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PSMA-ligand PET for early castration-resistant prostate cancer: a retrospective single-center study

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ABSTRACT

Low detection rate of conventional imaging and unspecific fluctuations of prostate-specific antigen can hamper early diagnosis of castration-resistant prostate cancer (CRPC). We thus assessed the value of PSMA-PET/CT in the detection of early CRPC (PSA ≤3 ng/mL).

Methods: We identified 55 patients with early CRPC from our institutional database. PSMA-PET/CT and its CT component were interpreted independently by three blinded readers. Primary endpoint was the per-patient detection rate, secondary endpoints were interobserver agreement, and predictors of PET-positivity.

Results: PSMA-PET/CT was positive in 41/55 (75%) patients. 16/55 (29%) patients had local disease only, 25/55 (45%) had M1-disease. Overall PSMA-PET/CT interobserver agreement was substantial by Landis and Koch criteria (Fleiss' kappa 0.77).

Conclusions: PSMA-PET/CT localized prostate cancer lesions in 75% and M1-disease in 45% of patients. Detection of early CRPC facilitates disease-delaying therapies for local/oligometastatic disease. PSMA-PET/CT is of value in early CRPC and should be included in EAU/PCWG3 CRPC entry criteria.

INTRODUCTION

Castration-resistant prostate cancer (CRPC) is characterized by biochemical or radiographic disease progression despite effective androgen deprivation therapy (*1*). Biochemical progression is defined as three consecutive prostate-specific antigen (PSA) rises, each at least one week apart with two 50% increase over the nadir. However, pharmacologic androgen axis treatment was demonstrated to result in potentially disconnected effects on PSA expression and tumor growth (*2-4*). This is of importance in patients with low but rising PSA as the only evidence of disease progression (*5*). Therefore, the diagnosis of CRPC requires repeat measurements and a bottom PSA threshold of 2.0 ng/mL (EAU)/1.0 ng/mL (PCWG3) (*1,5*). In addition, the assessment of radiographic progression is hampered considerably by low detection rates for PSA≤3 ng/mL. In recent years, systemic treatment in CRPC patients who are non-metastatic by conventional imaging (nmCRPC) showed improvements in metastasis-free survival for apalutamide, darolutamide and enzalutamide. In a prior study by our group, PSMA PET uncovered disease burden in almost all nmCRPC patients demonstrating distant disease in 55% and locoregional disease only in 44% of nmCRPC patients (*6*). Hence, in the era of precision medicine the unprecedented accuracy of PSMA PET could lead the way towards a more personalized treatment strategy. We hypothesize that PSMA PET will improve stratification of nmCRPC candidates for local and/or systemic treatment even before PCWG3/EAU thresholds (PSA≤3 ng/mL).

MATERIALS AND METHODS

Through screening of n=1965 prostate cancer patients at our institutional database we identified 55 patients with (a) histopathologically proven adenocarcinoma of the prostate, (b) status post prostatectomy / primary radiotherapy, (c) rising PSA during continuous androgen deprivation therapy, (d) PSA <3 ng/mL at the time of PSMA-PET/CT. Patients were stratified according to PSA level at imaging, into (a) <1.0 ng/mL (pre-PCWG group); (b) 1.0-<2.0 ng/mL (early PCWG group); (c) 2.0-≤3.0 ng/mL (early EAU group). 9 patients were reported previously (*6*).

PSMA-PET/CT was performed on a Siemens Biograph mCT after the administration of a median of 110 (interquartile range: 35) Megabecquerel ^{68}Ga-PSMA11 with a median uptake time of 70 (interquartile range: 31) minutes.

PET/CT and the CT component were anonymized separately and interpreted visually by three independent blinded readers at random order with ≥2 weeks between PET/CT and CT reading sessions. Lesion number, size and standardized uptake values were assessed separately for 4 regions (prostate bed, pelvic lymph nodes, soft tissue including extrapelvic lymph nodes, bones) and 21 subregions, as published previously (*7*). Statistical consensus was positive, when ≥2/3 readers rated a region positive.

Primary endpoint was PSMA-PET/CT versus CT lesion detection rate on a per-patient basis. Secondary endpoints were reproducibility, lesion detection stratified by PSA, and predictors for PET-positivity or PET-M1 disease.

Interobserver agreement was determined by Fleiss' kappa and interpreted by the criteria of Landis and Koch (*6*). Odds ratio and corresponding 95% confidence interval for PET-positivity were assessed for different variables using multivariate analyses. Statistical analysis was performed with R version 3.5.1 and SPSS software version 24.0.

RESULTS

Median PSA at the time of PET was 1.5 ng/mL; median patient age was 70 years. 27/44 patients (61%) had a PSA doubling time ≤6 months. Gleason Score was ≥8 in 28/47 patients (60%). 44/55 patients (80%) had undergone primary prostatectomy, 11 patients had primary radiotherapy (20%) (Supplemental Table 1).

PSMA-PET/CT detected prostate cancer lesions in 41/55 (75%) patients, CT alone in 18/55 (33%) of patients. All CT lesions were also seen on PET/CT. Per-patient detection rate for PSMA-PET/CT stratified by PSA is shown in Table 1. In summary, 29% (16/55) patients had locoregional disease only, 45% (25/55) M1 disease. 23/34 (68%) patients with N/M findings had uni- or oligometastatic (2-5 lesions) disease extent. Interobserver agreement for PSMA-PET/CT was superior to CT (overall: κ 0.77 vs. 0.29; local tumor recurrence: κ 0.75 vs. 0.14; N1-disease: κ 0.79 vs. 0.53; M1a/c-disease: κ 0.91 vs. 0.14; M1b-disease: κ 0.80 vs. 0.47).

DISCUSSION

In line with prior publications, PSMA-PET/CT detected lesions in 75% of patients with early CRPC even below PCWG3/EAU thresholds and reliably distinguished local versus distant disease while CT demonstrated low detection rate and slight reproducibility (*8*). Of note, PSMA PET resulted in stage migration to PET-M1 disease in 45% of patients, potentially affecting management. Of the assessed risk factors, only primary radiation therapy was significantly associated with a lower rate of PET-M1-disease (p=0.02, OR 0.1), which may be biased by an expected higher PSA nadir in this group; no other risk factor predicted PET-positivity indicating additional value of PSMA-PET/CT (Table 2).

In our prior study PSMA-PET localized extra-pelvic disease in about half of nmCRPC patients with biochemical or histopathologic risk features (*6*). A joint post-hoc analysis including Fendler et al. (*6*) and the presented patients demonstrated a higher proportion of metastatic disease and lower proportion of uni- to oligometastatic findings with increasing PSA (Figure 1). Thus, early diagnosis by PSMA-PET/CT may provide additional value for disease-delaying metastasis-directed therapies. While such treatments may postpone the start of other more toxic regimens their impact on overall survival was not demonstrated, yet (*9*). Inversely, identification of distant disease on PSMA-PET/CT may be an indicator of poor prognosis as shown previously by Emmett et al in patients with biochemical recurrence (BCR) (*10*). Consequently, the results of our study contribute to the growing body of evidence for high prevalence of PET-M1 disease in patients nonmetastatic by conventional imaging. Degree of upstaging by PSMA-PET/CT depends on extent of conventional imaging, however prior head-to-head comparison indicates low impact of additional MRI and/or bone scan on early detection of metastases (*11-13*). In the light of recent clinical trials showing improved outcome in nmCRPC patients, such as SPARTAN (*14*) or ARAMIS (*15*), we assume that about half of subjects enrolled in these trials did indeed have metastatic disease detectable by PET. The clinical significance of PET-M1-disease in CRPC patients, however, has yet to be determined.

PSMA-PET/CT has become standard of care imaging for BCR following prostatectomy or radiotherapy. We anticipate large patient groups with available PSMA-PET/CT staging at baseline of subsequent PSA rise. Initial to follow-up PSMA-PET/CT progression may serve as new criteria for CRPC. Frameworks to assess PSMA-PET/CT disease progression have been proposed previously (*16*). Given limitations of PSA, such as unspecific fluctuations in the low detection

range, PSMA-PET/CT may serve as complementary or even independent biomarker of early CRPC tumor load (*2*).

Limitations of our study include its retrospective single-center design, small sample size, as well as the lack of serum testosterone levels at the time of PET and missing correlational bone scan or magnetic resonance imaging in all patients.

CONCLUSION

PSMA-PET/CT detects prostate cancer in most patients with early CRPC even below the valid EAU/PCWG3 PSA thresholds. Early staging is associated with a higher rate of targetable local or uni- to oligometastatic disease, which may provide value for metastasis-directed therapy. Now most patients with BCR will undergo baseline PSMA-PET/CT and any PET-based disease progression under effective androgen-deprivation may serve as new entry criteria for CRPC. These aspects need attention in future clinical trials on CRPC imaging and targeted therapy.

DISCLOSURE:

Manuel Weber is on the speakers' bureau for Boston scientific. Claudia Kurek has nothing to disclose. Boris A. Hadaschik reports advisory roles for ABX, Bayer, Lightpoint Medical, Inc., Janssen R&D, Bristol-Myers-Squibb and Astellas; research funding from Profound Medical, German Cancer Aid, German Research Foundation, Janssen R&D, Bristol-Myers-Squibb and Astellas; and travel support from AstraZeneca, Janssen R&D and Astellas. Wolfgang P. Fendler is a consultant for Ipsen, Endocyte, and Boston scientific, and he received personal fees from RadioMedix outside of the submitted work; Wolfgang P. Fendler received financial support from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, grant FE1573/3-1 / 659216), Mercator Research Center Ruhr (MERCUR, An-2019-0001), IFORES (D/107-81260, D/107-30240), Doktor Robert Pfleger-Stiftung, and Wiedenfeld-Stiftung/Stiftung Krebsforschung Duisburg. Tobias Maurer reports advisory role for BlueEarth Diagnostics, ROTOP. Matthias Eiber reports an advisory role for Blue Earth Diagnostics and patent application for rhPSMA.

KEY FINDINGS

Question: Can PSMA PET accurately localize prostate cancer in nonmetastatic patients with beginning castration resistance?

Pertinent findings: PSMA PET reveals prostate cancer in the majority of patients and metastatic disease in almost half of the study cohort.

Implications for patient care: PSMA PET has the potential to complement PSA and radiographic assessment in the detection of disease progression.

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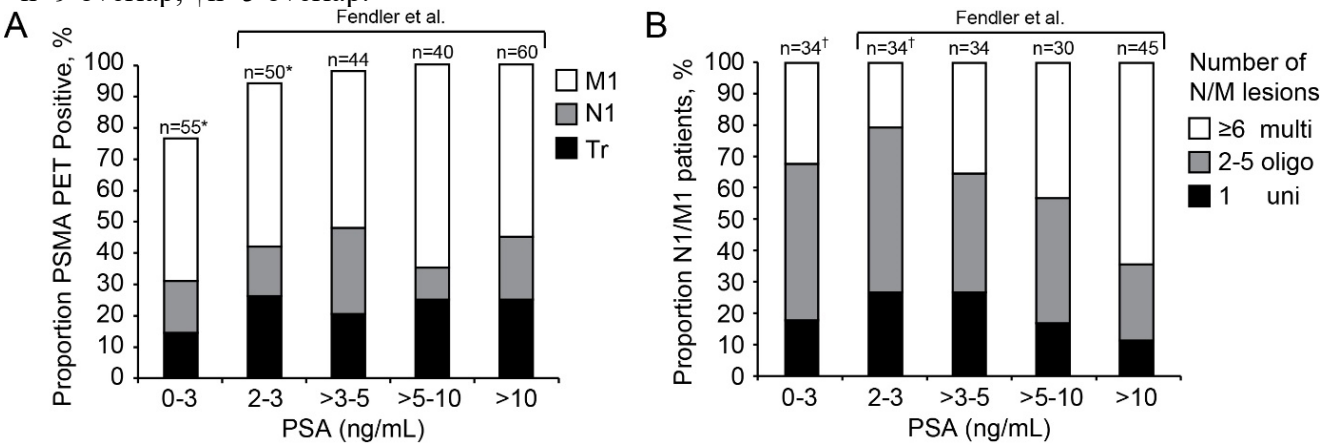
FIGURES

Figure 1: Proportion of local (Tr), nodal (N1) or distant (M1) disease **(A)** and N/M disease extent **(B)** stratified by PSA range for the presented patients including previous data by Fendler et al. (*6*). Six patients in the Fendler et al. study were excluded due to PSA ≥8 weeks before PET. *n=9 overlap; †n=5 overlap.



TABLES

Table 1: Disease extent stratified by PSA at time of imaging according to PROMISE (n=55) (*17*). Data are number of patients (%).

PSMA-PET/CT findings	**Total (n=55)**	**Pre-PCWG3 PSA: <1.0 ng/mL (n=21)**	**Early PCWG3 PSA: 1.0-<2.0 ng/mL (n=11)**	**Early EAU PSA: 2.0-≤3.0 ng/mL (n=23)**
Negative	**14 (25)**	**10 (48)**	**0 (0)**	**4 (17)**
Tr/N1 only	**16 (29)**	**6 (29)**	**3 (27)**	**7 (30)**
Local recurrence (Tr)	9 (16)	3 (14)	1 (9)	5 (22)
Pelvic lymph nodes (N1)	9 (16)	3 (14)	2 (18)	4 (17)
Any M1	**25 (45)**	**5 (24)**	**8 (73)**	**12 (52)**
Extrapelvic lymph nodes (M1a)	15 (27)	3 (14)	3 (27)	9 (39)
Bone (M1b)	13 (24)	3 (14)	4 (36)	6 (26)
Soft tissue/ visceral (M1c)	2 (4)	0 (0)	2 (18)	0 (0)
N/M disease extent	**n=34**	**n=8**	**n=10**	**n=16**
Unifocal (1)	6 (18)	2 (25)	1 (10)	3 (19)
Oligometastatic (2-5)	17 (50)	4 (50)	9 (90)	4 (25)
Multiple/ disseminated (≥6)	11 (32)	2 (25)	0 (0)	9 (56)

Table 2: Regression analysis of clinical parameters and their respective risk for PSMA-PET/CT detection (n=55).

Variable	n (%)	OR for PET positive (95% CI)	p-value	OR for PET M1 (95% CI)	p-value
Age ≥65	40 of 55 (73)	1.3 (0.3-4.9)	0.75	0.9 (0.3-3.1)	0.91
Gleason score ≥8	28 of 47 (60)	1.3 (0.2-5.1)	0.70	1.2 (0.4-3.9)	0.77
PSA ≥1.5 ng/mL	28 of 55 (51)	3.0 (0.8-11.3)	0.11	2.0 (0.7-5.8)	0.22
PSA doubling time ≤6 months	27 of 44 (61)	0.8 (0.2-3.5)	0.82	1.3 (0.4-4.2)	0.70
Loco-regional disease pT3/pT4*	20 of 31 (65)	1.5 (0.2-9.4)	0.60	1.2 (0.3-5.2)	0.81
Loco-regional disease pN1**	12 of 30 (40)	1.4 (0.2-9.4)	0.71	0.6 (0.1-2.5)	0.46
Primary radiation therapy	11 of 55 (20)	0.5 (0.1-2.1)	0.36	0.1 (0.0-0.7)	0.02*

OR=Odds Ratio; CI=Confidence Interval
*analyzed for all patients post prostatectomy with known pT-stage
**analyzed for all patients post lymphadenectomy with known pN-stage
indicated.

SUPPLEMENTAL MATERIAL

Supplemental Table 1: Patient characteristics.

	All patients (n=55)
Age (years)	**(n=55)**
Median (range)	70 (56–86)
Prostate-specific antigen (ng/mL)	**(n=55)**
Median (range)	1.5 (0.1 – 3.0)
Prostate-specific antigen doubling time (months)	**(n=44)**
≤6	27 (61)
>6	17 (39)
Gleason score	**(n=47)**
< 8	19 (40)
≥ 8	28 (60)
Initial treatment	**(n=55)**
Prostatectomy	44 (80)
Lymph node resection	32 (58)
Radiation therapy	11 (20)

Data are number of patients (%) unless otherwise indicated.