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A Prospective Study on ^{18}F-DCFPyL PSMA PET/CT Imaging in Biochemical Recurrence of Prostate Cancer

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ABSTRACT

^{18}F-DCFPyL, a prostate specific membrane antigen targeting radiotracer, has shown promise as a prostate cancer imaging radiotracer. We evaluated the safety, sensitivity and impact on patient management of ^{18}F-DCFPyL in the settings of biochemical recurrence of prostate cancer. **Methods:** Subjects with prostate cancer and biochemical recurrence post radical prostatectomy/curative intent radiotherapy were included in this prospective study. The subjects underwent ^{18}F-DCFPyL PET/CT imaging. The localisation and number of lesions were recorded. The uptake characteristics of the five most active lesions were measured. A pre- and post-test questionnaire was sent to treating physicians to assess the impact on management. **Results:** One-hundred and thirty subjects were evaluated. ^{18}F-DCFPyL PET/CT localized recurrent prostate cancer in 60% (PSA ≥0.4 to <0.5), 78% (≥0.5 to <1.0), 72% (≥1.0 to <2.0), and 92% (≥2.0) of cases. Many subjects had few lesions: one lesion (40.8%), two (8.5%), three (4.6%). The number of lesions was significantly related to PSA by ANOVA analysis, but there was a large overlap in the PSA values for number of lesions categories. Total lesion uptake was also significantly related to PSA values. Change in treatment intent occurred in 65.5% of subjects. Disease stage changed in 65.5%. Management plans changed in 87.3% of subjects. Twenty-two subjects reported mild adverse events after the scan; all resolved completely. **Conclusion:** ^{18}F-DCFPyL PET/CT is safe and sensitive for the localization of biochemical recurrence of prostate cancer. This test improved decision making for referring oncologists and changed management for the majority of subjects.

Key Words: Prostate cancer, prostate specific membrane antigen, biochemical recurrence

INTRODUCTION

Prostate cancer (PC) is the most prevalent cancer in men in Canada and is the cause of one third of cancer deaths in that population (*1*). While identification of biochemical recurrence (BR) post-therapy can be achieved with the prostate specific antigen (PSA) test, localisation of recurrence can be challenging with conventional imaging modalities that can't match the sensitivity of this blood test (*2,3*). Precise localisation of sites of recurrence is important, as there are options available to treat localized or oligometastatic disease (*4,5*).

With a new class of positron emission tomography (PET) radiopharmaceuticals targeting the prostate specific membrane antigen (PSMA), it has become feasible to detect recurrent or metastatic prostate cancer that is otherwise occult on conventional imaging modalities (*6-9*). ^{18}F-DCFPyL, a radiotracer based on the glutamate-ureido-lysine motif, has the advantage of the longer 110-minute half-life of ^{18}F compared to ^{68}Ga, and of ease of regional distribution; it has been used successfully for detection of PSMA-expressing prostate cancer lesions (*10-12*).

In this study, we aimed to determine the proportion and characteristics of participants with BR that present with limited extent disease (localized or oligometastatic) and would be potentially amenable to surgical resection or localized irradiation, to assess the clinical impact of ^{18}F-DCFPyL PET/CT in patient management, and to evaluate the safety of this radiopharmaceutical for clinical use.

MATERIALS AND METHODS

Selection of Subjects

Participants with any of the following criteria were enrolled: (1) Known prostate cancer with biochemical recurrence after initial curative therapy with radical prostatectomy, with a PSA > 0.4 ng/mL and an additional measurement showing increase; (2) Known prostate cancer with biochemical recurrence after initial curative therapy with radiation therapy, with a PSA level > 2 ng/mL above the nadir after therapy; (3) Castration resistant prostate cancer with PSA ≥2.0 ng/mL with 2 consecutive rises above nadir and castrate levels of testosterone (<1.7 nm/L); (4) Participants with findings on other examinations (such as plain x-ray, CT, magnetic resonance imaging (MRI), or bone scintigraphy and others) that are suspicious for metastatic disease but not conclusive. Participants were excluded if: (1) Medically unstable; (2) Unable to lie supine for imaging; (3) Unable to provide written consent; (4) Exceed the safe weight of the PET/CT bed (204.5 kg) or unable to fit through the PET/CT bore (70 cm diameter); (5) ECOG > 2. No treatment was discontinued before the ^{18}F-DCFPyL scan.

This is an interim analysis of the first 208 participants of an investigator-initiated clinical trial (clinicaltrials.gov NCT03181867). Only participants meeting inclusion criteria (1) and (2) were analyzed for this paper (130/208), but all 208 are included in the safety analysis. Repeat scans in the same subjects were not included. The study has been approved by the UBC/BC Cancer Research Ethics Board and by Health Canada. All subjects signed an informed consent form prior to inclusion in the study.

Study Procedures

Patient demographics were recorded, along with relevant oncological history, laboratory values, and tumour pathology data. Referring physicians completed a questionnaire describing the intended course of treatment before the ^{18}F-DCFPyL PET/CT scan. Participants were followed-up 24h after radiotracer administration to identify adverse events. A second questionnaire was sent to referring physicians a few weeks after the scan to assess changes in management.

^{18}F-DCFPyL was synthesized according to a previously published method (*13*). The administered activity was scaled by body weight (range: 237-474 MBq), allowing a 10% variation in target activity. After a 4-hour fast, participants were injected intravenously with ^{18}F-DCFPyL. Vital signs were measured before, 5-15 minutes after injection, and after the uptake phase. The subjects could eat between radiotracer injection and the scan. After a 120-minute uptake period, patients were imaged from top-of-head to mid-thigh on a Discovery PET/CT 600 or 690 (GE Healthcare). A CT scan for localization and attenuation correction (120 kV, automatic mA selection (30-200 mA range) and noise index of 20) was acquired. PET data were acquired immediately after the CT over 2-4 minutes/bed position, adjusted for participant girth, and reconstructed with the ordered subset expectation maximization algorithm and point-spread-function modeling.

Qualitative Image Analysis

Images were interpreted by experienced nuclear medicine physicians on Oasis (Segami) or AW Workstation (GE Healthcare). Physicians completed a qualitative interpretation case report form recording the number of positive lesions (0, 1, 2, 3, 4, 5, 6-10, >10) and site of recurrence (local, regional nodes, distant nodes, bone, liver, lung, other). Regional nodes were considered: pelvic, hypogastric, obturator, iliac (internal, external), and sacral; other nodal locations were considered distant. Physicians had access to all clinical data; they recorded scans as positive or

negative and rated their confidence in the diagnosis for a total of 6 possible qualitative results (negative: high, moderate, low; positive: high, moderate, low).

Quantitative Image Analysis

Quantitative data was extracted on AW Workstation by a nuclear medicine physician, on images reconstructed without the time-of-flight option for consistency between the two scanners. Mean and standard deviation of cardiac blood-pool activity in a 3-cm spherical volume of interest in the left ventricle was recorded in standardized uptake value (SUV) and lean body mass SUV (SUL). Peak and maximum SUV/SUL as well as total lesion uptake (TLG) of the five most active lesions of each scan were recorded using manually-corrected semi-automatic contours.

Statistical Analysis and Computations

Analysis was exploratory. Statistics were computed in R 3.5.1 (R Foundation for Statistical Computing). Descriptive statistics included mean, standard deviation, or proportions, as appropriate. Vital signs were analysed using a mixed effects model (paired data). PSA doubling time was calculated by fitting to a linear model with logarithmic transformation. Negative doubling times due to treatment effects were excluded from calculation. Subjects were not excluded from the study on the basis of missing data; rather, for each variable or multivariate analysis, the maximum number of evaluable subjects (that had all required variables) was used and reported. Comparison of continuous distributions was done with Welch's t-test. When analysing the effect of categorical variables against another categorical variable, the Pearson's χ^2 test was used with *p*-values estimated by Monte-Carlo simulation (10^6 repetitions). When the effect of categorical variables was assessed against a continuous variable, a linear model with ANOVA was used.

SUV_{max}/SUL_{max} dispersion was assessed by coefficient of variation. Statistical significance was defined as a *p*-value ≤ 0.05.

RESULTS

Demographic Characteristics

One hundred thirty subjects were included in the analysis with demographic parameters reported in Table 1 and Supplemental Table 1. There were 94 subjects (72.3%) with BR after radical prostatectomy and 37 (28.5%) with BR after radiation therapy. Prior treatments included surgery (72.3% of cases), radiotherapy (34.6%), androgen deprivation therapy (ADT) (47.7%), or chemotherapy (0.8%), with some participants having received more than one type of therapy. Forty-five subjects received one or more types of radiotherapy: brachytherapy was administered to 27/45, external beam radiotherapy to 20/45, intensity-modulated radiation therapy (IMRT) to 4/45, and proton therapy to 1/45. Overall, the subjects had a mean PSA of 5.20±6.50 ng/mL with a doubling time of 12.2±11.8 (n=113) months.

Initial Tumor Characteristics

The distribution of Gleason scores was skewed towards intermediate to high grades (6: 13.2%, 3+4=7: 21.7%, 4+3=7: 28.7%, 8: 10.1%, 9: 25.6%, 10: 0.8%; n=129). Most had advanced pathological T stage: with pT3 and pT4 representing 59.4% (n=64) (Supplemental Table 2).

Clinical Assessment of PET/CT Scans

Representative ^{18}F-DCFPyL PET/CT scans are shown in Fig. 1; 84.6% were positive with varying certainty levels: 81.5% high, 13.1% moderate, 5.4% low, demonstrating a good confidence of readers in their findings (Table 2; Supplemental Table 3). A high proportion of participants (53.9%) had 3 lesions or fewer, with only 1 (40.8%), 2 (8.5%), or 3 (4.6%) lesions detected.

In an ANOVA of a linear model where PSA was analysed with the number of lesions and Gleason score factors, the number of lesions had a significant effect ($p < 0.01$). However, there was substantial overlap in PSA values for differing number of lesions. The initial Gleason score was not significantly associated with PSA. To evaluate for potential association of PSA to lesion localisation, Gleason score, and number of lesions, participants with disease in only one area were selected (n=75). ANOVA of a linear model of PSA against lesion localisation, Gleason score, and number of lesions was computed. In that subgroup, no significant association was found. There was, also, substantial overlap in PSA values when plotted against those factors (Supplemental Figs. 1-3). The Gleason score was not related to the number of lesions when evaluated by χ^2 but there was lack of independence when evaluated against sites of relapse (χ^2; $p < 0.01$).

The proportion of positive scans increased with PSA level (Fig. 2; Supplemental Table 4). The PSA values for positive scans (5.80±6.87 ng/mL) were significantly different (Welch's t-test; $p < 0.001$) from that of negative scans (1.86±1.62 ng/mL), however there is a large overlap in PSA values across those two categories.

Active disease was most often identified in regional nodes (43.9%) followed by prostate bed/seminal glands (26.9%), distant nodes (24.6%), bone (20.0%), lung (2.3%), and other sites (0.8%); no liver lesions were identified (Supplemental Fig. 4). A number of participants had disease in more than one site. Previous treatments had an influence on lesion distribution which differed, notably, between those that previously had surgery with or without androgen-deprivation therapy (ADT) and those that had radiotherapy with or without ADT (χ^2 test; $p < 0.01$) (Supplemental Fig. 5). In the subset of participants treated with radiotherapy with or without ADT there was trend for a differing distribution of lesion localisation between brachytherapy and

external beam radiotherapy treatment types (χ^2 test; $p = 0.051$); this was calculated while excluding subjects who had multiple radiotherapy treatment types.

Evaluation of Lesions

Background uptake was low (SUV_{mean} 1.22±0.22) in the cardiac blood pool. The distribution of lesion uptake had a range of SUV_{max} 1.15-85.04 (mean: 12.43±12.34). SUV_{peak} yielded distributions with a smaller range 0.86-61.2 (mean: 7.60±7.98). Coefficients of variation of SUL_{max} (97%) and SUL_{peak} (106%) were comparable to those of SUV_{max} (99%) and SUV_{peak} (105%) (Supplemental Table 5). When selecting patients that had five or fewer lesions (the maximum recorded on the quantitative assessment), there was a significant relationship between PSA and sum of TLG ($p < 0.05$) when assessed by ANOVA of a linear model that also accounted for the Gleason score (which also had a significant association with PSA in this reduced dataset; $p < 0.01$). Lesion SUV_{max} and SUL_{max} were significantly related to the initial Gleason score when evaluated by a linear model ($p < 0.05$)

Adverse Events

Vital signs varied at different time-points: blood pressure changed from 142±19/82±13 to 146±19/80±9 mmHg between pre-injection values and immediately before the scan. Heart rate changed from 65±14 to 75±16 bpm, and pulse oximetry from 97.6±2.1 to 97.6±2.6%. Those values were statistically significant (except for pulse oximetry) but not considered clinically significant. There were no adverse events during scans. A total of 22 subjects reported mild adverse events after the scan; all resolved completely (Supplemental Table 6).

Changes in Management

At this point in time, referring physicians had completed post-scan assessments of changes in management for 55/130 subjects (Table 3;Supplemental Table 7). Change in treatment intent occurred in 65.5% of subjects: 50.0% directed to palliative care and 50.0% to curative treatment. Disease stage changed in 65.5% (97.1% of which were upstaged). Findings on ^{18}F-DCFPyL scans prompted additional imaging in 23.6% of cases, changed plans for surgery or biopsy in 25.5%, changed plans for systemic therapy in 56.4%, and those for radiotherapy in 47.3%. Physicians indicated that imaging results improved decision-making in 89.1% and changed management plans in 87.3%.

DISCUSSION

This study aimed to determine the sensitivity and safety of ^{18}F-DCFPyL PET/CT for the detection of prostate cancer relapse in the context of biochemical recurrence. Since the initial publication by Rowe et al. in 2015 on nine patients, several small studies have been published on this tracer for prostate cancer, many of them by the same groups (*8,10-12,14-20*). This interim analysis evaluated a large prospective cohort of subjects that participated in an investigator-initiated ^{18}F-DCFPyL PET/CT imaging study in Vancouver, Canada.

While the definition of oligometastatic disease in prostate cancer is still evolving, many participants had a low number of lesions that would fall under this category (53.9% had 1-3 lesions) (*21-23*). Although more research is needed to assess its efficacy, there is a potential for localized therapy (i.e.: resection, stereotactic body radiation therapy) with minimal risk of serious adverse events (*23,24*). In this setting, ^{18}F-DCFPyL PET/CT may be useful to identify disease occult on other imaging modalities that could be amenable to more aggressive treatment (*25*). Furthermore, in 65.4% of participants, disease was located in regional nodes and/or presented as local recurrence. For subjects that were treated surgically, this would potentially be amenable to salvage pelvic irradiation.

Although the number of lesions reported on imaging was significantly related to PSA values at baseline for the participants, there was an important overlap in PSA range between groupings based on the number of lesions. This is likely because the number of lesions is not a good indicator of tumor burden due to size variations. Conversely, there was a significant relation between TLG and PSA. However, no PSA value was predictive of oligometastatic disease in this population.

Compared with the detection rates presented by Eiber for ^{68}Ga-PSMA HBED-CC: 57.9%, 72.7%, 93%, and 96.8%, with PSA 0.2 to 0.5 ng/mL, 0.5 to 1.0 ng/mL, 1.0 to 2.0 ng/mL, and >= 2.0 ng/mL, our study achieved similar results with 60% (± 80%; exact 95% confidence interval), 78% (± 36%), 72% (± 37%), and 92% (± 14%) in equivalent intervals (≥0.4 to <0.5; ≥0.5 to <1.0; ≥1.0 to <2.0; ≥2.0), respectively (*26*). The lower detection rate in the 1.0 to 2.0 interval for ^{18}F-DCFPyL may be attributable to random variations and remains within the 95% confidence interval for the proportion. This is also similar to other ^{68}Ga-PSMA studies reported in a review by Evans et al. and to detection rates reported for ^{18}F-PSMA-1007 (61.5%, 74.5%, 90.1%, 94.1%) (*27,28*). ^{18}F-DCFPyL, in the context of the inclusion criteria of the present analysis, appears to have an overall similar sensitivity to other radiotracers.

The distribution of active disease was dependant on prior therapy. There was a greater proportion of local recurrence after radiotherapy compared to surgery. This study was not designed to evaluate primary treatment modalities. Referral patterns for inclusion into the study might account for some of these differences.

Change in treatment intent occurred in 65.5% of subjects and that disease stage changed in 65.5%. In comparison with ^{68}Ga-PSMA-11, Afaq reported changes in management plans post in 39% of patients and Hope et al. in 59.6%. Koerber reported changes in radiotherapeutic management of 56.3% in patients with PSA persistence after surgery or recurrence after definitive therapy (*29-31*). A systematic review by Han et al. reported a change in management of 54% (95% confidence interval 47-60%) (*32*). PSA at baseline was determined not to be a significant factor for change in management, in treatment intent, disease stage, or for ordering additional diagnostic studies when assessed by logit analysis. In the meta-analysis by Han et al., the meta-regression had not shown PSA to be a significant factor for change in management either, but there was a

tendency for greater proportion of management changes in studies with greater PSA levels before PET (*32*).

Although a small proportion of participants reported undesirable events, they were all mild, and resolved completely. There was no serious adverse event. Our results indicate that ^{18}F-DCFPyL can be considered safe for injection in humans (*10,11*).

As a limitation to this study, not all referring physicians (55/130) had completed the questionnaire for change in management at time of analysis, which could reflect reporting bias in favor of helpful scans.

CONCLUSION

^{18}F-DCFPyL PET/CT imaging identified sites of recurrent prostate cancer in the majority of subjects and was well tolerated, with no serious adverse events. A large proportion of subjects meeting the inclusion criteria for this analysis had three or fewer lesions identified on the scan. ^{18}F-DCFPyL PET/CT imaging improved decision making for referring oncologists and changed management plans for a majority of subjects.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

The trial was conducted in compliance with the protocol, with good clinical practice guidelines as set out by Health Canada and the institutional Research Ethics Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

KEY POINTS

Question

What is the impact on patient management of ^{18}F-DCFPyL PET/CT in settings of biochemical recurrence of prostate cancer?

Pertinent Findings

In this analysis of a prospective clinical trial, ^{18}F-DCFPyl changed management plans of patients in 87.3% and disease stage in 65.5% with no serious adverse events.

Implications for Patient Care

^{18}F-DCFPyL PET/CT is safe and changed management of a majority of subjects.

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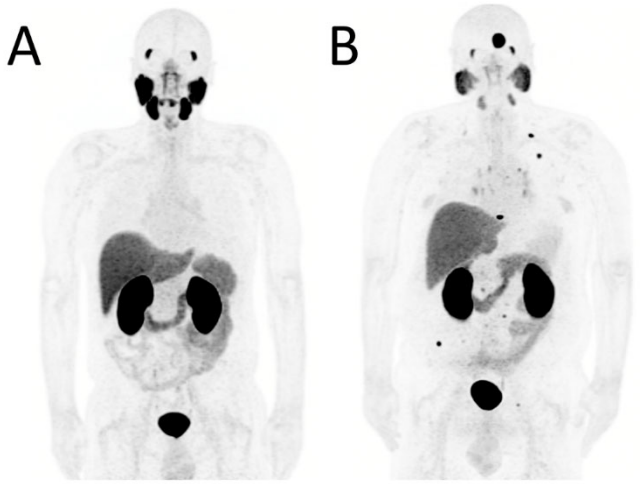

Figure 1.[18]F-DCFPyL PET Maximum Intensity Projection images representative of tracer distribution. A: normal biodistribution (significant uptake of lacrimal glands, salivary glands, kidneys, liver, spleen, bowel, and bladder content); B: metastatic prostate cancer.

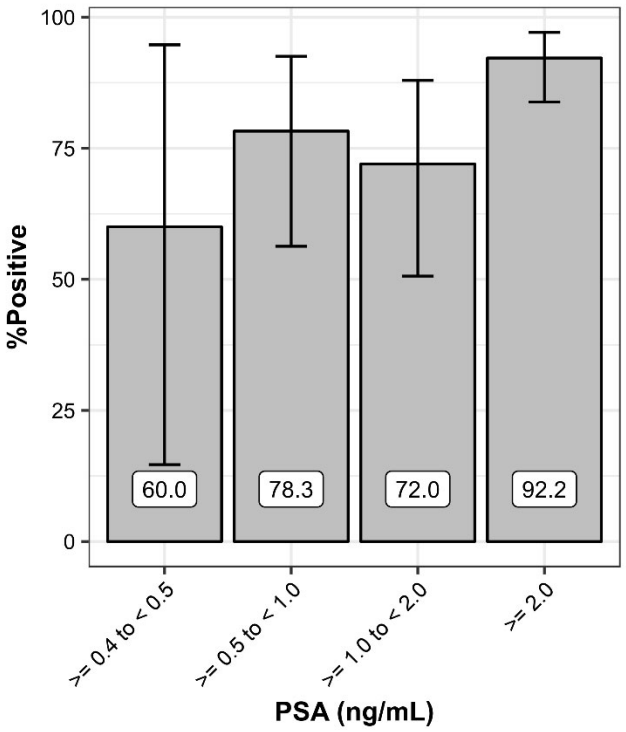

Figure 2. Proportion of positive scans based on PSA levels. Error bars represent 95% confidence interval.

Table 1: Patient Characteristics

	All included		BR post RP only*		BR post RT only*	
Variable	**Value**	**n**	**Value**	**n**	**Value**	**n**
Age (years)	69.1±6.5	130	68.4±6.3	92	70.8±6.9	35
Body weight (kg)	87.4±14.4	130	86.9±14.4	92	87.7±13.5	35
Height (cm)	177.3±6.8	130	176.9±6.8	92	177.5±6.6	35
Injected activity (MBq)	369.2±47.2	130	367.8±47.1	92	371.1±46.0	35
Uptake time (min)	120.4±1.5	130	120.5±1.7	92	120.2±0.6	35
Inclusion criteria†						
Known PC after radical prostatectomy with BR	94 (72.3%)	130	92 (100%)	92	0 (0.0%)	35
Known PC after radiation therapy with BR	37 (28.5%)	130	0 (0.0%)	92	35 (100%)	35
PSA at baseline (ng/mL)	5.20±6.50	130	3.03±3.40	92	11.11±8.94	35
PSA doubling time (months)	12.2±11.8	113	12.0±12.3	78	12.9±11.1	32
Treatment history†						
Surgery	94 (72.3%)	130	92 (100%)	92	0 (0.0%)	35
Radiotherapy†	45 (34.6%)	130	7 (7.6%)	92	35 (100%)	35
Brachytherapy	27 (60.0%)	45	0 (0.0%)	7	26 (74.3%)	35
External beam	20 (44.4%)	45	5 (71.4%)	7	13 (37.1%)	35
IMRT	4 (8.9%)	45	2 (28.6%)	7	2 (5.7%)	35
Proton	1 (2.2%)	45	0 (0.0%)	7	1 (2.9%)	35
Radium-223	0 (0.0%)	45	0 (0.0%)	7	0 (0.0%)	35
ADT	62 (47.7%)	130	39 (42.4%)	92	22 (62.9%)	35
Chemotherapy	1 (0.8%)	130	1 (1.1%)	92	0 (0.0%)	35

Values are presented as mean ± std. dev. or proportions. PC: prostate cancer; BR: biochemical recurrence; RP: radical prostatectomy; RT: radiation therapy; ADT: Androgen deprivation therapy; IMRT: Intensity-modulated radiation therapy. *Inclusion criteria; †Categories are not mutually exclusive.

Table 2: Qualitative Assessment of Scans

	All included		BR post RP only*	BR post RT only*
Variable	**Value**	**n**		
Number of lesions		130	92	35
0	20 (15.4%)		19 (20.7%)	0 (0.0%)
1	53 (40.8%)		35 (38.0%)	18 (51.4%)
2	11 (8.5%)		6 (6.5%)	5 (14.3%)
3	6 (4.6%)		6 (6.5%)	0 (0.0%)
4	3 (2.3%)		3 (3.3%)	0 (0.0%)
5	7 (5.4%)		5 (5.4%)	2 (5.7%)
6-10	14 (10.8%)		10 (10.9%)	3 (8.6%)
>10	16 (12.3%)		8 (8.7%)	7 (20.0%)
Sites of relapse†		130	92	35
Local	35 (26.9%)		13 (14.1%)	22 (62.9%)
Regional nodes	57 (43.9%)		41 (44.6%)	14 (40.0%)
Distant nodes	32 (24.6%)		21 (22.8%)	10 (28.6%)
Bone	26 (20.0%)		20 (21.7%)	6 (17.1%)
Lung	3 (2.3%)		2 (2.2%)	1 (2.9%)
Liver	0 (0.0%)		0 (0.0%)	0 (0.0%)
Other	1 (0.8%)		1 (1.1%)	0 (0.0%)
Diagnosis		130	92	35
Positive	110 (84.6%)		73 (79.3%)	35 (100%)
Negative	20 (15.4%)		19 (20.7%)	0 (0.0%)
Certainty of diagnosis		130	92	35
High	106 (81.5%)		73 (79.3%)	31 (88.6%)
Moderate	17 (13.1%)		14 (15.2%)	3 (8.6%)
Low	7 (5.4%)		5 (5.4%)	1 (2.9%)

*Inclusion criteria; †Categories are not mutually exclusive.

Table 3: Changes in Treatment Intent, Disease Stage, Investigation, Decision-Making or Management Plan

	All included		BR post RP only*		BR post RT only*	
Variable	**Value**	**n**	**Value**	**n**	**Value**	**n**
Change in treatment intent	36 (65.5%)	55	21 (56.8%)	37	13 (86.7%)	15
To Palliative	18 (50.0%)	36	10 (47.6%)	21	6 (46.2%)	13
To Curative	18 (50.0%)	36	11 (52.4%)	21	7 (53.9%)	13
Change in disease stage	36 (65.5%)	55	24 (64.9%)	37	10 (66.7%)	15
Upstaged	34 (97.1%)	35	23 (100%)	23	9 (90.0%)	10
Downstaged	1 (2.9%)	35	0 (0.0%)	23	1 (10.0%)	10
Ordering of additional diagnostic studies†	13 (23.6%)	55	6 (16.2%)	37	7 (46.7%)	15
Computed tomography	4 (30.8%)	13	2 (33.3%)	6	2 (28.6%)	7
Magnetic resonance imaging	5 (38.5%)	13	3 (50.0%)	6	2 (28.6%)	7
Nuclear medicine	1 (7.7%)	13	1 (16.7%)	6	0 (0.0%)	7
Ultrasound	0 (0.0%)	13	0 (0.0%)	6	0 (0.0%)	7
Biopsy	4 (30.8%)	13	0 (0.0%)	6	4 (57.1%)	7
Other‡	1 (7.7%)	13	0 (0.0%)	6	1 (14.3%)	7
Imaging results changed plans for surgery or biopsy	14 (25.5%)	55	6 (16.2%)	37	8 (53.3%)	15
	NA: 13 (23.6%)		NA: 10 (27.0%)		NA: 1 (6.7%)	
Surgery or biopsy added	9 (64.3%)	14	4 (66.7%)	6	5 (62.5%)	8
Surgery or biopsy cancelled	5 (35.7%)	14	2 (33.3%)	6	3 (37.5%)	8
Other	0 (0.0%)	14	0 (0.0%)	6	0 (0.0%)	8
Imaging results changed plans for systemic therapy	31 (56.4%)	55	20 (54.1%)	37	9 (60.0%)	15
	NA: 3 (5.5%)		NA: 2 (5.4%)		NA: 1 (6.7%)	
Systemic therapy started	23 (74.2%)	31	15 (75.0%)	20	6 (66.7%)	9
Systemic therapy not initiated/cancelled	8 (25.8%)	31	5 (25.0%)	20	3 (33.3%)	9
Systemic therapy changed	0 (0.0%)	31	0 (0.0%)	20	0 (0.0%)	9
Imaging results changed plans for radiotherapy	26 (47.3%)	55	22 (59.5%)	37	4 (26.7%)	15
	NA: 9 (16.4%)		NA: 6 (16.2%)		NA: 1 (6.7%)	
Radiotherapy added	13 (52.0%)	25	11 (52.4%)	21	2 (50.0%)	4
Radiotherapy cancelled	9 (36.0%)	25	8 (38.1%)	21	1 (25.0%)	4
Radiotherapy prescription changed	3 (12.0%)	25	2 (9.5%)	21	1 (25.0%)	4
Imaging results improved decision-making	49 (89.1%)	55	33 (89.2%)	37	14 (93.3%)	15
Imaging results changed subject's management plan	48 (87.3%)	55	32 (86.5%)	37	14 (93.3%)	15

*Inclusion criteria; †Categories are not mutually exclusive. NA: not applicable; ‡Repeat PET a few months after the start of androgen deprivation therapy.

A Prospective Study on ^{18}F-DCFPyL PSMA PET/CT Imaging in Biochemical Recurrence of Prostate Cancer — Supplemental Material

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Supplemental Table 1: Patient characteristics (additional subgroups)

	ADT naive		Prior or ongoing ADT	
Variable	**Value**	**n**	**Value**	**n**
Age (years)	69.1±6.3	68	69.0±6.8	62
Body weight (kg)	86.8±15.1	68	88.2±13.6	62
Height (cm)	177.3±6.0	68	177.3±7.6	62
Injected activity (MBq)	366.4±45.6	68	372.4±49.0	62
Uptake time (min)	120.5±1.8	68	120.3±0.9	62
Inclusion criteria†				
Known PC after radical prostatectomy with BR	54 (79.4%)	68	40 (64.5%)	62
Known PC after radiation therapy with BR	14 (20.6%)	68	23 (37.1%)	62
PSA at baseline (ng/mL)	3.55±3.61	68	7.01±8.29	62
PSA doubling time (months)	15.3±13.8	55	9.3±8.7	58
Treatment history†				
Surgery	54 (79.4%)	68	40 (64.5%)	62
Radiotherapy†	17 (25.0%)	68	28 (45.2%)	62
Brachytherapy	13 (76.5%)	17	14 (50.0%)	28
External beam	5 (29.4%)	17	15 (53.6%)	28
IMRT	0 (0.0%)	17	4 (14.3%)	28
Proton	0 (0.0%)	17	1 (3.6%)	28
Radium-223	0 (0.0%)	17	0 (0.0%	28
Other	0 (0.0%)	17	0 (0.0%)	28
ADT	0 (0.0%)	68	62 (100%)	62
Chemotherapy	0 (0.0%)	68	1 (1.6%)	62

PC: prostate cancer; BR: biochemical recurrence; ADT: Androgen deprivation therapy; IMRT: Intensity-modulated radiation therapy. †Categories are not mutually exclusive.

Supplemental Table 2: Staging and Gleason Score. Includes pathological TNM and Gleason score when available.

	All included		BR post RP only		BR post RT only		ADT Naive		Prior or ongoing ADT	
Variable	**Value**	**n**	**Value**	**n**	**Value**	**n**	**Value**	**n**	**Value**	**n**
Pathological TNM		64		63		0		38		26
pT2*	0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)	
pT2a	2 (3.1%)		2 (3.2%)		0 (0.0%)		0 (0.0%)		2 (7.7%)	
pT2b	3 (4.7%)		3 (4.8%)		0 (0.0%)		1 (2.6%)		2 (7.7%)	
pT2c	21 (32.8%)		21 (33.3%)		0 (0.0%)		14 (36.8%)		7 (26.9%)	
pT3a	11 (17.2%)		11 (17.5%)		0 (0.0%)		7 (18.4%)		4 (15.4%)	
pT3b	27 (42.2%)		26 (41.3%)		0 (0.0%)		16 (42.1%)		11 (42.3%)	
pT4	0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)	
pNx	7 (10.9%)		7 (11.1%)		0 (0.0%)		3 (7.9%)		4 (15.4%)	
pN0	46 (71.9%)		46 (73.0%)		0 (0.0%)		29 (76.3%)		17 (65.4%)	
pN1	11 (17.2%)		10 (15.9%)		0 (0.0%)		6 (15.8%)		5 (19.2%)	
Gleason score		129		91		35		67		62
6	17 (13.2%)		8 (8.8%)		8 (22.9%)		8 (11.9%)		9 (14.5%)	
7 (3+4)	28 (21.7%)		17 (18.7%)		11 (31.4%)		19 (28.4%)		9 (14.5%)	
7 (4+3)	37 (28.7%)		27 (29.7%)		9 (25.7%)		19 (28.4%)		18 (29.0%)	
8	13 (10.1%)		12 (13.2%)		1 (2.9%)		7 (10.4%)		6 (9.7%)	
9	33 (25.6%)		26 (28.6%)		6 (17.1%)		13 (19.4%)		20 (32.3%)	
10	1 (0.8%)		1 (1.1%)		0 (0.0%)		1 (1.5%)		0 (0.0%)	

*Data not available to specify a or b stage.

Supplemental Table 3: Qualitative assessment of scans (additional subgroups)

	ADT naive		Prior or ongoing ADT	
Variable	**Value**	**n**		
Number of lesions		68		62
0	14 (20.6%)		6 (9.7%)	
1	26 (38.2%)		27 (43.5%)	
2	7 (10.3%)		4 (6.5%)	
3	0 (0.0%)		6 (9.7%)	
4	1 (1.5%)		2 (3.2%)	
5	6 (8.8%)		1 (1.6%)	
6-10	10 (14.7%)		4 (6.5%)	
>10	4 (5.9%)		12 (19.4%)	
Sites of relapse†		68		62
Local	17 (25.0%)		18 (29.0%)	
Regional nodes	33 (48.5%)		24 (38.7%)	
Distant nodes	14 (20.6%)		18 (29.0%)	
Bone	9 (13.2%)		17 (27.4%)	
Lung	1 (1.5%)		2 (3.2%)	
Liver	0 (0.0%)		0 (0.0%)	
Other	1 (1.5%)		0 (0.0%)	
Diagnosis		68		62
Positive	54 (79.4%)		56 (90.3%)	
Negative	14 (20.6%)		6 (9.7%)	
Certainty of diagnosis		68		62
High	52 (76.5%)		54 (87.1%)	
Moderate	11 (16.2%)		6 (9.7%)	
Low	5 (7.4%)		2 (3.2%)	

Supplemental Table 4: Proportion of positive scans based on PSA levels

	All included		BR post RP only		BR post RT only	
Variable	**Value**	**n**	**Value**	**n**	**Value**	**n**
Proportion of positive scans						
>= 0.4 to < 0.5	60.0%	5	60.0%	5	-	0
>= 0.5 to < 1.0	78.3%	23	81.8%	22	-	0
>= 1.0 to < 2.0	72.0%	25	72.0%	25	-	0
>= 2.0	92.2%	77	85.0%	40	100%	35
>= 2.0 to < 5.0	84.8%	33	79.2%	24	100.0%	7
>= 5.0 to < 10.0	96.2%	26	90.9%	11	100.0%	15
>= 10.0 to < 15.0	100.0%	11	100.0%	4	100.0%	7
>= 15.0 to < 20.0	100.0%	2	-	0	100.0%	2
>= 20.0 to < 25.0	100.0%	2	100.0%	1	100.0%	1
>= 25.0 to < 30.0	-	0	-	0	-	0
>= 30.0	100.0%	3	-	0	100.0%	3

Supplemental Table 5: Characteristics of the five most active lesions of each scan and blood pool activity.

Variable	SUV	SUL	n
Cardiac blood pool (mean uptake)	1.22±0.22	0.93±0.15	130
Lesion (max uptake)			290
Mean	12.43	9.29	
Minimum	1.15	0.90	
Maximum	85.04	62.39	
Standard deviation	12.34	9.01	
Lesion (peak uptake)			282
Mean	7.60	5.77	
Minimum	0.86	0.69	
Maximum	61.2	48.3	
Standard deviation	7.98	6.11	

Supplemental Table 6: List of adverse events

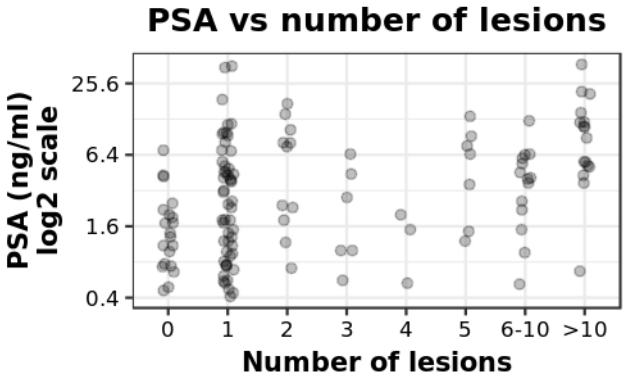
Adverse event	Severity	Resolved	Related
Tiredness after scan, resolved after sleeping	mild	yes	Unlikely
Tiredness	mild	yes	Not related
Tiredness & diarrhea overnight	mild	yes	Not related
Flu-like symptoms	mild	yes	Unlikely
Tiredness	mild	yes	Unlikely
'Floaters' in right eye	mild	yes	Not related
Headache and tired	mild	yes	Unlikely
Dark red blood blisters on left arm where injection made, no pain or discomfort.	mild	yes	Possibly
Tiredness	mild	yes	Unlikely
Palpitations	mild	yes	Not related
Felt vertigo symptoms	mild	yes	Unlikely
Felt dizzy/nauseous	mild	yes	Possibly
Dizzy/nauseous - for 5 - 10 minutes after leaving the department.	mild	yes	Possibly
Tired	mild	yes	Unlikely
Chest pain*	mild	yes	Possibly
Metallic taste in mouth	mild	yes	Possibly
Dizzy first thing in the morning	mild	yes	Possibly
Tired	mild	yes	Unlikely
Tired and a bit 'worn out', loose stool, no nausea	mild	yes	Unlikely
Diarrhea	mild	yes	Unlikely
Light headed about 1 hour after the injection. Felt better after laying down for 30 minutes on the scanner bed, during the scan.	mild	yes	Unlikely
Headache	mild	yes	Unlikely
Right lower back muscle ache.	mild	yes	Unlikely
Extra tired	mild	yes	Unlikely
Tiredness/slightly dizzy*	mild	yes	Possibly
Low appetite/slight nausea*	mild	yes	Possibly
Arm sore from IV	mild	yes	Probably

* The subjects did not think the symptoms were related to scan.
Some subjects experienced more than one symptom.

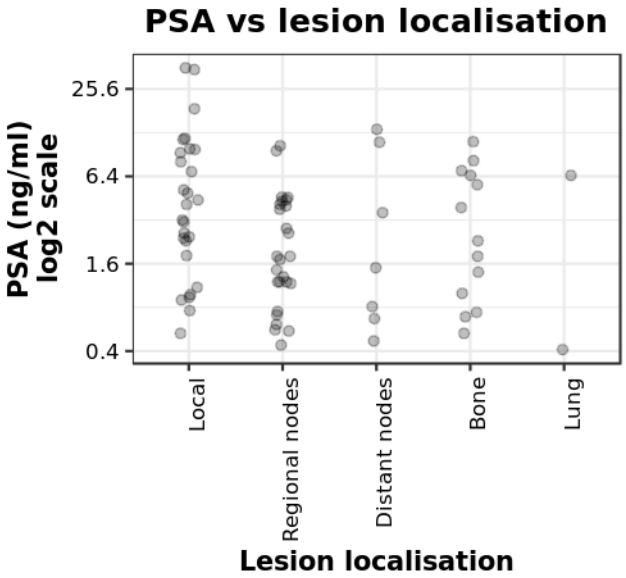
Supplemental Table 7: Changes in treatment intent, disease stage, investigation, decision-making or management plan (additional subgroups)

	ADT naive		Prior or ongoing ADT	
Variable	**Value**	**n**		
Change in treatment intent	20 (66.7%)	30	16 (64.0%)	25
To Palliative	9 (45.0%)	20	9 (56.3%)	16
To Curative	11 (55.0%)	20	7 (43.8%)	16
Change in disease stage	20 (66.7%)	30	16 (64.0%)	25
Upstaged	18 (94.7%)	19	16 (100%)	16
Downstaged	1 (5.3%)	19	0 (0.0%)	16
Ordering of additional diagnostic studies†	8 (26.7%)	30	5 (20.0%)	25
Computed tomography	2 (25.0%)	8	2 (40.0%)	5
Magnetic resonance imaging	4 (50.0%)	8	1 (20.0%)	5
Nuclear medicine	1 (12.5%)	8	0 (0.0%)	5
Ultrasound	0 (0.0%)	8	0 (0.0%)	5
Biopsy	2 (25%)	8	2 (40.0%)	5
Other*	0 (0.0%)	8	1 (20.0%)	5
Imaging results changed plans for surgery or biopsy	8 (26.7%) NA: 7 (23.3%)	30	6 (24.0%) NA: 6 (24.0%)	25
Surgery or biopsy added	5 (62.5%)	8	4 (66.7%)	6
Surgery or biopsy cancelled	3 (37.5%)	8	2 (33.3%)	6
Other**	0 (0.0%)	8	0 (0.0%)	6
Imaging results changed plans for systemic therapy	14 (46.7%) NA: 2 (6.7%)	30	17 (68.0%) NA: 1 (4.0%)	25
Systemic therapy started	11 (78.6%)	14	12 (70.6%)	17
Systemic therapy not initiated/cancelled	3 (21.4%)	14	5 (29.4%)	17
Systemic therapy changed	0 (0.0%)	14	0 (0.0%)	17
Imaging results changed plans for radiotherapy	12 (40.0%) NA: 5 (16.7%)	30	14 (56.0%) NA: 4 (16.0%)	25
Radiotherapy added	6 (54.6%)	11	7 (50.0%)	14
Radiotherapy cancelled	3 (27.3%)	11	6 (42.9%)	14
Radiotherapy prescription changed	2 (18.2%)	11	1 (7.1%)	14
Imaging results improved decision-making	26 (86.7%)	30	23 (92.0%)	25
Imaging results changed subject's management plan	25 (83.3%)	30	23 (92.0%)	25

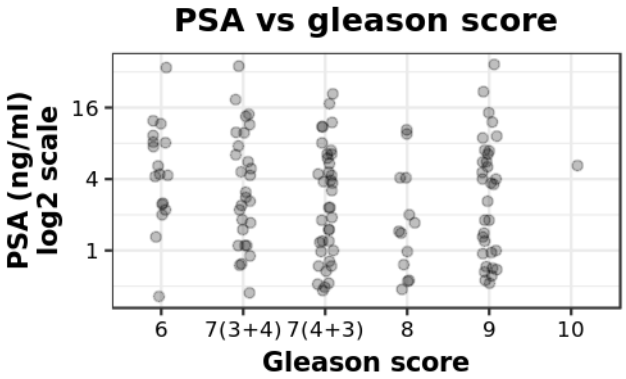
Note: one referring physician did not indicate on follow-up the detailed change in disease stage / plans for radiotherapy (awaiting biopsy).



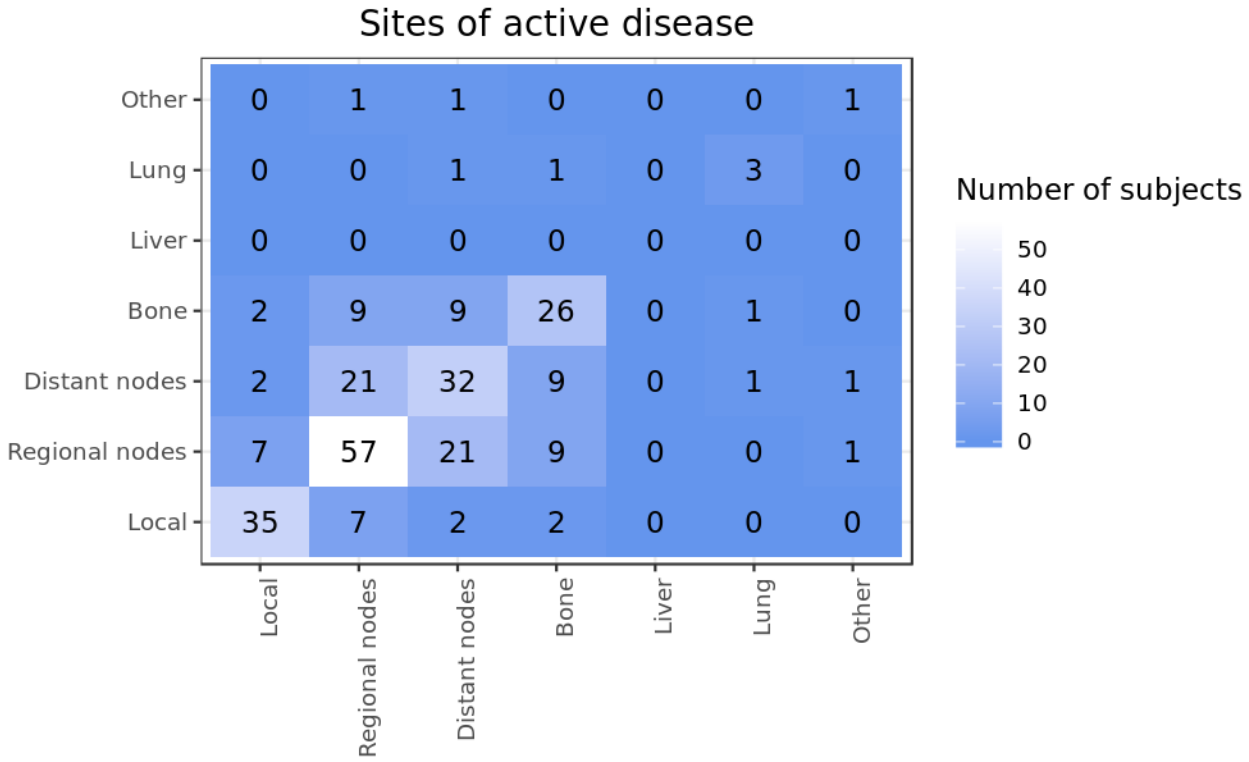
Supplemental Figure 1. PSA vs number of lesions. This represents the PSA values (on a $\log_2$ scale) in each number of lesions category.



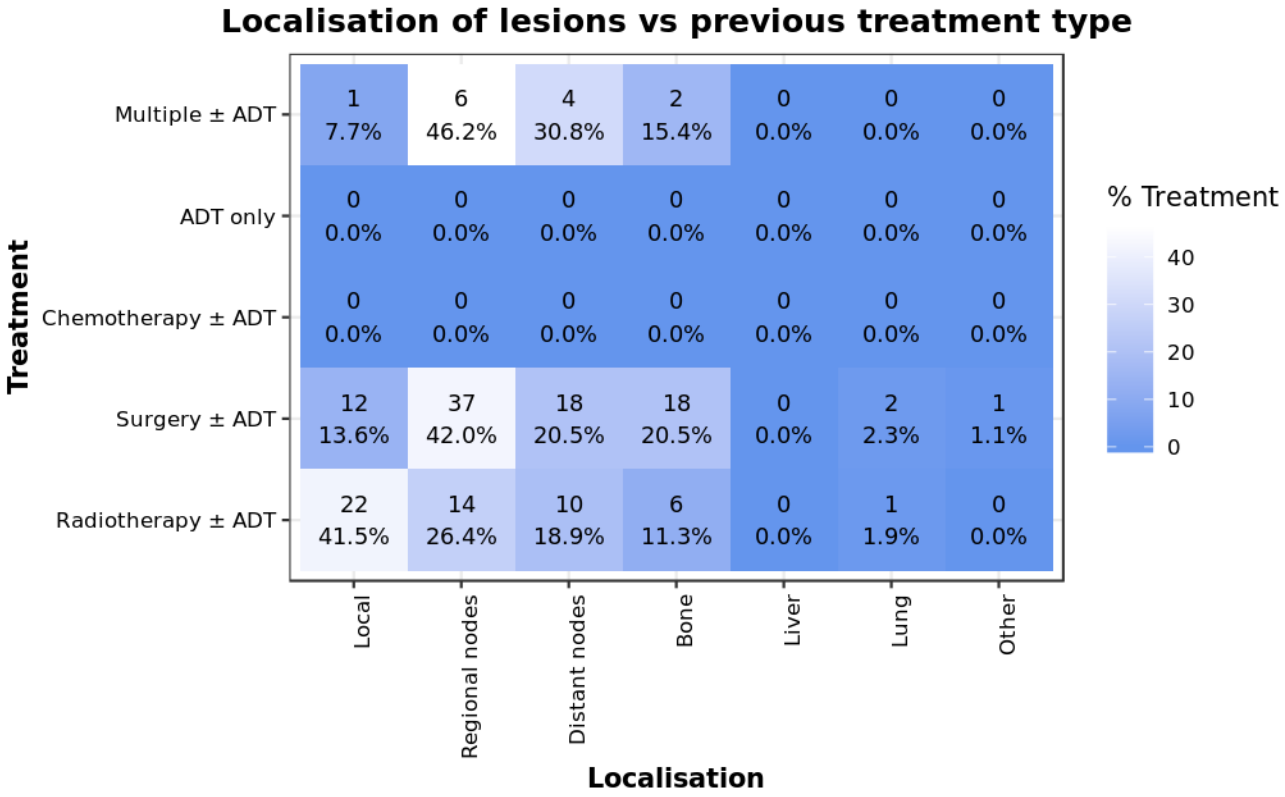
Supplemental Figure 2. PSA vs lesion localisation. Presented lesion localisation are mutually exclusive (i.e. those subjects had lesions in only one localisation).



Supplemental Figure 3. PSA vs Gleason score.



Supplemental Figure 4. Joint histogram of lesion distribution. The graph shows on the diagonal the number of subjects that had disease in the specified location. Each cell shows the number of subjects that had disease simultaneously in those two locations. Categories are not mutually exclusive (a subject may have disease in more than one location, some in more than two).



Supplemental Figure 5. Localization of lesions versus previous treatment types. The number in the cells represents the number of subjects that had a recurrence in the region specified on the horizontal axis for each treatment type. A subject may have had recurrence in more than one site. Calculated percentages are cumulative for treatments (calculated by adding cells in each row and dividing by total). When subjects had more than one treatment, they were aggregated in the "Multiple ± ADT" category and excluded from the other categories. ADT: androgen deprivation therapy.

STARD STATEMENT CHECKLIST

Section & Topic	No	Item	Item included
Title or abstract			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Yes
Abstract			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Yes
Introduction			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Yes
	4	Study objectives and hypotheses	Yes
Methods			
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Yes
Participants	6	Eligibility criteria	Yes
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Yes
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Yes Study start date: August 3, 2017. Can be derived from clininicaltrial.gov identifier.
	9	Whether participants formed a consecutive, random or convenience series	Yes
Test methods	10a	Index test, in sufficient detail to allow replication	Yes
	10b	Reference standard, in sufficient detail to allow replication	Not applicable (no reference test)
	11	Rationale for choosing the reference standard (if alternatives exist)	Not applicable (no reference test)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Yes Cutoffs not applicable Result categories defined in methods.
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Not applicable (no reference test)

	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Yes
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Not applicable (no reference test)
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy	Yes
	15	How indeterminate index test or reference standard results were handled	Not applicable (no reference test)
	16	How missing data on the index test and reference standard were handled	Yes
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Yes (analyses were performed on data collected prospectively specified by study protocol).
	18	Intended sample size and how it was determined	Yes. Stated that this is an interim analysis.
Results			
Participants	19	Flow of participants, using a diagram	Described textually.
	20	Baseline demographic and clinical characteristics of participants	Yes
	21a	Distribution of severity of disease in those with the target condition	Yes
	21b	Distribution of alternative diagnoses in those without the target condition	Not applicable (no reference test)
	22	Time interval and any clinical interventions between index test and reference standard	Not applicable (no reference test)
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Not applicable (no reference test)
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Yes
	25	Any adverse events from performing the index test or the reference standard	Yes (There were no adverse events)
Discussion			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Yes
	27	Implications for practice, including the intended use and clinical role of the index test	Yes
Other information			
	28	Registration number and name of registry	Yes

	29	Where the full study protocol can be accessed	Yes (information accessible on clinicaltrials.gov)
	30	Sources of funding and other support; role of funders	Yes.