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Prostate Cancer

Magnetic Resonance Imaging and Targeted Biopsies Compared to Transperineal Mapping Biopsies Before Focal Ablation in Localised and Metastatic Recurrent Prostate Cancer After Radiotherapy

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Abstract

Background: Recurrent prostate cancer after radiotherapy occurs in one in five patients. The efficacy of prostate magnetic resonance imaging (MRI) in recurrent cancer has not been established. Furthermore, high-quality data on new minimally invasive salvage focal ablative treatments are needed.
Objective: To evaluate the role of prostate MRI in detection of prostate cancer recurring after radiotherapy and the role of salvage focal ablation in treating recurrent disease.
Design, setting, and participants: The FORECAST trial was both a paired-cohort diagnostic study evaluating prostate multiparametric MRI (mpMRI) and MRI-targeted biopsies

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in the detection of recurrent cancer and a cohort study evaluating focal ablation at six UK centres. A total of 181 patients were recruited, with 155 included in the MRI analysis and 93 in the focal ablation analysis.

Intervention: Patients underwent choline positron emission tomography/computed tomography and a bone scan, followed by prostate mpMRI and MRI-targeted and transperineal template-mapping (TTPM) biopsies. MRI was reported blind to other tests. Those eligible underwent subsequent focal ablation. An amendment in December 2014 permitted focal ablation in patients with metastases.

Outcome measurements and statistical analysis: Primary outcomes were the sensitivity of MRI and MRI-targeted biopsies for cancer detection, and urinary incontinence after focal ablation. A key secondary outcome was progression-free survival (PFS).

Results and limitations: Staging whole-body imaging revealed localised cancer in 128 patients (71%), with involvement of pelvic nodes only in 13 (7%) and metastases in 38 (21%). The sensitivity of MRI-targeted biopsy was 92% (95% confidence interval [CI] 83–97%). The specificity and positive and negative predictive values were 75% (95% CI 45–92%), 94% (95% CI 86–98%), and 65% (95% CI 38–86%), respectively. Four cancer (6%) were missed by TTPM biopsy and six (8%) were missed by MRI-targeted biopsy. The overall MRI sensitivity for detection of any cancer was 94% (95% CI 88–98%). The specificity and positive and negative predictive values were 18% (95% CI 7–35%), 80% (95% CI 73–87%), and 46% (95% CI 19–75%), respectively. Among 93 patients undergoing focal ablation, urinary incontinence occurred in 15 (16%) and five (5%) had a grade $\geq$3 adverse event, with no rectal injuries. Median follow-up was 27 mo (interquartile range 18–36); overall PFS was 66% (interquartile range 54–75%) at 24 mo.

Conclusions: Patients should undergo prostate MRI with both systematic and targeted biopsies to optimise cancer detection. Focal ablation for areas of intraprostatic recurrence preserves continence in the majority, with good early cancer control.

Patient summary: We investigated the role of magnetic resonance imaging (MRI) scans of the prostate and MRI-targeted biopsies in outcomes after cancer-targeted high-intensity ultrasound or cryotherapy in patients with recurrent cancer after radiotherapy. Our findings show that these patients should undergo prostate MRI with both systematic and targeted biopsies and then ablative treatment focused on areas of recurrent cancer to preserve their quality of life.

This trial is registered at ClinicalTrials.gov as NCT01883128.

1. Introduction

For the 45 000 patients diagnosed with nonmetastatic prostate cancer in the UK and 180 000 in the USA every year, radiotherapy is a common and effective treatment. However, with the increasing number of patients receiving radiotherapy and one in five experiencing recurrence of their cancer at 5–10 yr, there are a significant number of men living with recurrent cancer [1]. Currently, most are managed on watchful waiting with immediate or delayed androgen deprivation therapy (ADT). ADT has side effects such as lethargy, weight gain, metabolic syndrome leading to diabetes or heart disease, and osteopenia and fractures. In addition, after 2–3 yr, many men develop castrate-resistant prostate cancer requiring second- and third-line medications [2,3]. Salvage prostatectomy is an alternative strategy but is not often carried out owing to significant side effects such as urinary incontinence in almost all patients and rectal injury in up to one in 20 [4].

It has been shown that localisation via magnetic resonance imaging (MRI) and targeted biopsy is highly accurate in diagnosing prostate cancer in patients presenting with elevated prostate specific antigen (PSA) [5–7]. There is little high-level evidence demonstrating whether such an approach is accurate for suspected recurrences after radiotherapy. Furthermore, there is a lack of prospective evidence as to whether targeted focal ablation to areas of localised cancer recurrence within the prostate is effective.

2. Patients and methods

2.1. Trial overview

The FORECAST (Focal Recurrent Assessment and Salvage Treatment) trial (NCT01883128) assessed a combined diagnostic and treatment pathway in six centres. The trial first evaluated the diagnostic accuracy of prostate MRI and targeted biopsy in comparison to the reference standard of transperineal template prostate mapping (TTPM) biopsy (Standards for the Reporting of Diagnostic Accuracy [STARD] checklist in the Supplementary material). TTPM biopsy is highly accurate in patients for whom whole-prostate surgical pathology cannot be obtained [5,8]. Second, FORECAST evaluated functional and oncological outcomes after focal ablation in eligible and consenting patients with localised cancer alone and those with intraprostatic recurrence of cancer in the presence of metastases (Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] checklist in the Supplementary material). Full details are available in the previously published full protocol [9] and the Supplementary material.

2.2. Patients

All patients with biochemical failure detected as a rising PSA level after prior external beam radiotherapy (EBRT) or interstitial low-dose-rate or

high-dose-rate brachytherapy with or without neoadjuvant/adjuvant ADT were eligible. Exclusion criteria were ADT within 6 mo of enrolment, a PSA doubling time of ≤3 mo, total PSA ≥20 ng/ml, inability to undergo MRI, and receipt of salvage therapy. There were no restrictions on stage (provided there were no distant extrapelvic metastases), Gleason grade, or PSA before radiotherapy. Oversight was provided by an independent trial steering committee.

2.3. Trial procedures

All patients underwent staging investigations that consisted of ^{18}F-choline positron emission tomography/computed tomography (PET/CT) and a radioisotope bone scan (^{99m}Tc-methyl diphosphonate) for assessment of nodal and distant disease (^{68}Ga or ^{18}F prostate-specific membrane antigen [PSMA] PET/CT was not available or approved for clinical use in the UK at the time of the study). This was followed by a prostate multiparametric MRI (mpMRI) study (T2-weighted imaging, diffusion-weighted imaging, precontrast T1-weighted MRI, and dynamic contrast-enhanced sequences; Supplementary material). Seven expert radiologists with 5–15 yr of experience in reading prostate MRI scans scored the MRI findings before biopsy using a 5-point Likert scale, where 1 denotes "highly unlikely" and 5 "highly likely" to show clinically significant prostate cancer. MRI findings were reported blind to other tests; clinicians were unblinded to the MRI at the time of biopsy in order to carry out targeted biopsy. The targeted biopsy and TTPM biopsy were conducted in that order in one session under sedation or general anaesthetic. The recommendation was to take four to six cores from any lesions scoring 3, 4, or 5 using visual estimation targeting. Commonly referred to as cognitive targeting, this involves the operator looking at the MRI on a separate screen to determine where to deploy the needle under ultrasound guidance. There were no image fusion devices available at the time of this study, although recent studies have shown that in expert hands, visual estimation seems comparable to image fusion targeting [10]. TTPM biopsy involves taking a biopsy every 5 mm using a brachytherapy template grid placed against the perineum, with additional biopsies taken to sample the full craniocaudal prostate length. The technique has previously been described [5,11].

All nuclear medicine scans (choline PET and bone scans) were reviewed centrally. The MRI scans and pathology were reviewed at local multidisciplinary cancer board meetings but were not reviewed centrally.

Subsequent eligibility for focal ablation was confirmed in a protocol-mandatory tumour board meeting. Eligible patients consenting to focal ablation then underwent either cognitively targeted high-intensity focused ultrasound (HIFU) or cryotherapy to target areas of recurrence alone, with a 3–5-mm margin of normal tissue. Initially, only patients with imaging-confirmed localised disease underwent targeted and TTPM biopsy with a view to undergoing focal ablation. An ethical amendment in December 2014 permitted focal ablation in patients with metastases.

The energy modality for each patient was chosen on the basis of the tumour location on mpMRI and biopsies. Patients underwent focal cryotherapy (SeedNet or Visual ICE, Boston Scientific, Marlborough, MA, USA) for anterior tumours, larger prostates with an anterior-posterior distance of >3.5 cm, and cases with prostatic calcifications or previous brachytherapy seeds. All other patients with peripheral zone or posterior tumours underwent HIFU (Sonablate, Sonacare, Charlotte, NC, USA).

After focal ablation, follow-up consisted of PSA measurement at 1, 3, 6, 9, and 12 mo and at 6-mo intervals thereafter, with completion of validated questionnaires including the International Prostate Symptom Score (IPSS) and IPSS Quality of Life score, the Expanded Prostate Cancer Index Composite (EPIC) Urinary and Bowel, and the International Index of Erectile Function 15-point (IIEF-15).

Further repeat focal ablation of residual disease was permitted on the basis of mpMRI and biopsy findings after review in a multidisciplinary tumour board meeting.

2.4. Outcomes

There were two primary outcomes: (1) the sensitivity of MRI and MRI-targeted biopsies in comparison to the reference test of TTPM biopsy; and (2) urinary incontinence, defined as the use of any pads at 12 mo, in patients who were continent before focal ablation.

A key secondary outcome was progression-free survival (PFS) in all patients undergoing focal ablation. Progression was defined as any new metastases or hormone use or chemotherapy or further local treatment. In those with nodal or metastatic disease, use of hormone therapy was allowed according to the protocol and did not constitute a failure event. Other secondary outcomes were metastasis-free survival (MFS), biochemical disease–free survival (bDFS; assessed using the Phoenix criterion of PSA +2 ng/ml above the nadir value after treatment), and cancer-specific mortality. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) classification system. In addition, we assessed the time to return of urinary continence, lower urinary tract symptoms according to IPSS results at 12 mo, and erectile dysfunction, measured as the overall IIEF-15 change and an inability to have erections sufficient for penetrative sexual activity at 12 mo (IIEF-15 question 2) with or without the use of phosphodiesterase-5 inhibitors, in those without erectile dysfunction at baseline.

2.5. Statistical analysis

To determine whether MRI-targeted prostate biopsies can accurately identify areas of radiorecurrent cancer compared to TTPM biopsies, the minimum number of patients undergoing biopsy needed to evaluate the proportion of agreement between MRI, MRI-targeted biopsies, and the reference test given a marginal error of 0.05 and 90% disease prevalence would be 81. Given that an estimated 50% of those recruited would subsequently undergo MRI-targeted biopsies, the overall target was set at 162 patients. To obtain a precision-based estimate of the rate of urinary incontinence after focal ablation, we estimated that the rate of incontinence (any pad usage) would be 20%. Thus, a sample size of 60 would give a 95% confidence interval (CI) of ±10%. If incontinence was slightly lower (15%), then the 95% CI would be ±9%. If incontinence was higher (25%), then the 95% CI would be ±11%.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for MRI and MRI-targeted biopsies compared to TTPM biopsies in detecting any cancer were calculated using an MRI score of ≥3 to designate positive MRI findings. In addition, MRI positivity was also defined as a score of ≥4 as a secondary outcome. Cumulative incidence analysis was performed to determine the time to recovery of urinary continence. Kaplan-Meier analyses were used to assess PFS, MFS, and bDFS. All analyses were performed using Stata v16.1 (StataCorp, College Station, TX, USA) with the *diagt* package.

3. Results

3.1. Patient characteristics

Between April 2014 and January 2018, 181 patients were enrolled (Fig. 1), of whom 157 (87%) had previously undergone EBRT, 15 (8%) brachytherapy, and six (3%) brachytherapy with EBRT boost (data missing for 3/181, 2%). Neo/adjuvant ADT was used in 142/181 (79%) (data missing for 10/181, 6%). The most common radiotherapy protocols were

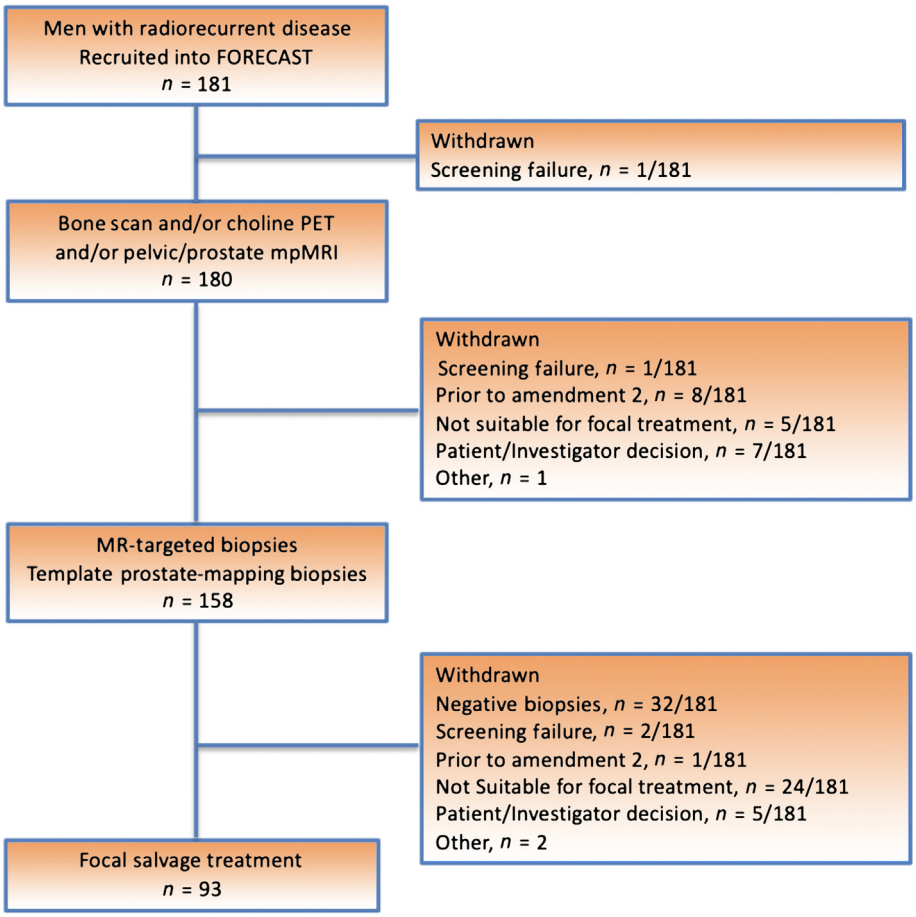

Fig. 1 – Flow diagram for the FORECAST trial. mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography.

74 Gy in 37 fractions (61/157, 39%) and 55–60 Gy in 19–20 fractions (16/157, 10%); data were missing for 80/157 patients (51%) because of the long time since radiotherapy was delivered and the fact that treatment was often performed at other hospitals (Table 1).

3.2. Primary outcomes

3.2.1. Assessment of prostate MRI and MRI-targeted biopsy

Matched data for comparison of prostate MRI and TTPM biopsies were available for 155 patients. When Likert 3–5 was used to denote MRI positivity, the MRI sensitivity for detection of cancer recurrence was 94% (95% CI 88–98%). The specificity, PPV, and NPV were 18% (95% CI 7–35%), 80% (95% CI 73–87%), and 46% (95% CI 19–75%), respectively. Using Likert 4–5 to denote MRI positivity, the MRI sensitivity for detection of cancer recurrence was 81% (95% CI 73–88%). The specificity, PPV, and NPV were 88% (95% CI 73–98%), 96% (95% CI 90–99%), and 57% (95% CI 42–70%), respectively (Table 2). Likert scores on MRI were 1–2 in 13/155 patients (8%), 3 in 40/155 (25%), 4 in 24/155 (15%), and 5 in 78/155 (50%); cancer detection increased with increasing Likert score (Supplementary information).

Matched data were available for 87 patients (56%) for comparison between MRI-targeted and TTPM biopsies. A median of six (interquartile range [IQR] 4–9) targeted cores were taken, with cancer detected in 72 patients (83%, 95% CI 73–90%). The sensitivity of MRI-targeted biopsy for cancer detection was 92% (95% CI 83–97%). The specificity, PPV, and NPV were 75% (95% CI 45–92%), 94% (95% CI 86–98%), and 65% (95% CI 38–86%), respectively. Overall, four cancers (6%) were detected by MRI-targeted biopsy that were missed on TTPM biopsies; six cancers (8%) were detected by TTPM biopsy that were missed by MRI-targeted biopsy (Supplementary material).

3.2.2. Urinary incontinence

Of 93 patients undergoing focal ablation, 64 (69%) had HIFU and 29 (31%) underwent cryotherapy. Focal ablation was performed in 73 patients (78%) who had nonmetastatic disease, while 20 (21%) had intraprostatic recurrences involving nodal or distant metastases. After excluding patients who did not complete a baseline questionnaire, 3/84 (3.6%) were wearing a pad at baseline; this changed to 20/67 (30%), 10/58 (17%), 7/56 (13%), and 8/45 (18%) at 1, 6, 9, and 12 mo, respectively. The probability of return of continence for all those who returned a questionnaire was 84% (95% CI 74–91%) at 12 mo (Supplementary material).

3.3. Secondary outcomes

During median follow-up of 27 mo (IQR 18–34), overall PFS was 66% (95% CI 54–75%) at 24 mo for the 93 patients

Table 1 – Patient characteristics for the overall and focal salvage therapy cohorts.

Cohort	Overall cohort	Focal therapy	Localised cancer	Nodal/metastatic
Patients (*N*)	181	93	73	20
Radiotherapy type, *n*/*N* (%)				
External beam radiotherapy	157/181 (87)	81/93 (87)	68/73 (93)	15/20 (75)
Brachytherapy	21/181 (12)	10/73 (14)	5/20 (25)	5/20 (25)
Neo/adjuvant hormone use, *n* (%)	142/181 (79)	69/93 (74)	55/73 (75)	14/20 (70)
Median disease-free survival interval, yr (IQR)	7 (5–10)	8 (5–11)	7 (5–11)	8 (7–11)
Parameters at original diagnosis				
Median age, yr (IQR)	63 (59–68)	63 (59–66)	63 (59–68)	61.5 (58–64)
Median PSA, ng/ml (IQR)	12 (8–24)	12 (8–23)	12 (8–23)	10 (7–21)
Disease characteristics, *n*/*N* (%)				
Gleason $\leq$ 3 + 3	45/181 (25)	28/93 (30)	23/73 (32)	4/20 (20)
Gleason 7	88/181 (49)	40/93 (43)	32/73 (44)	8/20 (40)
Gleason $\geq$8	38/181 (21)	19/93 (20)	11/181 (6)	8/20 (40)
Stage T1	15/181 (8)	9/93 (10)	7/73 (10)	2/20 (10)
Stage T2	51/181 (28)	24/93 (26)	21/73 (29)	3/20 (15)
Stage T3	80/181 (44)	37/93 (40)	29/73 (40)	8/20 (40)
Stage T4	2/181 (1)	0/93 (0)	0/73 (0)	0/20 (0)
Parameters at enrolment				
Median age, yr (IQR)	72 (67–77)	71 (67–76)	72 (68–77)	70 (66–72)
Median PSA, ng/ml (IQR)	4 (2–6)	4 (3–7)	5 (3–7)	4 (3–6)
Disease characteristics, *n*/*N* (%)				
Localized N0M0 disease	128/181 (71)	73/93 (78)	73/73 (100)	0/73 (0)
Nodal N1 disease	13/181 (7)	5/93 (5)	0/73 (0)	5/20 (25)
Metastatic M1+ disease	38/181 (21)	15/93 (16)	0/73 (0)	15/20 (75)
Prostate MRI performed, *n*/*N* (%)	175/181 (97)	93/93 (100)	73/73 (100)	20/20 (100)
MRI stage, *n*/*N* (%)				
Stage T1/2	144/175 (82)	80/93 (86)	61/73 (84)	20/20 (100)
Stage T3	27/175 (15)	10/93 (11)	10/73 (14)	0/20 (0)
Stage T4	4/175 (2)	2/93 (2)	2/73 (3)	0/20 (0)
Transperineal biopsy, *n*/*N* (%)	158/181 (87)	93/93 (100)	73/73 (100)	20/20 (100)
Median number of cores, *n* (IQR)	36 (28–47)	37 (29–49)	39 (29–59)	31 (26–42)
Positive biopsy, *n*/*N* (%)	126/158 (80)			
Median number of positive cores, *n* (IQR)	7 (4–12)	7 (3–11)	8 (4–12)	4 (2–7)
Median MCCL, mm (IQR)	8 (4–11)	8 (4–10)	8 (4–11)	6 (4–8)
Gleason score, *n*/*N* (%)				
Gleason 3 + 3	3/124 (2)	2/93 (2)	2/73 (3)	0/20 (0)
Gleason 3 + 4	18/124 (15)	15/93 (16)	12/73 (16)	3/20 (15)
Gleason 4 + 3	36/124 (29)	32/93 (34)	25/73 (34)	7/20 (35)
Gleason 4 + 4	27/124 (22)	20/93 (22)	17/73 (23)	3/20 (15)
Gleason 4 + 5	24/124 (19)	13/93 (14)	10/73 (14)	3/20 (15)
Not reported	16/124 (13)	11/93 (125)	7/73 (10)	4/20 (20)
Focal therapy, *n*/*N* (%)				
High-intensity focused ultrasound		64/93 (69)	51/73 (70)	12/20 (60)
Cryotherapy		29/93 (31)	21/73 (29)	8/20 (40)

IQR = interquartile range; MCCL = maximum cancer core length; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Table 2 – Magnetic resonance imaging performance in the diagnosis of radiorecurrent cancer.[a]

	Positivity threshold score	
	Likert 3–5	Likert 4–5
Sensitivity, % (95% CI)	94 (88–98)	81 (73–88)
Specificity, % (95% CI)	18 (7–35)	88 (73–98)
Positive predictive value, % (95% CI)	80 (73–87)	96 (90–99)
Negative predictive value, % (95% CI)	46 (19–75)	57 (42–70)
AUC (95% CI)	0.56 (0.49–0.63)	0.85 (0.78–0.91)

AUC = area under the receiver operating characteristic curve; CI = confidence interval.
[a] Further 2 $\times$ 2 cross tabulations can be found in the Supplementary material.

undergoing focal ablation (Fig. 2). There were no cancer-specific deaths.

For the patients undergoing focal ablation for localised disease, median follow-up was 26 mo (IQR 18-36). At 24 mo, PFS, MFS, and bDFS were 65% (95% CI 51–75%), 80% (95% CI 68–88%), and 68% (95% CI 55–78%), respectively (Supplementary material).

For the 20 patients undergoing focal ablation for nodal or metastatic disease, median follow-up was 27 mo (IQR 20–31) and PFS was 76% (95% CI 48–91%) at 24 mo (Supplementary material). Four patients (20%) had evidence of disease progression on follow-up whole-body imaging. Fifteen (75%) started on ADT by the end of the follow-up period, of whom three (15%) received docetaxel chemotherapy.

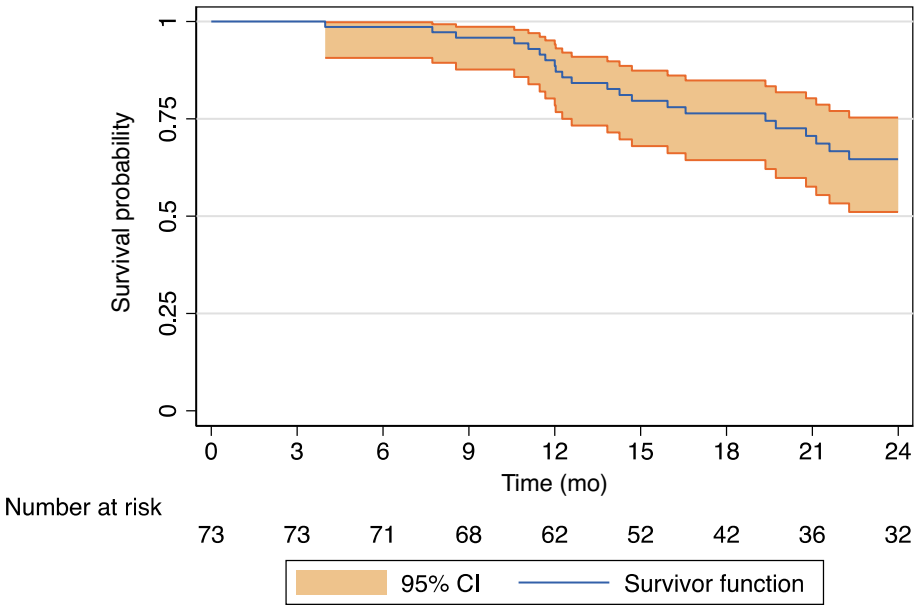

Fig. 2 – Progression-free survival after salvage focal ablation. Progression-free status was defined as no new metastases or hormone use (localised group only) or chemotherapy or further local treatment. CI = confidence interval.

One patient (5%) had repeat focal ablation for residual disease within the prostate. All 20 patients (100%) were alive at last follow-up.

Lower urinary tract symptoms measured using the IPSS questionnaire (higher score indicating worse symptoms) showed a median score at baseline of 7 (IQR 5–14; 10th worst score 19), increasing to 13 (IQR 8–19; 10th worst score 24) at 4 wk after ablation and then decreasing to 10 (IQR 5–13; 10th worst score 18) by 12 mo. At baseline, only 33/93 patients (35%) had erections sufficient for penetrative sexual activity (with or without oral phosphodiesterase type 5 inhibitors). Among the patients who had erections at baseline and for whom questionnaire data were available, the proportion with erectile dysfunction was 14/24 (58%), 11/21 (52%), 9/17 (53%), and 9/15 (60%) at 1, 6, 9, and 12 mo, respectively. The probability of having erections sufficient for penetrative sexual activity at 12 mo was 64% (95% CI 43–84%).

3.4. *Safety*

Adverse events were recorded for 22/93 patients (24%, 95% CI 16–34%) and CTCAE grade 3 adverse events for 5/93 patients (5%, 95% CI 2–12%) undergoing focal ablation (Supplementary material).

4. Discussion

Our results demonstrate that MRI and MRI-targeted biopsy are able to detect recurrent cancer within the prostate in patients with a clinical suspicion of failure after radiotherapy, with sensitivity of 81% and 92%, and specificity of 88% and 75%, respectively. The high PPV and lower NPV suggest that MRI is able to rule in rather than rule out disease in the postradiotherapy setting. Evaluation of patients in this manner is only desirable if the diagnostic information impacts on treatment. Thus, we have shown that for the patients who had focal ablation of recurrent cancer that was identified in the first part of the study (with or without synchronous metastases), there was 80% probability of preserving urinary continence and 60% probability of retaining erectile function. Early cancer control was also reassuring, with PFS of 66% for the overall focal ablation cohort, which included patients with metastatic disease. For those who were treated for localised recurrence alone, PFS was 65% and MFS was 80%. The diagnostic performance indicates that MRI followed by MRI-targeted biopsy can rule in recurrent prostate cancer, while focal ablation to those areas seems to represent a treatment option with a favourable therapeutic ratio.

Patients who have recurrence after radiotherapy currently have limited options. Most are placed on a strategy of watchful waiting, often with the addition of ADT. While ADT can control disease for a median of 2–3 yr, castrate resistance requiring second-line therapies occurs, with these agents providing a median of 3–6 mo of additional overall survival. Avoidance of this so-called lineage crisis, whereby systemic drug effects on cancer cells lead to clonal evolution of drug resistance, may be a key aim in this population [12]. Neither ADT nor other systemic agents are without significant side effects such as weight gain, obesity, osteopenia, fractures, diabetes, and ischaemic heart disease. Currently, if patients wish to avoid ADT, salvage prostatectomy can be used. This can lead to significant adverse events and side effects [13] such as urinary incontinence (≥1 pads in almost all patients and >1 pad in 20–78.1%), anastomotic strictures (0–41.8%), rectal injury (0–12.5%), and erectile dysfunction (29–100%) [14]. It is in this context that the FORECAST trial findings are particularly pertinent.

The strengths of our study are the use a paired cohort design, with blinding where appropriate, and application of the reference test in all eligible patients; this design

represents level 1 evidence for diagnostic test validation. Furthermore, we have coupled the validation of the diagnostic test to a novel treatment paradigm—focal ablation—that incorporates additional diagnostic information. Our prospective enrolment of patients with very few exclusion criteria makes the results generalisable. Finally, we conducted the first known analysis of focal ablation of prostatic recurrence despite the presence of nodal and/or metastatic cancer. These data can now be used to develop future research strategies for this group of patients. PFS appeared to be better in this group than for those with localised disease, but this was because ADT use was not counted as a failure event for those with metastatic disease. While further evaluation with larger numbers and longer follow-up is needed, this concept of cytoreduction of visible disease even when cancer is disseminated is increasingly being postulated as a means to improve cancer control in primary disease [15].

The study has some limitations. First, our staging work-up relied on ^{18}F-choline PET/CT and radioisotope bone scans, which were the accepted standard at the time of recruitment. Novel functional imaging such as ^{68}Ga PSMA PET/CT might have led to better outcomes in the nonmetastatic group as a result of the identification of occult metastases. Second, although all those scoring the MRI scans were experts and had previously recruited patients into the PROMIS trial, no formal adaptive training was given for the detection of radiorecurrent disease. Furthermore, at the time there was no mpMRI scoring system for recurrent disease such as Prostate Magnetic Resonance Imaging for Local Recurrence Reporting (PI-RR), and thus Likert scoring was utilised. MRI scanning parameters have also improved over time, and it is quite possible that the accuracy of mpMRI may be better than reported here with the use of more contemporary protocols, adaptive training, and PI-RR [16,17]. The use of cognitive targeting rather than fusion targeting may have also had an impact, in particular for smaller lesions. In addition, a more detailed conclusion on the exact biopsy protocol beyond the need for both systemic and targeted cores cannot be drawn from our current analysis. Third, not all patients completed their 12-mo outcome questionnaires and thus there may be some inaccuracy in the estimates. However, we did adjust for this by assessing the cumulative probability of return to continence. Fourth, we did not have a comparative arm to focal ablation and even for this high-risk group our evaluation of focal ablation was limited by the follow-up duration. One previous attempt at randomisation has been unsuccessful, although the use of focal ablation rather than whole-gland ablation as in the current setting may lead to higher rates of physician and patient equipoise to facilitate randomisation [18]. Finally, our analysis of diagnostic accuracy is based on sensitivity and specificity, which may be difficult to interpret in a clinical setting. An alternative methodology such as decision curve analysis may be more meaningful [19]. With respect to our data, the high prevalence of cancer in biopsies when patients develop biochemical recurrence after radiotherapy does preclude the use of MRI as a triage test. However, MRI does allow targeting of lesions that might otherwise be missed on systematic biopsy alone. Overall, four cancers (6%) were missed on systematic biopsies and six (8%) were missed on MRI-targeted biopsy. As recurrent disease is generally considered "high risk", the importance of not missing disease is to prevent potential overtreatment using systemic therapy such as hormones when local treatment may suffice.

5. Conclusions

In conclusion, MRI and targeted biopsy can detect prostate cancer recurring after radiotherapy. Patients should undergo prostate MRI with both systematic and targeted biopsies to optimise cancer detection. Focal ablation preserves urinary continence in the majority of patients, with good early cancer control. The FORECAST trial results highlight a pathway in which prostate mpMRI and targeted biopsies can be used to identify recurrent cancer before offering patients focal ablative treatment.

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Study concept and design: Ahmed, Arya, Kanthabalan, Emberton.
Acquisition of data: All authors.
Analysis and interpretation of data: Shah, Omar, Pavlou.
Drafting of the manuscript: Shah, Ahmed.
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Peer Review Summary

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