Platinum Priority – Prostate Cancer
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# The Role of Multiparametric MRI and MRI–targeted Biopsy in the Diagnosis of Radiorecurrent Prostate Cancer: An Analysis from the FORECAST Trial

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## Article info

## Abstract

*Background:* The role of multiparametric magnetic resonance imaging (MRI) for detecting recurrent prostate cancer after radiotherapy is unclear.

*Objective:* To evaluate MRI and MRI-targeted biopsies for detecting intraprostatic cancer recurrence and planning for salvage focal ablation.

*Design, setting, and participants:* FOcal RECurrent Assessment and Salvage Treatment (FORECAST; NCT01883128) was a prospective cohort diagnostic study that recruited

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181 patients with suspected radiorecurrence at six UK centres (2014 to 2018); 144 were included here.

*Intervention:* All patients underwent MRI with 5 mm transperineal template mapping biopsies; 84 had additional MRI-targeted biopsies. MRI scans with Likert scores of 3 to 5 were deemed suspicious.

*Outcome measurements and statistical analysis:* First, the diagnostic accuracy of MRI was calculated. Second, the pathological characteristics of MRI-detected and MRI-undetected tumours were compared using the Wilcoxon rank sum test and chi-square test for trend. Third, four biopsy strategies involving an MRI-targeted biopsy alone and with systematic biopsies of one to two other quadrants were studied. Fisher's exact test was used to compare MRI-targeted biopsy alone with the best other strategy for the number of patients with missed cancer and the number of patients with cancer harbouring additional tumours in unsampled quadrants. Analyses focused primarily on detecting cancer of any grade or length. Last, eligibility for focal therapy was evaluated for men with localised ($\leq$T3bN0M0) radiorecurrent disease.

*Results and limitations:* Of 144 patients, 111 (77%) had cancer detected on biopsy. MRI sensitivity and specificity at the patient level were 0.95 (95% confidence interval [CI] 0.92 to 0.99) and 0.21 (95% CI 0.07 to 0.35), respectively. At the prostate quadrant level, 258/576 (45%) quadrants had cancer detected on biopsy. Sensitivity and specificity were 0.66 (95% CI 0.59 to 0.73) and 0.54 (95% CI 0.46 to 0.62), respectively. At the quadrant level, compared with MRI-undetected tumours, MRI-detected tumours had longer maximum cancer core length (median difference 3 mm [7 vs 4 mm]; 95% CI 1 to 4 mm, $p < 0.001$) and a higher grade group ($p = 0.002$). Of the 84 men who also underwent an MRI-targeted biopsy, 73 (87%) had recurrent cancer diagnosed. Performing an MRI-targeted biopsy alone missed cancer in 5/73 patients (7%; 95% CI 3 to 15%); with additional systematic sampling of the other ipsilateral and contralateral posterior quadrants (strategy 4), 2/73 patients (3%; 95% CI 0 to 10%) would have had cancer missed (difference 4%; 95% CI –3 to 11%, $p = 0.4$). If an MRI-targeted biopsy alone was performed, 43/73 (59%; 95% CI 47 to 69%) patients with cancer would have harboured undetected additional tumours in unsampled quadrants. This reduced but only to 7/73 patients (10%; 95% CI 4 to 19%) with strategy 4 (difference 49%; 95% CI 36 to 62%, $p < 0.0001$). Of 73 patients, 43 (59%; 95% CI 47 to 69%) had localised radiorecurrent cancer suitable for a form of focal ablation.

*Conclusions:* For patients with recurrent prostate cancer after radiotherapy, MRI and MRI-targeted biopsy, with or without perilesional sampling, will diagnose cancer in the majority where present. MRI-undetected cancers, defined as Likert scores of 1 to 2, were found to be smaller and of lower grade. However, if salvage focal ablation is planned, an MRI-targeted biopsy alone is insufficient for prostate mapping; approximately three of five patients with recurrent cancer found on an MRI-targeted biopsy alone harboured further tumours in unsampled quadrants. Systematic sampling of the whole gland should be considered in addition to an MRI-targeted biopsy to capture both MRI-detected and MRI-undetected disease.

*Patient summary:* After radiotherapy, magnetic resonance imaging (MRI) is accurate for detecting recurrent prostate cancer, with missed cancer being smaller and of lower grade. Targeting a biopsy to suspicious areas on MRI results in a diagnosis of cancer in most patients. However, for every five men who have recurrent cancer, this targeted approach would miss cancers elsewhere in the prostate in three of these men. If further focal treatment of the prostate is planned, random biopsies covering the whole prostate in addition to targeted biopsies should be considered so that tumours are not missed.

## 1. Introduction

Radiotherapy is the most common prostate cancer treatment for localised disease; over 13 000 with localised disease undergo external beam radiotherapy in the UK annually with overall excellent long-term survival [1,2]. However, approximately 25% with localised disease will biochemically fail within 10 yr, and this subset of patients will have comparatively poorer outcomes [3]. Within 5 yr of biochemical failure, approximately 50% develop metastases and 20 to 30% die from their cancer [4,5]. Specifically, recurrence localised to the prostate affects 10% of radiotherapy patients and is independently predictive of further developing metastases, cancer-specific mortality, and all-cause mortality [6]. Currently, most radiorecurrence is managed with watchful waiting or noncurative androgen-deprivation therapy (ADT), a treatment with unpleasant adverse effects and potentially significant metabolic consequences. For biopsy-proven localised recurrences, European guidelines recommend that local salvage

treatment can be performed for select patients [7]. Some centres offer whole-gland salvage, for example, radical prostatectomy. Although effective, this carries considerable toxicity [8,9]. Salvage focal therapy targeting the recurrent lesion(s) alone as an alternative may offer good cancer control with reduced toxicity [10,11].

Patient selection for salvage focal therapy is particularly important; beyond detecting the overall presence of radiorecurrent cancer within the gland, recurrent tumours require accurate characterisation and mapping within the prostate. The utility of multiparametric magnetic resonance imaging (MRI) and MRI-targeted biopsies here is unclear. Furthermore, after radiotherapy, MRI interpretation is challenging given factors such as glandular atrophy, reactive inflammation, reduced zonal differentiation, diffuse hypointense T2 signal, and artefact from brachytherapy seeds if present [12–14]. In addition, unlike in the primary diagnostic setting, there currently exists no robustly validated recommendations for the conduct or reporting of MRI after radiotherapy. An evaluation of the diagnostic performance of MRI with MRI-targeted biopsies is therefore needed, alongside investigating the added value of systematic biopsies, and describing the characteristics of tumours overlooked by MRI. These aims were addressed in a secondary analysis of the FOcal RECurrent Assessment and Salvage Treatment (FORECAST) trial [11].

## 2. Patients and methods

### 2.1. Study population

FORECAST was a prospective paired-cohort diagnostic study coupled with an evaluation of adverse events, side effects, and early cancer control following salvage focal ablation (NCT01883128) [11,15]. From 2014 to 2018, 181 patients from six UK centres were enrolled. The inclusion criteria were biochemical failure defined by rising prostate-specific antigen (PSA) levels after external beam radiotherapy or brachytherapy with or without (neo)adjuvant ADT. Biochemical failure was defined by the referring clinician; whilst some oncologists use the Phoenix criteria for this, the study protocol did not insist on a specific threshold [15,16]. Those taking ADT within 6 mo of enrolment, with a PSA doubling time of ≤3 mo, a total PSA value of ≥20 ng/ml, unable to undergo MRI, or who had undergone salvage treatment were excluded. For this analysis, patients were required to have MRI and biopsy data available at the prostate quadrant level.

Gleason grade and PSA before radiotherapy were not exclusion criteria. In FORECAST, patients also underwent MRI with biopsy regardless of N and M staging. Consistent with this, nodal and/or metastatic spread was not an exclusion criterion here. However, a subgroup analysis was performed by repeating analyses in patients with prostate-confined radiorecurrence (N0M0).

### 2.2. Trial procedures

Following ^{18}F-choline positron emission tomography/computed tomography (PET/CT) and ^{99m}Tc methylene diphosphonate bone scan, patients underwent prostate MRI. All MRI scans were performed using a 1.5 or 3.0 Tesla scanner and a pelvic phased array coil with no endorectal coil. The likelihood of intraprostatic radiorecurrent cancer was reported with a five-point Likert score by one of seven blinded radiologists with at least 5 yr of experience in reporting prostate MRI. The Likert system was used as the Prostate Imaging Reporting and Data System score, which is not validated for this setting, and the Prostate Magnetic Resonance Imaging for Local Recurrence Reporting (PI-RR) score was published only recently [14]. Participants then underwent a cognitive MRI-targeted biopsy for lesions with a Likert score of ≥3, with a recommendation to take four to six cores per target. This was followed in the same session by a transperineal template prostate mapping (TTPM) biopsy, where a biopsy was taken every 5 mm using a brachytherapy grid, in addition to further biopsies to sample the full craniocaudal length. The Supplementary material describes further details on trial procedures.

### 2.3. Outcomes

First, the diagnostic accuracy of MRI for radiorecurrence at the patient and prostate quadrant levels was calculated. Second, the pathological characteristics of MRI-detected versus MRI-undetected tumours were compared. At the patient level, PSA, T stage, and NM stage were also compared. Third, an MRI-targeted biopsy alone was compared with three other biopsy strategies involving an MRI-targeted biopsy with additional systematic biopsies of adjacent quadrants. This aimed to investigate the added diagnostic value of perilesional sampling, as has been shown to be important in the primary diagnostic setting, and whether this could be performed in lieu of whole-gland sampling [17]. Figure 1 illustrates how biopsies were performed in FORECAST and the specific strategies tested here. At the patient level, for each strategy, the number of patients with cancers missed was determined, in addition to the number of these patients with cancer that harboured additional tumours in unsampled quadrants. The reference standard for these calculations was whole-gland TTPM and MRI-targeted biopsies. As a secondary outcome, the suitability of patients for focal ablative techniques was evaluated based on their biopsy and staging data.

As the precise role of Gleason grading in radiorecurrence has not been established, analyses primarily focused on the detection of cancer of any grade or length. However, the following protocol-described definitions were also used, which are considered definitions of clinically significant disease requiring treatment in the primary setting: (1) grade group ≥3 and/or maximum cancer core length (MCCL) ≥6 mm of any grade (PROMIS definition 1) and (2) grade group ≥2 and/or MCCL ≥4 mm of any grade (PROMIS definition 2) [15,18].

### 2.4. Statistical analysis

The prostate was divided into quadrants (left/right; anterior/posterior), with a line crossing anterior to the urethral margin marking the anterior/posterior boundary (Fig. 1). Further information on the rules used to allocate biopsy cores to quadrants is detailed in the Supplementary material.

Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for MRI lesion visibility against the reference standard of 5 mm TTPM with MRI-targeted biopsies. At the quadrant level, 95% confidence intervals (95% CIs) were derived using cluster bootstrapping with 10 000 resamples. With each patient representing a cluster, this technique was performed to handle correlated quadrant-level data from individual patients. Analyses were performed primarily using MRI visibility thresholds of Likert ≥3 and then adjusted to ≥4. The proportion of patients who had cancer detected and missed at each Likert threshold was also determined.

The characteristics of MRI-detected and MRI-undetected tumours were compared using the Wilcoxon rank sum test for continuous variables (PSA, total biopsy cores, positive biopsy cores, and MCCL). For ordinal variables (grade group, T stage, and NM stage), the chi-square test for trend was used to assess whether these had a linear relationship with MRI visibility.
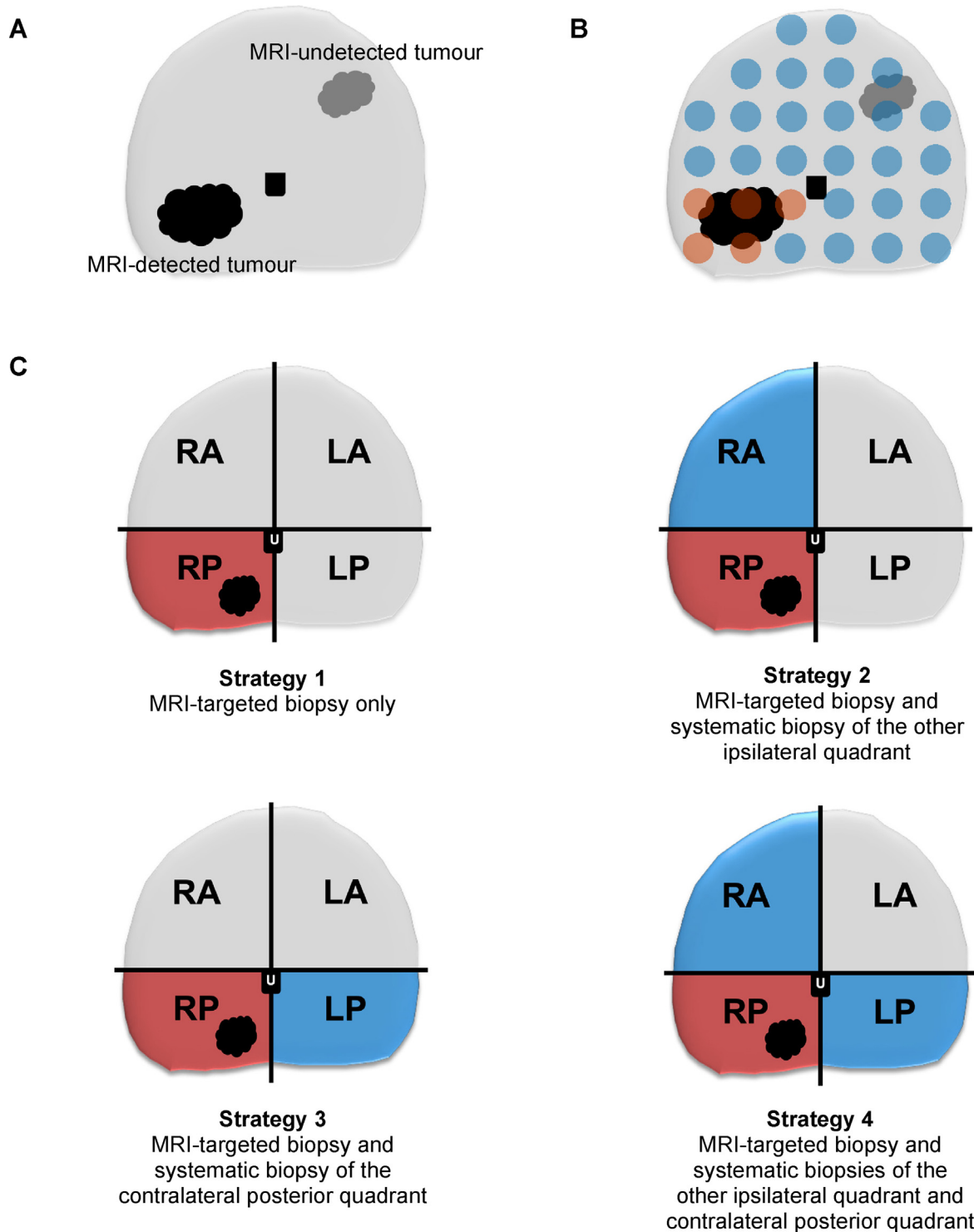
Fig. 1 – (A) Schematic illustrating a patient with two tumours, one of which was detected on MRI and one was not detected. (B) Schematic illustrating how this prostate would have been biopsied in FORECAST. Blue cores represent TTPM biopsy cores, and red cores represent sampling by both MRI-targeted and TTPM biopsy. MRI-targeted biopsy would have identified the MRI-detected tumour but would not have identified the MRI-undetected tumour. (C) Schematic of the biopsy strategies tested and quadrant anatomical position relative to the urethra, using an example of a patient with an mpMRI target in the right posterior quadrant. Red shading indicates an area undergoing MRI-targeted biopsy. Blue shading indicates an area undergoing systematic biopsy. Grey shading indicates an area not biopsied. FORECAST = FOcal RECurrent Assessment and Salvage Treatment; LA = left anterior; LP = left posterior; MRI = magnetic resonance imaging; RA = right anterior; RP = right posterior; U = urethra; TTPM = transperineal template prostate mapping.

For a biopsy strategy analysis, only patients with both MRI-targeted and TTPM biopsies were included. If patients had an MRI target in several quadrants, the strategy's rules were applied to each quadrant. For example, consider a patient with targets in the right posterior and left posterior quadrants; in strategy 2, the patient would undergo MRI-targeted biopsies of both posterior quadrants with systematic biopsies of both anterior quadrants. The proportions of missed cancer and proportions of cancers in unsampled quadrants were determined with

95% CIs calculated using the modified Wald method [19]. For each of these metrics, Fisher's exact test was used to make a pairwise comparison between an MRI-targeted biopsy alone (strategy 1) and the best performing strategy among strategies 2–4.

Suitability for focal ablation was assessed for men with localised disease (≤T3bN0M0) for the following focal techniques: quadrant, bilateral quadrant, left or right hemigland, posterior hemigland, and hockey stick. Bilateral quadrant ablation was indicated for cancer in two nonadjacent quadrants. Hockey stick ablation was indicated for cancer in three quadrants. If cancer was present in all quadrants, whole-gland ablation was recommended. Eligibility was made purely based on pathological and staging criteria; other clinical criteria, for example, patient fitness, were not considered. However, being unfit for general anaesthesia was an exclusion criterion during FORECAST recruitment; 95% CIs was calculated using the modified Wald method [19].

All analyses were performed using R v.4.2.2. Statistical significance was set at $p < 0.05$.

## 3. Results

### 3.1. Patient characteristics

Figure 2 details the flow chart for patient eligibility, with patient characteristics shown in Table 1. Of 144 eligible patients, 84 (58%) underwent MRI-targeted biopsy in addition to 5 mm TTPM biopsy. The median PSA nadir was 0.30 ng/ml (interquartile range [IQR] 0.10 to 0.52), and the median PSA at trial enrolment was 3.80 ng/ml (IQR 2.40 to 6.17); the median increase of PSA from nadir was 3.50 ng/ml (IQR 2.10 to 6.00). Of the 109 men for whom it was possible to calculate the PSA increase from nadir, 86 (79%) met the Phoenix criteria [16]. In all, 130 patients (90%) previously underwent external beam radiotherapy and 15 (10%) brachytherapy. Of 136 patients with available data, 79 patients (58%) received neoadjuvant ADT and 31/136 (23%) received adjuvant ADT. The median age at enrolment was 71 yr (IQR 67 to 76), and there was a median of 7 yr (IQR 5 to 10) between the points of original diagnosis and enrolment in FORECAST.

### 3.2. MRI diagnostic accuracy

Following 5 mm TTPM with or without MRI-targeted biopsies, 111/144 (77%) patients had cancer diagnosed. Of 144 patients, 93 (65%) and 108 (75%) had definition 1 and 2 cancers diagnosed, respectively. At the patient level, using the Likert ≥3 threshold, five of all 111 (5%) cases of cancer were undetected by MRI, with 2/93 (2%) definition 1 and 5/108 (5%) definition 2 cancers being undetected. Supplementary Table 1 details the diagnostic accuracy of MRI for each cancer definition at the patient and quadrant levels, and Table 2 details the number of cancers detected and missed by a biopsy at different Likert thresholds. At the patient level, using the Likert ≥3 threshold, sensitivity was very high across all cancer definitions (0.95 to 0.98). However, specificity was very poor (0.19 to 0.21). Across the whole cohort, among 144 patients, 91 to 106 (63 to 74%) had cancer detected and two to five (1 to 3%) had cancer missed at the Likert ≥3 threshold following TTPM with or without MRI-targeted biopsies.
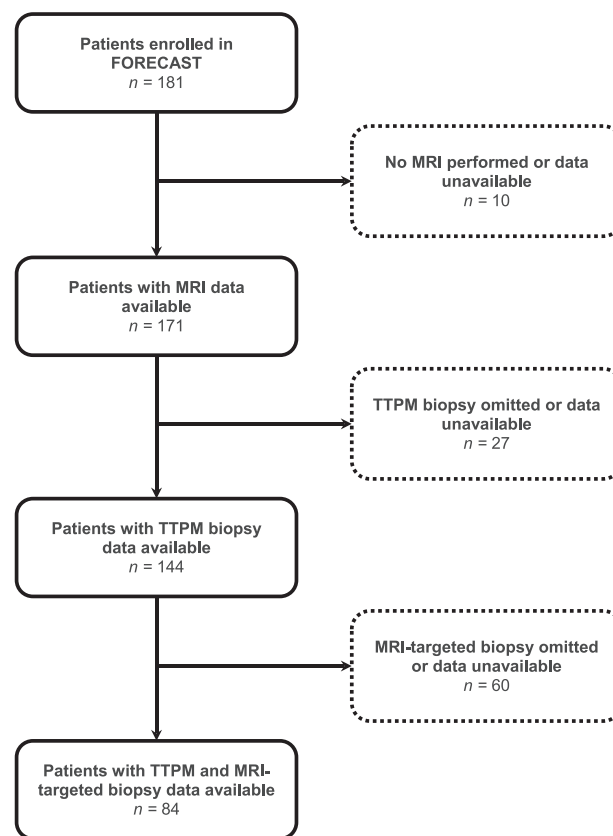


Fig. 2 – Flow chart detailing the exclusion and inclusion processes of patients in this analysis. FORECAST = FOcal RECurrent Assessment and Salvage Treatment; MRI = magnetic resonance imaging; TTPM = transperineal template prostate mapping.

At the quadrant level, of 576 quadrants, 258 (45%) had any cancer, 195 (34%) had definition 1 cancer, and 235 (41%) had definition 2 cancer. Using the Likert ≥3 threshold, 87 of all 258 (34%) cases of cancer were overlooked by MRI, compared with 61/195 (31%) definition 1 cancers, and 79/235 (34%) definition 2 cancers. Sensitivity was 0.66 to 0.69, with specificity 0.52 to 0.54. Across the whole cohort, among 576 quadrants, 134 to 171 quadrants (23 to 30%) had cancer diagnosed and 61 to 87 (11 to 15%) had cancer missed at the Likert ≥3 threshold following TTPM with or without MRI-targeted biopsies.

With the Likert ≥4 threshold, at the patient level, 19 of all 111 (17%) cases of cancer were undetected by MRI, with 14/93 (15%) and 19/108 (18%) definition 1 and 2 cancers undetected, respectively. Sensitivity was 0.82 to 0.85 and specificity improved to 0.63 to 0.82. Across the whole cohort, among 144 patients, 79 to 92 (55 to 64%) had cancer detected and 14 to 19 patients (10 to 13%) had cancer missed at the Likert ≥4 threshold following TTPM with or without MRI-targeted biopsies. With the Likert ≥4 threshold, at the quadrant level, 145 of all 258 (56%) cases of cancer were overlooked by MRI, compared with 102/195 (52%) definition 1 cancers and 131/235 (56%) definition 2 cancers. Sensitivity was poorer (0.44 to 0.48) but specificity very high (0.89 to 0.94). Across the whole cohort, among 576 quadrants, 93 to 113 (16 to 20%) had cancer diagnosed

**Table 1 – Patient and tumour characteristics of the 144 included men, both at initial diagnosis and during the FORECAST study**

| Characteristic | n = 144[a] |
|---|---|
| *At original diagnosis* | |
| Age (yr) | 63 (59 to 68) |
| Unknown | 3 |
| PSA (ng/ml) | 12.0 (7.8 to 23.2) |
| Unknown | 12 |
| Gleason score, n (%) | |
| ≤6 | 37 (27) |
| 7 | 70 (51) |
| ≥8 | 31 (22) |
| Unknown | 6 |
| T stage, n (%) | |
| T1 | 13 (11) |
| T2 | 41 (34) |
| T3 | 65 (55) |
| Unknown | 25 |
| *At enrolment in FORECAST* | |
| Prior EBRT, n (%) | 130 (90) |
| Prior brachytherapy, n (%) | 15 (10) |
| Low-dose rate | 10 (67) |
| High-dose rate | 3 (20) |
| Unknown | 2 |
| Hormone use, n (%) | |
| None | 26 (19) |
| Neoadjuvant | 79 (58) |
| Adjuvant | 31 (23) |
| Unknown | 8 |
| Age (yr) | 71 (67 to 76) |
| Unknown | 4 |
| Years from original diagnosis | 7 (5 to 10) |
| Unknown | 2 |
| PSA nadir (ng/ml) | 0.30 (0.10 to 0.52) |
| Unknown | 32 |
| PSA at enrolment (ng/ml) | 3.80 (2.40 to 6.17) |
| Unknown | 7 |
| PSA increase from nadir (ng/ml) | 3.50 (2.10 to 6.00) |
| Unknown | 35 |
| T stage, n (%) | |
| T1/2 | 117 (81) |
| T3a | 17 (12) |
| T3b | 7 (4.9) |
| T4 | 3 (2.1) |
| NM stage, n (%) | |
| N0M0 | 108 (75) |
| N1M0 | 10 (6.9) |
| M1 | 26 (18) |
| MRI Likert score, n (%) | |
| 1 | 0 (0) |
| 2 | 12 (8.3) |
| 3 | 34 (24) |
| 4 | 25 (17) |
| 5 | 73 (51) |

EBRT = external beam radiotherapy; FORECAST = FOcal RECurrent Assessment and Salvage Treatment; IQR = interquartile range; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.
[a] Median (IQR); n (%).

and 102 to 145 (18 to 25%) had cancer missed at the Likert ≥4 threshold following TTPM with or without MRI-targeted biopsies.

### 3.3. MRI-detected versus MRI-undetected cancers

At the patient level (n = 144), with the Likert ≥3 threshold, no statistically significant difference was observed between patients with MRI-undetected and MRI-detected tumours with respect to PSA, T stage, or NM stage at trial enrolment (Supplementary Table 2).

Table 3 details the comparison of MRI-detected versus MRI-undetected tumours at the quadrant level, using the

Likert ≥3 threshold (n = 576). MRI-detected tumours had significantly longer MCCL (median difference 3 mm [7 vs 4 mm]; 95% CI 1 to 4 mm, p < 0.001). In addition, with higher-grade group, a significantly greater proportion of tumours were detected by MRI (chi-square test for trend p = 0.002). Specifically, MRI-detected disease comprised 3/7 (43%) grade group 1 tumours, 24/43 (56%) grade group 2 tumours, 50/80 (63%) grade group 3 tumours, 27/39 (69%) grade group 4 tumours, and 40/49 (82%) grade group 5 tumours. This trend was also observed at the whole-gland level (Supplementary Table 2).

### 3.4. Biopsy strategies

Of the 84 patients with matched TTPM and MRI-targeted biopsies included for a biopsy analysis, 33 (39%) had one targeted quadrant at the Likert ≥3 threshold, 34 (40%) had two targeted quadrants, 14 (17%) had three targeted quadrants, and three (4%) had four targeted quadrants.

Of 84 patients, any cancer was diagnosed in 73 (87%), whilst 67 (80%) and 73 (87%) had definition 1 and 2 cancers, respectively. Supplementary Table 3 details the performance of MRI-targeted biopsies only (strategy 1) stratified by the Likert score threshold, and Table 4 details the number of missed cancers per biopsy strategy at the patient level.

For cancer of any grade or length, with MRI-targeted biopsies only, 5/73 patients (7%; 95% CI 3 to 15%) would have had their cancer missed. For definition 1 and 2 cancers, respectively, 7/67 (10%; 95% CI 5 to 20%) and 8/73 patients (11%; 95% CI 5 to 20%) would have had cancer missed. Across cancer definitions, with other biopsy strategies, the number of patients with missed cancer ranged from 3 to 8% for strategies that systematically sampled one additional quadrant per target (strategies 2 to 3) to 1 to 3% for strategy 4, which systematically sampled two additional quadrants per target. In a pairwise comparison between MRI-targeted biopsy only and the best performing strategy, strategy 4, there was no statistically significant differences in the proportion of patients with missed cancer, for each cancer definition.

For the 73 patients with biopsy-confirmed cancer, for each biopsy strategy, the number of patients harbouring additional tumours in nonbiopsied quadrants was next calculated (Table 4). Across definitions, MRI-targeted biopsy only resulted in the highest proportion of patients with cancer in unsampled quadrants, affecting 59% of patients (95% CI 47 to 69%) for cancer of any grade or length, 45% (95% CI 33 to 57%) for definition 1 cancer, and 49% (95% CI 38 to 61%) for definition 2 cancer. Sampling one additional quadrant lowered this to 24 to 38% (strategies 2 to 3), and sampling two additional quadrants lowered this to 7 to 10% (strategy 4). In a pairwise comparison of MRI-targeted biopsy only with strategy 4, the best alternative strategy, there were statistically significant reductions in the proportion of patients with additional cancers for each cancer definition. For cancer of any grade or length, this difference was 49% (59% vs 10%; 95% CI 36 to 62%, p < 0.0001); for definition 1 cancer, the difference was 37% (45% vs 7%; 95% CI

**Table 2 – The number of patients and quadrants who had cancer detected on TTPM with or without MRI-targeted biopsy at different MRI Likert score thresholds**

| Likert threshold | No. biopsied (%) | Any cancer | | PROMIS definition 1 Grade group ≥3 and/or MCCL ≥6 mm of any grade | | PROMIS definition 2 Grade group ≥2 and/or MCCL ≥4 mm of any grade | |
|---|---|---|---|---|---|---|---|
| | | No. detected (%) | No. missed (%) | No. detected (%) | No. missed (%) | No. detected (%) | No. missed (%) |
| *Whole gland* | | | | | | | |
| All patients | 144 (100) | 111 (77) | 0 (0) | 93 (65) | 0 (0) | 108 (75) | 0 (0) |
| Likert ≥2 | 144 (100) | 111 (77) | 0 (0) | 93 (65) | 0 (0) | 108 (75) | 0 (0) |
| Likert ≥3 | 132 (92) | 106 (74) | 5 (3) | 91 (63) | 2 (1) | 103 (72) | 5 (3) |
| Likert ≥4 | 98 (68) | 92 (64) | 19 (13) | 79 (55) | 14 (10) | 89 (62) | 19 (13) |
| Likert 5 | 73 (51) | 72 (50) | 39 (27) | 64 (44) | 29 (20) | 71 (49) | 37 (26) |
| *Quadrant* | | | | | | | |
| All quadrants | 576 (100) | 258 (45) | 0 (0) | 195 (34) | 0 (0) | 235 (41) | 0 (0) |
| Likert ≥2 | 566 (98) | 255 (44) | 3 (1) | 192 (33) | 3 (1) | 232 (40) | 3 (1) |
| Likert ≥3 | 317 (55) | 171 (30) | 87 (15) | 134 (23) | 61 (11) | 156 (27) | 79 (14) |
| Likert ≥4 | 134 (23) | 113 (20) | 145 (25) | 93 (16) | 102 (18) | 104 (18) | 131 (23) |
| Likert 5 | 91 (16) | 84 (15) | 174 (30) | 72 (13) | 123 (21) | 79 (14) | 156 (27) |

MCCL = maximum cancer core length; MRI = magnetic resonance imaging; TTPM = transperineal template prostate mapping.
For percentage calculations, the denominator was the total number of patients or quadrants included (*n* = 144 and *n* = 576, respectively).

**Table 3 – Comparison of pathological characteristics between prostate quadrants with MRI-undetected and MRI-detected cancer, according to the Likert ≥3 visibility threshold**

| Characteristic | MRI undetected (*n* = 87) [a] | MRI detected (*n* = 171) [a] | Difference (95% CI) | *p* value [b] |
|---|---|---|---|---|
| Total biopsy cores | 10 (8 to 16) | 12 (9 to 15) | 2 (–2 to 3) | 0.2 |
| Positive biopsy cores | 3 (1 to 6) | 4 (2 to 7) | 1 (0 to 1) | 0.004 |
| Grade group, *n* (%) | | | | 0.002 |
| 1 | 4 (5) | 3 (2) | | |
| 2 | 19 (22) | 24 (14) | | |
| 3 | 30 (35) | 50 (29) | | |
| 4 | 12 (14) | 27 (16) | | |
| 5 | 9 (10) | 40 (24) | | |
| Undeterminable/irradiation effect | 13 (15) | 27 (16) | | |
| MCCL (mm) | 4 (2 to 8) | 7 (4 to 10) | 3 (1 to 4) | <0.001 |
| Undeterminable | 2 | 15 | | |

CI = confidence interval; IQR = interquartile range; MCCL = maximum cancer core length; MRI = magnetic resonance imaging.
This analysis pertains to all 144 men included, equating to 576 prostate quadrants.
[a] Median (IQR); *n* (%).
[b] Wilcoxon rank sum test (total biopsy cores, positive biopsy cores, and MCCL); chi-square test for trend (grade group).

24 to 51%, *p* < 0.0001); and for definition 2 cancer, the difference was 40% (49% vs 10%; 95% CI 26 to 53%, *p* < 0.0001).

### 3.5. Eligibility for salvage focal ablation

Of 73 patients, 43 (59%; 95% CI 47 to 69%) had biopsy-confirmed localised (≤T3bN0M0) radiorecurrent cancer and were suitable for a form of focal ablation. This included eight (11%) for quadrant ablation, one (1%) for bilateral quadrant ablation, 11 (15%) for left or right hemigland ablation, eight (11%) for posterior hemigland ablation, and 15 (21%) for a hockey stick ablation. Ten (14%) patients would have required whole-gland ablation.

### 3.6. N0M0 subgroup analysis

Analyses were repeated for the 108 men with localised N0M0 radiorecurrent disease, of whom 64 underwent an MRI-targeted biopsy (Supplementary Fig. 1 and Supplementary Table 4). Findings were consistent with our main analysis. At the Likert ≥3 threshold, sensitivity and specificity at the patient level were 0.95 to 0.99 and 0.17 to 0.19, respectively (Supplementary Table 5). Across the subgroup, 66 to 77% patients had cancer detected, and 1 to 4% had cancer missed at the Likert ≥3 threshold following TTPM with or without MRI-targeted biopsies (Supplementary Table 6).

At the quadrant level, sensitivity and specificity were 0.68 to 0.71 and 0.56 to 0.60, respectively (Supplementary Table 5). Of the quadrants, 25 to 32% had cancer detected, and 10 to 15% had cancer missed at the Likert ≥3 threshold following TTPM with or without MRI-targeted biopsies (Supplementary Table 6).

At the quadrant level, with increasing grade group, tumours were more likely to be MRI visible (chi-square test for trend *p* = 0.006). MRI-visible tumours also had longer MCCL (median difference 3 mm [7 vs 4 mm]; 95% CI 0 to 4 mm, *p* < 0.001; Supplementary Tables 7 and 8).

Overall, with MRI-targeted biopsy only (strategy 1), 2/56 (4%; 95% CI 0 to 13%) patients had cancer of any grade or length missed, 4/51 (8%; 95% CI 3 to 19%) had definition 1 cancer missed, and 5/56 (9%; 95% CI 3 to 20%) had definition 2 cancer missed (Supplementary Tables 9 and 10). In men with biopsy-confirmed cancer, performing an MRI-targeted biopsy would have missed cancer in other quadrants in 49 to 59%, reducing to 27 to 39% with systematic sampling of one additional quadrant (strategies 2 to 3) and 10 to 13% with systematic sampling of two additional quadrants (strategy 4; Supplementary Table 10). On comparison of strategy 4 with strategy 1, this was a significant reduction for each cancer definition (*p* < 0.0001 for each definition).

Table 4 – Comparison of biopsy strategies, calculating the number of patients with cancer missed by the strategy and the number of patients with cancer who also harboured tumours in quadrants not sampled by that particular biopsy strategy

| Cancer definition | Strategy 1 | Strategy 2 | Strategy 3 | Strategy 4 | Difference between strategy 1 and best other strategy | p value[a] |
|---|---|---|---|---|---|---|
| Any cancer (n = 73) | | | | | | |
| Patients with cancer missed | 5; 7% (3 to 15%) | 4; 5% (2 to 14%) | 2; 3% (0 to 10%) | 2; 3% (0 to 10%) | 4% (–3 to 11%)[b] | 0.4[b] |
| Patients with cancer harbouring additional tumours in unsampled quadrants | 43; 59% (47 to 69%) | 28; 38% (28 to 50%) | 20; 27% (18 to 39%) | 7; 10% (4 to 19%) | 49% (36 to 62%)[c] | <0.0001[c] |
| PROMIS definition 1Grade group ≥3 and/or MCCL ≥6 mm cancer of any grade (n = 67) | | | | | | |
| Patients with cancer missed | 7; 10% (5 to 20%) | 5; 7% (3 to 17%) | 3; 4% (1 to 13%) | 1; 1% (0 to 9%) | 9% (1 to 17%)[c] | 0.061[c] |
| Patients with cancer harbouring additional tumours in unsampled quadrants | 30; 45% (33 to 57%) | 17; 25% (16 to 37%) | 16; 24% (15 to 35%) | 5; 7% (3 to 17%) | 37% (24 to 51%)[c] | <0.0001[c] |
| PROMIS definition 2Grade group ≥2 and/or MCCL ≥4 mm cancer of any grade (n = 73) | | | | | | |
| Patients with cancer missed | 8; 11% (5 to 20%) | 6; 8% (4 to 17%) | 2; 3% (0 to 10%) | 2; 3% (0 to 10%) | 8% (0 to 16%)[b] | 0.1[b] |
| Patients with cancer harbouring additional tumours in unsampled quadrants | 36; 49% (38 to 61%) | 24; 33% (23 to 44%) | 18; 25% (16 to 36%) | 7; 10% (4 to 19%) | 40% (20 to 53%)[c] | <0.0001[c] |

LA = left anterior; LP = left posterior; MCCL = maximum cancer core length; mpMRI = multiparametric magnetic resonance imaging; RA = right anterior; RP = right posterior; TTPM = transperineal template prostate mapping.
The denominator for these calculations is the number of cancers present (any cancer: n = 73; PROMIS definition 1: n = 67; PROMIS definition 2: n = 73). The reference in these calculations is whole-gland TTPM and MRI-targeted biopsies. The values in parentheses represent 95% CIs. This analysis pertains only to the 84 patients who underwent mpMRI-targeted biopsy in addition to TTPM biopsy. A schematic of each biopsy strategy is detailed in the table, using an example of a patient with an mpMRI target in the right posterior quadrant.
[a] Fisher's exact test for a pairwise comparison of proportions between mpMRI-targeted biopsy alone (strategy 1) and the best performing strategy of strategies 2 to 4.
[b] Pairwise comparison of strategy 1 with strategies 3 to 4.
[c] Pairwise comparison of strategy 1 with strategy 4.

# 4. Discussion

## 4.1. Summary

Whilst multiparametric MRI has excellent sensitivity for the diagnosis of radiorecurrence at the patient level, sensitivity is modest at the quadrant level, and 31 to 34% of tumours were undetected by MRI. This suggests that although MRI is likely to detect the overall presence of radiorecurrent cancer, it may not accurately localise all lesions in the gland or the extent of these lesions. MRI-undetected tumours, however, were comparatively smaller and of lower grade.

Given the modest sensitivity of MRI at the quadrant level, whether an MRI-targeted biopsy was sufficient to detect radiorecurrence without additional systematic biopsies was next tested. At the patient level, if only MRI-targeted biopsies were performed, this would have missed disease in 7 to 11% of patients with radiorecurrent cancer. Additional sampling of the other ipsilateral quadrant and contralateral posterior quadrant (strategy 4) reduced this to 1 to 3%. An MRI-targeted biopsy therefore detected the overall presence of radiorecurrent cancer in the majority and is possibly improved further with perilesional sampling.

MRI-targeted biopsies alone, however, were not sufficient for localising all cancerous lesions within the gland. Of patients with radiorecurrent cancer, as many as 45 to 59% would have harboured cancer in unsampled quadrants if only an MRI-targeted biopsy was performed. With strategy 4, this proportion reduced, but only to 7 to 10%, which may still represent an unacceptable miss rate in the context of the aggressive cancer phenotypes observed in radiorecurrent disease [4,5]. Given this, systematic sampling of all quadrants in addition to an MRI-targeted biopsy is recommended to capture MRI-undetected disease for accurate prostate mapping. This would be important for planning salvage focal ablation such that any MRI-undetected cancers are not missed inappropriately during treatment.

## 4.2. Implications for practice

With the emerging use of salvage focal treatments, it is vital not only to exclude metastases, but also to identify, map, and characterise any intraprostatic disease [20]. Relevant studies are scarce and heterogeneous in design and quality. Our findings, however, agree with other groups that MRI has good sensitivity for detecting radiorecurrence at the patient level, but poorer sensitivity at the level of prostate subdivisions [21–26]. At the patient level, if the primary aim is to detect the overall presence of recurrent cancer, then our work demonstrates that MRI-targeted biopsies with perilesional sampling will identify the majority of patients with recurrence, in keeping with data from the primary diagnostic setting [17,27,28]. MRI-undetected disease here was smaller and of lower grade, also consistent with the findings from primary diagnostic MRI [29,30]. However, although

low-volume, clinically insignificant disease detected on systematic biopsies can often be left untreated in the primary setting, whether the same can be done with equivalent tumours in the radiorecurrence setting is presently unknown. If focal ablation is to be planned, performing MRI-targeted biopsies alone will potentially miss cancer elsewhere in the prostate in three of five patients. This finding aligns with those of a recent study of salvage radical prostatectomy whole-mount histology, where 22/41 (54%) prostates were found to have at least two cancer foci [31]. Thus, the addition of systematic sampling of the whole prostate seems necessary so that any and all MRI-undetected lesions are captured and can be considered for subsequent ablation.

Our group has previously proposed that eligible cancers should be unifocal or unilateral, or bilateral/bifocal with at least one neurovascular bundle spared, or bilateral/multifocal with one dominant index lesion, and secondary lesions having no more than 3 mm of grade group 1 disease [20]. Beyond detecting the presence versus absence of radiorecurrent cancer, accurate prostate mapping is therefore crucial to distinguish treatment candidates versus those who should receive whole-gland or other management strategies. Toxicity is also higher following whole-gland versus focal treatments, whether extirpative or ablative [32,33]. Salvage radical prostatectomy can be particularly morbid, associated with erectile dysfunction in nearly 100%, urinary incontinence in nearly 80%, and rectal injury in nearly 10% [8,9].

Irrespective of toxicity, however, the most important reason underpinning a well-planned focal ablation is the oncological outcome. It is established that patients with biochemical failure after radiotherapy have poor outcomes [6,34,35]. The 5-yr incidence of distant metastases and that of cancer-specific death after biochemical failure are approximately 50% and 20 to 30%, respectively [4,5]. Furthermore, localised failures are independently associated with a higher risk of metastases and mortality [6]. It follows that accurate identification and targeted treatment of lesions could confer an oncological benefit versus surveillance or hormone therapy. One systematic review found a 48 to 72% 3-yr disease-free survival rate after salvage focal therapy, whilst FORECAST demonstrated a 66% 2-yr progression-free survival rate [11,36]. Furthermore, prospective UK registry data after salvage focal high-intensity focused ultrasound and cryotherapy has shown a 6-yr failure-free survival rate of 75% and overall survival rate of 88% [37]. Longer-term, comparative randomised data versus other salvage treatments are certainly needed, but current evidence, though of modest quality, supports good early-medium cancer control for salvage focal ablation. Robust prostate mapping and identification of all lesions via MRI-targeted and whole-gland systematic biopsies are therefore crucial for planning any successful focal ablation, or referring patients for whole-gland treatments if found to be ineligible.

### 4.3. Limitations

The FORECAST trial was a prospective, multicentre, paired-cohort study representing level 1 evidence for diagnostic test validation. This analysis, however, is subject to several limitations. One encompasses quadrant-level analyses, where data points are inherently nonindependent. However, we mitigated against this using cluster bootstrapping at the individual patient level.

Second, 84 patients underwent an MRI-targeted biopsy despite more men having Likert scores of 3 to 5. The reasons for omission of a targeted biopsy were not collected. However, as a TTPM biopsy was performed in the same session, it is likely that an additional targeted biopsy was omitted if a target lesion had already been sampled systematically. The 84 men who underwent an MRI-targeted biopsy had a significantly higher increase in PSA from nadir than those who did not (median difference 1.6 ng/ml [4.4 vs 2.8 ng/ml], $p = 0.043$). Higher Likert scores ($p < 0.001$) and higher T stages were also observed in this group ($p = 0.046$; Supplementary Table 11). No statistically significant difference was observed for other variables such as PSA at trial enrolment and NM stage.

Next, with a median of 7 yr between diagnosis and trial enrolment, our cohort is less representative of modern radiotherapy cohorts. At the initial diagnosis, participants would likely have received a systematic transrectal ultrasound (TRUS)-guided biopsy only, which may have affected the management of the patient [18,38]. On a related note, 27% also had Gleason ≤6 disease at the initial diagnosis. This may represent the sampling limitations of a TRUS biopsy, but regardless, most patients with Gleason ≤6 disease would now be offered active surveillance [7,39]. In addition, a 1.5 Tesla scanner provides reduced signal-to-noise ratio and spatial resolution compared with modern 3.0 Tesla scanners. However, at least in the primary diagnostic setting, it is not clear whether this technical improvement translates to improved outcomes [40]. Furthermore, there is currently no evidence to suggest that magnet strength improves diagnostics in the radiorecurrent setting. Last, staging was done with bone scan and $^{18}$F-choline PET/CT, the standard during study recruitment. Prostate-specific membrane antigen (PSMA) PET/CT may better identify occult intraprostatic and extraprostatic recurrences and alter management options [41].

### 4.4. Further directions

This work would benefit from supplementary analyses using data not collected in FORECAST. For example, studying biopsy complications and post-biopsy functional outcomes relative to the biopsy route, number of cores taken, and quadrants sampled would contribute to the discussion of the optimal biopsy strategy. It is known that a TTPM biopsy with 5 mm sampling, at least in the primary diagnostic setting, frequently mandates a general anaesthetic and is associated with acute urinary retention in approximately one-quarter, as well as deterioration in erectile and sexual function [42]. The functional impact of previous interventions for benign prostatic obstruction, for example, transurethral resection of the prostate, is also not known. The toxicity of biopsy strategies is an important consideration in this population of older men (here, a median age of 71 yr with a median of 7 yr from completing radiotherapy) who have already sustained toxicity from radiotherapy with or without ADT.

Another important analysis is a comparison of location of the primary lesion(s) versus radiorecurrent lesion(s). Radiological and pathological data regarding the site of the original index tumour were not collected, and many cases would have been diagnosed without accurate localisation data because of the pre-MRI diagnostic pathway employed at the time. Nonetheless, others have shown that radiorecurrent disease usually develops at the site of the original index tumour [43,44]. The value of biopsying the index tumour site irrespective of imaging findings should therefore be considered in future work.

Third, to compare a biopsy after radiotherapy versus the primary setting, it would also be useful to identify the rate of core fragmentation and how this varies between prostate zones. Furthermore, collecting data on the presence of other pathologies, such as prostatic intraepithelial neoplasia or inflammation, would improve the understanding of how these correlate with MRI findings. This is especially important considering the high rate of false positive MRI examinations associated with its low specificity.

Further research is also warranted in optimising image interpretation. Robust, multicentre prospective validation of the recently published PI-RR score will be important and could optimise MRI use [14]. There is also growing observational evidence that $^{68}$Ga-PSMA-11 PET/CT has high sensitivity for the detection of radiorecurrent intraprostatic cancer and could therefore be used not only to rule out metastases, but also to identify candidates for salvage focal therapies, as has also been suggested in the primary treatment setting [45–48]. This warrants robust evaluation of the diagnostic accuracy of PSMA PET/CT in isolation and combined with MRI alongside the evaluation of cost effectiveness for a healthcare system.

## 5. Conclusions

For patients with recurrent prostate cancer after radiotherapy, MRI, and MRI-targeted biopsy, with or without perilesional sampling, will diagnose cancer in the majority where present. MRI-undetected cancers, defined as Likert scores of 1 to 2, were found to be smaller and of lower grade. However, if salvage focal ablation is planned, an MRI-targeted biopsy alone is insufficient for prostate mapping; approximately three of five patients with recurrent cancer found on an MRI-targeted biopsy alone harboured further tumours in unsampled quadrants. Systematic sampling of the whole gland should be considered in addition to an MRI-targeted biopsy to capture both MRI-detected and MRI-undetected disease.

## Peer Review Summary and Supplementary data

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2023.09.001.

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