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ORIGINAL ARTICLE

Correlation of [^{68}Ga]Ga-PSMA PET/CT response and PSA decline in first-line enzalutamide for metastatic castration-resistant prostate cancer patients

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Abstract

Purpose to assess the utility of response monitoring to enzalutamide by using [^{68}Ga]Ga-PSMA PET in mCRPC patients treated with enzalutamide as first-line therapy.

Methods patients underwent [^{68}Ga]Ga-PSMA PET less than 8 weeks before and 3 months after starting enzalutamide. On the basis of EAU/EANM criteria, patients were categorized as PSMA responders (PET-R) or PSMA non-responders (PET-NR), whilst, based on PSA, they were classified as biochemical responders (PSA-R) or non-responders (PSA-NR). Survival analysis was performed using the Cox regression hazard model and the Kaplan-Meier method.

Results 69 patients were considered fully evaluable. We observed 47.8% of concordance between [68Ga]Ga-PSMA PET and PSA monitoring at 3 months after starting enzalutamide. For discordant cases, the PSA reduction has a weak impact on PFS and a significant impact on OS in PET-NR patients, whilst this change has no impact either for PFS and OS in PET-R ones.

Conclusions [^{68}Ga]Ga-PSMA PET could be a useful imaging tool for monitoring response to enzalutamide in mCRPC patients, being more informative than PSA in this setting, and possibly better guiding clinicians in therapeutic decisions.

Keywords Prostate cancer · Enzalutamide · PSMA PET · Monitoring response.

Introduction

Metastatic prostate cancer is still a lethal disease, being less than half of patients alive after 5 years from diagnosis [1]; in the last two decades, many efforts in both diagnostic and therapeutic scenarios led to an improvement in the survival of these patients. Among diagnostic tools, prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has gained a more and more relevant role in prostate cancer management [2]. PSMA, also known as folate hydrolase 1 and glutamate carboxypeptidase II (GCP-II), is a transmembrane protein that is predominantly expressed in the prostate and proximal renal tubules, but it is expressed also in salivary glands, small bowel, and some glial cells in the brain [3]; apart from normal tissues, it is also highly expressed in almost all primary prostate cancers - being its expression associated with higher prostate-specific antigen (PSA) values - but also on the neo-vasculature of epithelial

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malignancies, such as renal cell, bladder, and colon cancers [4].

PSMA PET is currently used for several purposes in prostate cancer, from staging to theranostic application [5]; the most studied PSMA-targeted PET tracers are [^{18}F]F-DCFPyL and [^{68}Ga]Ga-PSMA-11, both of which are currently approved for diagnostic use. Among new potential uses, response monitoring to anticancer therapy by using PSMA PET is certainly of great interest, since it could overcome the limited predictive and diagnostic value of standard imaging tools in the castration-resistant setting [6]; however, a recently published systematic review has pointed out that data are still insufficient to assess the role of [68Ga]Ga-PSMA PET in this specific field [7].

Among new-generation hormonal agents (NHA) administered in metastatic castration-resistant prostate cancer (mCRPC), enzalutamide has shown to prolong survival in both chemotherapy-naïve and pretreated patients [8, 9]. Enzalutamide is an oral agent targeting multiple steps in the androgen receptor (AR) signaling pathway, which is the major molecular driver of prostate carcinogenesis [10]. It has been shown that enzalutamide is able to induce PSMA upregulation in mCRPC patients, as assessed by PSMA PET scan performed at baseline and after approximately two weeks from enzalutamide starting date [11].

Several studies demonstrated that [^{18}F]F-choline-PET imaging could be useful in evaluating response to enzalutamide in the mCRPC setting [12–14]. Based on these studies, PSMA PET has been investigated for monitoring response to NHA – including enzalutamide.

In the retrospective work by Plouznikoff and colleagues [15], 11 and 15 mCPRC patients received enzalutamide and abiraterone, respectively, and the responses observed by PSMA PET totally agreed with the PSA response. In the prospective trial by Zukotinsky and colleagues [16], 14 patients started abiraterone while only 2 patients started enzalutamide; interestingly, the authors have evaluated changes in specific metabolic parameters between baseline and follow-up PET/CT scans, including the sum of the percentage change in SUVmax in PET-positive disease sites, finding an association with the probability of changing treatment. In the retrospective analysis by Shagera et al. [17], 14 and 16 mCPRC patients received abiraterone and enzalutamide, respectively, showing a high concordance between PSMA PET and Prostate-Specific Antigen (PSA) response and also a clear correlation between PSMA PET response and overall survival (OS). In the work by Sonni et al., 9 mCPRC patients starting NHA underwent PSMA PET monitoring by repeating the scans after 1 week and after 3 months from starting NHA [18]; despite the low enrollment rate, this study has pointed out the absence of a significant modulation of PSMA expression induced by NHA after 1 week of treatment.

In our study, we evaluated the impact of adopting [^{68}Ga]Ga-PSMA PET/CT to assess therapeutic response, as compared to PSA response, in patients treated with enzalutamide as first-line therapy for mCRPC.

Materials and methods

Patients and treatment evaluation

We prospectively included mCRPC patients which received enzalutamide in first-line for mCRPC at our institution, between August 2017 and May 2022. This prospective study was approved by the Institutional Review Board and Ethics Committee of IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori," Meldola, Italy (protocol code: IRST B073). The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference of Harmonization. Eligibility criteria included: patients age > 18 years; patients willing and able to give informed consent for participation in the study; patients with histologically confirmed adenocarcinoma of the prostate; progressive disease despite androgen deprivation therapy (ADT) as defined by rising PSA levels despite testosterone suppression (castration-resistant disease); patients must have metastatic disease at the time of castration-resistant disease; patients must not have received previous chemotherapy for mCRPC, but they could have received docetaxel in the hormone-sensitive setting. All enrolled patients underwent [^{68}Ga]Ga-PSMA PET/computed tomography ([^{68}Ga]Ga-PSMA PET/CT) less than 8 weeks before starting enzalutamide; subsequent scans were performed after 3 months, during follow-up (as per routine clinical practice) and at PSA/clinical progression. Patients were evaluated on a monthly basis for serological PSA response and safety.

Treatment consisted of orally administered enzalutamide, 160 mg once daily, and was continued until there was documented evidence of disease progression or unacceptable toxicity. Figure 1 presents the study flowchart.

Response evaluation by PSMA PET

Preparation of [^{68}Ga]Ga- PSMA-11

[^{68}Ga]Ga-HBED-CC-PSMA was prepared in accordance with national regulations, good radiopharmaceutical practices (GRPs), defined by EANM guidelines and "Good Manufacturing Procedures" (GMPs).(Eder 2014).

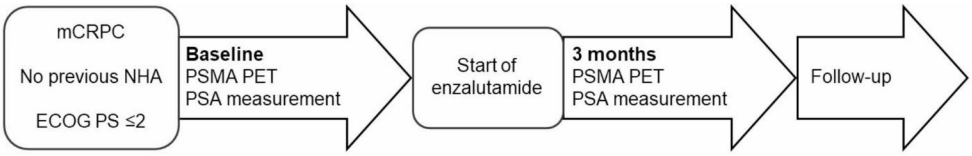

Fig. 1 Study flowchart. ECOG PS, Eastern Cooperative Oncology Group Performance Status; NHA, new hormonal agents; mCRPC, metastatic castration-resistant prostate cancer

[^{68}Ga]Ga-PSMA-11 was synthesized with the ModularLab Eazy kit (Eckert & Ziegler Radiopharma GmbH, Berlin, Germany) without organic solvents and with sterile disposable cassettes. The 68 Gallium (^{68}Ga) radionuclide was routinely obtained as a solution of gallium chloride (^{68}GaCl3) by eluting a commercial solution of ^{68}Ge/^{68}Ga, 1.11 GBq (GalliaPharm®, Eckert & Ziegler Radiopharma GmbH, Berlin, Germany).

PSMA-11 was obtained from Advanced Biochemical Compounds, ABX (Radeberg, Germany).

[^{68}Ga]Ga-PSMA PET/CT scan acquisition

[^{68}Ga]Ga-PSMA PET/CT scans were performed on a Biograph mCT Flow® machine (Siemens Healthineers, Erlangen, Germany). Acquisition was done in Flow mode (0.7 mm/sec). Body-weighted [^{68}Ga]Ga-PSMA-11 activity was administered intravenously (activity range: 100–200 MBq). Patients were asked to drink 0.5 to 1 L of water during the absorption time to dilute the concentration of [^{68}Ga]Ga-PSMA-11 concentration in the urinary tract. According to EANM guidelines, imaging began 60 ± 10 min after injection of [^{68}Ga]Ga-PSMA (Fendler 2017]. PET/CT scanning was carried out with patients in the supine position. The PET/CT scan was performed from the top of the skull to mid-thigh. A low-dose CT scan was conducted to correct the attenuation of PET emission data.

Image analysis

All [^{68}Ga]Ga-PSMA PET/CT images were analyzed with dedicated, commercially available software (Syngovia; Siemens Healthcare, Erlangen, Germany), which permitted review of PET, CT, and fused image data. Physiological [^{68}Ga]Ga-PSMA-11 uptake was considered in the lacrimal and salivary glands, liver, spleen, kidney, and small intestine. Focal uptake of Ga-PSMA above the background and uncorrelated with the physiological tracer uptake sites was classified as suggestive of PCa recurrence. PET/CT images were reviewed by two nuclear medicine physicians, who had at least 5 years of experience in reading PET/CT images and were not blinded to all available clinical data, and [^{68}Ga]Ga-PSMA-11 data were reported according to the guidelines of the procedure [19].

We measured at baseline and after 3 months of the beginning of Enzalutamide the sum of metabolic total volume (SMTV), mean standardized uptake volume (SSUVmean), maximum standardized uptake volume (SSUVmax), and total lesion activity (STLA), which is the product of SMTV and SSUVmean, for a maximum of 20 lesions.

Response assessment

[68Ga]Ga-PSMA-11 PET response criteria at three months was defined as:

- complete response (CR), in case of any pathological PSMA uptake in all lesions;
- partial response (PR), in case of a decrease of PET parameters ≥ 25%;
- progression disease (PD), in case of an increase of PET values ≥ 25% and/or new PSMA + lesion(s);
- stable disease (SD) an intermediate change PET parameters between − 25% and + 25% without the appearance of new target lesions.

Response evaluation by PSA

PSA response was defined as a decrease in PSA value ≥ 50% after 3 months of therapy compared to baseline. We have further divided the PSA response in partial response (PR) in case of a reduction between 50 and 99%, and complete response (CR) in case of a reduction higher than 99% (which corresponds to undetectable PSA). In all other cases, patients were classified as non-responders (NRs). Among NRs, we divided stable disease (SD) in case of a variation between − 50% and + 30% after 3 months of therapy compared to baseline, while progressive disease (PD) was defined as an increase of 30% or higher.

Statistical analysis

Progression-free survival (PFS) was defined as the time elapsed between the date of the start of enzalutamide and the date of progression disease (PD) detection - either radiographic or clinical - or the date of death for any cause within 168 days after treatment discontinuation or the date of the last tumor evaluation, whichever occurred first.

Overall Survival (OS) was defined as the time elapsed between the date of the start of enzalutamide and the date of either death for any cause or the last follow-up.

Table 1 Main patients' characteristics at the time of mCRPC diagnosis of the 69 patients included in the analysis. ECOG PS, Eastern Cooperative Oncology Group Performance Status; GS, Gleason score; IQR, Interquartile Range; PSA, prostate-specific Antigen; PSMA PET, prostate-specific membrane Antigen Positron Emission Tomography

Age - median (IQR)	75 (68–81)
ECOG PS - no. (%)	55 (79.7)
0	14 (20.3)
1–2	
GS at diagnosis - no. (%)	24 (34.8)
6–7	37 (53.6)
8–10	8 (11.6)
Not available	
Median baseline PSA level - ng/ml (IQR)	2.57 (1.09–6.19)
Site of disease (at baseline PSMA PET) - no. (%)	25 (36.2)
Prostate	46 (66.7)
Nodes	37 (53.6)
Bone	6 (8.7)
Lung	1 (1.4)
Liver	

Categorical variables were reported as frequency and percentage whereas continuous variables were summarized using median value and interquartile range (IQR).

The Kaplan-Meier method was used to estimate the OS function and the logrank test was used for survival curves comparison. Estimated Hazard ratios (HRs) and their 95% confidence intervals (CIs) were obtained applying the Cox proportional hazards model.

The impact of PSA reduction from baseline to 3 months on survival outcomes was evaluated by the landmark analysis at 3 months. With landmark analysis, patients with a survival event (progression or death) within or precisely at 3 months were excluded. All statistical analyses were carried out with SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

We enrolled consecutive mCRPC patients who were candidates for enzalutamide. At the data cut-off (31st Dec 2023), 69 mCRPC patients were considered fully evaluable. Patient characteristics are presented in detail in Table 1.

Baseline [68Ga]Ga-PSMA PET scans were performed at a median of 26 days (IQR, 15–34 days) before enzalutamide starting; the first PSMA PET scans were performed at a median of 13.2 weeks (IQR, 11.8–15 weeks) after enzalutamide initiation. Concerning baseline [68Ga]Ga-PSMA PET parameters, we observed a median SSUVmax of 41.6 (IQR, 26.6–95.2), a median SSUVmean of 28.2 (IQR, 15.3–58.8), a median STLA of 44.8 (IQR, 26.2-151.4) and a median SMTV of 7.4 (IQR, 3.4–15.9).

Concordance between PSMA PET and PSA response

In Fig. 2 we reported the contingency table correlating response assessment obtained by both PSMA PET and PSA monitoring after 3 months from starting enzalutamide (Fig. 2); a global concordance of 33 (47.8%) was observed.

On the basis of European Association of Urology/European Association of Nuclear Medicine (EAU/EANM) criteria, as carried out in the abovementioned work by Shagera et al. [17], patients were categorized as PSMA responders (PET-R, in case of CR, PR or SD) or PSMA non-responders (PET-NR, in case of PD). Based on prostate-specific antigen (PSA), patients were classified as biochemical responders (PSA-R) or non-responders (PSA-NR in all other cases). Thereafter, patients have been divided into 4 groups: PSA-R/PET-R, PSA-R/PET-NR, PSA-NR/PET-R and PSA-NR/PET-NR. In Fig. 2 we resumed the division in

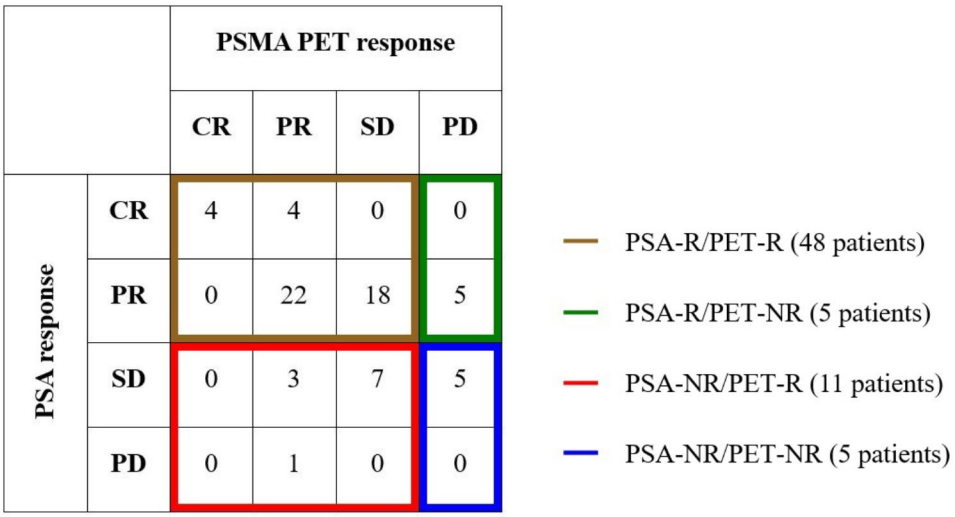

Fig. 2 Contingency table and the 4 groups obtained according to PSA and [^{68}Ga]Ga-PSMA PET response at 3 months after starting enzalutamide. CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; R, Responder; NR, Non-Responder.

Table 2 Impact of PSA response (reduction of 50% or higher after 3 months from starting enzalutamide) on PFS and OS, according to PSMA PET response. CI, confidence interval; HR, hazard ratio; OS; overall survival; PET-NR, PSMA PET non-responder patients; PET-R, PSMA PET responder patients; PFS, progression-free survival

PSA response (reduction of ≥ 50%) after 3 months from starting enzalutamide	PFS		OS	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Overall	0.36 (0.18–0.71)	0.003	0.32 (0.14–0.71)	0.005
PET-R group	0.52 (0.11–2.40)	0.406	0.66 (0.08–5.55)	0.701
PET-NR group	0.48 (0.21–1.08)	0.075	0.36 (0.14–0.92)	0.033

the 4 groups. PFS and OS according to the division in the 4 aforementioned groups are presented in Figure S1.

Discordant groups: the role of PSMA PET and PSA monitoring

Overall, at a median follow-up of 57 months (range 3–74 months), median PFS was 37 months (95% CI 26–66) and median OS was 66 months (95% CI 38-not reached). Details of discordant patients are presented in Table S1, according to PSMA PET and PSA response at 3 months after starting enzalutamide.

The impact of PSA reduction from baseline to 3 months from starting enzalutamide on both PFS and OS was evaluated through landmark analysis. Overall, PSA response (PSA reduction of 50% or higher after 3 months) appears to have a significant impact on both PFS and OS, reducing the risk of progression and death (Table 2); however, it is interesting to note that this impact is weaker when dividing the patients based on the PET response: in PET-NR patients, the PSA reduction has a weak impact on PFS and a significant impact on OS, whilst in PET-R patients this change has no impact either for PFS and OS. An example of a discordant case from our cohort of patients is reported in Fig. 3.

Discussion

[^{68}Ga]Ga-PSMA PET is gaining ground in the management of prostate cancer, replacing conventional imaging - namely, CT scan and bone scintigraphy - in tumor response evaluation. In this perspective, our study gives an insight in the possible use of [^{68}Ga]Ga-PSMA PET to monitor treatment response in prostate cancer patients receiving enzalutamide in the castration-resistant setting.

First of all, [^{68}Ga]Ga-PSMA PET could be informative from the prognostic point of view. In a retrospective study that included 54 mCRPC patients receiving first-line therapy, whole-body PSMA-derived tumor volume

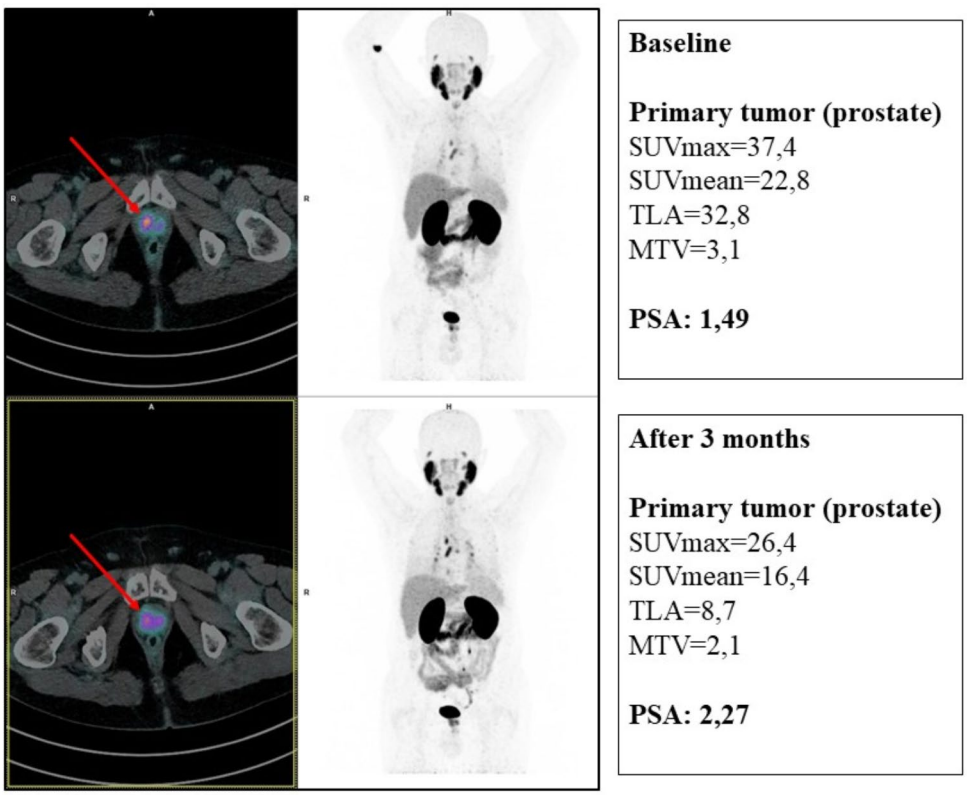

Fig. 3 63-year-old patient with discordance between PSMA PET and PSA response 3 months after starting enzalutamide. In detail, at baseline he had bone metastases (S4 and S5 vertebrae) and prostatic disease, both of which responded to enzalutamide (the response on the primary tumor is represented in the figure)

(wbPSMA-TV) was associated with survival as a parameter reflecting tumor burden - being the survival lower in case of higher disease volume [20]. Another retrospective series of 151 prostate cancer patients confirmed the prognostic role of whole-body metabolic tumor volume assessed by PSMA PET [21]; from the same group, another work specifically focused on mCRPC patients receiving taxane furtherly supported this hypothesis [22]. In a previous report from the same cohort of mCRPC patients receiving enzalutamide and evaluated in this current work [23], we have observed that some parameters - namely, SSUVmax and STLA - were significant for PFS and OS. The role of these two PET parameters has already been reported to be prognostic for OS in mCRPC patients [22, 24]. A multivariable prognostic risk score including total, bone, and visceral tumor volumes from PSMA PET has been recently reported to be prognostic for survival in metastatic prostate cancer patients: notably, in this study, the prostate cancer patients were included independently from the therapeutic setting [25].

PSMA PET is currently being studied for its predictive role in mCPRC patients receiving [^{177}Lu]Lu-PSMA-617 as radioligand therapy: in the TheraP phase II randomized trial, SUVmean values of 10 or higher were associated with higher odds of PSA response to radioligand therapy than those observed with cabazitaxel [26]; SUVmax and SUVmean values obtained from the baseline [^{68}Ga]Ga-PSMA PET were associated with lesion response to [^{177}Lu]Lu-PSMA-617 in a retrospective single-center series [27]. The wider use of [^{177}Lu]Lu-PSMA-therapy also led clinicians to the development of a novel framework for treatment response evaluation by using PSMA PET scans and PSA measurements, called Response Evaluation Criteria In PSMA-imaging (RECIP) 1.0 [28].

Apart from the theranostic use for radionuclide targeted therapy, PSMA PET is also being evaluated in prostate cancer patients receiving other therapeutic options, as already stated before, but with a specific focus on monitoring response to them.

PSMA PET was evaluated in monitoring response to docetaxel in 23 metastatic prostate cancer patients (both castration sensitive and resistant), suggesting a potential role in patients receiving chemotherapy [29]. In a retrospective analysis of 43 mCRPC patients whose response to systemic therapies were monitored by PSMA PET, the authors conclude that changes in some metabolic parameters correlate with response [6].

Enzalutamide is an AR signaling inhibitor (ARSI); in detail, enzalutamide inhibits androgen binding to the AR but also inhibits the nuclear translocation and the DNA binding of this receptor [10]. Several works showed an in-vitro and in-vivo upregulation of PSMA during AR-targeted treatment, specifically with enzalutamide [30–32]; however, this upregulation is usually transient and could be responsible for the "flare phenomenon" that has been described in the article by Aggarwal et al. [31]. In our study, the observed PSMA PET response after 3 months from starting enzalutamide probably reflects the volume reduction of metastatic lesions due to the antitumoral effect of the drug, which does not exclude the possible upregulation on residual tumor cells: further preclinical and clinical studies are needed to validate our hypothesis.

Currently, guidelines do not support the systematic use of PSMA PET to evaluate disease progression in mCRPC patients, due to several reasons - lack of specific data, the possible absence of cost-effectiveness, and limited PSMA PET availability in some countries [33]; it remains however a potential clinical application for the future [34], and the need for standardized response assessment led to the development of the PSMA PET Progression (PPP) criteria [35] and the aforementioned RECIP 1.0 [28] (the latter specifically developed for [^{177}Lu]Lu-PSMA-therapy).

PSA level is the easiest and most widely adopted parameter for disease monitoring in mCRPC patients, even if with well-known limitations. Early PSA response, defined as a decline > 50% after 4 weeks from starting an NHA, was associated with better PFS and OS as shown by Fuerea and colleagues in a cohort of mCRPC patients enrolled in clinical trials [36]. The decline in PSA after 3 months from starting enzalutamide was associated with improved survival in mCRPC patients enrolled in the PREVAIL trial [37]. An increase in PSA level does not mandate therapy change in mCRPC patients enrolled in clinical trials, according to the Prostate Cancer Working Group 3 (PCWG3) criteria [38]. On the other hand, the possibility of clinical and/or radiographic progression despite a reduction in PSA level has been described: in a post hoc analysis of the aforementioned PREVAIL trial, one out of four patients receiving enzalutamide at the time of radiographic progression had a non-rising PSA [39].

In our study we mainly focused on the patients belonging to the two discordant groups (16 out of 69 patients: 23.2% of the cohort, in line with previous reports [40], since it is not an infrequent situation in clinical practice, possibly leading clinicians to uncertainty in therapeutic choices. Our results show that PSMA PET monitoring is more informative than PSA monitoring, especially in the case of response to PSMA PET without simultaneous response to PSA, in which the survival is predicted by PSMA PET and not by PSA, as shown before. Our results are in contrast to those reported by Shagera et al. [17]: the authors reported a high concordance rate (89%) between PSMA PET and PSA response, but the sample size was lower than our study, and it must be noted that the discordance varied based on the criteria chosen (~10% with EAU/EANM vs. ~20% with RECIP 1.0);

moreover, the authors acknowledged that the mechanism of PSA secretion is different and not associated to the mechanism responsible for PSMA expression in PCa cells, and our findings further support this statement. Our study is the first to assess – on a larger scale if compared to previous reports – that PSA is less informative than PSMA PET in patients receiving ARSI in a castration-resistant environment. We therefore suggest abandoning the use of PSA alone for disease monitoring in this context.

Lastly, despite the above-mentioned limitations, PSMA PET adoption is increasing in mCRPC patients, also because it is necessary for assessing [^{177}Lu]Lu-PSMA eligibility: the use of PSMA PET with the double aim of monitoring NHA/docetaxel response and also identifying the right moment to start [^{177}Lu]Lu-PSMA-therapy - which has been recently approved by Food and Drug Administration (FDA) [41] - is becoming reality.

Among the limitations of our work, we acknowledge that the mCRPC disease presentation could vary significantly among cohorts of PCa patients, and our cohort included patients with a relatively low burden of metastases, potentially influencing the applicability of our findings.

Conclusions

Our results indicate that [^{68}Ga]Ga-PSMA PET could be a useful imaging tool for monitoring response to enzalutamide in mCRPC patients. PSA monitoring is less informative than [^{68}Ga]Ga-PSMA PET in this setting, and in case of a discordant response after 3 months from starting enzalutamide, [^{68}Ga]Ga-PSMA PET could better guide clinicians in therapeutic choices.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-024-06887-4.

Author contributions All authors contributed to the study conception and design. Data collection was performed by Emilio Francesco Giunta, Paola Caroli and Amelia Altavilla, analysis was performed by Emilio Francesco Giunta and Emanuela Scarpi. The first draft of the manuscript was written by Emilio Francesco Giunta, Paola Caroli and Emanuela Scarpi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This prospective study was approved by the Institutional Review Board and Ethics Committee of IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori," Meldola, Italy (protocol code: IRST B073). The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference of Harmonization A written informed consent was obtained from all the enrolled patients.

Consent for publication All patients participating in the present study and the authors consent to publish and print the information contained in this article.

Competing interests Financial interests: EFG reports honoraria from Astellas and travel support from Janssen-Cilag and Bayer. CL reports honoraria for advisory boards or speaker fees from Ipsen, BMS and MSD. GS reports honoraria from Bayer, BMS and Ipsen. NB reports travel support from Ipsen, Novartis, Janssen-Cilag, Pfizer and Advanced Accelerator Applications, speaker honoraria from BMS. MCC reports travel accommodation from Ipsen. UDG reports honoraria for advisory boards or speaker fees from Pfizer, BMS, MSD, PharmaMar, Astellas, Bayer, Ipsen, Roche, Novartis, Clovis, GSK, AstraZeneca, institutional research grants from AstraZeneca, Sanofi and Roche. The other authors do not report any conflicts of interest.

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