changing practice. This meant that as well as using TPM plus mpMRI, we permitted entry to the study if a TRUS-guided biopsy proved to be concordant with mpMRI. We feel that this was the right decision, as there is now a substantial body of evidence supporting a high negative predictive value for mpMRI (≥95%) in ruling out prostate cancer with Gleason ≥7 and/or lesion volume ≥0.5 ml [24,25]. This is in fact the performance characteristic seen with TPM [26]. This might be consistent with our results, since we detected two cases of clinically significant cancer in untreated areas at follow-up. These lesions might have been missed at baseline by the inherent 5% false-negative rate of mpMRI and TPM, although progression of untreated cancer lesions may also have occurred. However, we also acknowledge that there may be bias introduced in allowing TRUS biopsy with mpMRI concordance, as the more detailed histological mapping proffered by TPM biopsies may lead to different cancer control outcomes. The disease control rates by method of cancer localisation were as follows. For the 26 men undergoing TPM biopsies, 3/26 (11.5%; 95% CI 3.2–29.8%) had histological presence of clinically significant cancer in the treated area and 1/26 (3.8%; 95% CI 0.01–20.5%) had histological presence of clinically significant cancer in untreated areas. For the TRUS biopsy group of 22 men, these proportions were 5/22 (22.7%; 95% CI 9.7–43.8%) and 1/22 (4.5%; 95% CI 0.01–23.5%), respectively. Although this subgroup analysis demonstrates that TRUS biopsy may yield important clinical differences in histological outcomes, the difference between these proportions was not statistically significant. Third, our study population is likely to have limited external validity. We estimated a 10% baseline incontinence rate and a 40% baseline rate of erectile dysfunction, yet our data reveal rates of 0% and 24%,

respectively. We applied no selection criteria, but it is likely that patients who were continent and on the whole had better than average erectile function at diagnosis sought out focal therapy in this trial in the hope of gaining access to a treatment that might preserve their function. Fourth, while our initial rate of endoscopic intervention (5.4%) within the first year is low, with further follow-up and potentially further repeat treatments, this rate might increase. This is clearly an issue that needs to be considered if focal therapy is recommended as standard care in the future. Fifth, while we report the overall rate of the absence of clinically significant disease as the primary cancer control measure to reflect the study design and rationale, it must be remembered that 43% of men had persistent disease at the study end. These men may exhibit progression with time.

4.1. Clinical implications

The outcome from other focal therapy studies in which treatment was applied to all known cancer lesions was recently reviewed [9]. Rates of 95–100% for pad-free, leak-free continence preservation, 54–100% for potency, and 83–100% for overall absence of clinically significant cancer were observed after treatment. Most of these studies applied strict selection criteria for disease risk, biopsy cancer burden, and function at baseline, and therefore have limited external validity. In our current study—in a group of men who were not selected by the investigators on the basis of good baseline function—the functional preservation outcomes were not as high as we have previously reported. Indeed, our trifecta rate is also lower than previously reported, and may not be as encouraging when compared to the rates reported after surgery. With greater numbers in our ongoing larger multicentre trials, we may be to identify men who are unlikely to have good functional outcomes after focal therapy and would be better treated using a radical approach. Our study is unique in that known cancer of low malignant potential was left untreated. We recently showed that if such a strategy were to be adopted, more than 90% of newly diagnosed men with localised prostate cancer might be eligible for focal therapy [27].

Some have argued that because mpMRI and TPM biopsies are not accurate enough to detect all areas of prostate cancer, the concept of selective therapy lacks legitimacy [28]. However, in most other solid organs, cancer is diagnosed when a clinical manifestation of disease (a lump or an imaging signal) is verified histologically. Inevitably, therapy is directed at the clinical phenotype plus the addition of a margin. This was recently seen in the administration of radiotherapy to the breast after lumpectomy. Historically, whole-breast irradiation was favoured because of the known multifocality of breast cancer. The finding that intraoperative local irradiation of the surgical site was not inferior to whole-breast irradiation challenges the idea that recurrence is due to residual subclinical multifocal lesions away from the index lesion [29]. There is also concern that inclusion of intermediate- and high-risk cases for focal therapy may represent undertreatment for those men who harbour microscopic nodal metastases.

It is yet to be determined whether an RCT of focal therapy compared to radical therapy is deliverable [23]. Previous trials have attempted to compare different interventions in localised prostate cancer; however, many have failed because of a lack of physician and patient equipoise. There are additional concerns regarding appropriate endpoints and the follow-up time frame, especially as a minimum of 10-yr follow-up would be required to evaluate metastases and mortality. The UK National Institute of Health Research has recently funded a pilot RCT to determine whether recruitment might be feasible (ISRCTN99760303). This RCT will evaluate rates of transition to local salvage therapies within a 5-yr period between focal therapy and radical prostatectomy in men with intermediate-risk prostate cancer.

Our findings have implications for prostate cancer management. Some have suggested that low-risk disease should be relabelled as a benign entity because of the rarity of progression and metastases from these lesions [10–12]. If this hypothesis proves to be true, we could concentrate on targeting measurable disease based on mpMRI considering the high negative predictive values for clinically significant disease that it confers. However, the notion that Gleason 6 disease cannot metastasise has recently been brought into question following the findings of Haffner et al [30], who reported on a case in which a small area of Gleason 6 disease within a tumour of very high-grade cancer was responsible for a distant metastasis. There has been considerable debate regarding the validity of these findings [31].

Our study also represents an *in vivo* human model for better understanding of the determinants of progression of low-grade disease in a manner that is not predicated on removing the whole organ. This might allow us to determine if such lesions do progress and, if so, whether they can be identified at the time of diagnosis using detailed molecular typing approaches such as immunohistochemistry and -omics techniques.

5. Conclusions

Prostate cancer is multifocal in the majority of men. Current treatment options deal with such multifocality by applying treatment to the entire gland, and this can lead to urinary incontinence and impotence in some men. It has been shown that treatment targeted to the index lesion is feasible, safe, and well tolerated, with high rates of genitourinary functional preservation. Comparative effectiveness studies are needed.

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Acquisition of data: Ahmed, Dickinson, Weir, McCartan, Hindley, Freeman, Kirkham, Sahu, Scott, Allen.
Analysis and interpretation of data: Ahmed, Dickinson, Charman, van der Meulen, Emberton.
Drafting of the manuscript: Ahmed, Dickinson, Charman, Weir, McCartan, Hindley, Freeman, Kirkham, Sahu, Scott, Allen, Van der Meulen, Emberton.

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Appendix A. Supplementary data

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