available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Early-Medium-Term Outcomes of Primary Focal Cryotherapy to Treat Nonmetastatic Clinically Significant Prostate Cancer from a Prospective Multicentre Registry

Taimur T. Shah [a,b,c,*], *Max Peters* [d], *David Eldred-Evans* [a], *Saiful Miah* [a,b,c], *Tet Yap* [e], *Nicholas A. Faure-Walker* [e], *Feargus Hosking-Jervis* [a], *Benjamin Thomas* [c], *Tim Dudderidge* [f], *Richard G. Hindley* [g], *Stuart McCracken* [h], *Damian Greene* [i], *Raj Nigam* [l], *Massimo Valerio* [j], *Suks Minhas* [b], *Mathias Winkler* [a,b], *Manit Arya* [a,b,c,k,†], *Hashim U. Ahmed* [a,b,†]

[a] *Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK;* [b] *Department of Urology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK;* [c] *Division of Surgery and Interventional Sciences, University College London, London, UK;* [d] *Department of Radiotherapy, University Medical Centre, Utrecht, The Netherlands;* [e] *Department of Urology, Guy's Hospital, Great Maze Pond, London, UK;* [f] *Department of Urology, University Hospital Southampton NHS Trust, Southampton, UK;* [g] *Department of Urology, Basingstoke and North Hampshire Hospital, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK;* [h] *Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK;* [i] *Department of Urology, Sunderland Royal Hospital, Sunderland, UK;* [j] *Department of Urology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland;* [k] *Department of Urology, The Princess Alexandra Hospital NHS Trust, Harlow, UK;* [l] *Department of Urology, Royal Surrey County Hospital NHS Trust, UK*

Article info

Article history:
Accepted December 18, 2018

Associate Editor:
Giacomo Novara

Keywords:
Clinically significant prostate cancer
Cryotherapy
Focal therapy

Abstract

Background: Focal cryotherapy can be used to treat patients with clinically significant nonmetastatic prostate cancer to reduce side effects.
Objective: Early-medium-term cancer control and functional outcomes.
Design, setting, and participants: A prospective registry-based case series of 122 consecutive patients undergoing focal cryotherapy between October 1, 2013, and November 30, 2016, in five UK centres. Median follow-up was 27.8 mo [interquartile range (IQR) 19.5–36.7]. A total of 35 patients (28.7%) had National Comprehensive Cancer Network (NCCN) high risk and 87 (71.3%) had intermediate risk disease. Risk and zonal stratification included multiparametric magnetic resonance imaging (mpMRI) with targeted and systematic biopsies, or transperineal mapping biopsies.
Intervention: Focal cryoablation of MR-visible tumours.
Outcome measurements and statistical analysis: Follow-up involved prostate-specific antigen (PSA) monitoring, mpMRI, and for-cause biopsies. Primary outcome was failure-free survival (FFS), defined as transition to radical, whole-gland, or systemic therapy, or metastases/death. Secondary outcomes included adverse events and functional outcomes.
Results and limitations: A total of 80 (65.6%) had anterior ablation, 23 (19.7%) combined posterior and anterior ablation, and two (1.6%) posterior ablation alone (SeedNet or Visual-ICE, BTG plc). Median age was 68.7 yr (IQR 64.9–73.8) and preoperative PSA 10.8 ng/ml (IQR 7.8–15.6). Overall FFS at 3 yr was 90.5% [95% confidence interval (CI) 84.2–97.3]. When stratified for the NCCN risk group, 3-yr outcomes were 84.7% (95% CI 71.4–100) in high risk and 93.3% (95% CI 86.8–100) in intermediate risk. At last

[†] Joint senior authors.
[*] Corresponding author. Imperial Prostate, Room 5L28, 5th Floor, Laboratory Block, Charing Cross Hospital Campus, Imperial College London, Fulham Palace Road, W6 8RF, UK. Tel. +44 7713245739.
E-mail address: t.shah@imperial.ac.uk (T.T. Shah).

https://doi.org/10.1016/j.eururo.2018.12.030

follow-up, incontinence defined as any pad use was 0/69 (0%) and erectile dysfunction (defined as erections insufficient for penetration) was 5/31 (16.1%). Limitations include lack of long-term outcomes.
Conclusions: Focal cryotherapy primarily for anterior intermediate and high-risk prostate cancer results in good rates of cancer control and low rates of treatment-related side effects.
Patient summary: In this multicentre study of 122 patients undergoing focal cryotherapy for medium- to high-risk prostate cancer, at 3 yr, no patient died from their cancer whilst failure-free survival, was approximately 90%. None of the patients needed pads for managing urine leakage, although 16% had erection problems.

1. Introduction

Currently, patients with nonmetastatic clinically significant localised prostate cancer are offered either radical prostatectomy or radiotherapy. Both interventions have robust long-term cancer control outcomes, but due to targeting the entire prostate confer significant negative effects on genitourinary function, particularly with regard to incontinence, urinary symptoms, erectile function, and rectal side effects (radiotherapy) [1,2].

Recently, promising functional and oncological outcomes have been reported from minimally invasive treatments performed in a focal approach that targets areas of cancer rather than the entire prostate [3–5].

Much of the previously published studies have focused on low-risk patients being offered focal therapy as an alternative to active surveillance. However, multiple consensus groups have highlighted that low-risk patients should not routinely be offered focal therapy and that the ideal patient is one with localised intermediate-risk disease [6–8]. In this study, we report the cancer control and functional outcomes in patients with intermediate- and high-risk prostate cancer, from our prospective, multicentre, focal cryotherapy registry, compliant with the UK's National Institute of Clinical Excellence guidance.

2. Patients and methods

2.1. Study design

We implemented a focal cryotherapy program to complement focal high-intensity focussed ultrasound (HIFU); October 1, 2013, to November 30, 2016 with data collected prospectively in five centres. Ethics committee review exemption was granted by our institution.

2.2. Patient selection

Preoperatively, all patients underwent a prostate multiparametric magnetic resonance imaging (mpMRI) followed by either transperineal template mapping or MRI-targeted biopsy with systematic nontargeted sampling. A minority of patients were included on the basis of concordant mpMRI with systematic transrectal ultrasound (TRUS)-guided biopsy. The Likert MRI grading system was used (further details in the Supplementary data).

All patients were reviewed in a multidisciplinary team meeting. Our general inclusion criteria for focal therapy were patients requiring active treatment with a nonmetastatic cancer lesion of Gleason grade group (GGG) 2 or 3 (Gleason 3 + 4, 4 + 3) or high-volume GGG 1 (3 + 3) disease based on review of imaging and/or maximum cancer core length (MCCL) of $\geq$6 mm. All patients with anterior disease or factors that made focal HIFU unsuitable such as large prostates (anterior–posterior height $>$3 cm) or widespread calcifications were considered for focal cryotherapy. Patients with multiple lesions were permitted. There were no specific exclusion criteria based on tumour size. However, apical lesions invading or abutting the sphincter were excluded.

2.3. Surgical procedure

All patients underwent a standardised focal cryotherapy procedure using either the SeedNet or Visual ICE cryotherapy device (BTG plc, London, UK) [9]. The majority of patients underwent a general anaesthetic with a small number undergoing a spinal anaesthetic with sedation. During the procedure, real-time ultrasound was used to visualise the growing ice ball, and duty-cycle (gas flow) settings were adjusted to control the ice-ball dimensions (Figs. 1 and 2; further details and full protocol in the Supplementary data).

2.4. Follow-up

Follow-up consisted of serum prostate-specific antigen (PSA) testing every 3–6 mo in the 1st yr (6 mo thereafter) and mpMRI at 12 mo after focal cryotherapy. Subsequently, mpMRI and "for-cause" biopsies were performed when a recurrence was suspected due to rising PSA. When there was suspicion of recurrence, biopsies were targeted to the previous treatment site and to any new lesion/s seen on follow-up MRI. Systematic biopsies were not carried out as standard. Up to one further session of cryotherapy was permissible as part of the focal intervention. Patient-reported outcome measures [PROMs; International Prostate Symptoms Score (IPSS), Expanded Prostate Cancer Index (EPIC) Urinary, and 15-question International Index of Erectile Function (IIEF-15)] were sent to patients preoperatively and postoperatively (pre- and post-MRI and further information in the Supplementary data).

2.5. Outcome measures

Our primary outcome was failure-free survival (FFS), defined as transition to radical, whole-gland, or systemic therapy, or metastases/death (cancer specific) as used in our previous reports of focal therapy (definition 1) [10,11]. This is also the primary end point used in the PART (Partial prostate Ablation vs Radical prosTatectomy in intermediate-risk unilateral clinically localised prostate cancer) randomised control trial (RCT) comparing focal with radical therapy [12]. Secondary outcomes included histological failure, adverse events (Clavien-Dindo Classification), and functional outcomes (PROMs questionnaires: IIEF, EPIC, and IPSS). We also secondarily evaluated rate of a second focal therapy session within the definition of our composite cancer control outcome as well as cancer-specific, metastases-free, and overall survival rates (definition 2).

2.6. Statistical analyses

Continuous variables are presented as medians with interquartile ranges (IQRs) and categorical variables as absolute numbers with percentages.

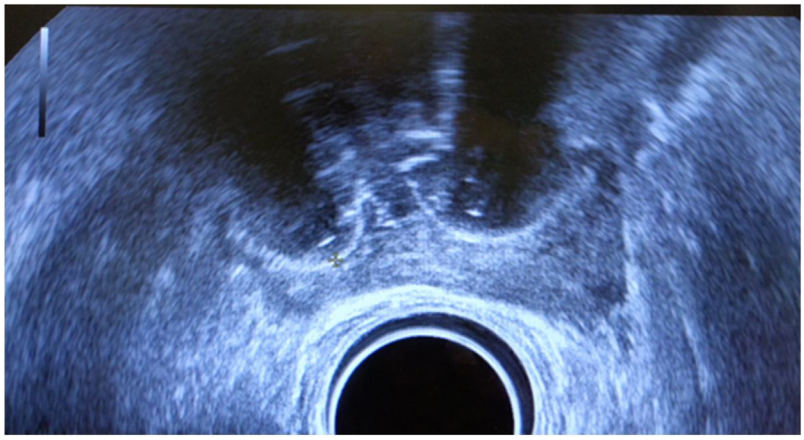

Fig. 1 – Real-time ultrasound image of a growing ice ball during a bilateral anterior ablation for a predominantly left anterior tumour with histology showing bilateral anterior Gleason 3 + 4 and baseline prostate-specific antigen of 17 ng/ml. The hypoechoic ice-ball edge can be clearly seen.

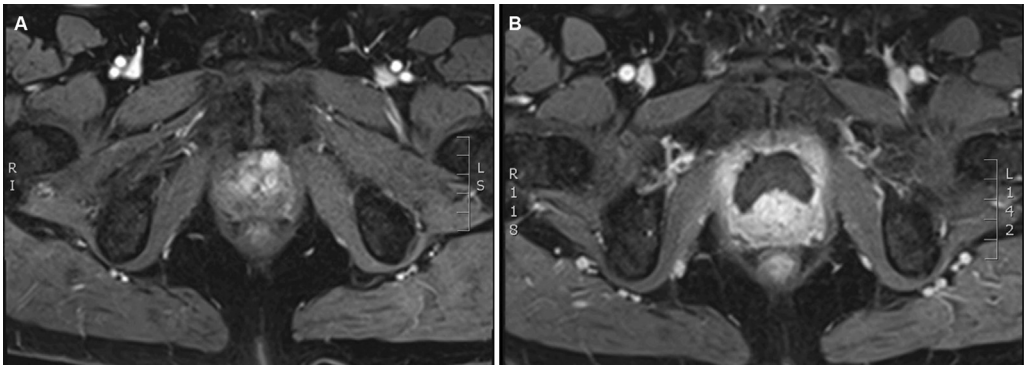

Fig. 2 – (A) Pre and (B) 2-wk post focal cryotherapy dynamic contrast-enhanced magnetic resonance imaging images of a predominantly left anterior tumour with histology showing bilateral anterior Gleason 3 + 4 and baseline prostate-specific antigen of 17 ng/ml.

Patients who returned questionnaires were compared with those who did not to assess if any differences existed in these populations. Differences in continuous variables were tested with Mann-Whitney *U* tests and categorical variables with the Fisher exact test. A comparison was made between National Comprehensive Cancer Network (NCCN) risk groups to assess differences in clinical characteristics. Kaplan-Meier (KM) analyses was performed to assess FFS, metastases-free survival, and overall survival. FFS was assessed for NCCN risk category (version 3.2018), PSA, T-stage, and GGG. Subgroups were compared using the log-rank test statistic. 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 characteristics and descriptive results

A total of 122 consecutive patients underwent primary focal cryotherapy with median follow-up of 27.8 mo (IQR 19.5–36.7) with 10/122 patients having less than 12 mo follow-up and no patient with less than 12-mo follow-up experiencing failure. Median age was 68.7 yr (IQR 64.9–73.8 yr), preoperative PSA 10.8 ng/ml (IQR 7.8–15.6 ng/ml), prostate volume 45 cc (IQR 33.8–64.0 cc), and MCCL 8 mm (IQR 6–10 mm). As much as 87 (71%) had intermediate risk and 35 (28.7%) high risk; 92.6% (113/122) patients underwent a transperineal mapping biopsy prior to treatment, 1.6% (2/122) had treatment based on their TRUS biopsy, and in 5.7% (7/122) this information was missing. In addition, 43.4% (53/122) had undergone a TRUS biopsy in the past. A total of 80 (65.6%) had anterior ablation, 24 (19.7%) combined posterior and anterior ablation, and two (1.6%) had posterior ablation alone (Table 1). Ablation data were missing in 16 (13.1%).

3.2. Primary outcome

Overall FFS at 3 yr was 90.5% [95% confidence interval (CI) 84.2–97.3]. When stratified for the NCCN risk group, 3-yr outcomes were 84.7% (95% CI 71.4–100) in high risk and 93.3% (95% CI 86.8–100) in intermediate risk (Fig. 3, Table 3). At last follow-up, five underwent radical prostatectomy, four radical radiotherapy, and four were started on systemic therapy. Three of those started on systemic therapy had developed metastatic disease. Four died of a nonprostate cancer-related cause and none of these four had developed metastatic disease.

3.3. Secondary outcomes

First, at last follow-up, eight patients underwent a further focal cryotherapy procedure. FFS incorporating further focal

Table 1 – Baseline characteristics in 122 patients who underwent focal cryotherapy for clinically significant nonmetastatic prostate cancer

Variable	Median	Interquartile range
Follow-up time (mo)	27.8	19.5–36.7
Age (yr)	68.7	64.9–73.8
PSA (ng/ml)	10.8	7.8–15.6
Prostate volume (cc)	45.0	33.8–64.0
MCCL (mm)	8	6–10
Positive cores	5	3–8
Total cores	25	12–47

Variable	*N*	%
T-Stage		
T2a	32	26.2
T2b	3	2.5
T2c	60	49.2
rT3a	13	10.7
T3a	9	7.4
Missing	5	4.1
Grade		
Grade group 1 (3 + 3)	12	9.8
Grade group 2 (3 + 4)	89	73
Grade group 3 (4 + 3)	19	15.6
Grade group 4 (4 + 4)	2	1.6
Ablation pattern		
Unilateral anterior ablation	29	23.8
Bilateral anterior ablation	51	41.8
Bilateral posterior ablation	2	1.6
Anterior and posterior ablation	24	19.7
Missing	16	13.1

MCCL = maximum cancer core length; PSA = prostate-specific antigen.

cryotherapy at 3 yr was 83.2% (95% CI 75.1–92.1). When stratified for the NCCN risk group, 3-yr outcomes were 68.4% (95% CI 51.4–90.9) in high risk and 90.1% (95% CI 82.6–98.2) in intermediate risk (Fig. 4).

Second, cancer-specific survival, metastases-free survival, and overall survival at 3 yr were 100% (95% CI 100–100), 98% (95% CI 95.3–100), and 96.1% (95% CI 92.3–100), respectively (Fig. 5).

Third, 29/122 patients underwent "for-cause" biopsies due to rising PSA and suspicious mpMRI scans with 20 having clinically significant cancer (Gleason grade ≥3 + 4 = 7), one having insignificant cancer (Gleason 3 + 3 = 6, 1 mm), and eight no cancer. Of those with positive biopsies (n = 21), nine had infield disease, nine had out-of-field disease, and three had both infield and out-of-field disease.

Fourth, as the decision for radical therapy following focal cryotherapy was based on a discussion with the patient along with clinical parameters, rather than a defined histological criterion, for the purposes of the comparative analysis FFS incorporating a further cryotherapy treatment was used to determine if any factors predicted the requirement for further treatment. Even though the KM curves diverged, the NCCN risk group was not found to be significantly different. There was also no difference found in FFS for GGGs or T-stage. However, a difference was found for PSA at the clinically accepted cut-off of 10 ng/ml (Table 2 and Fig. 6).

Finally, PROMs questionnaires return rate for one preoperative and at least one postoperative questionnaire was 69/124 (55.6%) for urinary function and 58/124 (47.5%) for erectile function (further data in the Supplementary information). Incontinence defined as any pad usage occurred in 4/69 (6%) at 3 mo and 0/69 (0%) by 6 mo. Overall, only 31 patients had preoperative erections sufficient for penetration defined as "erections with sexual stimulation hard enough for penetration a few times over the past 4-weeks" and postoperatively 26/31 (83.8%) were still potent. Comparing the baseline characteristics of those that did return a questionnaire with those that did not, we found no statistically significant differences apart from a higher proportion of TRUS biopsies in those

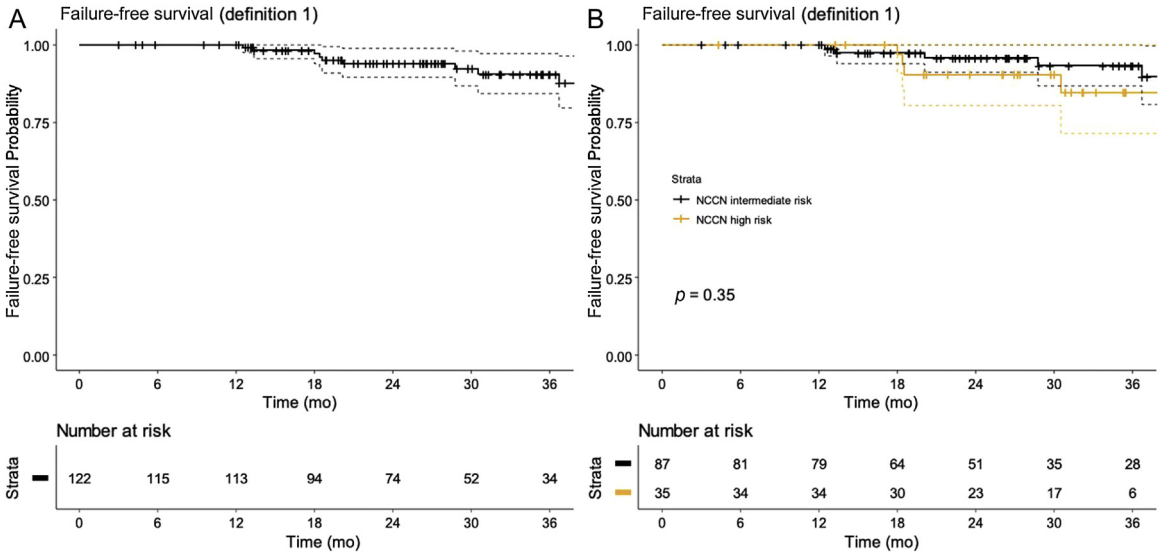

Fig. 3 – (A) Kaplan-Meier curve showing failure-free survival (FFS) defined as transition to radical, whole-gland, or systemic therapy, and metastases/death in patients undergoing focal cryotherapy for clinically significant nonmetastatic prostate cancer (definition 1). (B) Kaplan-Meier curve showing FFS defined as transition to radical, whole-gland, or systemic therapy, and metastases/death in patients undergoing focal cryotherapy for clinically significant nonmetastatic prostate cancer stratified by the National Comprehensive Cancer Network (NCCN) risk category (intermediate risk, high risk).

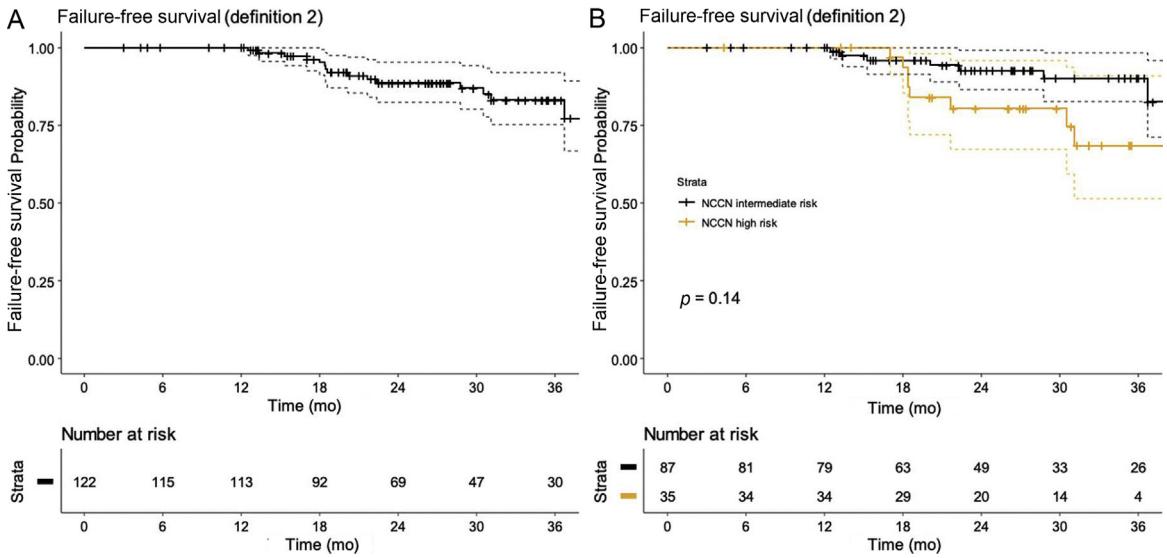

Fig. 4 – (A) Kaplan-Meier curve showing failure-free survival (FFS) defined as transition to any further focal, radical, whole-gland, or systemic therapy and metastases/death in patients undergoing focal cryotherapy for clinically significant nonmetastatic prostate cancer. (B) Kaplan-Meier curve showing FFS defined as transition to further focal, radical, whole-gland, or systemic therapy and metastases/death in patients undergoing focal cryotherapy for clinically significant nonmetastatic prostate cancer (definition 2) stratified for the National Comprehensive Cancer Network (NCCN) risk category (intermediate risk, high risk).

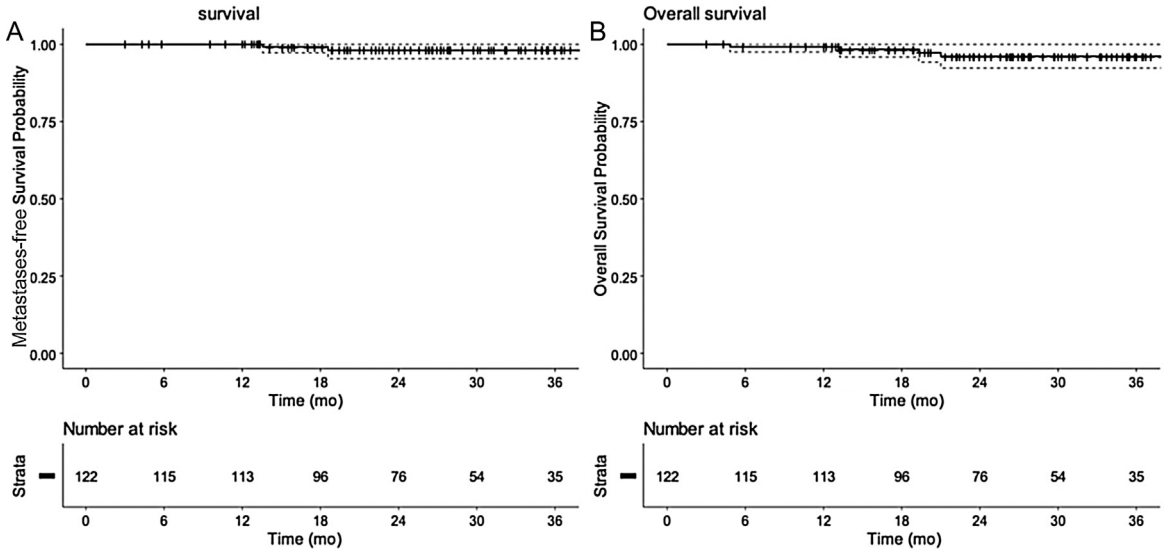

Fig. 5 – Kaplan-Meier curves showing (A) metastases-free survival and (B) overall survival in patients undergoing focal cryotherapy for clinically significant nonmetastatic prostate cancer.

returning a PROMs questionnaire, which could be a type I error.

Other adverse events occurred in 27.8% (*N* = 34) of patients and included cystoscopic interventions (Clavien-Dindo 3) in 1.6% (*N* = 2) with none needing bladder neck or prostatic resection, urinary retention managed with a short-term catheter in 4.1% (*N* = 5), urinary tract infections (Clavien-Dindo 2) in 9% (*N* = 11), penile numbness/penoscrotal swelling in 9.8% (*N* = 12; Clavien-Dindo 2), osteomyelitis of the pubic symphysis managed conservatively with antibiotics (Clavien-Dindo 2) in 0.8% (*N* = 1). There was no case of rectal fistulae (0%).

4. Discussion

In summary, our results show good early-medium-term cancer control outcomes with low rates of adverse events and side effects. At 3 yr, nine of 10 patients being treated with focal cryotherapy for largely intermediate-high-risk anterior prostate cancer were free from requiring radical or systemic therapy. No incontinence requiring any pad use was reported at last follow-up whilst approximately one in six patients reported erections insufficient for penetration. There were no rectal adverse events.

Table 2 – Kaplan-Meier estimates of freedom (24 and 36 mo, respectively) from failure definition 1 (transition to radical, whole-gland, or systemic therapy and metastases/death) and definition 2 (transition to any further focal, radical, whole-gland, or systemic therapy and metastases/death), stratified for the NCCN risk group (intermediate and high) and PSA (<10 ng/ml and ≥10 ng/ml) following focal cryotherapy in men treated for nonmetastatic prostate cancer

	Kaplan-Meier estimate, % (95% confidence interval)			
	24 mo		36 mo	
	Definition 1	Definition 2	Definition 1	Definition 2
Overall failure-free survival	94.0 (89.4–98.8)	88.6 (82.4–95.2)	90.5 (84.2–97.3)	83.2 (75.1–92.1)
By NCCN risk group				
Intermediate risk	95.7 (91.0–100)	92.6 (86.5–99.1)	93.3 (86.8–100)	90.1 (82.6–98.2)
High risk	90.3 (80.5–1)	80.3 (67.3–95.8)	84.7% (95% CI 71.4–100)	68.4 (51.4–90.9)
By baseline PSA				
PSA < 10 ng/ml	97.7 (93.4–100)	95.5 (89.6–100)	97.7 (93.4–100)	95.5 (89.6–100)
PSA ≥ 10 ng/ml	90.8 (83.3–98.9)	82.7 (73.0–93.7)	84.5 (74.2–96.4)	72.8 (60.2–88.2)

CI = confidence interval; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen.

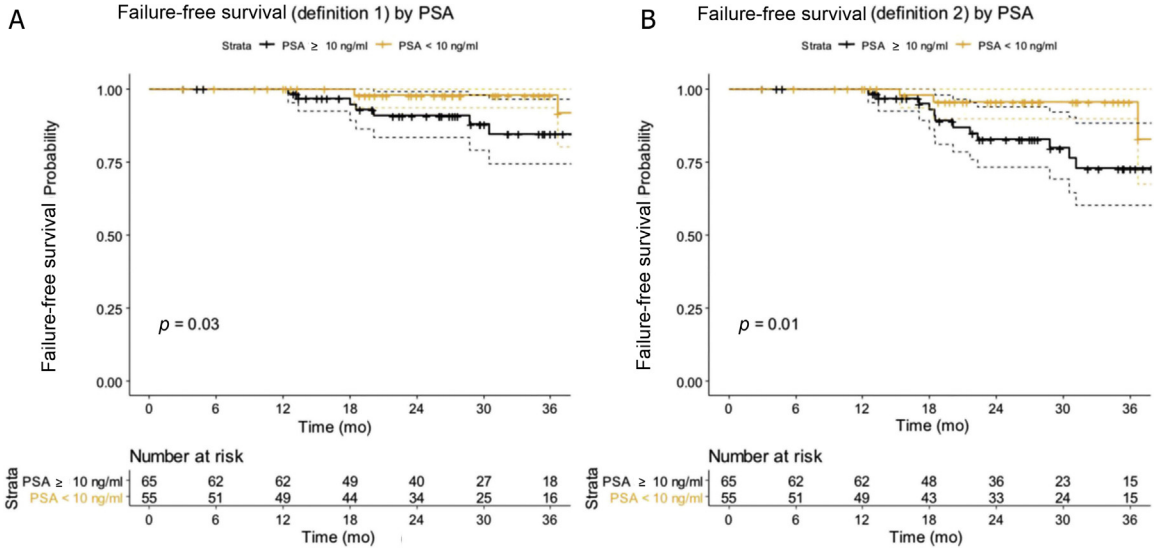

Fig. 6 – Kaplan-Meier curves of freedom from failure (A) definition 1 (transition to radical, whole-gland, or systemic therapy and metastases/death) and (B) definition 2 (transition to any further focal, radical, whole-gland, or systemic therapy and metastases/death), stratified for prostate-specific antigen (PSA; <10 ng/ml and 10 ng/ml) following focal cryotherapy in men treated for nonmetastatic prostate cancer.

When comparing our data with other energy modalities, the use of our definitions for the primary and secondary outcomes may make comparisons more difficult but is entirely in keeping with our recently published series which showed, using the same definition of FFS in a 625-patient multicentre focal HIFU registry, FFS was 92% at 3 yr and 88% at 5 yr [10].

For a similar reason, direct comparison with other cryotherapy series is difficult but our results do appear comparable with the published series [3]. The results from a review of 1582 primary focal cryotherapy patients incorporating 1160 patients from the Cryo On-Line Database (COLD) registry showed biochemical disease-free survival between 71% and 93% at 9–70 mo follow-up. Incontinence rates were 0–3.6% and erectile dysfunction (ED) 0–42% whilst rectourethral fistula occurred in only two patients [3,13–15].

Another factor to consider when comparing our data with the available literature is our use of the previously described “a la carte” [16] patient-stratified approach to energy selection, whereby focal HIFU was used for glands with mainly posterior tumours or anterior tumours in small glands, whilst cryotherapy was used for large glands with anterior tumours or those unsuitable for focal HIFU.

A major strength of our data comes from the fact that the majority of our cohort had intermediate- and high-risk prostate cancer in contrast to the early cryotherapy cohorts in patients with predominately low-risk disease [17,18]. Almost one-third of our series was NCCN high risk. More reassuring is that patients being selected were those needing active treatment rather than active surveillance, with only two patients treated for low-risk disease (high-volume Gleason 6 excluded from the analysis). Our cohort is in line with current consensus guidelines stating that focal therapy should only be directed towards localised intermediate-grade cancer and not offered to patients suitable for active surveillance unless in extenuating circumstances (high-volume Gleason 6, family history, psychological distress to surveillance) [8]. It must be noted that the

Table 3 – A comparison of baseline characteristics between NCCN intermediate and high risk[a]

Variable	Median (IQR)/*N* (%) intermediate risk (*n* = 87)	Median (IQR)/*N* (%) high risk (*n* = 35)	*p* value
Follow-up time (mo)	27.2 (18.2–38.3)	29.7 (21.0–35.4)	
Age (yr)	68.9 (64.5–73.7)	68.3 (65.9–73.7)	0.65
PSA (ng/ml)	9.2 (7.0–13.7)	17 (11.0–22.3)	<0.0001
PSAD (ng/ml/cc)	0.2 (0.1–0.3)	0.3 (0.2–0.4)	0.003
Prostate volume (cc)	44 (31.8–59.3)	48.5 (39.0–66.3)	0.14
MCCL (mm)	8 (6–10)	9 (6–11)	0.17
Positive cores	6 (3–9)	5 (3–7)	0.29
Total cores	27 (12–49)	21 (10–39)	0.29
T-stage			<0.0001
T2a	25 (28.7%)	7 (20%)	
T2b	3 (3.4%)	9 (0%)	
T2c	53 (60.9%)	7 (20.0%)	
rT3a	1 (1.1%)	8 (37.1%)	
T3a	0 (0%)	13 (22.9%)	
	Missing: *n* = 5 (5.7%)		
Grade			0.17
Grade group 1 (3 + 3)	10 (11.5%)	2 (5.7%)	
Grade group 2 (3 + 4)	63 (72.4%)	26 (74.3%)	
Grade group 3 (4 + 3)	14 (16.1%)	5 (14.3%)	
Grade group 4 (4 + 4)	0 (0%)	2 (5.7%)	
Ablation pattern			0.13
Unilateral anterior ablation	21 (24.1%)	8 (22.9%)	
Bilateral anterior ablation	32 (36.8%)	19 (54.3%)	
Bilateral posterior ablation	1 (1.1%)	1 (2.9%)	
Anterior and posterior ablation	21 (24.1%)	3 (8.6%)	
	Missing: *n* = 12 (13.8%)	Missing: *n* = 4 (11.4%)	
PSA nadir post-treatment	1.3 (0.7–2.5)	1.1 (0.6–2.2)	0.60

IQR = interquartile range; MCCL = maximum cancer core length; *N* = absolute number; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; PSAD = PSA density.

[a] Differences between continuous variables are tested using the Mann-Whitney *U* test. Differences in categorical variables are tested using the Fisher exact test.

majority of our patients were deemed high risk due to early T3 disease and/or a PSA over 20 ng/ml. Only two patients had GGG 4 disease, which is in keeping with our eligibility criteria for focal cryotherapy. At the study institutions, patients with high-risk GGG 4 and 5 disease were recommended and underwent whole-gland radical treatments.

There are some limitations that also need highlighting. First, there are no defined PSA criteria that are representative of failure. Our follow-up strategy is heavily reliant on mpMRI as we have previously shown high negative predictive values of 86–97% for significant disease postfocal therapy [19]. This is the main limitation as patients with negative MR (and nonspecific PSA kinetics) may still harbour clinically significant cancer. Therefore, histological failure could be underestimated. Ideally, 1-yr protocol biopsies would have been performed on the ablated area. However, in a routine clinical setting this was not possible and from experience is often not accepted by patients with a low PSA and negative MRI. Second, we used a pragmatic definition of transition to radical or systemic treatment or metastases/death. This takes into account the fact that our focal therapy treatment protocols allow for one further session of focal treatment to either an in-field or out-of-field recurrence. For completeness we also presented a second more conservative definition of failure. Third, it is possible that the true rates of incontinence and ED may differ as we had incomplete PROM data. However, our figures appear comparable to results in the literature of 0–3.6% incontinence and 0–42% ED [3]. Fourth, due to the low number of failures (events) and large number of exploratory variables a Cox-regression model is not presented as it was deemed inaccurate. KM analysis showed that preoperative PSA was a potential predictor of failure whilst NCCN risk category was not. A possible reason for NCCN risk category being not significant may stem from unmeasured factors influencing patient selection or due to the low number of overall events. The 95% CIs between the intermediate- and high-risk groups were very wide and do overlap. With longer follow-up and a larger cohort, tighter estimates can potentially be found. Fifth, the results are from a highly selected group of patients with predominantly anterior disease. Although this limits generalisability, it does indicate that focal cryotherapy in this cohort of patients is a potential treatment option. In addition, one-quarter did have both an anterior and posterior ablation.

There is little randomised comparative data on focal therapy. The only RCT on focal therapy found lower progression with focal vascular target photodynamic therapy against active surveillance. However, as the cohort of patients in this study were all low risk diagnosed using only transrectal systematic biopsies with an end point that was likely reflective of the misclassification error of the baseline biopsy rather than progression, extrapolating the data to our own series is problematic. Although RCTs in intermediate and high-risk disease are being piloted, these may be difficult to recruit especially considering that many previous trials have struggled to complete when attempting to compare current radical therapy approaches [20].

5. Conclusion

Focal cryotherapy used primarily for anterior intermediate and high-risk prostate cancer results in good rates of cancer control and low rates of treatment-related side effects in the early to medium term. Patient selection should be based on accurate index lesion and tumour characterisation using mpMRI and targeted biopsies or systematic transperineal biopsies. The ideal patient should have a localised GGG 2 or 3 lesion that is not abutting or invading the urethral sphincter. Based on the presented data and on the evidence within the literature, it would be reasonable to counsel eligible patients about focal cryotherapy prior to RCT data becoming available as long as they are made aware of the alternative radical treatments and that currently long-term 10-yr outcomes are not available on focal therapy.

Author contributions: Taimur T. Shah 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.

Study concept and design: Shah, Valerio, Arya, Ahmed.
Acquisition of data: Shah, Valerio, Hosking-Jervis, Eldred-Evans, Peters, Yap, Arya, Ahmed.
Analysis and interpretation of data: Shah, Peters, Yap, Valerio, Hosking-Jervis, Arya, Ahmed.
Drafting of the manuscript: Shah, Peters, Eldred-Evans, Miah, Arya, Ahmed.
Critical revision of the manuscript for important intellectual content: Shah, Peters, Eldred-Evans, Miah, Yap, Valerio, Hosking-Jervis, Faure-Walker, Thomas, Dudderidge, Hindley, McCracken, Greene, Nigam, Valerio, Minhas, Winkler, Arya, Ahmed.
Statistical analysis: Shah, Peters.
Obtaining funding: Arya, Ahmed.
Administrative, technical, or material support: Shah, Hosking-Jervis.
Supervision: Minhas, Winkler, Arya, Ahmed.
Other: None

Financial disclosures: Taimur T. Shah certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Shah would like to acknowledge funding from Prostate Cancer UK and the St Peters Trust for clinical research and has received funding for conference attendance from Astellis, Ferring, and Galil Medical. Ahmed's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. Ahmed currently receives funding from the Wellcome Trust, Prostate Cancer UK, Sonacare Inc., Trod Medical, and Sophiris Biocorp for trials in prostate cancer. Ahmed is a paid medical consultant for Sophiris Biocorp and Sonacare Inc. Winkler receives a travel grant and a loan of device from Zicom Biobot. G. Hindley has received proctor fees for training surgeons in HIFU and owns loan notes/stock options in Nuada Medical. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.12.030.

References

[1] Menon M, Dalela D, Jamil M, et al. Functional recovery, oncologic outcomes and postoperative complications 12 months following robot-assisted radical prostatectomy: follow-up of an evidence-based analysis comparing the Retzius sparing and standard approaches. J Urol 2018;199:1210–7.
[2] Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. New Engl J Med 2016;375:1415–24.
[3] Shah TT, Ahmed H, Kanthabalan A, et al. Focal cryotherapy of localized prostate cancer: a systematic review of the literature. Expert Rev Anticancer Ther 2014;14:1337–47.
[4] Valerio M, Cerantola Y, Eggener SE, et al. New and established technology in focal ablation of the prostate: a systematic review. Eur Urol 2017;71:17–34.
[5] Ahmed HU, Pendse D, Illing R, Allen C, van der Meulen JH, Emberton M. Will focal therapy become a standard of care for men with localized prostate cancer? Nat Clin Pract Oncol 2007;4:632–42.
[6] van den Bos W, Muller BG, Ahmed H, et al. Focal therapy in prostate cancer: international multidisciplinary consensus on trial design. Eur Urol 2014;65:1078–83.
[7] Donaldson IA, Alonzi R, Barratt D, et al. Focal therapy: patients, interventions, and outcomes—a report from a Consensus Meeting. Eur Urol 2014;67:771–7.
[8] 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;20:294–9.
[9] Shah TT, Arbel U, Foss S, et al. Modeling cryotherapy ice ball dimensions and isotherms in a novel gel-based model to determine optimal cryo-needle configurations and settings for potential use in clinical practice. Urology 2016;91:234–40.
[10] 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.
[11] Dickinson L, Arya M, Afzal N, et al. Medium-term outcomes after whole-gland high-intensity focused ultrasound for the treatment of nonmetastatic prostate cancer from a multicentre registry cohort. Eur Urol 2016;70:668–74.
[12] Elliott D, Hamdy FC, Leslie TA, et al. Overcoming difficulties with equipoise to enable recruitment to a randomised controlled trial of partial ablation vs radical prostatectomy for unilateral localised prostate cancer. BJU Int 2018;122:970–7.
[13] Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int 2012;109:1648–54.
[14] Ahmed HU, Emberton M. Benchmarks for success in focal therapy of prostate cancer: cure or control? World J Urol 2010;28:577–82.
[15] Ahmed HU, Moore C, Lecornet E, Emberton M. Focal therapy in prostate cancer: determinants of success and failure. J Endourol 2010;24:819–25.
[16] Sivaraman A, Barret E. Focal therapy for prostate cancer: an “a la carte” approach. Eur Urol 2016;69:973–5.
[17] Ellis DS, Manny Jr TB, Rewcastle JC. Focal cryosurgery followed by penile rehabilitation as primary treatment for localized prostate cancer: initial results. Urology 2007;70:9–15.
[18] Ellis DS, Manny Jr TB, Rewcastle JC. Cryoablation as primary treatment for localized prostate cancer followed by penile rehabilitation. Urology 2007;69:306–10.
[19] Dickinson L, Ahmed HU, Hindley RG, et al. Prostate-specific antigen vs. magnetic resonance imaging parameters for assessing oncological outcomes after high intensity-focused ultrasound focal therapy for localized prostate cancer. Urol Oncol 2017;35:30e9–30e15.
[20] Ahmed HU, Berge V, Bottomley D, et al. Can we deliver randomized trials of focal therapy in prostate cancer? Nat Rev Clin Oncol 2014;11:482–91.