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Assessing Interlesional Tumor Response and Patient Outcomes with Sequential PSMA PET/CT in Metastatic Castration-Resistant Prostate Cancer

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The impact of heterogeneous interlesional tumor response on outcomes in patients with metastatic castration-resistant prostate cancer (mCRPC) remains unclear. We aimed to evaluate the role of prostate-specific membrane antigen (PSMA) PET/CT in assessing patient outcomes on the basis of global tumor response and interlesional tumor response. **Methods:** We retrospectively analyzed data for 24 patients with mCRPC treated with androgen receptor pathway inhibitors who underwent [^{68}Ga]Ga-PSMA-11 PET/CT at baseline and at weeks 4 and 12 of therapy as well as conventional imaging at baseline and week 12 of therapy. Global PET/CT response was evaluated in accordance with the European Association of Urology/European Association of Nuclear Medicine criteria, classifying patients as having progressive disease (PD) or nonprogressive disease (non-PD) (i.e., complete response, partial response, or stable disease) and was correlated with overall survival (OS), prostate-specific antigen–progression-free survival (PSA-PFS) (i.e., time from diagnosis to PSA progression or death from any cause), radiologic progression-free survival, and time to no longer clinically benefiting from treatment. For interlesional assessment, a subset of PSMA-positive lesions was extracted from each patient and compared longitudinally. Patients classified as having either interlesional progression or interlesional homogeneous response were included in the OS and PSA-PFS analyses. **Results:** The median OS was 22 mo for patients with PD ($n = 8$) and 51 mo for those with non-PD ($n = 16$) (hazard ratio [HR], 28.2; $P < 0.0001$). PSMA PET/CT–based response was significantly associated with median PSA-PFS (6.5 mo vs. not reached [NR]; HR, 20.5; $P = 0.0001$), radiologic progression-free survival (9 mo vs. NR; HR, 12.2; $P = 0.002$), and time to no longer clinically benefiting from treatment (12 mo vs. NR; HR, 18.6; $P = 0.0002$) for patients with PD versus non-PD, respectively. The results were similar at week 12 and remained statistically significant. Interlesional assessment was performed for 125 PSMA-positive lesions in 20 (83%) patients. At week 12, 9 (45%) of 20 patients had interlesional progression, which was significantly associated with worse outcomes compared with patients who had an interlesional homogeneous response (median PSA-PFS, 7 mo vs. NR; HR, 19.2; $P < 0.0001$; median OS, 16 mo vs. 52 mo; HR, 31.2; $P < 0.0001$, respectively). **Conclusion:** Assessment of interlesional tumor response at week 12 by sequential PSMA PET/CT enabled the identification of patients with mCRPC who had worse outcomes after treatment with an androgen receptor pathway inhibitor.

Key Words: PSMA; PET/CT; interlesional; ARPI; prostate cancer

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Metastatic castration-resistant prostate cancer (mCRPC) is a heterogeneous and lethal disease. Complex primary or secondary resistance mechanisms inevitably develop, contributing to the poor prognosis associated with this disease (*1*). Therapy sequencing remains challenging for patients with mCRPC, and selecting the most appropriate first-line treatment is essential, as fewer than 50% of patients will receive 2 or more treatments (*2*). Improving patient selection to guide treatment choice is key to extending survival in this population.

Emerging data on the prognostic value and use of prostate-specific membrane antigen (PSMA) PET/CT imaging for monitoring systemic therapy response in patients with mCRPC seem promising when compared with that of conventional imaging, including CT and bone scintigraphy (*3–5*). By enabling earlier and more accurate identification of disease progression, molecular imaging has the potential to improve individualized treatment for patients with mCRPC. However, as most data are retrospective and based on small cohorts (*6*), the use of PSMA PET/CT is not yet recommended in clinical practice, where conventional imaging remains the gold standard. Moreover, various evaluation criteria have been proposed to standardize the use of PSMA PET/CT for therapy response assessment for patients with mCRPC (*7,8*). These criteria classify patients' disease on the basis of the global tumor response, primarily analyzing volumetric changes in tumor burden and the appearance of new lesions, both of which are associated with patient outcomes (*7,9–11*). However, despite the availability of semiautomatic segmentation software, evaluation of whole-body tumor burden remains time-consuming. Recent studies suggest that one way to simplify PSMA PET/CT interpretation may lie in the evaluation of a limited number of lesions, which seems feasible and comparable to whole-body segmentation (*12,13*). Additionally, not all evaluation criteria include PSMA tumor uptake modifications, and none specifically address interlesional tumor response heterogeneity, in which patients may have a favorable global response despite the presence of oligoprogressive lesions. The presence of the

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latter is frequently encountered in clinical practice and presents a challenge, as it is unknown whether patients with these lesions are prone to respond less favorably to therapy or if a heterogeneous interlesional tumor response could predict worse outcomes. Recent data in the hormone-sensitive setting and in patients with mCRPC treated with an androgen receptor pathway inhibitor (ARPI) suggest that interlesional heterogeneous responses during therapy were linked to worse outcomes and raised the question of whether to escalate treatment in that context (*13*,*14*). These observations also led to questions about whether evaluating tumor response at the interlesional level instead of the global (i.e., whole-body) level could improve the detection of resistant tumor clones, which may influence patient outcomes. In this study, we used PSMA PET/CT to evaluate the association between survival outcomes and both global tumor response and interlesional tumor response in patients with mCRPC receiving first-line therapy with an ARPI.

MATERIALS AND METHODS

Patients

Data from patients with mCRPC starting first-line therapy with an ARPI between January 2018 and January 2024 at the University Hospital of Liège (Belgium) were retrospectively extracted from an internal database. Patients were included if they had histologically confirmed prostate adenocarcinoma; progressive castration-resistant disease, as defined by castration levels of testosterone (<1.7 nmol/L) and clinical, biologic, or radiographic progression conforming to Prostate Cancer Clinical Trials Working Group 3 criteria (*15*); documented evidence of metastatic disease (on conventional imaging or [^{68}Ga]Ga-PSMA-11 PET/CT) before treatment initiation; a serum prostate-specific antigen (PSA) level measured within 10 d of treatment initiation and at week 4 ± 10 d and week 12 ± 10 d, undergone [^{68}Ga]Ga-PSMA-11 PET/CT within 6 wk of treatment initiation and at week 4 ± 10 d and week 12 ± 10 d; and undergone conventional imaging at baseline (within 6 wk of treatment initiation) and at week 12 ± 10 d. Patients who did not meet all inclusion criteria were excluded. This study was approved by the institutional review board of the University Hospital of Liège. Informed consent was obtained from all patients.

PSMA PET/CT and Conventional Imaging

Chest–abdomen–pelvis CT scans and bone scintigraphy (including SPECT), performed as part of the clinical routine, were analyzed in accordance with Prostate Cancer Clinical Trials Working Group 3 criteria (*15*). Radiolabeling of [^{68}Ga]Ga-PSMA-11, [^{68}Ga]Ga-PSMA-11 PET/CT image acquisition, tumor volume delineation (thresholds included SUV > 3.0 and PSMA-positive lesion volume > 0.5 mL), and analysis were performed as previously reported (*16*). The following semiquantitative variables were extracted for each patient: SUV_{max} of the hottest lesion, total PSMA–positive tumor volume (PSMA-TV), and SUV_{mean} of PSMA-TV. For interlesional tumor response assessment, semiquantitative parameters were extracted from each PSMA-positive delineated lesion and described as lesional SUV_{max}, lesional SUV_{mean}, and lesional PSMA volume.

Global Response Assessment

Global response (i.e., whole-body tumor burden) was assessed in accordance with the European Association of Urology/European Association of Nuclear Medicine recommendations for PSMA PET/CT–based response (*8*) and Prostate Cancer Clinical Trials Working Group 3 criteria for responses based on conventional imaging and PSA. PSMA PET/CT data were used to further categorize patients as having progressive disease (PD) or nonprogressive disease (non-PD) (i.e., complete response, partial response, or stable disease). All retrospective image interpretations ([^{68}Ga]Ga-PSMA-11 PET/CT and conventional imaging) were compared with the report issued prospectively as part of the follow-up. Discordances were resolved by an additional nuclear medicine specialist and radiologist, both of whom were masked to the clinical and imaging data and reevaluated the images to reach a consensus majority (2 vs. 1).

Interlesional Response Assessment

To analyze the sequential behavior of PSMA-positive lesions during therapy, a subset of lesions was selected from each patient. As many as 11 lesions were chosen per patient: a maximum of 8 lesions at baseline, including 4 with the highest lesional SUV_{max} and 4 with the lowest lesional SUV_{max} (referred to as target lesions 1–8) and a maximum of 3 more lesions, with the highest lesional SUV_{max} at week 12, if they were not already included in the baseline target lesions (referred to as nontarget lesions 1–3) (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org). PET parameters derived from each lesion were analyzed individually and compared sequentially at baseline and weeks 4 and 12.

Individual lesion response was based on lesional PSMA volume and lesional SUV_{max} and categorized as stable (≤30% decrease or increase in lesional SUV_{max} and lesional PSMA volume), partial (>30% decrease in lesional SUV_{max} or lesional PSMA volume), complete (lesion disappearance), or progressive (new lesion not detected at baseline or below delineation thresholds or an increase of >30% in lesional SUV_{max} or lesional PSMA volume). This analysis enabled interlesional tumor response assessment, which categorized responses as either interlesional homogeneous response (ILHR; all lesions showing a stable, partial, or complete response without the appearance of new lesions) or interlesional progression (ILP; at least 1 new or progressive lesion, regardless of the response of other lesions).

Statistical Analysis

Statistical analyses were performed using Prism version 10.4.0 (GraphPad). Categoric variables were presented as relative frequencies, and continuous data were expressed as median and interquartile range (IQR), unless otherwise specified. Overall survival (OS) was defined as the time from ARPI initiation until death from any cause or the last follow-up visit. The other endpoints were radiologic progression-free survival (rPFS; time from ARPI initiation to radiographic progression on conventional imaging or death from any cause), PSA–progression-free survival (PSA-PFS; time from diagnosis to PSA progression or death from any cause), and time to no longer clinically benefiting from treatment (time to NLCB; defined as the time from diagnosis to the clinical need to terminate or change treatment or death from any cause). Kaplan–Meier analysis was used to determine survival probabilities. For interlesional analyses, a χ^2 test was used to compare PET parameters at weeks 4 and 12. All tests were 2-sided, and a P value of less than 0.05 was considered statistically significant.

RESULTS

Patient and Imaging Characteristics

Data for 24 patients with mCRPC were extracted from our database (Table 1). The mean age of patients was 72 ± 8 y, with a median PSA level at baseline of 8.68 ng/mL (IQR, 5.83–23.29 ng/mL). Eleven patients (46%) had International Society of Urological Pathology grade 4 or 5 disease. Seven patients (29%) had de novo metastatic prostate cancer, 3 of whom benefited from chemotherapy with docetaxel in the hormone-sensitive setting. Most patients (23/24) were treated with first-line enzalutamide; 1 patient received abiraterone. The median follow-up time was 32 mo (IQR, 23–41 mo).

Three patients with up-front metastatic prostate cancer at diagnosis had no residual metastasis visible on baseline imaging

TABLE 1
Patient Characteristics at Study Entry (n = 24)

Characteristic	Value
Age (y)	72 ±8
PSA at baseline (ng/mL)	8.68 (5.83–23.29)
ISUP grade group version 8.0 at time of diagnosis	
Grade 1	3 (13)
Grade 2	2 (8)
Grade 3	6 (25)
Grade 4	6 (25)
Grade 5	5 (21)
Unknown	2 (8)
De novo metastatic prostate cancer	7 (29)
Systemic therapy before study entry	
ADT only	21 (88)
ADT with up-front docetaxel	3 (13)
First-line treatment for mCRPC	
Enzalutamide 160 mg daily	23 (96)
Abiraterone 1000 mg daily	1 (4)
Site of distant metastasis at study entry	
LN only	6 (25)
Bone with or without LN	12 (50)
Visceral, bone, or LN	3 (13)
Micrometastatic	3 (13)

ISUP = International Society of Urological Pathology; ADT = androgen-deprivation therapy; LN = lymph node. Qualitative data are number and percentage. Continuous data are mean ± SD or median and interquartile range.

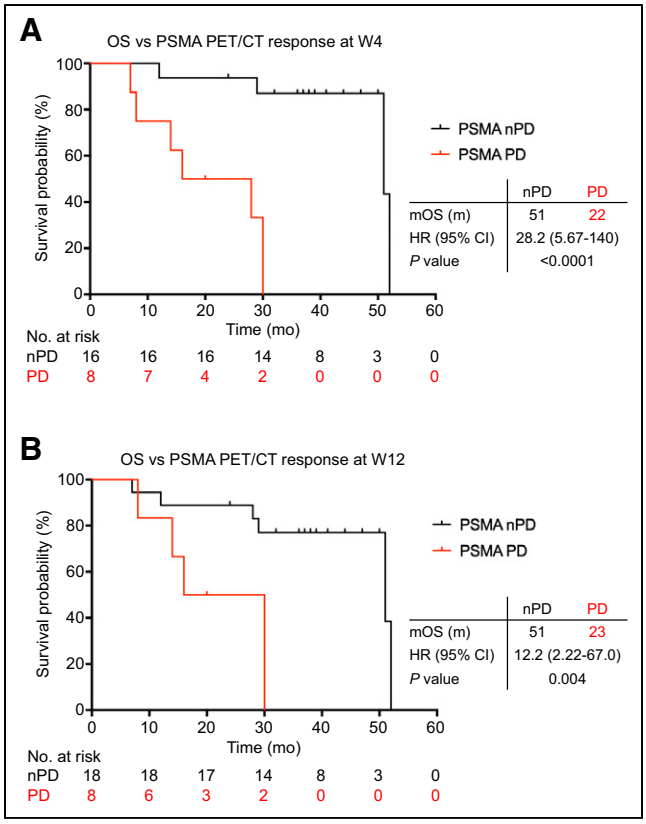

FIGURE 1. Kaplan–Meier curves of OS according to PSMA PET/CT–based global tumor response (PD vs. non-PD) evaluated at 4 (A) and 12 (B) wk. mOS = median OS; nPD = non-PD; W4 = week 4; W12 = week 12.

(by conventional imaging and PSMA PET) when becoming resistant to castration after first-line treatment in the hormone-sensitive setting. These patients were still considered to have micrometastatic disease and were included in the study.

Median time intervals between systemic treatment initiation and baseline PSMA PET/CT, bone scintigraphy, and CT scans were 7 d (IQR, 6–22 d), 5 d (IQR, 4–11 d), and 5 d (IQR, 4–13 d), respectively. Follow-up imaging with PSMA PET/CT was performed at week 4 after 29 d (IQR, 29–31 d) and at week 12 after 85 d (IQR, 85–85 d). Bone scintigraphy and CT scans were acquired at week 12, with a median time from systemic treatment initiation of 86 d (IQR, 86–86 d) and 86 d (IQR, 86–87 d), respectively. No discordances were observed between prospective and retrospective image interpretations.

Association of Global Tumor Response and OS

At week 4, 16 patients were classified as having non-PD and 8 had PD based on PSMA PET/CT. At week 12, conventional imaging showed that 20 patients had non-PD and 4 had PD; PSA testing showed that 23 had non-PD and 1 had PD, and PSMA PET/CT showed that 18 patients had non-PD and 6 had PD.

Patient outcomes were significantly associated with PSMA PET/CT–based global response at weeks 4 and 12 (Fig. 1). The median OS for patients with PD versus non-PD was 22 mo versus 51 mo at week 4, respectively (HR [hazard ratio], 28.2; 95% CI, 5.67–140; $P < 0.0001$) and 23 mo versus 51 mo at week 12, respectively (HR, 12.2; 95% CI, 2.22–67.0; $P = 0.004$). All patients with PD at week 12 ($n = 6$) were also classified as having PD at week 4 ($n = 8$). Only 2 of 8 patients were classified as having PD at week 4 but not at week 12.

The characteristics of patient subgroups were analyzed on the basis of their PSMA PET/CT–based response at week 12 (Supplemental Table 1). When compared with patients with non-PD, patients with PD had a higher serum PSA level at study entry (median, 40.8 ng/mL vs. 7.24 ng/mL), higher baseline PSMA-TV (median, 109.1 mL vs. 13.8 mL), and higher baseline SUV_{max} (median, 33.9 vs. 9.44).

Association of Global Tumor Response with PSA-PFS, rPFS, and Time to NLCB

At week 4, PSMA PET/CT–based global tumor response was significantly associated with patient outcomes (Supplemental Fig. 2A). The median time to PSA progression was not reached (NR) for patients with non-PD and was 6.5 mo for patients with PD (HR, 20.5; 95% CI, 4.32–96.8; $P = 0.0001$). The median rPFS was 9 mo versus NR (HR, 12.2; 2.47–60.3; $P = 0.002$), and time to NLCB was 12 mo versus NR (HR, 18.6; 95% CI, 4.02–85.6; $P = 0.0002$) for patients with PD versus those with non-PD, respectively.

At week 12, PSMA PET/CT–based response was significantly associated with median PSA-PFS (6.5 mo vs. NR; HR, 12.2; 95%

CI, 2.21–67.1; $P = 0.004$), rPFS (9 mo vs. NR; HR, 6.45; 95% CI, 1.11–37.4; $P = 0.038$), and time to NLCB (15 mo vs. NR; HR, 8.96; 95% CI, 1.76–45.7; $P = 0.008$) for patients with PD versus non-PD, respectively (Supplemental Fig. 2B).

Interlesional Tumor Response Assessment and Survival Outcomes

Tumor volume delineation was successfully performed in 20 (83%) of 24 patients (3 patients had PSMA-negative lesions, and 1 had PSMA-positive lesions below delineation thresholds), resulting in over 350 individually delineated PSMA-avid lesions. A total of 125 lesions (119 target lesions at baseline [69 with the highest lesional SUV_{max} and 50 with the lowest lesional SUV_{max}] and 6 nontarget lesions at week 12) were extracted and sequentially analyzed at the 3 time points (baseline and weeks 4 and 12). Most lesions with the highest lesional SUV_{max} at baseline ($n = 69$) persisted through week 12 (41/69), and only 6 nontarget lesions were delineated at week 12. Of those, 4 lesions were initially present at baseline but were not among the most intense lesions and 2 were new lesions that appeared at week 4 and persisted through week 12.

Individual lesion characteristics were compared with global tumor response at week 12 (PD vs. non-PD) (Fig. 2). Of the 125 lesions, 82 (66%) were from patients with non-PD and 43 (34%) were from patients with PD.

Thirteen (65%) of 20 patients were classified as having ILP at week 4 versus 9 patients (45%) at week 12. All patients with PD at week 12 were classified as having ILP at weeks 4 and 12. ILP was significantly associated with worse patient outcomes at both time points. The median PSA-PFS and OS for patients classified as having ILP versus ILHR at week 4 were 11 mo versus NR (HR, 6.04; 95% CI, 1.68–21.7; $P = 0.006$), respectively, and 30 mo versus NR (HR, 6.11; 95% CI, 1.47–25.4; $P = 0.013$), respectively. The results were more significant for patients classified as having ILP versus ILHR at week 12 (Fig. 3), with a median OS of 16 versus 52 mo (HR, 31.2; 95% CI, 6.63–147; $P < 0.0001$), respectively, and a median PSA-PFS of 7 mo versus NR (HR, 19.2; 95% CI, 4.38–83.8; $P < 0.0001$), respectively. The use of lesional SUV_{max}, lesional PSMA volume, or both criteria to categorize individual lesion response was significantly correlated with OS and PSA-PFS, especially at week 12 (Supplemental Table 2).

Finally, the behavior of stable lesions at week 12 was analyzed. Compared with baseline, 10 (50%) of 20 patients had at least 1 persistent stable lesion after 3 mo of therapy. Of these patients, 6 had non-PD and 4 had PD (assessed by PSMA PET/CT). The presence of at least 1 stable lesion at week 12 was associated with a significantly worse median OS (22 mo vs. 52 mo; HR, 9.43; 95% CI, 2.17–41.0; $P = 0.003$) when compared with patients without any stable lesions.

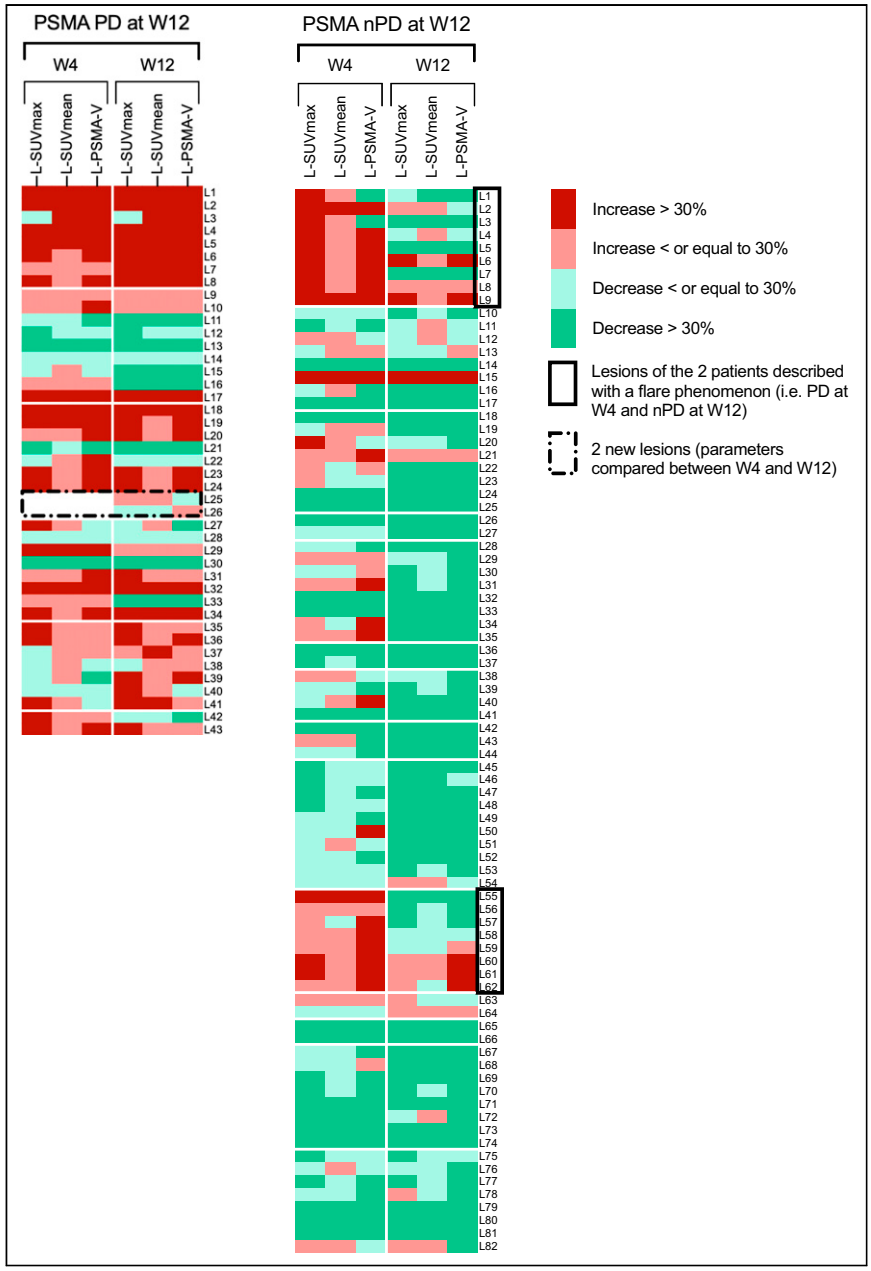

FIGURE 2. Heat map representing modifications in PSMA PET–derived parameters for each lesion (PD [$n = 43$], non-PD [$n = 82$]) compared with baseline (unless otherwise specified) for patients classified as having PD or non-PD at week 12. Each white intersection between groups of lesions represents different patient. L = lesion; L-PSMA-V = lesional PSMA volume; L-SUV_{max} = lesional SUV_{max}; L-SUV_{mean} = lesional SUV_{mean}; nPD = non-PD; W4 = week 4; W12 = week 12.

PSMA Upregulation with ARPIs

When comparing all lesions at weeks 4 and 12, a global increase (>0%) in PSMA uptake was observed in more lesions at week 4 than at week 12 (46% at week 4 vs. 33% at week 12 [$P = 0.03$] for lesional SUV_{max} and 53% at week 4 vs. 36% at week 12 [$P = 0.01$] for lesional SUV_{mean}). This was also observed for lesional PSMA volume (33% at week 4 vs. 19% at week 12; $P = 0.02$).

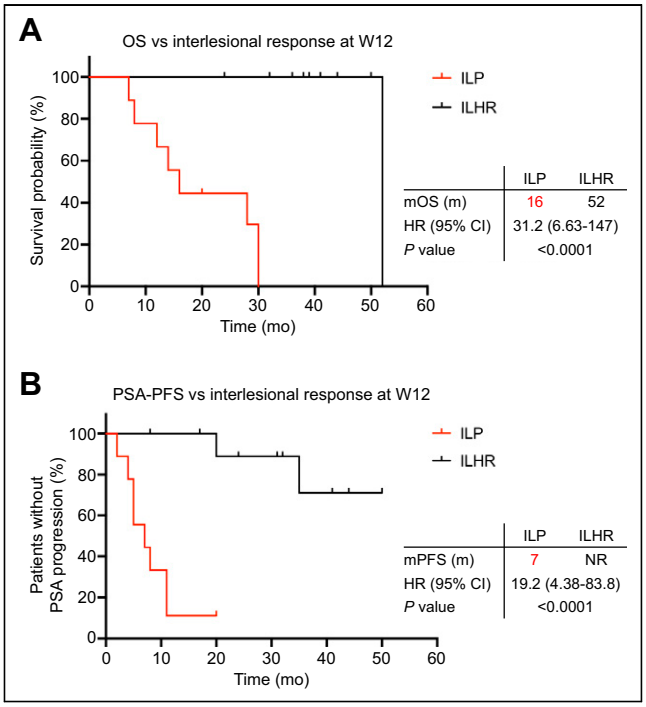

FIGURE 3. Kaplan–Meier curves of OS (A) and PSA-PFS (B) according to type of interlesional response (ILP vs. ILHR) evaluated at week 12 (W12). mOS = median OS; mPFS = median progression-free survival.

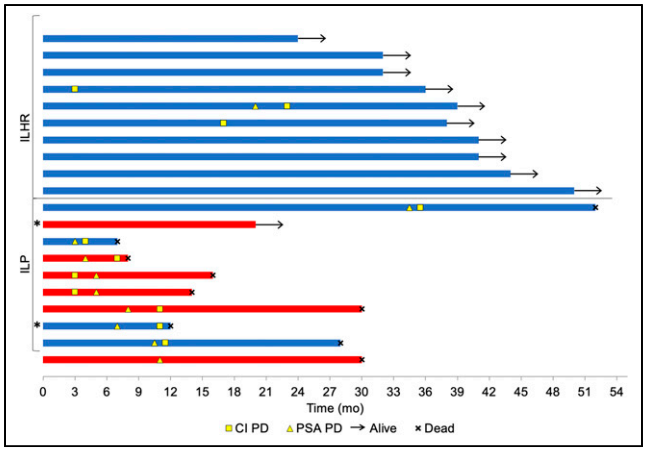

FIGURE 4. Swimming plot of individual patient data (n = 20), stratified between patients with ILP or ILHR at week 12. Colored bars represent global tumor response obtained at week 12 (non-PD in blue; PD in red). Patients described with flare phenomenon at week 4 and considered non-PD with favorable response at week 12 (*). CI = conventional imaging.

Lesions with a global increase (>0%) and a significant increase (>30%) in lesional SUV_{max}, lesional SUV_{mean}, and lesional PSMA volume were compared at weeks 4 and 12 in patients classified as having PD or non-PD at week 12 (Supplemental Table 3). Overall, PSMA upregulation was more frequent and significant in patients with PD, starting from week 4 and persisting at week 12, whereas the phenomenon seemed to resolve by week 12 in patients with non-PD.

Global Versus Interlesional Tumor Response Assessment at Week 12

For the 20 patients for whom PSMA PET/CT data enabled both a global response and an interlesional tumor response assessment, 6 cases were considered progressive by both analyses (i.e., PD and ILP) and 11 nonprogressive by both (i.e., non-PD and ILHR) at week 12. However, discordances were observed in the non-PD subgroup, in which 3 of 20 patients showed ILP (Fig. 4). Illustrated examples are provided in Supplemental Figure 3. Further analyses were performed on the interlesional assessment of patients classified as having non-PD at week 12. At week 4, 23 (28%) of 82 lesions showed a modification of over 30% in at least 1 PET parameter. Six lesions had modifications in lesional PSMA volume of small lesions (<1 mL at baseline) that normalized by week 12. The remaining 17 lesions were from the 3 patients classified as having ILP at weeks 4 and 12. When examining the global tumor response criteria, 2 of these 3 patients had disease that was classified as progressive at week 4 but not at week 12, as the global response was favorable compared with baseline. Therefore, these 2 patients were thought to have a transient flare phenomenon at week 4. However, when assessing interlesional tumor response, both patients had oligoprogressive lesions that were confirmed as progressive at week 12. One patient had 2 bone lesions with increases in their lesional SUV_{max} (43% and 110% increases) and lesional PSMA volume (66% and 36% increases). The other patient had 3 bone lesions with a persistent increase in lesional PSMA volume (166%, 166%, and 97% increases), whereas their lesional SUV_{max} was stable. A detailed description of these 2 patients is provided in Supplemental Table 4.

DISCUSSION

In this retrospective study, survival outcomes of patients with mCRPC treated with ARPIs as first-line therapy were evaluated using 2 different PSMA PET/CT–based responses: global response (derived from whole-body tumor burden) and interlesional response (derived from a subset of lesions tracked longitudinally for each patient).

Few studies have evaluated the use of early PSMA PET/CT, as the underlying mechanisms of PSMA expression are not yet well understood. Previous research found that PSMA receptors were rapidly upregulated after the initiation of androgen blockade in patients with mCRPC (*17*) and that a transient flare phenomenon could appear on early imaging, contributing to the complexity of response interpretation at these time points (*8*,*16*). In this study, when focusing on the global response, all patients with PD at week 12 (n = 6) were already described as such at week 4, but a flare phenomenon seemed to occur in 2 patients. Although the latter were classified as having non-PD at week 12, they individually had a shorter OS and PFS compared with the other patients with non-PD (Fig. 4). When analyzing the interlesional tumor response of these 2 patients, a clear ILP was observed with oligoprogressive lesions, which may explain why their outcomes were worse. This example highlights one of the limits of global response evaluation, as current response criteria involve whole-body tumor modifications but omit the possibility of heterogeneous interlesional response and the presence of oligoprogressive lesions, which may alter patient outcome.

The question of interlesional heterogeneity of tumor response has been raised in only a few articles (*13*,*14*,*18*) but may provide

potentially crucial information about disease progression and patient outcome, underscoring the question of treatment escalation in that context. Recently, complex interactions were highlighted between PSMA expression and genomic alterations. Spatial heterogeneity of PSMA uptake seems to be associated with circulating tumor DNA characteristics (such as androgen receptor and TP53 alterations, which have been associated with worse prognoses (*19*,*20*) and response to ARPIs (*21*,*22*)). In our cohort, 45% of patients showed ILP at week 12, which was already observed at week 4. This was significantly associated with worse OS (16 mo vs. 52 mo; $P < 0.0001$) and PSA-PFS (7 mo vs. NR; $P < 0.0001$) compared with that of patients with ILHR. This aligns with previous observations (*13*,*14*), further highlighting how early intrinsic resistance seems to occur and may be detectable using molecular imaging.

In this study, interlesional analysis enabled a more detailed evaluation of early PSMA modulation with ARPIs. At week 4, more lesions showed a global increase in their lesional SUV_{max} ($P = 0.03$) and lesional SUV_{mean} ($P = 0.01$), regardless of the global response (Fig. 2; Supplemental Table 3). However, the number of lesions showing an increase in PSMA uptake was much higher in the PD subgroup at week 4, with almost half (47%) of the lesions exhibiting an increase of more than 30% in lesional SUV_{max} versus 17% of lesions in the non-PD subgroup. This difference increased by week 12 (51% for PD vs. 4% for non-PD), suggesting early divergence in PSMA response dynamics between PD and non-PD subgroups. Similarly, at week 12, most of the lesions with the highest lesional SUV_{max} had the highest lesional SUV_{max} at baseline, and the presence of stable lesions at week 12, independently of the global PET response, was associated with worse median OS. Similar observations were reported by Dell'Oro et al. (*13*) in a cohort of 163 men with biochemical recurrence of prostate cancer. In their work, the heterogeneity features most strongly associated with OS were the extent and intensity of lesions increasing in PSMA activity, suggesting that PSMA expression has a role in driving disease progression and patient outcome.

An in vitro study demonstrated that antiandrogenic drugs led to an upregulation in PSMA tracer uptake per cell (*23*). However, by reducing cell proliferation, the overall PSMA uptake of the tumor decreased, as the number of cells with targetable PSMA was reduced. It would therefore be plausible to suggest that, by week 12, a stable or increased uptake of PSMA compared with baseline may indicate resistance to ARPIs, without the confounding effect of a flare phenomenon. It also raises the question as to whether patients with a global stable response, who are currently classified as responders, should now be considered nonresponders.

PD, according to global PSMA PET/CT–based response at both weeks 4 and 12, was also significantly associated with worse OS and PFS, consistent with previous reports (*4*,*10*,*24*). PSA-based PD was observed later than PSMA PET/CT–based PD and was found in only 1 patient at week 12 (who was also classified as having PD). Although our study emphasizes the prognostic value of PSMA PET/CT response, PSA-PFS was a key endpoint and showed significant associations with PSMA PET/CT findings. Nonetheless, our findings support prior observations that PSA kinetics, representing the global tumor burden response, may not fully capture the complexity of tumor response, particularly in the context of disease heterogeneity, which may explain why PSMA PET/CT–based response seems to outperform PSA-based response for both the detection of disease progression and prediction of OS (*25*). For instance, we identified cases in which patients demonstrated a favorable PSA and global response on PSMA PET/CT (non-PD) despite a limited ILP. Such patterns, consistent with the concept of oligoprogression, illustrate potential discordances between biochemical- and imaging-based assessments, which could have therapeutic implications (i.e., considering metastasis-directed therapy to progressive lesions while continuing systemic therapy).

Our analysis also confirms that patients with PD generally had higher baseline PSMA-TV, consistent with prior studies showing that PSMA-TV was a strong independent predictor of OS (*3*). However, our work also highlights that interlesional response heterogeneity, independent of PSMA-TV, is a significant prognostic factor. For instance, even among patients with lower baseline PSMA-TV, the presence of ILP at week 12 was associated with significantly worse outcomes compared with those with ILHR. These findings suggest a complementary relationship: while PSMA-TV reflects overall tumor burden, interlesional heterogeneity captures the variability in treatment response among metastatic sites, potentially allowing earlier identification of subclonal resistance. Integrating both parameters may therefore provide a more nuanced assessment of disease biology, with implications for both prognostication and therapeutic tailoring.

The main limitations of the present study include the small number of patients with mCRPC, limiting statistical power and generalizability, particularly in subgroup analyses, as well as its retrospective design and the exclusion of patients receiving first-line chemotherapy. The definition of tumor heterogeneity has not been prospectively validated and was based on a limited number of lesions per patient, selected by their SUV_{max}, for which data are lacking. The selection method aimed to capture interlesional variability while keeping the analysis clinically and technically feasible, similarly to the approach used in RECIST. Nonetheless, this method did not include all PSMA-positive lesions, which may underrepresent the full spectrum of tumor biology and spatial heterogeneity. Additionally, lesion location (e.g., visceral vs. bone vs. nodal) was not evaluated in the lesion analyses. Further prospective studies incorporating more comprehensive lesion sampling and advanced analytic approaches, such as artificial intelligence–driven methods, will be important to enhance the assessment of interlesional heterogeneity.

CONCLUSION

Assessment of interlesional tumor response at week 12 by sequential PSMA PET/CT enabled the identification of patients with mCRPC with worse outcomes after treatment with an ARPI, suggesting PSMA PET/CT's potential to enable early detection of ARPI-resistant clones. This interlesional-based response analysis should be considered when assessing treatment efficacy with PSMA PET/CT. Prospective research is warranted to confirm these observations and to assess whether treatment escalation in these patients could impact survival.

DISCLOSURE

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KEY POINTS

QUESTION: Are the outcomes of patients with mCRPC treated by ARPIs influenced by interlesional tumor response heterogeneity?

PERTINENT FINDINGS: We analyzed a subset of lesions for each patient and tracked their response longitudinally over 12 weeks of therapy. The presence of ILP, compared with ILHR, was associated with a worse median OS (16 mo vs 52 mo; $P < 0.0001$) and PSA-PFS (7 mo vs NR; $P < 0.0001$). This analysis highlighted one of the limits of global tumor response criteria, which may omit the presence of oligoprogressive lesions that can alter patient outcomes.

IMPLICATIONS FOR PATIENT CARE: Integrating interlesional-based assessment in the evaluation of therapy response for patients with mCRPC treated by ARPIs could improve patient selection for potential treatment escalation early in the course of disease. Prospective research is warranted to assess whether doing so would impact survival outcomes.

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