BJUI
BJU International

# Medium-term oncological outcomes in a large cohort of men treated with either focal or hemi-ablation using high-intensity focused ultrasonography for primary localized prostate cancer

Armando Stabile*†‡, Clement Orczyk*‡, Feargus Hosking-Jervis‡, Francesco Giganti‡§, Manit Arya*‡, Richard G. Hindley*, Louise Dickinson§, Clare Allen§, Shonit Punwani§, Charles Jameson¶, Alex Freeman¶, Neil McCartan‡, Francesco Montorsi†, Alberto Briganti†, Hashim U. Ahmed**††, Mark Emberton*‡ and Caroline M. Moore*‡

*Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK, †Department of Urology and Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy, ‡Division of Surgery and Interventional Science, University College London, §Department of Radiology, ¶Department of Pathology, University College London Hospitals NHS Foundation Trust, **Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, and ††Imperial Urology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK

## Objective

To report medium-term oncological outcomes in men receiving primary focal treatment with high-intensity focused ultrasonography ( HIFU) for prostate cancer (PCa).

## Patients and Methods

Consecutive patients with PCa treated with primary focal HIFU at two centres by six treating clinicians were assessed. Patients were submitted to either focal ablation or hemi-ablation using HIFU (Sonablate 500). The primary objective of the study was to assess medium-term oncological outcomes, defined as overall survival, freedom from biopsy failure, freedom from any further treatment and freedom from radical treatment after focal HIFU. The secondary objective was to evaluate the changes in pathological features among patients treated with focal HIFU over time. We also assessed the relationship between year of surgery and 5-year retreatment probability.

## Results

A total of 1032 men treated between November 2005 and October 2017 were assessed. The median age was 65 years and median prostate-specific antigen level was 7 ng/mL. The majority of patients had a Gleason score of 3 + 4 or above (80.3%). The median (interquartile range) follow-up was 36 (14–64) months. The overall survival rates at 24, 60 and 96 months were 99%, 97% and 97%, respectively. Freedom from biopsy failure, defined as absence of Gleason 3 + 4 disease, was 84%, 64% and 54% at 24, 60 and 96 months. Freedom from any further treatment was 85%, 59% and 46% at 24, 60 and 96 months, respectively. Approximately 70% of patients who were retreated received a second focal treatment. Freedom from radical treatment was 98%, 91% and 81% at 24, 60 and 96 months. During the study period, we observed an increase in the proportion of patients undergoing focal HIFU with Gleason 3 + 4 disease and with T2 stage disease as defined by multiparametric magnetic resonance imaging. Finally, there was a reduction over time in the proportion of patients undergoing re-treatment within 5 years of first treatment.

## Conclusions

Focal HIFU for PCa is a feasible therapeutic strategy, with acceptable survival and oncological results and a reduction in the 5-year retreatment rates over the last decade. Re-do focal treatment is a feasible technique whose functional and oncological outcomes have still to be evaluated.

## Keywords

focal therapy, high-intensity focused ultrasonography, #PCSM, #ProstateCancer, #HIFU


BJU International © 2019 BJU International | doi:10.1111/bju.14710
Published by John Wiley & Sons Ltd. www.bjui.org

## Introduction

Men with low- or intermediate-risk prostate cancer (PCa) often face a choice between active surveillance with the option of deferred radical treatment, and radical treatment using surgery or radiotherapy. In the UK, the number of diagnoses is highest in the age range 70–74 years [1], and the proportion of men diagnosed with intermediate-risk disease is increasing, whilst low-risk disease (Gleason 3 + 3) is decreasing.

Whilst radical treatment of low- and intermediate-risk PCa is associated with good oncological control, it can be associated with significant side effects, including problems with urinary, bowel and sexual function [2].

The aim of focal therapy is to provide oncological control whilst preserving urinary and erectile function [3,4].

A systematic review that included 2350 cases (from 30 studies) treated with focal therapy, reported an overall positive biopsy rate ranging from 3.7% to 23% at a median follow-up ranging from 0 to 11.1 years [5]. Azzouzi et al. [6], in a randomized controlled trial comparing focal photodynamic targeted therapy vs active surveillance for low-risk PCa, reported a lower rate of progression in the former group at 24 months (28% vs 58%). Despite the promising oncological effectiveness of focal therapy, critics have argued that studies have had a tendency to include men with low-risk PCa for whom active surveillance might be appropriate. The lack of comparator group analysis, the relatively small study samples, the short-term follow-up and single-centre nature of most studies, as well as the paucity of study registration has, to date, limited the strength of the published clinical evidence in terms of case selection and generalizability as well as failure to adjust for any confounding [7]. In terms of informed shared decision-making what has been missing so far are outcomes that matter to patients. These comprise: absolute rates of retreatment, likelihood of deferring or avoiding radical treatment, the probability of overall cancer control and cost-effectiveness [5].

The University College London Hospital (UCLH) high-intensity focused ultrasonography (HIFU) programme started in 2003 as a whole-gland intervention. The focal therapy programme began 2 years later in 2005. Today HIFU is almost exclusively used to administer focal treatments, in both primary and salvage settings.

In April 2012, the UK National Institute for Health and Care Excellence (NICE) published an Interventional Procedure Guidance on HIFU (IPG 424) [8], stating that whilst there are not many safety concerns, the evidence on efficacy was limited. It concluded that the procedure could be used within the UK NHS as long as, 'special arrangements for clinical governance, consent and audit or research', were in place.

The IDEAL framework for developing surgical interventions describes the manner in which the process of clinical innovation might be reported. It describes the following phases: Idea (1), Development (2a), Exploration (2b), Assessment (3) and Long-term monitoring (4) [9]. We report the long-term monitoring results of focal HIFU, including the changes in its use over time, in a cohort of >1000 men who underwent this procedure under the care of one team of clinicians working within two UK healthcare settings: the NHS and private practice.

## Materials and Methods

### Study Population

The study cohort comprised 1032 consecutive patients who received focal HIFU at one of two centres (University College London Hospital or Princess Grace Hospital) between November 2005 and October 2017. Two surgeons (M.E. and C.M.) operated at both centres, and a further four surgeons (H.U.A., M.A., L.D., C.O.) operated at UCLH. Data were retrospectively analysed. This cohort included men who were treated both within National Cancer Research Network-approved trials and clinical practice where data were collected.

### Disease Localization

Disease was localized using a combination of prostate multiparametric MRI (mpMRI) and biopsy. All patients underwent a 1.5-T or 3.0-T mpMRI study consisting of T2-weighted, dynamic contrast-enhanced and diffusion-weighted imaging sequences. No endorectal coil was used. Biopsy strategies changed over time, and included systematic TRUS-guided biopsy with additional targeted cores; transperineal template prostate mapping (TTPM) biopsies using a 5-mm sampling grid or a modified Barzell approach, and transperineal targeted biopsies with additional systematic sampling. Patients who had an MRI not concordant with initial pathology were offered additional sampling to determine their suitability for focal therapy.

### High-Intensity Focused Ultrasonography Treatment and Follow-up

Patients with either TRUS-guided biopsy or TTPM results concordant with a suspicious lesion detected at mpMRI, were offered focal therapy as an alternative to the standard options of radical treatment and active surveillance. Other focal treatments were also available at the two different centres at various time points during this cohort, including focal

cryotherapy, Nanoknife™ electroporation, photodynamic therapy (Tookad™) and radiofrequency ablation (Encage™).

The patients underwent treatment with a transrectal HIFU device (Sonablate 500; Sonacare Inc, Indianapolis, IN, USA). This procedure has been previously described in detail [10]. According to the mpMRI and biopsy report (lesion volume, extension, Gleason score and number of positive cores) patients underwent either an entire ablation of one prostatic lobe (hemi-ablation) or the ablation of the index lesion only, identified with a combination of mpMRI and biopsy (focal/quadrant ablation) [11]. A margin of at least 5 mm was adopted around a visible mpMRI-based tumour.

Based on our initial experience with whole-gland ablation, suprapubic catheterization was routinely used as a routine for focal treatments. As it became clear that most men re-established voiding less than a week after HIFU, urethral catheterization was adopted as the standard approach, with removal within 3–7 days.

After treatment, PSA level was assessed on a 3–4-monthly basis, and mpMRI was offered at 6 or 12 months. For-cause triggers for an earlier MRI were principally driven by sequential PSA rises. Later MRI scans were requested according to baseline risk and PSA kinetics, with routine practice to have an MRI at 1 and 3 years, and additional MRI scans based on PSA changes. Patients with a suspicion of residual or recurrent disease on MRI, or those in whom there was an unexplained PSA rise, were offered biopsy assessment. Men with a stable PSA and no concerns on MRI or biopsy could be discharged to their GP for PSA monitoring with a PSA interval (e.g. 6-monthly) and threshold set for re-referral.

### Variable Definition

Baseline variables regarding pre-treatment characteristics including age, PSA value, prostate volume, type of diagnostic biopsy (TRUS-guided vs TTPM), number of biopsy cores, number of positive cores, maximum cancer core length (MCCL), mpMRI T stage (T1 vs T2 vs T3) and Gleason score were available for all the patients.

Follow-up data included first PSA after treatment, percentage of PSA reduction, biopsy failure (defined as the presence of clinically significant PCa at post-treatment biopsy). Clinically significant PCa was defined as Gleason score ≥3 + 4. Biopsies were offered systematically to men taking part in National Cancer Research Network-approved studies, and to other men on the basis of concern over mpMRI findings or PSA kinetics; therefore, follow-up biopsies were not routinely performed across the whole population (41% of patients [424/1032] received a post treatment prostate biopsy; Table 2). Any additional treatment, including further focal therapy, radical treatment or hormone treatment alone, was recorded.

### Outcomes

The primary outcomes of interest in the present analysis were oncological: freedom from any additional further treatment; freedom from radical treatment (defined as radical prostatectomy, external beam radiotherapy and other whole-gland therapies); freedom from biopsy failure; and overall survival after focal HIFU. We also evaluated the rate of retreatment-free survival according to type of treatment (focal vs hemi-ablation), and Gleason score (3 + 3 vs 3 + 4 vs ≥4 + 3).

We report the trend in Gleason score and tumour stage in men having focal HIFU over the inclusion period. To assess for the effect of a learning curve in the domains of patient selection and treatment delivery, we evaluated the likelihood of retreatment within 5 years of initial treatment for each of the years in which treatments were administered, contingent on a minimum of 5-year follow-up (i.e. until 2012).

### Statistical Analysis

Statistical analyses comprised four main steps. First, medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables, respectively. Second, Kaplan–Meier curves were plotted to assess survival. A log-rank test was used to compare different groups. Third, locally weighted scatterplot smoothing was used for graphical representation of the year-by-year trends in pathological characteristics. Finally, multivariable logistic regression analysis was performed to test the relationship between year of surgery and 5-year retreatment probability after accounting for the following confounders: PSA level; primary Gleason score; secondary Gleason score; MCCL; number of positive cores; and mpMRI T stage (T1 vs T2 vs T3). Locally weighted scatterplot smoothing smoother function was used to assess graphically the multivariable effect of the year of surgery on the 5-year retreatment probability.

All statistical tests were performed using the RStudio graphical interface v.1.1.383 for R software environment v.3.4.2 (R Foundation, Vienna, Austria). All tests were two-sided with a significance level set at $P < 0.05$.

## Results

### Baseline Characteristics

Descriptive characteristics and follow-up data are reported in Tables 1 and 2, respectively. The median (interquartile range [IQR]) age was 65 (60–70) years. The median (IQR) PSA was 7 (4.9–9.7) ng/mL. Patients were diagnosed either with TRUS (22%) or TTPM (78%) and underwent either focal (71%) or hemi-ablation (29%; specifically, 15% of these patients [47/302] underwent a hemi-ablation that crossed the midline of the prostatic gland). The majority of patients had Gleason

**Table 1** Descriptive characteristics of 1032 patients undergoing primary focal high-intensity focused ultrasonography for prostate cancer.

| Characteristic | |
|---|---|
| **Age at treatment, years** | |
| Median | 65 |
| IQR | 60–70 |
| **PSA value, ng/mL** | |
| Median | 7 |
| IQR | 4.9–9.7 |
| **Prostate volume, mL** | |
| Median | 36.5 |
| IQR | 28–48 |
| **Number of biopsy cores** | |
| Median | 25 |
| IQR | 12–44 |
| **Number of positive biopsy cores** | |
| Median | 5 |
| Range | 3–8 |
| **Maximum cancer core length, mm** | |
| Median | 6 |
| IQR | 4–8 |
| **T stage, *n* (%)** | |
| 1 | 78 (7.6) |
| 2 | 802 (77.7) |
| 3 | 123 (11.9) |
| **Biopsy type, *n* (%)** | |
| TRUS | 230 (22.3) |
| TTPM | 802 (77.7) |
| **Gleason score, *n* (%)** | |
| 3 + 3 | 203 (19.7) |
| 3 + 4 | 654 (63.4) |
| 4 + 3 | 159 (15.4) |
| 4 + 4 | 16 (1.6) |
| **Treatment type, *n* (%)** | |
| Focal | 730 (70.7) |
| Hemi | 302 (29.3) |
| **Percentage of PSA reduction, %** | |
| Median | 60 |
| IQR | 30–80 |

*IQR, interquartile range; TTPM, transperineal template prostate mapping.*

**Table 2** Follow-up data of 1032 patients undergoing primary focal high-intensity focused ultrasonography for prostate cancer.

| Variable | |
|---|---|
| **Retreatment, *n* (%)** | |
| No | 761 (73.7) |
| Yes | 271 (26.3) |
| **Number of retreatments, *n* (%)** | |
| 1 | 271 |
| 2 | 71 |
| 3 | 18 |
| **Type of first additional treatment, *n*** | |
| Focal HIFU | 193 |
| Focal cryotherapy | 12 |
| EBRT | 9 |
| Radical prostatectomy | 30 |
| Whole gland HIFU | 4 |
| ADT | 20 |
| Other | 3 |
| **Radical treatment, *n* (%)** | |
| No | 964 (93.4) |
| Yes | 68 (6.6) |
| **Patients receiving a follow-up biopsy** | 424 (41.0) |
| **Patients with any PCa found at follow-up biopsy** | 325 (31.5) |
| **Biopsy failure, *n* (%)** | |
| No | 777 (75.3) |
| Yes | 255 (24.7) |
| **Gleason at biopsy failure*** *n* (%) | |
| 3 + 4 | 189 (18) |
| 4 + 3 | 52 (5) |
| 4 + 4 | 12 (1) |
| 4 + 5 | 2 (<1) |
| **Time to retreatment** | |
| Median | 26 |
| IQR | 13–46 |
| **Time to radical treatment** | |
| Median | 34 |
| IQR | 14–60 |
| **Time to last follow-up** | |
| Median | 36 |
| IQR (range) | 14–64 (0–131) |

*ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; HIFU, high-intensity focused ultrasonography; PCa, prostate cancer. *Presence of clinically significant PCa at follow-up biopsy.*

score of 3 + 4 (63%) and T2 stage (78%). The median (IQR; range) time to last follow-up was 36 (11–64; 0–131) months.

## Primary Outcome

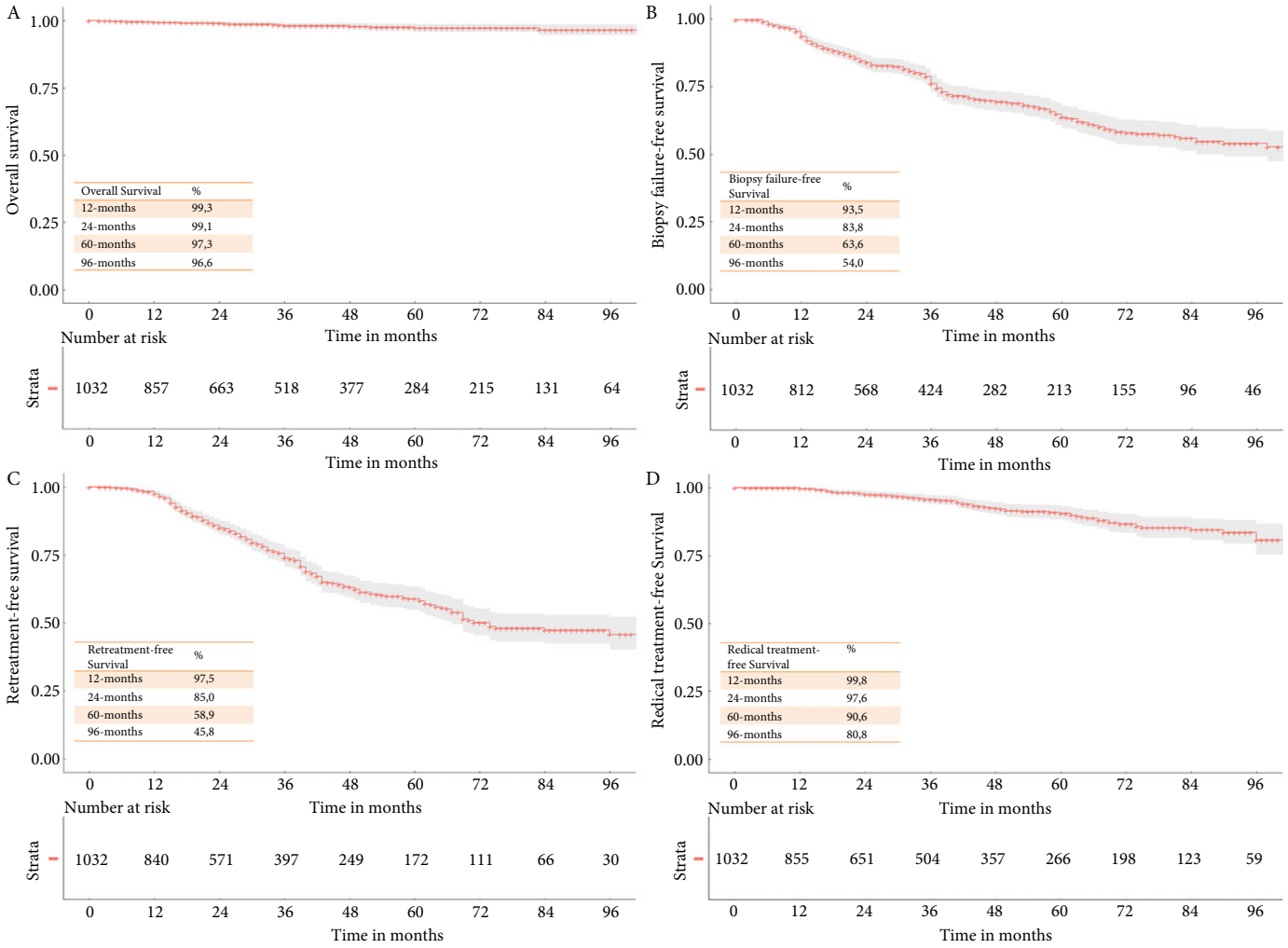
The overall survival rates at 12, 24, 60 and 96 months were 99%, 99%, 97% and 97%, respectively (Fig. 1A). Overall, freedom from biopsy failure was 94%, 84%, 64% and 54%, at 12, 24, 60 and 96 months, respectively (Fig. 1B). Freedom from any Gleason score PCa was 91%, 79%, 54% and 41% at 12, 24, 60 and 96 months, respectively (Fig. S1). The freedom from biopsy failure for patients who received a follow-up biopsy was 86%, 69%, 44% and 35% at 12, 24, 60 and 96 months (Fig. S2). Rate of freedom from any Gleason score PCa for these patients was 80%, 60%, 29% and 18% at 12, 24, 60 and 96 months (Fig. S3). Overall, the retreatment-free survival at 12, 24, 60 and 96 months was 98%, 85%, 59% and 46%, respectively (Fig. 1c). Freedom from radical treatment at 12, 24, 60 and 96 months was 100%, 98%, 91% and 81%, respectively (Fig. 1D).

When assessing the rate of retreatment-free survival according to treatment type (focal vs hemi-ablation), no significant differences were found between the two groups (Fig. 2A). The same analysis according to Gleason score showed a retreatment-free survival rate at 24 and 60 months for Gleason 3 + 3 vs 3 + 4 vs ≥4 + 3 of 86% and 66.5% vs 86.5% and 60.5% vs 77.8% and 37.4%, respectively (Fig. 2B). Retreatment rate of the Gleason ≥4 + 3 group was significantly different from men with ≤Gleason 3 + 4 disease (all $P < 0.001$). There was no significant difference in retreatment rates between Gleason 3 + 3 and 3 + 4 ($P = 0.13$).

## Change in Baseline Characteristics of the Population over Time

The trend in Gleason score treated over time is shown in Fig. 3A. We observed that Gleason 3 + 4 represented the

**Fig. 1** (**A**) Overall survival; (**B**) Biopsy failure-free survival; (**C**) Retreatment-free survival; (**D**) Radical treatment-free survival.




majority of the cases treated over the duration of the present study, starting from 50%, steadily increasing until ~75% in 2017. Patients with Gleason 3 + 3 diminished in prevalence over time, and the proportion of men attributed Gleason scores ≥4 + 3 remained stable over the period of study.

The trend in T stage treated over time is shown in Fig. 3B, with the majority of patients having T2 disease, a reduction over time of patients with T1 disease and a steady rate of T3 disease.

Multivariable analysis in patients with at least 5 years of follow-up does suggest a learning curve in patient selection and treatment delivery, as later year of surgery was significantly associated with a lower probability of 5-year retreatment (odds ratio [OR] 0.77, 95% CI 0.67–0.89; $P < 0.001$). We believe that the learning curve has two components, the first of which is learning about the capabilities of HIFU technology to ablate cancer in some anatomical areas of the gland. For example, extreme apical tumours are more likely to be undertreated given the lack of a 5-mm margin. The second is learning about the intrinsic disease characteristics: large-volume tumour crossing the midline, or bilateral Gleason 3 + 4 would no longer be offered focal therapy, where previously they may have been offered an extended hemi-ablation.

Furthermore, PSA (OR 1.07, 95% CI 1.01–1.12), T2 stage (OR 3.75, 95% CI 1.63–9.82) and T3 stage (OR 5.0, 95% CI 1.9–14.9) reached independent predictor status (all $P < 0.02$) (Table 3) for the probability of undergoing a re-treatment within 5 years of the primary treatment.

Finally, we depicted the multivariable effect of the year of surgery on the 5-year retreatment rate (Fig. 4). The likelihood of retreatment reduces with later year of surgery, as described in Table 3; specifically, in 2007, the multivariable predicted probability of being retreated within 5 years was ~50%, decreasing to ~30% in 2012.

**Fig. 2** (**A**) Retreatment-free survival according to the type of focal therapy strategy; (**B**) Retreatment-free survival according to Gleason score.

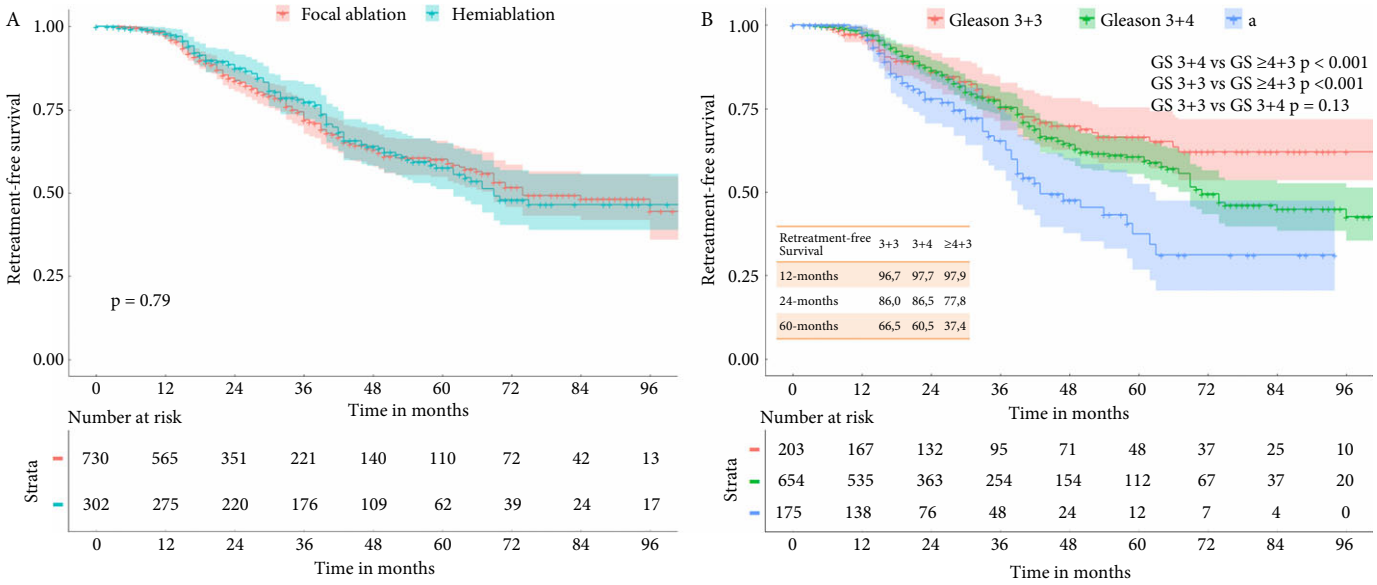
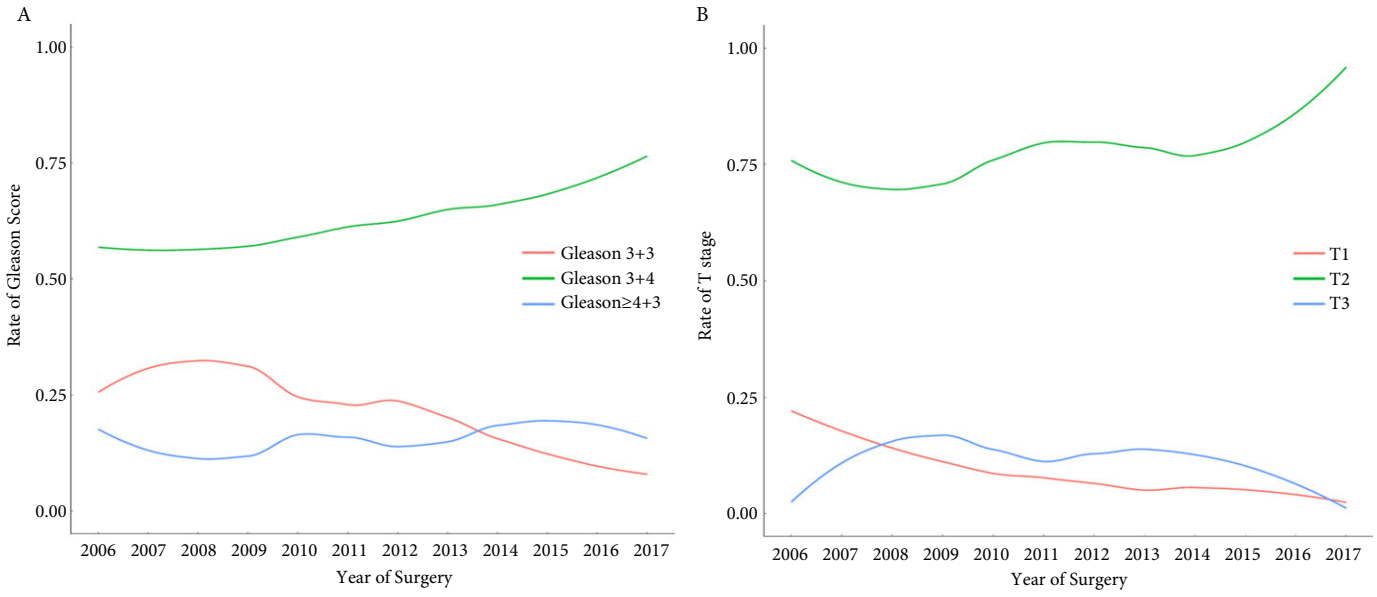



**Fig. 3** (**A**) Trend in Gleason score treated over time; (**B**) Trend in T stage treated over time.




## Discussion

Focal therapy has gained interest as a treatment option for clinically localized PCa with the aim of decreasing the side effects associated with radical treatment whilst offering greater oncological control than active surveillance [6], and allowing delayed radical treatment if needed. Early studies have shown promising results in terms of post-treatment side effects and related quality of life [3,4,12], but longer-term data are required [7].

The aim of the present analysis was to evaluate medium-term outcomes in a cohort of men treated at two expert centres using focal HIFU. To our knowledge, this is the largest cohort of patients ($n$ = 1032) treated with focal therapy using HIFU as an energy source with intermediate-term follow-up (median [IQR; range] 36 [14–64; 0–131] months).

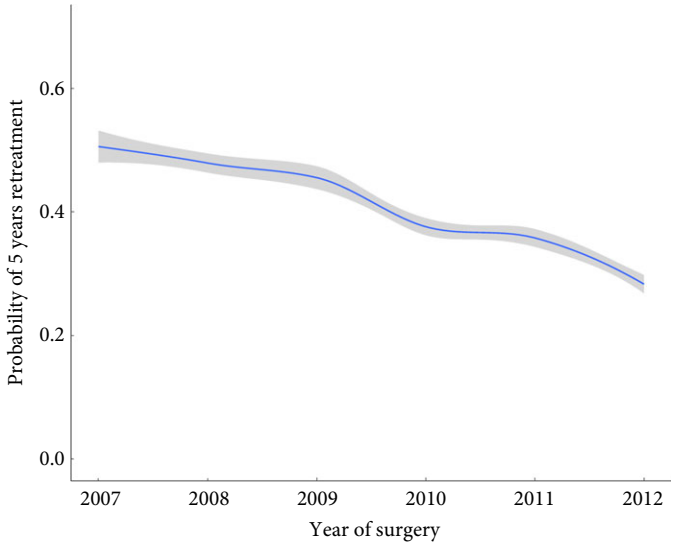
The study had several important findings. First, the overall survival of patients treated with focal HIFU was 99%, 99%,

**Table 3** Multivariable logistic regression model predicting 5-year retreatment probability after focal high-intensity focused ultrasonography for prostate cancer.

| Predictors | Multivariable analysis | |
|---|---|---|
| | OR (95% CI) | *P* |
| Year of surgery | 0.77 (0.67–0.89) | <0.001 |
| PSA | 1.07 (1.01–1.12) | 0.015 |
| Primary Gleason score | 1.76 (0.88–3.5) | 0.1 |
| Secondary Gleason score | 0.96 (0.60–1.54) | 0.8 |
| MCCL | 1.05 (0.98–1.12) | 0.18 |
| Number of positive cores | 1.01 (0.97–1.03) | 0.9 |
| T stage | | |
| T1 | Reference | – |
| T2 | 3.75 (1.63–9.82) | 0.003 |
| T3 | 5.0 (1.9–14.9) | 0.002 |

*HIFU, high-intensity focused ultrasonography; MCCL, maximum cancer core length; OR, odds ratio.*

**Fig. 4** Trend in multivariable 5-year retreatment probability over time.




97% and 97% at 12, 24, 60 and 96 months, respectively (Fig. 1A), in keeping with the low mortality expected in studies of men with low- and intermediate-risk PCa [13].

Second, the rates of detection of clinically significant cancer after treatment were 6%, 16%, 36% and 46% at 12, 24, 60 and 96 months – this is shown in the rate of biopsy-free failure across the whole cohort in Fig. 1B. When looking at the rate of biopsy failure exclusively in patients who received a follow-up biopsy, the rates of clinically significant disease detection were 14%, 31%, 56% and 65% at 12, 24, 60 and 96 months [Fig. S2]). Residual or recurrent disease after focal therapy can be attributable to a number of factors, and is affected by the follow-up protocol for the cohort. As there was no routine biopsy requirement for all men in the cohort, these data may underestimate the presence of Gleason ≥3 + 4 disease. Positive histology after treatment can occur either in the treated area, or in a new location, which could have been undersampled prior to treatment, or could have arisen *de novo* after treatment.

Shah et al. [14], in a review of histological outcomes after focal treatment, reported the presence of PCa in 22% of patients treated with focal HIFU at post-treatment biopsy (follow-up range 6–12 months). It is noteworthy as the majority (63%) of those positive biopsies were either insignificant (54%) or from the untreated part of the prostate (9%) [14]. In a recent systematic review, the median (IQR) overall presence of significant and insignificant cancer was 0 (0–13.5)% and 23.3 (10.4–38.1)%, respectively, with a median follow-up of 12 months [3]. In the present study, 74% of patients (189/255) had PCa with Gleason 3 + 4 score at biopsy failure, while 20%, 5% and <1% had Gleason score 4 + 3, 4 + 4 and 4 + 5, respectively.

Donaldson et al. [15], in a consensus conference, reported that the panellists were uncertain about whether post-treatment biopsy should also routinely sample the untreated gland. In the present study, follow-up biopsies were performed mostly 'for-cause' and the majority of patients had targeted sampling of MRI-suspicious areas. This might explain the considerable rate of presence of any PCa in post-treatment biopsies (77%; 325/424 [Table 2]). It is still not clear whether patients with a post-treatment positive biopsy have poorer oncological outcomes, and studies evaluating the presence of positive biopsy after radiotherapy showed discordant results [16,17].

Third, the overall retreatment rate showed that 98%, 85%, 59% and 46% of patients were free of any further treatment at 12, 24, 60 and 96 months, respectively. In previous studies providing retreatment data, reported rates of any retreatment ranged from 5% to 10.3%, with a median follow-up range of 12–38 months [18–20]. Interestingly, among the 271 patients who underwent a retreatment, 193 (71%) chose a repeat focal HIFU. Moreover, 51 out of 193 (26%) patients retreated with HIFU, underwent a second retreatment, with 74% of patients not having had further treatment to date.

There is a philosophical debate about whether a retreatment rate of this order is reasonable, given lower re-treatment rates for radical treatment; however, the preservation of urinary and sexual function is seen to a much greater extent in focal treatment than radical treatment, and many men consider this trade off a valuable option for them. Previous studies assessing the role of re-do whole-gland HIFU concluded that retreatment is associated with only a small increase in urinary side effects but further deterioration in potency from the initial treatment effect [21]. Nonetheless, the functional outcomes of re-do focal HIFU have yet to be addressed.

According to the present results, re-do HIFU is a feasible retreatment strategy which should be taken into account when a second treatment is necessary.

In terms of retreatment rates in the present study, we provided data regarding the radical treatment rate, defined as radical prostatectomy, external beam radiotherapy and other whole-gland therapies. In the context of focal therapy follow-up, a whole-gland treatment is proposed either for a disease upgrade to high-risk PCa or for a multifocal/bilateral clinically significant PCa which could not be controlled with a further focal approach. For these reasons, the rate of radical treatment after focal therapy might be considered a reliable outcome which mirrors the local control of the disease provided by a focal therapy strategy. In the present study, the overall rates of radical treatment were 0%, 2%, 9% and 19% at 12, 24, 60 and 96 months. Guillaumier et al. [12]recently published a report of oncological and functional outcomes in a cohort of 625 men across nine centres. This report differs in that it was carried out by one team of surgeons operating at two centres, and the number of men was higher. Guillaumier et al. [12] reported a failure-free survival after primary focal HIFU (defined as freedom from radical or systemic therapy, metastases, and cancer-specific mortality) of 99%, 92% and 88% at 1, 3 and 5 years. These rates are, as expected, concordant with the rate of radical treatment-free survival provided in the present study. Many concerns exist regarding the feasibility of radical prostatectomy after focal therapy. Nonetheless, results reported by studies evaluating outcomes of salvage radical prostatectomy after focal therapy seem to be promising [22,23]. In particular, Nunes-Silva et al. [22] reported a matched analysis of two groups submitted to radical prostatectomy and salvage radical prostatectomy after focal therapy. The authors reported a comparable rate of complications and incontinence; however, patients assigned to salvage radical prostatectomy had a lower rate of erectile function recovery and a higher probability of biochemical recurrence within 2 years of follow-up.

In a sub-analysis, we assessed the retreatment-free survival curves according to treatment type and Gleason score. In the present study, patients had been treated either with a focal ablation or with a hemi-ablation. The decision regarding to treat the entire lobe affected by PCa or to restrict the treatment to the index defined at mpMRI concordant with the presence of PCa is based on the results of a preoperative assessment in which multiple features of the disease are taken into account (i.e. Gleason score, MCCL, volume of the index lesion and number of positive cores). So far, to our knowledge, no study has directly compared the two techniques. In the present study we found that focal- and hemi-ablation had similar rates of retreatment-free survival. Tailoring the extension of the treatment to the disease's features seemed to be a feasible approach.

In a recent consensus meeting [24], the panelists agreed that focal therapy was an acceptable strategy for tumours of up to and including Gleason 4 + 3, with no clear agreement on the size of the tumour. Nonetheless, treatment of Gleason ≥4 + 4 disease was discouraged [24]. In the present study patients with Gleason ≥4 + 3 had a significantly higher retreatment rate as compared to lower Gleason categories. As a potential explanation, Le Nobin et al. [25] suggested that higher-grade tumours need a significantly higher margin around the mpMRI-visible lesion to achieve complete ablation. For these reasons, focal therapy for men with Gleason score ≥4 + 3 disease should not be routinely offered. However, there was no significant difference between men with Gleason 3 + 3 and Gleason 3 + 4 disease. This most likely reflects the fact that the majority of patients treated with Gleason 3 + 3 disease had visible disease on MRI, suggesting the presence of Gleason 3 + 4 disease. Patients were offered repeat biopsy to determine this, but not all patients accepted this, and treatment of Gleason 3 + 3 disease was permitted.

Fourth, when assessing the trend in pathological characteristics of patients over time (Fig. 3A,B), we observed a steady increase in the proportion of Gleason 3 + 4 and T2 disease treated compared with the other categories, with a growing tendency to treat patients with MRI-visible Gleason 3 + 4 disease. Patients with Gleason 3 + 3 disease are increasingly proposed for active surveillance and also are ever more likely to accept this strategy.

Finally, there was an improvement in the oncological outcomes over time, in terms of 5-year retreatment rates, falling from 50% for men treated in 2007 to 30% for men treated in 2012 (Fig. 4). We believe that this represents both the change in selection criteria, and in treatment delivery over time. Firstly, lesions very close to the apex are, nowadays, less likely to be treated with a focal approach because covering the whole lesion whilst sparing the sphincter is technically challenging and the risk of partially treated disease is higher. Secondly, the increasing inclusion of patients with a visible lesion at MRI over the study period (Fig. 3b) allowed the operator to more accurately select the area to treat with an appropriate margin. Thirdly, HIFU systems have significantly improved over the years, with subsequent improvement in long-term oncological outcomes [26]. Lastly, as in all other surgical procedures, the effect of the operator learning curve is likely to play a role.

The present study has the following limitations. First, it was based on retrospective data from a clinically managed cohort rather than a prospective study with mandated biopsy follow-up. Nonetheless, Anglemyer et al. [27] supported the reliability of retrospective studies demonstrating that observational reports did not significantly differ if compared to randomized controlled studies in terms of results. Second, in the context of pre-assessment, data regarding pre-treatment mpMRI report were not available. Consequently reporting and accounting for mpMRI lesion locations and volume was not possible. Third, data regarding disease localization at biopsy histological report were not available,

therefore, we were not able to account for the eventual presence of untreated disease. In this context, data regarding post-treatment biopsy PCa location were also not available, making the discrimination between in-field and out-of field recurrence impossible to figure. Moreover, as mentioned above, follow-up biopsies were not routinely carried out. Most patients underwent a 'for-cause' biopsy as a result of a rising PSA level or a prostate MRI suggestive of residual or recurrent disease. For these reasons, rate of biopsy failure must be interpreted with caution, nonetheless it mirrored the clinical practice over the study period. Finally, in this study we provided survival outcomes up to 96 months. Although the median (IQR) time to last-follow up in the present study was 36 (14–64) months, up to 14% ($n$ = 149) of patients had a follow-up > 80 months. Given the call for mid- to long-term oncological outcomes in the field of focal therapy [7] we deemed that data presented in this study might provide useful clinical information regarding the efficacy of focal HIFU. Moreover, with regard to the medium-term outcomes reported in the present study, the follow-up protocol for men who underwent HIFU included discharge to local hospitals or primary care when the mpMRI and PSA were stable after at least 5 years from latest treatment. Recommendations for PSA testing frequency and a re-referral threshold for PSA were given, and patients were referred back at this threshold for a further MRI and biopsies where indicated. Data were not always available on those patients who were managed locally, but the risk of treatment failure for patients continuing to be managed locally would be likely to be lower than for those referred back to our centres due to a concern over a rising PSA. The chosen methodology to censor the Kaplan–Meier analysis from those data could have induced a negative bias, potentially overestimating rates of failure. For clarity we also report that 73.7% of the whole cohort was free from further treatment (Table 2).

In conclusion, the present study involved a large retrospective series of patients treated with primary focal HIFU. Focal therapy for PCa using HIFU as an energy source is a feasible therapeutic strategy, with acceptable survival and oncological results in the medium term, at least for patients with low- or intermediate-risk disease. For patients treated in the later part of the cohort, a retreatment probability of 30% at 5 years was seen, with the majority of these patients having repeat focal treatment. Re-do focal treatment is a feasible technique whose functional and oncological outcomes are being studied. Moreover, the oncological control of the disease improved over time, meaning that better patient selection and surgeon expertise are crucial in the application of focal HIFU.

## Conflict of Interest

Caroline M. Moore has received research funding from the National Institute for Health Research, the European Association of Urology Research Foundation, Prostate Cancer UK, Movember, and the Cancer Vaccine Institute; advisory board fees from Genomic Health; and proctor fees for training surgeons in HIFU. Mark Emberton receives research support from the United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. He is an NIHR Senior Investigator. Mark Emberton also receives grant funding from the United Kingdom Medical Research Council (MRC), Prostate Cancer UK (PCUK) and Cancer Research UK. Industry support has been provided by Sonacare Inc., Trod Medical, the Cancer Vaccine Institute, Steba Biotech, Exact Imaging, and Profound Medical. Hashim U. Ahmed has received research funding from the Wellcome Trust, Prostate Cancer UK, Sonacare Inc., Trod Medical, and Sophiris Biocorp; consultant fees from Sophiris Biocorp and Sonacare Inc.; and proctor fees for training surgeons in HIFU. Richard G. Hindley has received proctor fees for training surgeons in HIFU. Manit Arya has received proctor fees for training surgeons in HIFU. Francesco Giganti is funded by the UCL Graduate Scholarship. The remaining authors have nothing to disclose.

## References

1 **NICE.** Prostate cancer: protocol for active surveillance. Implementing the NICE guideline on prostate cancer (CG175), 2014. Available at: https://www.nice.org.uk/guidance/cg175 Accessed November 2018.

2 **Donovan JL, Hamdy FC, Lane JA et al.** Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016; 375: 1425–37

3 **Valerio M, Cerantola Y, Eggener SE, Lepor H, Catto J.** New and established technology in focal ablation of the prostate : a systematic review. *Eur Urol* 2017; 71: 17–34

4 **Yap T, Ahmed HU, Hindley RG et al.** The effects of focal therapy for prostate cancer on sexual function: a combined analysis of three prospective trials. *Eur Urol* 2016; 69: 844–51

5 **Valerio M, Ahmed HU, Emberton M et al.** The role of focal therapy in the management of localised prostate cancer: a systematic review. *Eur Urol* 2014; 66: 732–51

6 **Azzouzi A-R, Vincendeau S, Barret E et al.** Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. *Lancet Oncol* 2017; 18: 181–91

7 **van der Poel HG, van den Bergh RCN, Briers E et al.** Focal therapy in primary localised prostate cancer : the European Association of Urology Position in 2018. *Eur Urol* 2018;74:84–91.

8 **NICE.** Focal therapy using high-intensity focused ultrasound for localised prostate cancer (IPG24), 2012: 1–6. Available at nice.org.uk/guidance/ipg424 Accessed November 2018.

9 **Ergina PL, Barkun JS, Mcculloch P, Cook JA, Altman DG.** IDEAL framework for surgical innovation 2: observational studies in the exploration and assessment stages. *BMJ* 2013; 346: f3011

10 **Ahmed HU, Cathcart P, Mccartan N et al.** Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy. *Cancer* 2012; 118: 4148–55

11 **Dickinson L, Ahmed HU, Kirkham AP et al.** A multi-centre prospective development study evaluating focal therapy using high intensity focused ultrasound for localised prostate cancer: the INDEX study. *Contemp Clin Trials* 2013; 36: 68–80

12 **Guillaumier S**, **Peters M**, **Arya M et al.** A multicentre study of 5-year outcomes following focal therapy in treating clinically significant nonmetastatic prostate cancer. *Eur Urol* 2018; 74: 422–9
13 **Hamdy FC**, **Donovan JL**, **Lane JA et al.** 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016; 375: 1415–24
14 **Shah TT**, **Kasivisvanathan V**, **Jameson C**, **Freeman A**, **Emberton M**, **Ahmed HU**. Histological outcomes after focal high-intensity focused ultrasound and cryotherapy. *World J Urol* 2015; 33: 955–64
15 **Donaldson IA**, **Alonzi R**, **Barratt D et al.** Focal therapy: patients, interventions, and outcomes - A report from a consensus meeting. *Eur Urol* 2015; 67: 771–7
16 **Zelefsky MJ**, **Reuter VE**, **Fuks Z**, **Scardino P**, **Shippy A**. Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. *J Urol* 2008; 179: 1368–73
17 **Alimonte LD**, **Helou J**, **Sherman C et al.** The clinical significance of persistent cancer cells on prostate biopsy after high-dose-rate brachytherapy boost for intermediate-risk prostate cancer. *Brachytherapy* 2015; 14: 309–14
18 **Ahmed HU**, **Freeman A**, **Kirkham A et al.** Focal therapy for localized prostate cancer: a phase I/II trial. *J Urol* 2011; 185: 1246–54
19 **Van Velthoven R**, **Aoun F**, **Limani K**, **Narahari K**, **Lemort M**, **Peltier A**. Primary zonal high intensity focused ultrasound for prostate cancer: results of a prospective phase IIa feasibility study. *Prostate Cancer* 2014; 2014: 1–6
20 **Ahmed HU**, **Hindley RG**, **Dickinson L et al.** Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. *Lancet Oncol* 2012; 13: 622–32
21 **Blana A**, **Rogenhofer S**, **Ganzer R**, **Wild PJ**, **Wieland WF**, **Walter B**. Morbidity associated with repeated transrectal high-intensity focused ultrasound treatment of localized prostate cancer. *World J Urol* 2006; 24: 585–90
22 **Nunes-Silva I**, **Barret E**, **Srougi V et al.** Effect of prior focal therapy on perioperative, oncologic and functional outcomes of salvage robotic assisted radical prostatectomy. *J Urol* 2017; 198: 1069–76
23 **Lebdai S**, **Villers A**, **Barret E**, **Nedelcu C**, **Bigot P**, **Azzouzi AR**. Feasibility, safety, and efficacy of salvage radical prostatectomy after Tookad® Soluble focal treatment for localized prostate cancer. *World J Urol* 2015; 33: 965–71
24 **Tay KJ**, **Scheltema MJ**, **Ahmed HU et al.** Patient selection for prostate focal therapy in the era of active surveillance : an International Delphi Consensus Project. *Prostate Cancer Prostatic Dis.* 2017; 3: 1–6
25 **Le Nobin J**, **Rosenkrantz AB**, **Villers A et al.** Image guided focal therapy for magnetic resonance imaging visible prostate cancer: defining a 3-dimensional treatment margin based on magnetic resonance imaging histology co-registration analysis. *J Urol* 2015; 194: 364–70
26 **Uchida T**, **Tomonaga T**, **Kim H et al.** Improved outcomes with advancements in high intensity focused ultrasound devices for the treatment of localized prostate cancer. *J Urol* 2015; 193: 103–10
27 **Anglemyer A**, **Horvath HT**, **Bero L**. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev* 2014: MR000034

Correspondence: Caroline M. Moore, Professor in Urology, Division of Surgery and Interventional Science, University College London, Honorary Consultant Urologist, University College London Hospitals Trust, London, 3rd Floor, Charles Bell House, 43-45 Foley Street, London, W1W 7TS, UK.

e-mail: caroline.moore@ucl.ac.uk

Abbreviations: HIFU, high-intensity focused ultrasonography; PCa, prostate cancer; mpMRI, multiparametric MRI; TTPM, transperineal template prostate mapping; MCCL, maximum cancer core length; IQR, interquartile range; OR, odds ratio.

## Supporting Information

Additional Supporting Information may be found online in the Supporting Information section at the end of the article:

**Fig. S1**. Any Gleason score biopsy failure-free survival.
**Fig. S2**. Biopsy failure free-survival in men receiving a follow-up biopsy.
**Fig. S3**. Any Gleason score biopsy failure-free survival in men receiving a follow-up biopsy.