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Brief Correspondence

Prostate-specific Membrane Antigen Positron Emission Tomography–detected Disease Extent and Overall Survival of Patients with High-risk Nonmetastatic Castration-resistant Prostate Cancer: An International Multicenter Retrospective Study

Manuel Weber[a,†], *Wolfgang P. Fendler*[a,†,*], *Aravind S. Ravi Kumar*[b,c,d], *Jeremie Calais*[e], *Johannes Czernin*[e], *Harun Ilhan*[f], *Fred Saad*[g], *Alexander Kretschmer*[h,i], *Turkay Hekimsoy*[j], *Sabine D. Brookman-May*[h,i], *Suneel D. Mundle*[k], *Eric J. Small*[l], *Matthew R. Smith*[m], *Paola M. Perez*[l], *Thomas A. Hope*[l], *Ken Herrmann*[a], *Michael S. Hofman*[b,c,d], *Matthias Eiber*[j,‡], *Boris A. Hadaschik*[n,‡]

[a] *Department of Nuclear M*
edicine, University of Duisburg-Essen and German Cancer Consortium (DKTK)–University Hospital Essen, Essen, Germany; [b] *Molecular Imaging and Therapeutic Nuclear Medicine, Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia;* [c] *Prostate Cancer Theranostics and Imaging Centre of Excellence (ProsTIC), Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia;* [d] *Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia;* [e] *University of California Los Angeles, Los Angeles, CA, USA;* [f] *Department of Nuclear Medicine, Ludwig-Maximilians-University, Munich, Germany;* [g] *Department of Surgery, Université de Montréal, Montréal, QC, Canada;* [h] *Department of Urology, Ludwig-Maximilians-University, Munich, Germany;* [i] *Janssen Research & Development, Spring House, PA, USA;* [j] *Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany;* [k] *Janssen Research & Development, Raritan, NJ, USA;* [l] *Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA;* [m] *Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA;* [n] *Department of Urology, University of Duisburg-Essen and German Cancer Consortium (DKTK)–University Hospital Essen, Essen, Germany*

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Abstract

Previously, we demonstrated that prostate-specific membrane antigen positron emission tomography (PSMA-PET) revealed distant metastases in 109/200 patients (39% distant nodes, 24% bone, and 6% visceral organ) with nonmetastatic castration-resistant prostate cancer (nmCRPC) and high-risk features (International Society of Urological Pathology score ≥4 and/or prostate-specific antigen doubling time ≤10 mo) without metastases by conventional imaging. However, the impact of disease extent determined by PSMA-PET on patient outcomes is unknown. We followed these 200 patients for a median of 43 mo after PSMA-PET and retrospectively assessed the association between patient characteristics, PSMA-PET findings, treatment management, and outcomes using a Kaplan-Meier model and Cox multivariable regressions. Among assessed disease characteristics, polymetastatic disease (five or more distant lesions on PET) was

† These authors contributed equally.

‡ These authors contributed equally.

* Corresponding author. University of Duisburg-Essen and German Cancer Consortium (DKTK)–University Hospital Essen, Hufelandstraße 55, 45147 Essen, Germany. Tel. +49 201 723 2032; Fax: +49 201 723 5658.
E-mail address: wolfgang.fendler@uk-essen.de (W.P. Fendler).

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resistant prostate cancer
SPARTAN
Prostate cancer

independently associated with shorter overall survival (OS; median 61 mo vs not reached; hazard ratio [95% confidence interval], 1.81 [1.00–3.27]; p = 0.050) and time to new metastases (median 38 vs 60 mo; 1.80 [1.10–2.96]; p = 0.019), and initial pN1 status with shorter OS (55 mo vs not reached; 1.94 [1.12–3.37]; p = 0.019). Following PSMA-PET, locoregional salvage therapies were used most commonly in no/local disease (58%), and androgen receptor signaling inhibitors were used in distant metastatic disease (51%). PSMA-PET provides additional risk stratification for patients with nmCRPC. Polymetastatic disease (five or more distant lesions) is associated with worse outcomes.
Patient summary: A novel sensitive imaging technology, called prostate-specific membrane antigen positron emission tomography (PSMA-PET), allows doctors to detect the spread of prostate cancer, known as distant metastases, earlier and more accurately than in the past. In our study, PSMA-PET detected none to many metastases in patients who were considered free of distant metastasis by conventional imaging. These findings predicted outcomes and were used to select appropriate treatment.

Nonmetastatic castration-resistant prostate cancer (nmCRPC) is defined by rising prostate-specific antigen (PSA) levels despite androgen deprivation therapy without evidence of metastasis on conventional imaging such as computed tomography or bone scintigraphy. The phase 3 trials SPARTAN, PROSPER, and ARAMIS have shown that apalutamide, enzalutamide, and darolutamide, respectively, prolonged metastasis-free survival and overall survival (OS) significantly in patients with nmCRPC and PSA doubling time (PSADT) <10 mo [1–6]. However, tumor detection by conventional imaging is limited by low sensitivity. In contrast, a growing body of evidence shows considerably higher detection rates, specificity, and subsequent impact on disease management for prostate-specific membrane antigen positron emission tomography (PSMA-PET) in various clinical scenarios [7].

In a retrospective multicenter study of 200 nmCRPC patients with inclusion criteria similar to those of SPARTAN, we demonstrated that PSMA-PET detected metastatic disease in 55% of patients, leading to considerable upstaging [8]. Yet, the clinical relevance of M1 disease by PSMA-PET remains uncertain without outcome data.

To address this knowledge gap, we evaluated our landmark nmCRPC cohort for an extended follow-up to assess PSMA-PET prognostic value for OS and time to new metastases (TTM) along with implemented patient disease management.

Patient enrollment, and image acquisition and interpretation have been described previously [8]. In brief, the databases of six high-volume PET centers were screened for patients with nmCRPC and (1) PSADT <10 mo and/or (2) International Society of Urological Pathology (ISUP) score ≥4, who underwent PSMA-PET. PSMA-PET was performed at a median of 59 min (interquartile range [IQR], 18) after the injection of a median of 143 MBq (IQR, 59) ^{68}Ga-PSMA-11 (n = 195), or 316 MBq (281–358) ^{18}F-DCFPyL (n = 5). Scans were interpreted by one unblinded local reader per the clinical standard and two blinded central readers according to the PROMISE criteria [9]. Whole-body PSMA-positive tumor volume (PSMA-TV) and per-region volume segmentation were performed using qPSMA, a semiautomatic software package for whole-body tumor burden assessment in patients with prostate cancer [10].

The primary endpoint was OS, defined as the time from PSMA-PET to death for any cause; the secondary endpoints were TTM, defined as the time from PSMA-PET to either death or new distant metastases on any imaging modality, and implemented first- and second-line treatment after baseline PSMA-PET. Time-to-events endpoints were censored at the last date of follow-up. The endpoints were assessed for a median follow-up of 43 mo (IQR, 18) after PSMA-PET.

The study was planned at the University of Duisburg-Essen (Essen, Germany) and approved by the local ethics committee (18-8044-BO).

A statistical analysis was performed with SPSS software version 20.0 (IBM, Armonk, NY, USA). The performance of metric variables including cutoff values was evaluated with the area under the curve (AUC) receiver operating characteristic (ROC) curves and Youden's index. Cutoffs for continuous variables were selected based on SPARTAN (age <65 yr, Gleason score ≥8, PSADT ≤6 mo) and AUC-ROC curves (PSA ≥5.5 ng/ml, high maximum standardized uptake value [SUV_{max}] ≥8.4, and PSMA-TV ≥7 ml). Survival among groups was compared by Kaplan-Meier models with log-rank test and univariate and multivariable Cox regression analyses. Multivariable analyses were performed using stepwise forward selection with a likelihood ratio test for entry at 0.05 and removal at 0.10.

Our patient cohort consisted of those 200 patients whose characteristics were reported previously [8] and are shown in Supplementary Table 1. The median age was 71 (range, 46–94) yr, and the median PSA level was 5.3 (range, 1.3–263.8) ng/ml. Of 200 patients, 115 (58%) had PSADT <10 mo, 66 of whom had ISUP ≥4; 85 (43%) had ISUP ≥4 only.

During a median follow-up of 43 mo, 56 OS and 83 TTM events occurred. TTM events were visual on conventional imaging in 71/83 patients. The median follow-up in patients without an OS event was 45 mo. The median OS was calculated to reach 74 mo (Fig. 1A).

Among the variables assessed in univariate analyses using Cox regression, median OS was significantly shorter

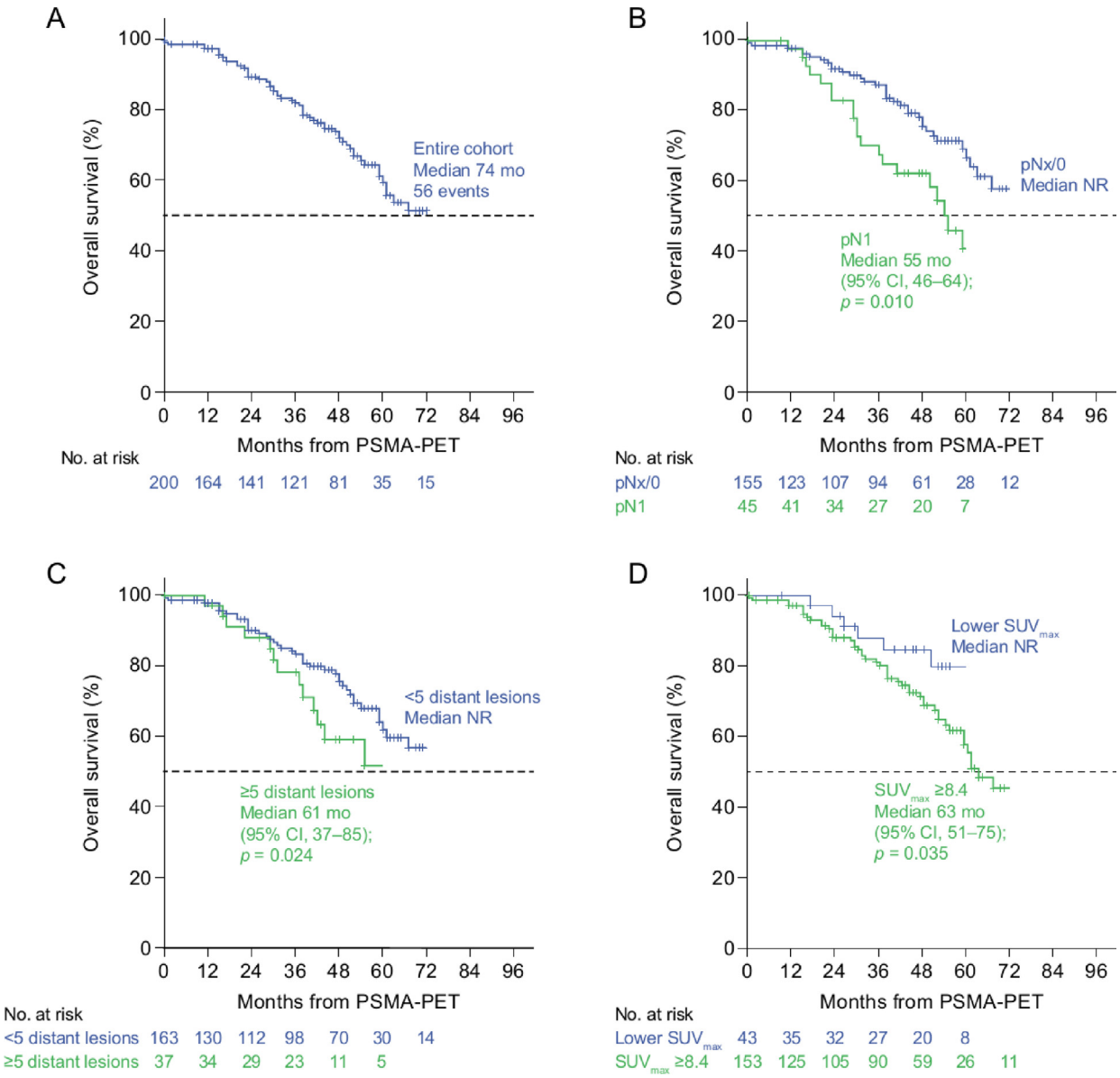

Fig. 1 – Overall survival by Kaplan-Meier modeling and log-rank test: (A) the entire cohort, (B) stratified by pN status, (C) stratified by number of extrapelvic metastases, and (D) stratified by maximum standardized uptake value (SUV_{max}). The curves are truncated for instances in which the number at risk in a group was <5. CI = confidence interval; NR = not reached; PSMA-PET = prostate-specific membrane antigen positron emission tomography.

in patients with pN1 versus pN0/pNx disease (55 mo vs not reached; p = 0.012), polymetastatic disease with five or more versus fewer than five PSMA-positive lesions (61 mo vs not reached; p = 0.027), and SUV_{max} ≥8.4 versus <8.4 (63 mo vs not reached; p = 0.043; Fig. 1 and Supplementary Table 2). Whole-body or per-region PSMA-TV was not associated with OS and TTM. The multivariable analysis using Cox regression confirmed pN1 disease (hazard ratio [HR] 1.94 [95% confidence interval {CI}, 1.12–3.37]; p = 0.019) and polymetastatic disease (HR 1.81 [95% CI, 1.0–3.27]; p = 0.05) as independent predictors of worse OS (Supplementary Table 3). Polymetastatic disease was also associated with shorter TTM in the univariate analysis (38 vs 60 mo; p = 0.021; Supplementary Fig. 1 and Supplementary Table 4) and was an independent predictor of shorter TTM in the multivariable analysis (Supplementary Table 5). Unifocal/oligometastatic disease on PET was not prognostic for OS or TTM (Supplementary Tables 2 and 4), which indicates that there is a diverse risk profile for high-risk nmCRPC. In a univariate analysis focusing on patients with PSADT ≤10 mo (n = 115), median OS was significantly shorter in patients with SUV_{max} ≥8.4 (HR 5.86 [95% CI, 1.14–30.03]; p = 0.034; Supplementary Table 6) of PET lesions, whereas pN1 or polymetastatic disease on PET were not predictive for OS. Most of these patients also had a Gleason score of ≥8 (61%; Supplementary Table 1) or PSADT ≤6 mo (74%), indicating that the prognostic value of some imaging features or pathology-based staging is lower in patients with multiple risk factors.

In contrast to our findings, any metastases were associated with shorter freedom from progression in patients with hormone-sensitive biochemical recurrence [11]. In line

with our findings, the negative prognostic impact of high SUV_{max} has been described previously for initial disease [12,13]. Notably, PSADT, an established marker in nmCRPC [14], was not prognostic in our patient cohort, possibly due to the small sample size and selection bias.

Information about treatment after PSMA-PET was available for 158/200 (79%) patients (Fig. 2). All patients were treated prior to approval of androgen receptor signaling inhibitors (ARSIs) for nmCRPC, and PET findings were discussed in multidisciplinary tumor boards to guide subsequent treatment. The use of locoregional salvage therapies decreased from 58% in patients with initially no disease/local disease to 39% in patients with locoregional disease, and to 12% in patients with distant disease only. Conversely, the usage of ARSIs increased from 25% in patients with not visible/local disease to 37% and 51% in those with locoregional and distant metastatic only disease, respectively. Stereotactic body radiation therapy was most prevalent in patients with locoregional (15%) and oligometastatic distant only (20%) disease, whereas chemotherapy (15%) and other systemic options were most commonly used in patients with molecular imaging (mi) N1M1 disease.

Despite focusing on patients with high-risk nmCRPC, PSMA-PET revealed heterogeneous disease extent, spanning from localized to advanced distant disease. The inclusion criteria for our study were similar to those for SPARTAN [5]. The median OS similar to that in the SPARTAN apalutamide treatment arm (74 mo [5]) points to similarity between our cohort and the SPARTAN population, suggesting that the disease spectrum in our cohort is comparable with that in SPARTAN. Disease characteristics defined by PSMA-PET associated with survival indicate that future clinical trials should implement PSMA-PET for an accurate assessment of patient risk. The main limitation of this study is its retrospective design, which reduces the degree of standardization of the collected data.

In summary, polymetastases (five or more lesions) by PSMA-PET and initial pN1 status were significantly associated with shorter OS in patients with nmCRPC in this exploratory analysis. PSMA-PET disease extent allowed for novel additional risk stratification in this patient cohort that should be replicated in other studies to confirm whether these, and potentially other risk factors identified by PSMA-PET, can be incorporated into future risk-adapted treatment algorithms.

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Study concept and design: Weber, Fendler, Calais, Czernin, Hope, Hofman, Eiber, Hadaschik.
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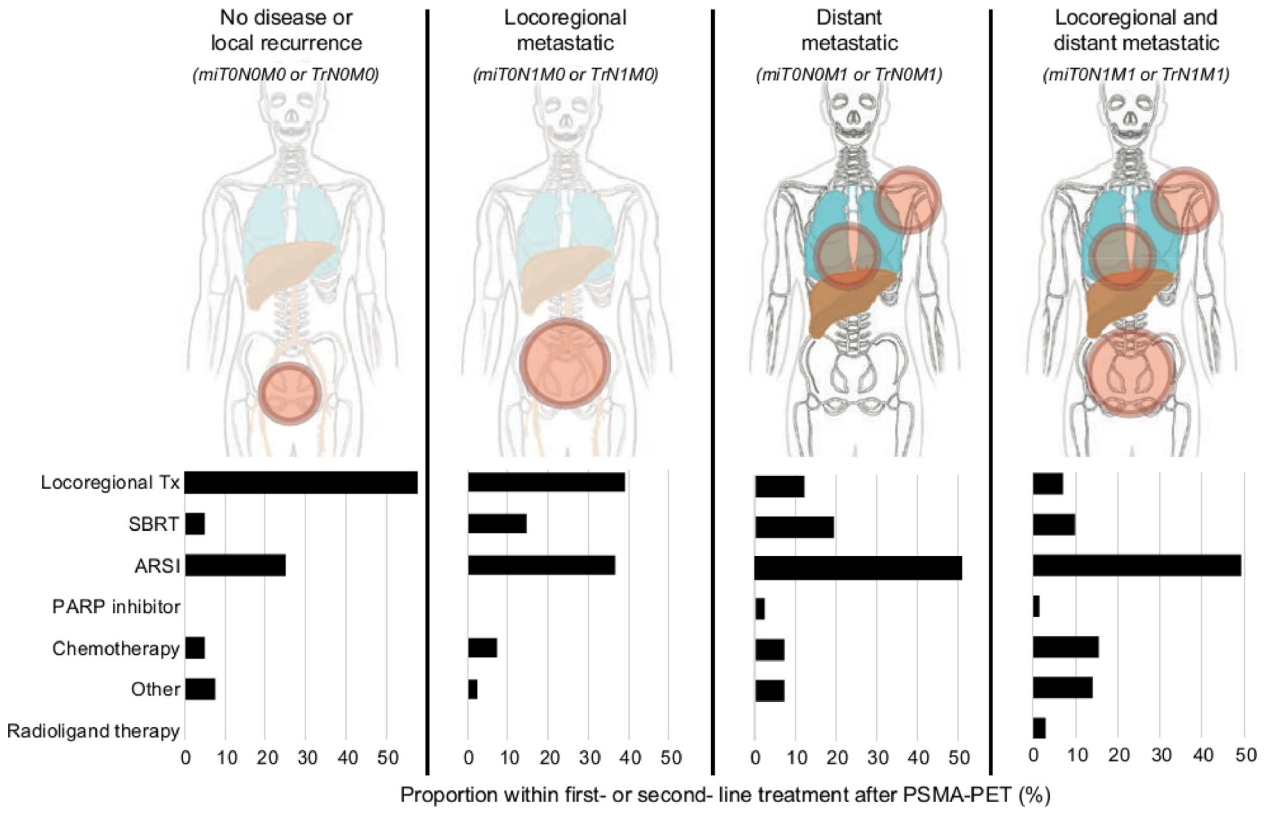

Fig. 2 – Pooled assessment of first- and second-line treatment implemented after PSMA-PET in four disease groups. ARSI = androgen receptor signaling inhibitor; PARP = poly (ADP-ribose) polymerase; PSMA-PET = prostate-specific membrane antigen positron emission tomography; RLT = radioligand therapy; SBRT = stereotactic body radiation therapy.

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Drafting of the manuscript: Weber, Fendler, Ravi Kumar, Calais, Czernin, Ilhan, Saad, Kretschmer, Hekimsoy, Brookman-May, Mundle, Small, Smith, Perez, Hope, Herrmann, Hofman, Eiber, Hadaschik.
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Supplementary data

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