Precision Medicine and Imaging

Clinical Cancer Research

Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer

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Abstract

Purpose: Systemic androgen-signaling inhibition added to ongoing androgen-deprivation therapy (ADT) improved clinical outcomes in patients with nonmetastatic castration-resistant prostate cancer without detectable metastases by conventional imaging (nmCRPC). Prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET) detects prostate cancer with superior sensitivity to conventional imaging, but its performance in nmCRPC remains largely unknown. We characterized cancer burden in high-risk patients with nmCRPC using PSMA-PET.

Experimental Design: We retrospectively included 200 patients with nmCRPC, prostate-specific antigen (PSA) >2 ng/mL, and high risk for metastatic disease [PSA doubling time (PSADT) of $\leq$10 months and/or Gleason score of $\geq$8] from six high-volume PET centers. We centrally reviewed PSMA-PET detection rate for pelvic disease and distant metastases (M1). We further evaluated SPARTAN patients stratified by risk factors for PSMA-PET-detected M1 disease.

Results: PSMA-PET was positive in 196 of 200 patients. Overall, 44% had pelvic diseases, including 24% with local prostate bed recurrence, and 55% had M1 disease despite negative conventional imaging. Interobserver agreement was very high (κ: 0.81–0.91). PSA $\geq$ 5.5 ng/mL, locoregional nodal involvement determined by pathology (pN1), prior primary radiation, and prior salvage radiotherapy independently predicted M1 disease (all $P < 0.05$).

Conclusions: PSMA-PET detected any disease in nearly all patients and M1 disease in 55% of patients previously diagnosed with nmCRPC, including subgroups with PSADT of $\leq$10 months and Gleason score of $\geq$8. The value of PSMA-PET imaging for treatment guidance should be tested in future studies.

Introduction

Nonmetastatic castration-resistant prostate cancer (nmCRPC) is characterized by a rising prostate-specific antigen (PSA) level, castrate testosterone levels, and no evidence of distant metastases by conventional bone scan and cross-sectional imaging of the chest, abdomen, and pelvis (1). Approximately one-third of patients with nmCRPC develop distant metastases on conventional imaging within 2 years despite ongoing androgen-deprivation therapy (ADT; ref. 2). Furthermore, in patients with nmCRPC, short PSA doubling time (PSADT) has been associated with worse clinical outcomes than longer PSADT (2–4). Delaying the development of metastasis is an important treatment goal that can be achieved with early inhibition of androgen receptor signaling. Several androgen receptor inhibitors added to ongoing ADT have recently been shown to improve outcomes in nmCRPC. Apalutamide and enzalutamide have been approved for the treatment of nmCRPC based on demonstration of a significant improvement in metastasis-free survival (MFS) in the SPARTAN and PROSPER studies (5, 6). Darolutamide has also been shown to significantly prolong MFS in nmCRPC in the ARAMIS study (7). All studies included patients with no detectable metastases by conventional imaging. However, with the recent advent of new PET technologies, conventional imaging is a diagnostic tool that

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Translational Relevance

Conventional imaging (bone imaging and various CT/MRI techniques) is currently used to confirm nonmetastatic castration-resistant prostate cancer (nmCRPC) and to categorize patients for clinical trials. In this study, prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET) detected any disease in nearly all patients and metastatic disease in a significant proportion of patients with nmCRPC as assessed by conventional imaging thereby redefining the patient population through considerable stage migration. Whether local salvage approaches guided by PSMA-PET can further improve outcomes of systemic androgen-signaling inhibition must be evaluated in the context of clinical studies with careful design. The value of PSMA-PET imaging in patients with high-risk nmCRPC requires continued studies in the near future.

may no longer be sensitive enough, especially in patients with low PSA levels (8, 9).

Prostate-specific membrane antigen ligand (PSMA) PET is a novel imaging technique that targets PSMA on prostate cancer cells with ^{68}Ga-labeled and ^{18}F-labeled PET agents (10, 11). In a recent prospective, multicenter trial designed for regulatory approval, PSMA-PET demonstrated high detection rate and positive predictive value for the localization of recurrent prostate cancer (9). Detection rate and reproducibility were significantly higher when compared with recently approved ^{18}F-fluciclovine PET (12). Superior accuracy has led to use of PSMA-PET in the localization of tumor tissue in patients with biochemical recurrence or metastatic disease and in clinical staging of high-risk initial disease (10, 13). The performance of PSMA-PET in nmCRPC remains largely unknown; however, it may detect metastases earlier and therefore lead to reclassification of disease and affect subsequent treatment decisions. There is an urgent need to understand the accuracy of PSMA-PET and its impact on stage migration of patients with nmCRPC.

We aimed to determine disease extent by PSMA-PET hybrid imaging in a group of patients with high-risk nmCRPC. We further evaluated the efficacy of systemic therapy in patients who had risk factors for distant metastases (M1 disease) detected by PSMA-PET in the SPARTAN study population.

Materials and Methods

Study design and participants

Databases at six participating high-volume PET centers were retrospectively screened for patients with prostate cancer who had histologically confirmed adenocarcinoma of the prostate; underwent PSMA-PET between 2013 and 2018; and had (i) documented CRPC during continuous ADT (physician note), (ii) PSA values >2 ng/mL (PET documentation) and were at high risk for developing metastases [PSADT of $\leq$10 months during continuous ADT and/or Gleason score of $\geq$8 (PET documentation and pathology report)], and (iii) no pelvic nodes $\geq$2 cm in the short axis or any extrapelvic metastases on prior conventional imaging and on the CT/MRI part of the PSMA-PET study. Conventional imaging was confirmed centrally by one blinded expert reader. Patients were assigned to one of two distinct subgroups: (i) those with PSADT of $\leq$10 months (PSADT of $\leq$10 months group), or (ii) those with Gleason score of $\geq$8 in the absence of PSADT or in patients with PSADT of >10 months (Gleason score of $\geq$8 only group). Enrollment criteria were chosen to be similar to those of the SPARTAN, PROSPER, and ARAMIS studies, which included castration-resistant patients at high risk for developing metastasis, defined as PSADT of $\leq$10 months during continuous ADT, but with the addition of a group of patients with Gleason score $\geq$8 due to increased risk of distant metastases for this group in previous studies (2, 4).

The retrospective, investigator-initiated, multicenter PSMA-PET study was planned at the University of Duisburg-Essen (Essen, Germany), approved by the University of Duisburg-Essen Ethics Committee (18-8044-BO), and conducted and analyzed by all participating academic investigators. Inclusion criteria and analyses were prespecified at baseline. All patients gave written consent to undergo the PET scan. The requirement to obtain informed consent for inclusion in the retrospective analysis was waived by the ethics committee. Anonymized data were collected in a central database at the University of Duisburg-Essen. Clinical SPARTAN analyses were contributed for comparison and discussion by Janssen Global Services, LLC, under a nonprofit data-sharing agreement.

Procedures

PET was acquired in accordance with the international guideline as part of a PET/CT (n = 191) or PET/MRI (n = 9) examination (14). Briefly, patients received, on average, 147 MBq (range: 54–274 MBq) ^{68}Ga-PSMA-11 (n = 195), or 316 MBq (281–358 MBq) ^{18}F-DCFPyL (n = 5) via a previously established peripheral venous access. Image acquisition was started after an average of 63 minutes (range: 39–139 minutes) postinjection. Of 200 examinations, 181 (91%) were performed with contrast enhancement of the CT/MRI. Images were acquired using GE Discovery 690 (n = 19), GE Healthcare Signa 3.0T (n = 8; GE Healthcare), Siemens Biograph 64 (n = 60), Siemens Biograph mCT (n = 112), and Siemens Biograph mMR (n = 1; Siemens Healthcare GmbH) scanners. The PET was reconstructed by ordered subset expectation maximization-based algorithms. Data from the CT scan or MR image were used for attenuation correction.

PSMA-PET/CT or PET/MRI was interpreted locally (one unblinded reader) and centrally (two blinded readers, who knew the patients' most recent PSA value and prior treatments but were blinded to other imaging findings and clinical data) using published visual criteria (15) by dedicated readers after training (13). In brief, visual focal uptake of the PSMA-ligand higher than the surrounding background and not associated with physiologic uptake or known pitfalls was considered suspicious for malignancy. Adjacent background was bloodpool/muscle for nodal lesions or local recurrence, bone (marrow) for osseous lesions, and respective organ uptake for visceral lesions. OsiriX MD (Pixmeo SARL) was used for the central readings. The presence of prostate cancer (PET positive vs. negative) was recorded separately for four regions (prostate bed, pelvic nodes, extrapelvic nonbone, and bone) and 21 subregions, as described previously (13). For each region, the highest lesion maximum standardized uptake value and diameter of the largest lesion were recorded. Findings were categorized by Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria (16). Consensus

(PET positive vs. negative) was determined by majority vote among the three reads.

Patient files were reviewed for correlative and follow-up information acquired during routine clinical practice. Lesions were confirmed by change in size, disappearance or appearance on follow-up imaging, or PSA drop of ≥50% after focal salvage therapy. The local investigators interpreted the composite reference standard after reviewing follow-up information. PSMA-PET–positive findings were validated as true- or false-positive on a region basis. New management after PSMA-PET was documented using standardized categories as described previously (17).

Outcomes

The primary outcome was the detection rate of lesions, on a per-patient basis, by PSMA-PET. Secondary outcomes were lesion locations stratified by subregion, per-region positive predictive value of PSMA-PET for detection of tumor location confirmed using a composite reference standard, and interobserver agreement. Multivariate analysis was used to identify predictors of M1 disease.

Statistical analysis

Findings are presented as descriptive statistics. Interobserver agreement was determined by Fleiss' κ and interpreted by the criteria of Landis and Koch (18). Optimal PSA cutoff to determine M1 disease was defined by Youden index. OR and corresponding 95% confidence interval (CI) for M1 disease were assessed for various clinical variables using multivariable analyses. Statistical analysis was performed with R version 3.5.1 and SPSS software version 15.0 (SPSS, Inc.).

Subgroup analyses of MFS in the intent-to-treat SPARTAN population were conducted using Cox proportional hazards models for various baseline clinical characteristics, including predictors of M1 disease as determined by the PSMA-PET study. Statistical analysis of the SPARTAN data was performed using SAS version 9.4 or higher (SAS Institute, Inc.).

Results

Patient characteristics

Between April and August 2018, 8,825 records of six high-volume PET center databases were screened; 200 patients were included [Technical University of Munich (Munich, Germany): 99 (50%); University Hospital Essen (Essen, Germany): 37 (19%); University of California Los Angeles (Los Angeles, California): 24 (12%); Peter MacCallum Cancer Centre (Melbourne, Australia): 20 (10%); University of California San Francisco (San Francisco, California): 16 (8%); and Ludwig-Maximilian-University, Munich (Munich, Germany): 4 (2%; see Supplementary Table S1 and CONSORT diagram in Supplementary Fig. S1)]. PSMA-PET scans were acquired between May 2013 and August 2018. Patient clinical characteristics are summarized in Table 1, including the subgroups with PSADT of ≤10 months and Gleason score of ≥8 only in an effort to allow comparison with the SPARTAN study population described previously and evaluated for *post hoc* analyses later (806 randomized to 240-mg apalutamide once daily plus ongoing ADT and 401 to placebo plus ongoing ADT; ref. 6).

Median PSA level was 5 ng/mL in the PSMA-PET dataset at the time of imaging and 8 ng/mL in the SPARTAN dataset at inclusion, and median PSADT was 4 months for both PSMA-PET and SPARTAN datasets.

Within 3 months before PSMA-PET or as a part of the PSMA-PET assessment, 91% of patients had a CT scan, 15% had an MR image, 11% had a bone scan/^{18}F PET, and 3% had other PET scans, all demonstrating M0 stage disease (Supplementary Table S2).

PSMA-PET prostate cancer locations

Table 2 shows stage, categorized by PSMA-PET PROMISE criteria, allowing patients to be counted under multiple M1 categories. PSMA-PET was positive in 196 of 200 (98%) study patients overall, 111 of 115 (97%) with PSADT of ≤10 months and 85 of 85 (100%) with Gleason score of ≥8 only. Four patients (2%) had no prostate cancer lesions demonstrated on PSMA-PET. Despite high rates of prior local therapy of the prostate with curative intent, 48 of 200 patients (24%) showed local recurrences only by PET imaging. Overall, 87 of 200 patients (44%) had disease limited to the pelvis and 109 of 200 patients (55%) had M1 disease (58% in the PSADT of ≤10 months subgroup and 49% in the Gleason score of ≥8 only subgroup). M1 disease was located in extrapelvic nodes [77 (39%)], bone [47 (24%)], and visceral organs [12 (6%)]. N/M disease extent in PSMA-PET was unifocal in 29 (15%), oligometastatic (2–3 metastases) in 28 (14%), and multiple/disseminated (≥4 lesions) in 91 patients (46%). Fig. 1A summarizes prostate cancer locations and subregions by PSMA-PET.

Interobserver agreement

Strength of agreement among the three independent PSMA-PET readers was "almost perfect" for all four regions analyzed [κ (95% CI) for prostate bed, 0.91 (0.83–0.99); pelvic nodes, 0.81 (0.73–0.89); extrapelvic soft tissue, 0.88 (0.80–0.96); and bone, 0.81 (0.74–0.89)].

PSMA-PET positive predictive value and management

Overall, 116 regions from 75 patients (38%) were validated by histopathology [30 of 116 (26%)], follow-up imaging [81 (70%)], or PSA follow-up after focal salvage therapy [5 (4%)]. The positive predictive value of PSMA-PET was 96% based on the composite reference standard and 97% based on histopathology correlation only (Table 3).

Clinical management after PSMA-PET was recorded for 148 of 196 (76%) PET-positive patients; 122 patients had new treatment after PSMA-PET (Supplementary Table S3).

Predictors of M1 disease and MFS in the SPARTAN study

Seven clinical variables previously associated with adverse outcomes were tested for association with PSMA-PET M1 disease (Table 4). PSADT, tested with univariable analysis, was available for 132 of 200 (66%) patients; other variables included in the multivariable analysis were available for all patients. ROC–derived cutoff for PSA at the time of PET ≥ 5.5 ng/mL (OR, 2.0; 95% CI, 1.1–3.6; $P = 0.03$), locoregional nodal involvement determined by pathology (pN1; OR, 2.7; 95% CI, 1.3–6.0; $P = 0.01$), primary radiotherapy of the prostate (OR, 3.1; 95% CI, 1.5–6.1; $P = 0.02$), and prior attempted salvage radiotherapy (OR, 4.6; 95% CI, 2.0–11.0; $P < 0.01$) were significantly associated with M1 disease.

Enzalutamide and apalutamide were shown to be consistently favorable for the primary endpoint of MFS (5, 6). Here, we

Table 1. Patient characteristics

	All PSMA-PET patients ($N = 200$)	PSADT of ≤10 months ($n = 115$)	Gleason score ≥8 only ($n = 85$)	SPARTAN ($N = 1,207$)
Age (years)				
Median (range)	71 (46–94)	71 (46–94)	73 (48–86)	74 (48–97)
Prostate-specific antigen (ng/mL)				
Median (range)	5.3 (1.3[a]–263.8)	5.2 (1.3[a]–263.8)	5.4 (2.0–99.1)	7.8 (0.1–294.8)
Prostate-specific antigen doubling time (months)	$n = 132$		$n = 17$	
Median (range)	4.0 (0.0–90.0)	3.6 (0.0–10.0)	Not applicable	4.4 (0.7–10.0)
≤6	85 (64)	85 (74)	Unknown	860 (71)
>6	47 (36)	30 (26)	17 (100)	347 (29)
Gleason score	$n = 193$	$n = 108$		$n = 1171$
<8	42 (22)	42 (39)	0 (0)	661 (56)
≥8	151 (78)	66 (61)	85 (100)	510 (44)
Prior therapy				
Prior prostate cancer–related surgery	130 (65)	79 (69)	51 (60)	682 (57)
Prior prostate cancer–related radiotherapy	104 (52)	69 (60)	35 (41)	696 (58)

NOTE: Data are number of patients (%) unless otherwise indicated.
[a]Two eligible patients had prostate-specific antigen ≤2 ng/mL at time of PSMA-PET.

evaluated the above predictors of M1 disease in *post hoc* SPARTAN subgroup analyses of MFS. In this *post hoc* analysis, apalutamide provided significant benefit in all clinically relevant subgroups of patients, including those with disease characteristics predictive of M1 disease as determined in the current PSMA-PET study (Fig. 1B).

Discussion

This study assessed disease extent detected by PSMA-PET in high-risk patients with CRPC defined as nonmetastatic by conventional imaging with characteristics similar to those of the recent phase III SPARTAN, PROSPER, and ARAMIS study patients. At the recruiting sites, PSMA-PET is used primarily in patients with hormone-sensitive prostate cancer for staging of biochemically recurrent disease or for advanced disease (Supplementary Fig. S1; refs. 19, 20). Thus, although we screened 8,825 records, only 200 patients fulfilled our inclusion criteria.

Table 2. Stage categorized by PSMA-PET PROMISE criteria (16)

miTNM stage, *n* (%)	All patients ($N = 200$)	PSADT of ≤10 months ($n = 115$)	Gleason score of ≥8 only ($n = 85$)
M0	**91 (46)**	**48 (42)**	**43 (51)**
T0N0M0	4 (2)	4 (3)	0 (0)
TrN0M0	48 (24)	22 (19)	26 (31)
T0N1M0	13 (7)	11 (10)	2 (2)
TrN1M0	26 (13)	11 (10)	15 (18)
M1	**109 (55)**	**67 (58)**	**42 (49)**
T0N0M1	31 (16)	15 (13)	16 (19)
TrN0M1	9 (5)	6 (5)	3 (4)
T0N1M1	42 (21)	30 (26)	12 (14)
TrN1M1	27 (14)	16 (14)	11 (13)
Extrapelvic disease[a]			
M1a (lymph node)	77 (39)	51 (44)	26 (31)
M1b (bone)	47 (24)	26 (23)	21 (25)
M1c[b] (visceral)	12[b] (6)	8 (7)	4 (5)
N/M disease extent			
Unifocal (1)	29 (15)	19 (17)	10 (12)
Oligometastatic (2–3)	28 (14)	16 (14)	12 (14)
Multiple/disseminated (≥4)	91 (46)	54 (47)	37 (44)

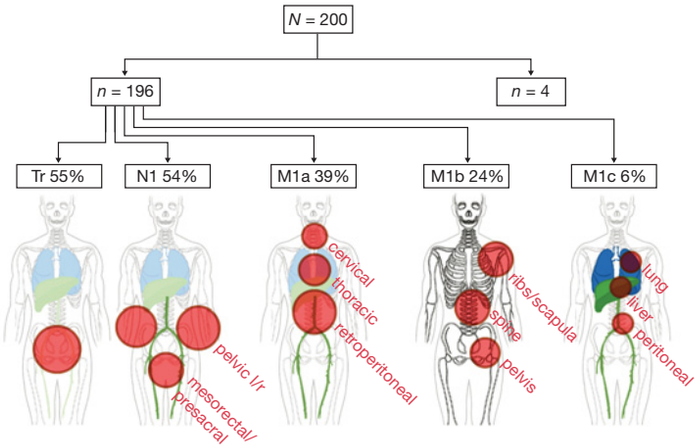
NOTE: Numbers in boldface represent the total.
Abbreviations: miTNM, molecular imaging TNM; TNM, tumor, nodes, metastases; Tr, local recurrence in the prostate bed.
[a]PROMISE allows patients to be counted under multiple M1 categories.
[b]Lung ($n = 4$), liver ($n = 5$), peritoneum ($n = 4$), and connective tissue ($n = 1$) with overlap.

PSMA-PET imaging was positive in 98% of patients, with similar detection rates in patients with PSADT of ≤10 months (97%) and those with a Gleason score of ≥8 (100%). After PSMA-PET, a significant proportion of patients had stage migration: 24% of patients had disease confined to the prostate bed, 44% had disease limited to the pelvis, and 55% had M1 disease. The latter included 58% of patients with a PSADT of ≥10 months and 49% of patients with a Gleason score of ≥8 only. M1 disease was located in extrapelvic nodes in 39%, bone in 24%, and visceral organs in 6% of patients. Multivariable analysis demonstrated several risk factors for M1 disease, including PSA. This is consistent with findings from a recent meta-analysis of PSMA-PET studies showing increasing positivity of PSMA-PET with increasing pre-PET PSA (21). Notably, the M1 detection rate did not correlate with PSADT or Gleason score. Thus, PSMA-PET provides valuable information in addition to known risk factors.

Interobserver agreement among the three independent PSMA-PET readers was "almost perfect" according to Landis and Koch criteria and the positive predictive value was high at 96% to 97%, similar to previous reports (13, 21, 22). Therefore, PSMA-PET can be considered an accurate and highly reproducible staging tool for nmCRPC and high risk of progression defined by short PSADT or high Gleason scores.

Patients in our study were imaged and treated before data from SPARTAN, PROSPER, and ARAMIS were reported and, thus, before approval of apalutamide and enzalutamide for nmCRPC. Following PSMA-PET, about two-thirds of patients with Tr/N1 disease underwent PET-targeted salvage therapy. The specific impact of PSMA-PET on management of the overall cohort cannot be evaluated with our retrospective study design as it lacked standardized questionnaires to assess disease management and the influence of imaging. However, considerable change in clinical management based on PSMA-PET results has been reported previously in the setting of biochemical recurrence (11, 17, 23, 24). Whether these changes in management lead to improved oncologic outcomes should be evaluated in the context of clinical trials (25).

A



B

Variable	Median (months) Placebo	Median (months) Apalutamide	Hazard ratio (95% CI)	Events/N Placebo	Events/N Apalutamide
All patients	16.2	40.5	0.30 (0.24–0.36)	194/401	184/806
Age, years					
<65	7.3	NE	0.14 (0.08–0.27)	25/43	19/106
≥65	18	40.5	0.33 (0.26–0.40)	169/358	165/700
Baseline ECOG					
0	15.7	40.5	0.27 (0.21–0.34)	150/311	133/623
1	18.4	27.8	0.40 (0.27–0.60)	44/89	51/183
Gleason score					
<8	21.2	40.5	0.36 (0.27–0.47)	95/218	98/443
≥8	11.1	NE	0.22 (0.16–0.30)	93/169	79/341
Baseline PSA					
<5.5	18.5	NE	0.25 (0.17–0.38)	60/148	40/298
≥5.5	14.5	40.5	0.30 (0.24–0.38)	134/253	144/508
PSA doubling time, months					
≤6	14.6	40.5	0.29 (0.23–0.36)	149/284	147/576
>6	22.8	NE	0.30 (0.20–0.47)	45/117	37/230
Locoregional disease					
N0	18.3	40.5	0.33 (0.26–0.41)	155/336	153/673
N1	10.8	NE	0.15 (0.09–0.25)	39/65	31/133
Prestudy local therapy					
RPE only	11.1	40.5	0.18 (0.12–0.27)	63/113	52/247
PRT only	14.6	NE	0.16 (0.08–0.33)	23/34	12/58
RPE and SRT	18.2	NE	0.32 (0.12–0.85)	10/19	7/29
No RPE/PRT	19	NE	0.41 (0.2–0.54)	98/235	113/472

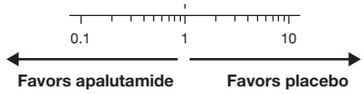


Figure 1.

Overview of prostate cancer lesion location depicted on PSMA-PET and subgroup analysis of SPARTAN patients. **A,** Three subregions with highest disease prevalence (red circles) are given for each miT/N/M stage. Circle area is proportional to prostate cancer lesion prevalence in the respective subregion. PSMA-PET PROMISE criteria allow patients to be counted under multiple categories. **B,** Metastasis-free survival in SPARTAN patients by subgroups including those stratified by risk factors of M1 disease by PSMA-PET. Baseline Eastern Cooperative Oncology Group (ECOG) performance status and variables associated with M1 disease in the PSMA-PET dataset were included. NE, not estimable; PRT, primary radiotherapy; RPE, radical prostatectomy; SRT, salvage radiotherapy.

Table 3. Lesion validation on a region basis[a]

PSMA-PET–positive regions	*n*	Prostate cancer confirmed	Prostate cancer ruled out	PPV (%)
Composite reference standard	116	111	5	96
Histopathology	30	29	1	97

Abbreviation: PPV, positive predictive value.
[a]A total of 116 regions from 75 patients (38%) were validated.

Results from this study have potential implications for the nmCRPC treatment paradigm. The SPARTAN, PROSPER, and ARAMIS studies have shown that proactive treatment of high-risk patients with nmCRPC with systemic therapies added to ongoing ADT can delay the transition to mCRPC (5–7, 20, 26). In our PSMA-PET study, baseline patient characteristics were generally similar to those of the SPARTAN, PROSPER, and ARAMIS study populations. In SPARTAN, the benefits of apalutamide were consistent in all prespecified subgroups (6). Not surprisingly, the benefit was observed in SPARTAN patient subgroups at high risk for distant metastases defined by PSMA-PET. Our data indicate that metastatic disease on PSMA-PET should not disqualify patients from receiving treatment with androgen receptor inhibitors. Intensified systemic treatment should be the standard of care for patients with nmCRPC and short PSADT. On the other hand, effective targeting of local–regional disease on PSMA-PET may further improve outcomes and should be evaluated in the context of clinical studies. Of note, not all patients included in our study had a bone scan prior to PET imaging at the time of castration resistance. However, at low PSA levels, bone scan positivity is unlikely (27). Some uncertainty in the interpretation of our findings arises from the inclusion of patients with Gleason score of $\geq$8 only and the analysis of separate datasets with potential overlap. Despite similar characteristics, patients retrospectively evaluated by PSMA-PET were not treated with apalutamide, and SPARTAN outcomes may not apply in patients in the Gleason score of $\geq$8 only group. Also, for the entire group, the value of PSMA-PET imaging for treatment guidance and clinically relevant oncologic outcomes remains unproven.

Results from this study have implications for the design of future clinical trials (20). Because of its excellent sensitivity and specificity compared with currently recommended workup for progression [X-ray, CT, MRI, or various PET technologies (20)], PSMA-PET may become a standard diagnostic tool for patients with recurrent/progressive prostate cancer. PSMA-PET should be implemented with conventional imaging for baseline staging and perhaps even follow-up in future clinical trials to evaluate the therapeutic benefit of new interventions with endpoints such as MFS or progression-free survival. Until then, clinicians must be aware that available clinical phase III trial data in patients with prostate cancer have been based on conventional imaging. Thus, disease stage (M0 vs. M1) as determined by conventional imaging should guide the decision for or against intensified systemic treatment.

In conclusion, we demonstrate extremely high PSMA-PET positivity and significant stage migration in patients with CRPC shown to be nonmetastatic by conventional imaging. Our study shows that 55% of patients had distant metastatic disease, and 44% had pelvic disease by PSMA-PET imaging. Stage migration was similar in patients with a PSADT of $\leq$10 months and Gleason score of $\geq$8. Future indication statements for systemic treatment may be adapted to accurately describe the respective trial populations, for example, nonmetastatic by conventional imaging. Patients who meet indication criteria should receive such treatment even if they have metastases detected by PSMA-PET. Future clinical trials correlating PSMA-PET staging and data on outcomes such as MFS and overall survival are clearly needed.

Table 4. Multivariable analysis of odds for PSMA-PET M1 disease ($n = 200$)

Variable	*n* (%)	OR	95% CI	*P*
Age $\geq$65 years	151 (76)	0.6	0.3–1.3	0.23
Gleason score of $\geq$8	151 (76)	1.1	0.5–2.3	0.80
PSA $\geq$5.5 ng/mL	97 (49)	2.0	1.1–3.6	0.03[a]
PSADT of $\leq$6 months ($n = 132$[b])	85 (43)	1.6	0.8–3.3	0.22
Locoregional disease pN1	45 (23)	2.7	1.3–6.0	0.01[a]
RPE and SRT	40 (20)	4.6	2.0–11.0	<0.01[a]
PRT	64 (32)	3.1	1.5–6.1	0.02[a]

Abbreviations: PRT, primary radiotherapy; RPE, radical prostatectomy; SRT, salvage radiotherapy.
[a]$P < 0.05$.
[b]On the basis of univariate analysis.

Disclosure of Potential Conflicts of Interest

W.P. Fendler is an employee/paid consultant for Endocyte and Ipsen and reports receiving other remuneration from RadioMedix. M. Weber reports receiving speakers bureau honoraria from BTG TheraSphere. M.S. Hofman reports receiving speakers bureau honoraria from Ipsen, Sanofi Genzyme, and Janssen, and is an unpaid consultant/advisory board member for Endocyte. J. Calais is an employee/paid consultant for Blue Earth Diagnostics and RadioMedix, and holds ownership interest (including patents) in Progenics Pharmaceuticals. J. Czernin holds ownership interest (including patents) in Sofie Biosciences and Trethera Corporation. H. Ilhan reports receiving commercial research grants from Novartis and reports receiving speakers bureau honoraria from Bayer. F. Saad is an employee/paid consultant for Janssen, Astellas, Sanofi, and Bayer. E.J. Small reports receiving speakers bureau honoraria from Fortis, Janssen, Harpoon Therapeutics, Beigene Therapeutics, and Tolero. M.R. Smith reports receiving speakers bureau honoraria from Astellas, Bayer, Pfizer, and Janssen. A. Londhe is an employee/paid consultant for Janssen Research & Development and holds ownership interest (including patents) in Johnson & Johnson. A. Lopez-Gitlitz is an employee/paid consultant for Janssen Research & Development and holds ownership interest (including patents) in Johnson & Johnson. S. Cheng is an employee/paid consultant for Janssen Research & Development and holds ownership interest (including patents) in Johnson & Johnson. T. Maurer reports receiving speakers bureau honoraria from Astellas, Janssen, Bayer, and Sanofi, and is an unpaid consultant/advisory board member for Blue Earth Diagnostics. K. Herrmann is an employee/paid consultant for Bayer, IPSEN, and Adacap; reports receiving speakers bureau honoraria from Bayer, Sirtex, Adacap, Curium, Endocyte, BTG, IPSEN, Siemens Healthineers, GE Healthcare, and Amgen; and holds ownership interest (including patents) in Sofie Biosciences. M. Eiber holds ownership interest (including patents) in rhPSMA and reports receiving other remuneration from BED/ABX. B. Hadaschik is an employee/paid consultant for Janssen, Lightpoint Medical, Uromed, Bristol-Myers Squibb, Bayer, Astellas, and AstraZeneca, and reports receiving commercial research grants from Janssen. No potential conflicts of interest were disclosed by the other authors.

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