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Prostate Cancer

Cancer Control Outcomes Following Focal Therapy Using High-intensity Focused Ultrasound in 1379 Men with Nonmetastatic Prostate Cancer: A Multi-institute 15-year Experience

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Abstract

Background: Focal therapy aims to treat areas of cancer to confer oncological control whilst reducing treatment-related functional detriment.
Objective: To report oncological outcomes and adverse events following focal high-intensity focused ultrasound (HIFU) for treating nonmetastatic prostate cancer.
Design, setting, and participants: An analysis of 1379 patients with ≥6 mo of follow-up prospectively recorded in the HIFU Evaluation and Assessment of Treatment (HEAT) registry from 13 UK centres (2005–2020) was conducted. Five or more years of follow-up was available for 325 (24%) patients. Focal HIFU therapy used a transrectal ultrasound-guided device (Sonablate; Sonacare Inc., Charlotte, NC, USA).
Outcome measurements and statistical analysis: Failure-free survival (FFS) was primarily defined as avoidance of no evidence of disease to require salvage whole-gland or systemic treatment, or metastases or prostate cancer–specific mortality. Differences in FFS

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Prostate cancer

between D'Amico risk groups were determined using a log-rank analysis. Adverse events were reported using Clavien-Dindo classification.

Results and limitations: The median (interquartile range) age was 66 (60–71) yr and prostate-specific antigen was 6.9 (4.9–9.4) ng/ml with D'Amico intermediate risk in 65% (896/1379) and high risk in 28% (386/1379). The overall median follow-up was 32 (17–58) mo; for those with ≥5 yr of follow-up, it was 82 (72–94). A total of 252 patients had repeat focal treatment due to residual or recurrent cancer; overall 92 patients required salvage whole-gland treatment. Kaplan-Meier 7-yr FFS was 69% (64–74%). Seven-year FFS in intermediate- and high-risk cancers was 68% (95% confidence interval [CI] 62–75%) and 65% (95% CI 56–74%; $p = 0.3$). Clavien-Dindo >2 adverse events occurred in 0.5% (7/1379). The median 10-yr follow-up is lacking.

Conclusions: Focal HIFU in carefully selected patients with clinically significant prostate cancer, with six and three of ten patients having, respectively, intermediate- and high-risk cancer, has good cancer control in the medium term.

Patient summary: Focal high-intensity focused ultrasound treatment to areas of prostate with cancer can provide an alternative to treating the whole prostate. This treatment modality has good medium-term cancer control over 7 yr, although 10-yr data are not yet available.

1. Introduction

Treatment of patients with nonmetastatic, clinically significant prostate cancer consists of whole-gland approaches using radical prostatectomy or radical radiotherapy [1–3]. In patients with intermediate- and high-risk disease, radical therapy leads to improvements in both progression-free and cancer-specific survival, but can confer some treatment-related complications including genitourinary and rectal side effects [4,5].

Improvements in diagnostic accuracy and localisation of clinically significant prostate cancer has allowed focal therapy to be considered in carefully selected patients [6]. Whilst initially seen as an alternative to active surveillance, it is now arguably seen as a potential treatment modality for patients diagnosed with intermediate- to high-risk localised prostate cancer who would otherwise undergo radical therapy [7–10] whilst minimising treatment-related complications and side effects [11–13].

Over the last 15 yr in the UK, focal high-intensity focused ultrasound (HIFU) has undergone a programme of health technology evaluation within trials or has been offered as a standard alternative in several centres where special arrangements included the requirement for prospective registries after multidisciplinary team review and informed consent with written patient information sheets. We report updated multicentre results in patients with nonmetastatic prostate cancer, reported in the "HIFU Evaluation and Assessment of Treatment" (HEAT) registry [14].

2. Patients and methods

A total of 1379 patients with a minimum of 6-mo follow-up reported within the HEAT registry following focal HIFU between November 2005 and July 2020, using the Sonablate (500 and 3G) device (Sonacare Inc., Charlotte, NC, USA) in 13 centres within the UK, were evaluated. Patients with Gleason score 6–9 prostate cancer and radiological stage up to T3bN0M0 were offered focal therapy. This study was exempt from ethics committee approval, and the requirement of informed consent of patients was waived as it is a registered audit of clinical outcomes after surgical intervention by local research and development departments for service and quality assurance. The study was performed in accordance with the Declaration of Helsinki.

Patients underwent 1.5 or 3 Tesla multiparametric magnetic resonance imaging (mpMRI) and transrectal or transperineal biopsy. In patients with MRI score (Likert or Prostate Imaging Reporting and Data System v1 or v2) ≥3, targeted and systematic biopsies were performed; some patients underwent transperineal 5–10 mm template mapping biopsies. To ensure suitability for focal therapy, patients with conflicting imaging and histology results underwent further biopsy. Only patients with MRI-visible lesions and no high-volume (≥6 mm) Gleason score 3 + 3 = 6 or any-volume Gleason score ≥3 + 4 = 7 disease in areas to be left untreated were considered suitable for focal ablation.

Patients were classified into D'Amico low-, intermediate-, or high-risk disease. Intermediate- and high-risk groups underwent radioisotope bone scan or cross-sectional imaging to rule out local nodal or distant disease as per local standard of care.

Ablative patterns considered focal are demonstrated in our previously published study [14]. Multiple lesions could be considered for treatment, provided the overall ablation area was in accordance with the maximum permitted ablative pattern. Ablation field was outlined using either intraoperative MRI–transrectal ultrasound fusion or expert-guided visual estimation, to allow a minimum of 5 mm margin for all MRI-visible lesions; this usually led to quadrant ablation or hemiablation. Patients were considered not suitable for focal treatment if the tumour abutted the urinary sphincter or urethra, or required ablation adjacent to neurovascular bundles bilaterally. The procedure was performed under antibiotic prophylaxis according to local guidance. A typical regime would entail gentamicin intravenously on induction of anaesthetic and ciprofloxacin continuing for 7 d.

Up to two focal therapy sessions were allowed. Neoadjuvant and adjuvant androgen deprivation therapy (ADT) within 12 mo of focal therapy was used as a temporising or cytoreductive strategy by some physicians, if it was felt that any delay in treatment would be detrimental. Patients underwent a trial without a catheter 7–10 d following treatment and were taught how to self-catheterise as a precaution.

Patients were clinically evaluated for signs or symptoms of disease progression or recurrence at all interactions. Recommended follow-up included 3–6 monthly prostate-specific antigen (PSA) follow-up in the 1st year and 6-monthly thereafter, with mpMRI at 6–12 mo. For-cause

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mpMRI was performed if consecutive PSA rises over three readings without predisposing causes were identified. A transperineal biopsy of typically three to six cores with further six to nine cores' systematic sampling was advised if MRI revealed a suspicion of recurrent or residual disease; referencing our previous publication demonstrating that negative mpMRI had a negative predictive value of 90–96% for significant cancer (cancer core length ≥3 mm of any grade or any pattern 4) when compared with protocol-mandated biopsy [15].

If a patient declined for-cause mpMRI or biopsy when clinically indicated, or mpMRI did not indicate the need for biopsy, they continued with PSA surveillance on a 3–6-monthly basis. In cases of continually rising PSA results, the indication for biopsy was rediscussed and often carried out.

If clinically significant cancer, defined as ≥3 + 4 disease occurred in field (residual disease) or out of field (de novo or progressive disease), was identified, patients were offered repeat focal treatment, radical radiotherapy, or radical prostatectomy. Any further treatment including hormone treatment, chemotherapy, or palliative treatments was recorded.

Adverse events were identified at all healthcare interactions. Follow-up time for oncological analyses was calculated according to the last clinical review evaluating the risk of disease recurrence/progression relative to treatment date and when evaluated overall survival included the date of death. Although patients were encouraged to return questionnaires for patient-reported outcome measure (PROM), rates of return were poor and robust analyses of these were not possible.

The primary outcome was failure-free survival (FFS) with failure defined as evidence of cancer requiring whole-gland salvage treatment or third focal therapy treatment, systemic treatment, development of prostate cancer metastases, or prostate cancer–specific death. Secondary outcomes included (1) any retreatment-free survival, (2) salvage whole-gland and systemic treatment-free survival, (3) ADT-free survival, (4) metastasis-free and prostate cancer-specific survival, (5) overall survival, and (6) adverse events and complications classified by the Clavien-Dindo system. Secondary analyses compared the above outcomes per D'Amico risk score, per International Society of Urological Pathology (ISUP) group 1–3, and separately for the cohort of patients with at least 5 yr of follow-up.

Baseline demographics are presented with descriptive statistics in which median and interquartile range (IQR), or absolute numbers and proportions were used as appropriate. FFS as well as other secondary cancer control outcomes, with 95% confidence intervals (CIs), were determined using the Kaplan-Meier method. The log-rank test was used to determine differences in failure rates between patient groups. All analyses were performed using IBM SPSS version 25 (Armonk, NY, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

3. Results

3.1. Baseline demographics

The overall median (IQR) follow-up was 32 (17–58) mo, and it was 82 (72–94) mo for the 325 patients with ≥5 yr follow-up. The median (IQR) follow-up for patients with no reported event (n = 1218) was 19 (5–43) mo and the median (IQR) time to failure event was 42 (27–63) mo. The median (IQR) age was 66 (60–71) yr and PSA 6.9 (4.9–9.4) ng/ml (Table 1). Most patients (65%, 896/1379) had intermediate-risk disease and diagnosed following transperineal biopsy (Table 1 and Supplementary Table 1). Of the patients, 79% (1093/1379) had ISUP group ≥2 (Table 1). Of 1379 patients, 13 (0.9%) received either neoadjuvant or cytoreductive ADT, and 850 (62%) underwent quadrant ablation (Table 1).

Table 1 – Baseline characteristics for patients undergoing focal HIFU for nonmetastatic prostate cancer

Characteristic	n = 1379
Age (yr), median (IQR)	66 (60–71)
Missing age data, n (%)	7 (0.5)
Pre-HIFU PSA (ng/ml), median (IQR)	6.9 (4.9–9.4)
Pre-HIFU PSA group, n (%)	
<10 ng/ml	1061 (77)
10–20 ng/ml	272 (20)
>20 ng/ml	24 (1.7)
Missing PSA data	22 (1.6)
Pre-HIFU prostate volume (ml), median (IQR)	36 (28–48)
Missing data, n (%)	154 (11)
Gleason score, n (%)	
3 + 3 = 6	257 (19)
3 + 4 = 7	851 (62)
4 + 3 = 7	225 (16)
≥8	17 (1.2)
Missing data	29 (2.1)
Pretreatment HIFU T stage, n (%)	
T1	95 (7)
T2	1023 (74)
T2a	276 (20)
T2b	140 (10)
T2c	209 (15)
Missing T2 subclassification	398 (29)
T3a/b	151 (11)
Missing data	110 (8.0)
D'Amico risk, n (%)	
Low	84 (6.1)
Intermediate	896 (65)
High	386 (28)
Missing data	13 (0.9)
Gleason 3 + 3 = 6, MCCL <6 mm, rT1	20 (1.5)
Ablative pattern, n (%)	
Quadrant	850 (62)
Hemiablation	487 (35)
Hockey-stick	42 (3.0)
Year of treatment, n (%)	
2005–2009	166 (12)
2010–2014	613 (45)
2015–2020	600 (44)

HIFU = high-intensity focused ultrasound; IQR = interquartile range; MCCL = maximum cancer core length; PSA = prostate-specific antigen.

3.2. Primary outcome

The FFS (95% CI) at 7 yr was 69% (64–74%; Table 2 and Fig. 1A). Seven-year FFS for intermediate- and high-risk cancers was 68% (95% CI 62–75%) and 65% (95% CI 56–74%, p = 0.3; Fig. 1B and Table 2).

3.3. Secondary outcomes

FFS (95% CI) at 7 yr for patients with at least 5-yr follow-up was 74% (69–80%), with no statistically significant difference demonstrated between intermediate- and high-risk disease (Supplementary Fig. 1A and 1B, and Supplementary Table 2). Significant differences in FFS (95% CI) at 7 yr between ISUP grade 2 and 3 were identified (p = 0.05; Supplementary Table 3). In patients followed up for at least 5 yr, 242 reported no failure event. The median (IQR) follow-up of these patients was 82 (71–92) mo.

During the 1st year following treatment, 1157 underwent at least two PSA tests. Throughout the study period, 2224 follow-up mpMRI examinations were undertaken by

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Table 2 – Kaplan-Meier estimates for failure outcomes after primary focal HIFU in patients with nonmetastatic prostate cancer and at least 6-mo follow-up

Kaplan-Meier estimate, % (95% confidence interval)							
	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr
Failure-free survival [a]	100 (100–100)	96 (95–98)	93 (91–95)	88 (85–90)	82 (79–86)	75 (71–79)	69 (64–74)
By D'Amico risk class							
Low	100 (100–100)	99 (96–100)	99 (96–100)	94 (88–100)	91 (84–100)	91 (84–100)	88 (77–99)
Intermediate	100 (100–100)	97 (96–98)	93 (91–95)	88 (85–91)	83 (79–87)	75 (70–81)	68 (62–75)
High	100 (99–100)	95 (93–97)	91 (88–94)	85 (81–90)	79 (73–85)	69 (62–78)	65 (56–74)
Salvage local whole-gland or systemic treatment-free survival	100 (100–100)	97 (96–98)	93 (91–95)	89 (86–91)	85 (83–88)	80 (77–84)	75 (71–80)
By D'Amico risk class							
Low	100 (100–100)	99 (96–100)	99 (96–100)	99 (96–100)	99 (96–100)	99 (96–100)	95 (87– 100)
Intermediate	100 (100–100)	97 (96–99)	94 (91–96)	89 (86–92)	84 (80–88)	79 (74–84)	73 (67–80)
High	100 (99–100)	95 (93–98)	91(87–94)	86 (82–91)	84 (79–89)	78 (71– 85)	73 (65–82)

HIFU = high-intensity focused ultrasound.
[a] Failure-free survival defined by transition to whole-gland salvage treatment, third focal therapy treatment, systemic treatment, development of prostate cancer metastases, or prostate cancer–specific death.

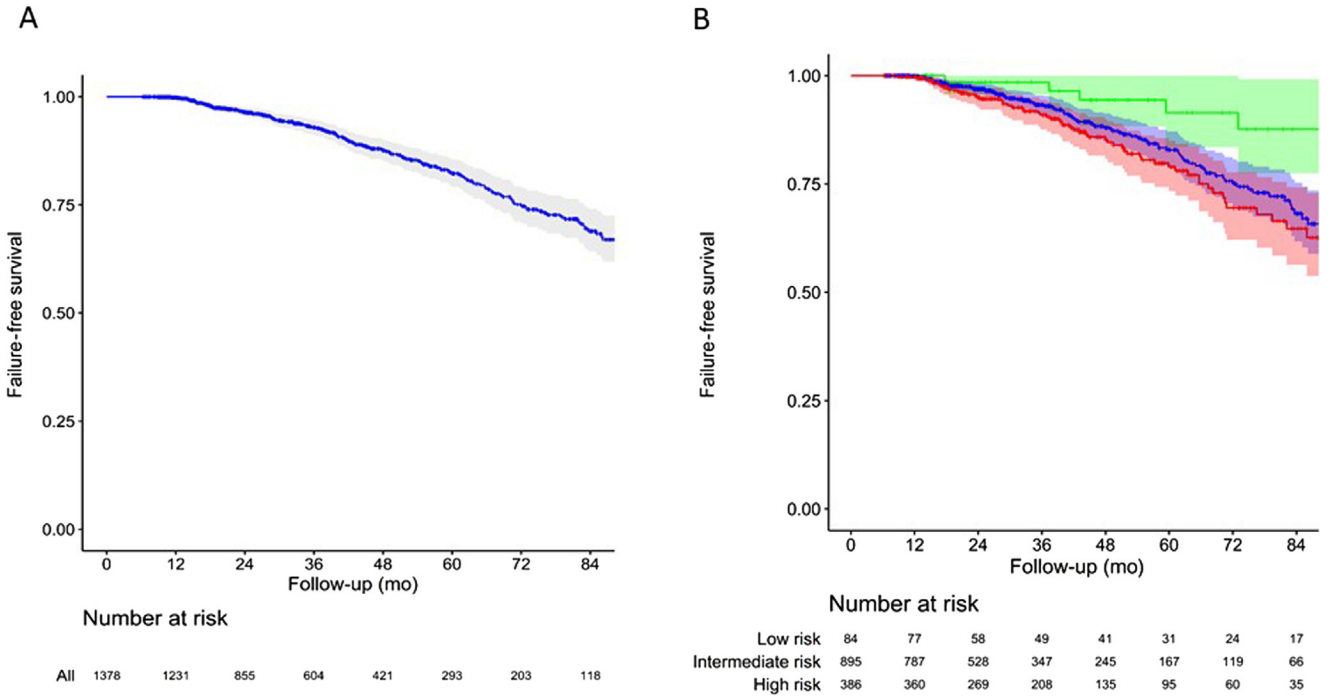

Fig. 1 – Kaplan-Meier curves of failure-free survival (FFS) with 95% confidence intervals. FFS is defined as transition to whole-gland salvage treatment or third focal therapy treatment, systematic treatment, and/or development of prostate cancer metastases and/or prostate cancer–specific death for (A) all patients with at least 6 mo of follow-up and (B) 1365 patients stratified per D'Amico low-risk (green line), intermediate-risk (blue line), and high-risk (red line) group (log-rank analysis of D'Amico intermediate- vs high-risk disease $p = 0.3$).

1123 patients; 544 underwent one, 285 underwent two, 159 underwent three, and 135 underwent four or more mpMRI examinations. A total of 256 patients did not undergo follow-up mpMRI, only ten of whom reported treatment failure.

Owing to concerns of recurrence or residual disease, 609 patients underwent 853 biopsy sessions, which were performed as either standard of care follow-up biopsies or for-cause biopsies. In all, 401 patients underwent one biopsy session after treatment, 175 patients underwent two biopsy sessions, and 33 underwent three or more biopsy sessions. Overall, recurrent/residual disease was reported in 488 biopsies performed, reflecting 403 patients. Subsequently, 352 biopsies performed, representing 314 patients, demonstrated Gleason grade $\geq$3 + 4 = 7 during their follow-up period (Supplementary Table 4).

In total, 252 patients underwent at least one repeat focal therapy session, 225 underwent one repeat session, 26 underwent two repeat sessions, and one underwent a total of four focal therapy sessions. Retreatment-free survival (95% CI) at 7 yr was 43% (39–49%; Supplementary Table 5 and Supplementary Fig. 2A). Statistically significant

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differences in retreatment-free survival were observed between D'Amico risk groups ($p < 0.0001$; Supplementary Fig. 2B and Supplementary Table 5).

Fifty-three patients transitioned to salvage radical prostatectomy and 39 underwent salvage radiotherapy or brachytherapy. Of the 53 patients undergoing salvage radical prostatectomy, nine did so after the second focal session. No patient undergoing salvage radical radiotherapy subsequently required any other treatment. Prior to salvage radical radiotherapy, 20 had two focal HIFU sessions and one had a whole-gland HIFU session.

Overall, 132 patients underwent salvage local whole-gland or systemic treatment. Salvage whole-gland and systemic treatment-free survival at 7 yr was 75% (71–80%; Supplementary Fig. 2C). Kaplan-Meier estimates at 7 yr are 95% (87–100%), 73% (67–80%), and 73% (65–82%) for low-, intermediate-, and high-risk disease, respectively ($p = 0.006$; Supplementary Fig. 2D). There was no statistically significant difference between intermediate- and high-risk disease outcomes ($p = 0.5$; Table 2 and Supplementary Fig. 2D).

Thirty-nine patients received ADT after focal therapy associated with salvage therapy. Seven-year ADT-free survival was 92% (89–96%; Supplementary Fig. 2E), with no statistically significant differences demonstrated between D'Amico risk groups ($p = 0.1$; Supplementary Fig. 2F and Supplementary Table 5).

Overall, three patients developed metastases, one of whom subsequently died from prostate cancer. All three patients had T3a disease; two of these had PSA 2.5 ng/ml and 0.73 ng/ml prior to focal HIFU, indicating that they might have been PSA nonsecretors. Seven-year metastasis-free and prostate cancer–specific survival was 100 (99–100%; Supplementary Fig. 2G). Statistically significant differences were observed between D'Amico risk groups ($p = 0.045$; Supplementary Fig. 2H and Supplementary Table 5).

During the study period, 20 patients were noted to have died from any cause, with overall survival (95% CI) at 7 yr being 97% (96–99%; Supplementary Fig. 2I) with no statistically significant differences observed between D'Amico risk groups ($p = 0.1$; Supplementary Table 5 and Supplementary Fig. 2J).

The rate of complications with Clavien-Dindo score >2 was 0.5% (7/1379), with most complications either self-resolving or not requiring admission or intervention (Supplementary Table 6). A total of 83/1379 (6.0%) postoperative complications were noted. Urinary tract infections and epididymo-orchitis were reported in 52 (3.8%) and 11 (0.8%) patients, respectively; one patient required resection of a prostatic abscess and one was admitted for subsequent urosepsis. Post-treatment retention was observed in ten (0.7%), with three requiring endoscopic intervention to be catheter free. One (0.1%) patient was treated under spinal anaesthetic, but had incomplete focal treatment due to patient movement; during his 1-yr follow-up, he required no further retreatment. There were two (0.1%) cases of rectourethral fistulae. One required management with urethral and suprapubic catheters for urinary diversion with subsequent spontaneous fistula healing, and the other required reconstructive surgery due to failure of conservative management.

4. Discussion

To our knowledge, this is the largest reported cohort for any form of focal ablative technique. Our multicentre UK-based study demonstrated 69% FFS at 7 yr after primary focal HIFU therapy for nonmetastatic prostate cancer. Metastasis-free survival and prostate cancer–specific mortality at 7 yr were 100%, and overall survival at 7 yr was 97% and compare similarly with recently published series [16]. These outcomes are more clinically relevant as over 90% of our cohort had intermediate- to high-risk cancer with modern imaging and biopsy strategies, compared with historical cohorts that had predominantly low-risk cancer or were diagnosed with transrectal systematic biopsies [16–18]. The oncological control demonstrated after focal HIFU is concordant with the rates seen in our earlier paper of 625 patients and continues to reinforce the acceptable medium-term outcomes [14]. Approximately one-fifth of cases needed a second session of focal HIFU over 7 yr. A second focal therapy treatment appears to be effective and remains part of our focal therapy intervention [19]. Patients are counselled that up to two sessions may be required to adequately treat their disease, whilst preserving at least one neurovascular bundle. Our UK-based group does not advocate the use of third focal HIFU therapy treatment, as recurrence or residual disease following two separate sessions would indicate that either the disease may be resistant to high temperatures (>70°C) or the energy cannot be delivered to the disease location.

The outcomes observed in this study allow clinicians to better counsel patients with clinically significant prostate cancer who are eligible for tissue-preserving strategies. Our recent COMPARE study findings showed that patients were willing to trade small detriments in cancer control in order to return to normal activities quicker, and maintain continence and erectile function in both intermediate- and high-risk cases [20]. Our data show that patients eligible for focal HIFU therapy need not make that compromise.

We have recently reported a propensity-matched analysis of focal therapy (HIFU or cryotherapy) in comparison with radical prostatectomy and radical radiotherapy and showed no clinically relevant differences in FFS [21,22]. Nonetheless, randomised controlled trials comparing radical strategies with focal therapy, such as IP4-CHRONOS and PART, are currently underway to test clinical and patient equipoise, although if successful at recruiting these will take another decade before primary outcomes are known [23,24].

A strength of our study is that very few low-risk patients were treated, with only 20 (1.5%) having low-risk, low-volume radiological ≤T1c disease treated about a decade ago; this was when our focal programme first started at a time when radical treatment for low-risk disease was considered appropriate and conducted widely. Further, complications following focal HIFU were reported in 6%, whilst serious adverse events were rare; there has previously been concern about rectal injury during HIFU, but we have

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confirmed the low number (0.1%) of patients developing a rectourethral fistula, which matches the rates of fistula following radiotherapy or rectal injury following prostatectomy [25]. In fact, one of these cases healed with conservative management with catheter diversion of urine. Such outcomes reinforce the safety profile of focal HIFU over time [26,27]. We accept that previous reports of a smaller number of cases observed higher urinary tract infection and retention rates. Patients' notes were reviewed for entry into the registry, so source data were verified in the majority. Lower urinary retention rates may be explained by the move from hemigland ablation to quadrant ablation and because patients were often taught self-catheterisation as a precaution following the initial trial without catheter.

There are limitations. First, despite the considerable time span in which patients were treated, our median follow-up was 32 mo due to the significant growth in numbers over the last 5 yr, which inevitably reduce the median. Further, patients are lost to follow-up or care transferred locally, limiting the long-term follow-up available within the registry. Second, we recognise that standard of care or protocolised biopsies providing histological confirmation of recurrence or lack of recurrence would be reassuring. The timings for MRI and biopsies after treatment were also dependent upon clinical parameters and patient decision. This reflects real-life practice and remains a limitation of observational series reported from registries where patients often do not consent to routine post-treatment biopsies with stable PSA and non-suspicious MRI results. High-level evidence in the form of cohort trials such as INDEX (NCT01194648) will better inform the most appropriate follow-up regimens. Nevertheless, for-cause mpMRI and/or biopsies due to clinical concern remain an accepted management pathway with mpMRI having previously been evaluated robustly [15]. Third, we recognise the value in reporting location of recurrence; however, our database registry did not capture this variable to a level that we were able to report on. Fourth, the rate of functional PROM completion was low, although we have previously reported PROM outcomes from our prospective trials that show pad-free continence of 98–99% and erectile function preservation of 85–95% in patients with good baseline function [19,28–30].

5. Conclusions

Focal HIFU in carefully selected patients with clinically significant prostate cancer, with six and three of ten patients having, respectively, intermediate- and high-risk cancer, has good cancer control in the medium term.

***Author contributions*:** Deepika Reddy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Peer Review Summary

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