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Systemic therapy response evaluation in prostate carcinoma with [^{68}Ga]Ga-PSMA-11 PET/CT

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Abstract

Background: Consensus statements was published by EAU and EANM to clarify some uncertainties on PSMA PET/CT response assessment in 2020. We aimed to investigate the response criteria for PSMA PET/CT according to published criteria by comparing with serum PSA changes and determine the factors affecting therapy response evaluation.

Results: A high concordance was found between [^{68}Ga]Ga-PSMA-11 PET/CT and serum PSA responses and 0.84 of Gamma coefficient was obtained. Between concordant and discordant group, statistically significant difference was not found in terms of received therapies and castration resistance status. Statistically significant but low correlation was found between serum PSA and SUV values of prostate, moderate correlation was found serum PSA and SUVmax values of metastatic lymph nodes and bones.

Conclusions: The response evaluation of PSMA PET/CT according to the published criteria shows high concordance with serum PSA values without being affected by received therapies or castration resistance. This criteria can be used with contribution of serum PSA values in response evaluation of prostate cancer according to our results and literature data.

Keywords: Prostate cancer, Prostate spesific antigen, PET scan, ^{68}Ga-PSMA

Background

Prostate adenocarcinoma is the second most frequent type of cancer and the fifth most frequent cause of cancer related death in men. While approximately 1.3 million people were diagnosed all over the world in 2018, the number of deaths due to prostate cancer was calculated about 359.000 [1]. According to United States data, the average 5-years survival is approximately 97.5%. At the time of diagnosis, the survival rate reaches 100% if the disease is localized to the prostate gland or spread to regional lymph nodes [2]. For this reason, determining the stage of the disease at the time of diagnosis is of great importance for prognosis. According to the D'Amico Risk Classification [3], while active monitoring or local treatments such as prostatectomy, external radiotherapy or brachytherapy are mainly used in patients in low and medium risk group, systemic first-line hormone therapy in addition to local treatments can be given in high-risk patients with distant metastasis [4]. The use of docetaxel or abiraterone in addition to systemic antiandrogenic agents is recommended in mCSPC, and these agents significantly increase survival [5, 6]. In mCRPC, there are systemic therapy options such as abiraterone, docetaxel, cabazitaxel, enzalutamide and [^{223}Ra]Ra for bone metastases. These options can be gradually and alternately used regarding prior received treatments, performance status, comorbidities and the extent of the disease [5]. [^{177}Lu]Lu-PSMA-617 is a radionuclide agent that has been used in many centers in the past decade and creates a cytotoxic effect with beta irradiation thanks

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to the increased PSMA ligand expression in target prostatic cells. A Phase II randomized clinical trial published on February 2021 showed that if [^{177}Lu]Lu-PSMA-617 is given to patients with mCRPC as a third line therapy instead of cabazitaxel, better PSA response and less Grade 3–4 adverse effects can be obtained [7]. In addition, international, prospective, open-label, randomized phase 3 trial (VISION study) revealed that when [^{177}Lu]Lu-PSMA-617 is added to standard care after at least one anti-androgenic therapy and one or two taxan regimens, both imaging-based progression free survival and overall survival are significantly prolonged. PSMA-targeted radionuclide therapy is gaining importance and will be a standard therapy regimen in near future [8].

PSMA is a type 2 transmembrane protein that is expressed 100–1000 fold more in prostate carcinoma cell membranes in comparison with other cells. The PSMA expression of prostate carcinoma cells increases in hormone resistant disease and advanced stages [9]. In recent years, PET/CT imaging with urea based PSMA inhibitor conjugated [^{68}Ga]Ga isotope has gained a wide place in diagnosis and follow-up of prostate cancer. The role of [^{68}Ga]Ga-PSMA-11 PET/CT in primary staging and biochemical recurrence was investigated with large patient series and high diagnostic rates were obtained even in case low serum PSA values [10]. However, there are limited number of studies evaluating the role of PSMA PET/CT in systemic therapy response of prostate cancer in the literature and there is still not a definitive criteria for therapy response evaluation. In order to resolve this ambiguity, a panel was held in the Netherlands in 2020 with the cooperation of EANM and EAU, and a joint text was published with participants specializing in prostate cancer from all over the world [11]. Eventually, the panelists were recommended a therapy response criteria very similar to PERCIST 1.0.

In this study, in light of the proposed criteria, we investigated role of [^{68}Ga]Ga-PSMA-11 PET/CT in the treatment response of prostate cancer in patients receiving antiandrogenic and other systemic therapies by comparing with the change of serum PSA values.

Methods

Patient Group

The study group was consisted of 50 patients who were given systemic antiandrogenic, chemotherapeutic or radionuclide therapy for prostate cancer and whose sufficient data about recieved therapies and serum PSA value were accessible in Cukurova University Balcali Hospital database. Subsequent to initiation of [^{68}Ga]Ga-PSMA-11 production in Nuclear Medicine Department of Cukurova University Balcali Hospital, 100 [^{68}Ga]Ga-PSMA-11 PET/CT images of 50 patients that were obtained between October 2018-March 2021 were evaluated comparatively. The therapy regimens of patients included first-line hormone therapy, enzalutamide, abirateron, radionuclide ([^{177}Lu]Lu-PSMA-617) and chemotherapeutic therapy with docetaxel or cabazitaxel. While second [^{68}Ga]Ga-PSMA-11 PET/CT images were obtained following suspicious biochemical or radiological findings during first-line hormone therapy only regimen, the end of therapy protocol was waited for other agents. Second PET/CT images for response evaluation were obtained three weeks later following last cycle of systemic therapy.

Serum PSA values were also recorded during first and second [^{68}Ga]Ga-PSMA-11 PET/CT. Care was taken to ensure that there was not more than two weeks between serum PSA measurement and PET/CT imaging. The study was approved by Cukurova University Non-Interventional Research Ethic Committee with the number of 21.01.2021/107. The informed consent was obtained from all participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, the Helsinki declaration and its later amendments or comparable ethical standards.

PET/CT Imaging

PET/CT imaging of all patients was performed at Nuclear Medicine Department of Cukurova University Balcali Hospital with the Biograph™ PET/CT system (Siemens Molecular Imaging, Hoffman Estates, IL, USA) consisting of a PET unit and 2-slice spiral CT. After 1,8–2,2 MBq/kg [^{68}Ga]Ga-PSMA-11 injection, PET/CT images were acquired about 60–75 min later. During rest period after injection, intravenous saline injection was provided and forced diuresis was suggested before imaging to overcome urinary system and bladder artifacts. The images were acquired from vertex to mid thigh when the patients were laid supin position and in normal tidal respiration rate. Obtained raw images were reconstructed by using iterative reconstruction method and 5 milimeter thick fusion sections of PET, CT and PET/CT were created for evaluation on high resolution workstations. Administered activity, administration time and patient weight were used to calculate maximum standardized uptake value (SUVmax) and mean standardized uptake value (SUVmean). On PET/CT images, SUVmax and SUVmean values were obtained from the prostate gland, SUVmax values were obtained from the involved lymph nodes, bones and distant organs by automatic isocontour with the General Electric AW VolumeShare® 7 workstation.

Response Evaluation

- *Biochemical Response*: Post-treatment serum PSA values were compared to those that measured in the time of diagnosis based on the Prostate Cancer Working Group 3 (PCWG3) criteria [12]. According to the criteria, ≥ 25% of increase in serum PSA compared to the first measurement represents biochemically progression, ≥ 50% of decrease in serum PSA or reggresion to below 2 ng/ml represents biochemically regression, < 25% of increase or < 50% decrease in serum PSA value represents biochemically stable disease.
- *[^{68}Ga]Ga-PSMA-11 PET/CT Response*: Absence of PSMA uptake in target foci indicates complete response, more than 30% decrease in uptake and tumor volume in target foci indicates partial response, less than 30% decrease or increase in uptake and tumor volume indicates stable disease and more than 30% increase in uptake and/or ≥ 2 new lesion indicates progressive disease in [^{68}Ga]Ga-PSMA-11 PET/CT [11].

Comparison of Alterations of Serum PSA Value and [^{68}Ga]Ga-PSMA-11 PET/CT Result

The concordance between serum PSA and [^{68}Ga]Ga-PSMA-11 PET/CT response after treatment was evaluated and the patients were divided into two groups as concordant and discordant in terms of progression, stable disease and regression. It was investigated whether there was a statistically significant difference between the groups in terms of the received treatments and castration resistance status. In addition, in order to determine the relationship between the change in serum PSA levels and the change in lesion-based PSMA expression, target foci with the highest PSMA expression from the prostate gland, lymph nodes and skeletal system were determined in all patients, and the SUV value changes were compared with the serum PSA changes.

Statistical Analysis

Categorical measurements were summarized as numbers and percentages, numerical measurements as mean and standard deviation (median and interquartile range (IQR) (25th percentile-75th percentile) where necessary). Chi-square test statistics were used to compare categorical measures between groups. Whether numerical measurements provided the assumption of normal distribution was tested with the Shapiro Wilk test. In the comparison of numerical measurements between concordant and discordant groups as a result of serum PSA and PET/CT findings, the T test of independent groups was used in if the assumptions were met and the Mann Whitney U test was used if the assumptions were not met. The concordance between serum PSA values and PET/CT results was analyzed by Gamma coefficient. Since the rate of alteration of the serum PSA and SUV values were not meet the assumption of normal distribution, the correlation between these continuous measurements was analyzed by Spearman Correlation Coefficient [13].

Results

The median interval between two PET/CT were 151 days (IQR: 118 days–233 days) in the group. The mean age of the patients was 67 ± 10 (48–87). The initial pathological features of some patients could not be accessed, because they were diagnosed in other health centers. The clinical and pathological features of the patient group are given in Table 1. The castration resistance status of the patients and the treatments that they received before the second [^{68}Ga]Ga-PSMA-11 PET/CTs are given in Table 2.

In light of EAU-EANM consensus criteria, 100 [^{68}Ga]Ga-PSMA-11 PET/CT images were evaluated comparatively and 25 (50%) progression, 5 (10%) stable disease and 20 (40%) partial regression were detected. Complete regression was not detected among the second PET/CT images. The obtained results were compared with the serum PSA changes after the therapy. The data of comparison are given in Table 3. PSMA PET/CT and serum PSA responses were concordant in 39 of 50 patients. 0.84 of Gamma coefficient which means high concordance was found between results (Fig. 1). Out of the 11 patients with discordant results, 4 have regression of serum PSA and progression of PET/CT, 2 have progression of serum PSA and stable disease with PET/CT. Of the rest 5 patients with stable serum PSA, 2 have progression and 3 have regression in PET/CT (Table 3). There was no statistically significant difference between the patients with concordant and discordant results in terms of received therapies ($p = 0.313$) and castration resistance status ($p = 0.74$) (Table 4). When the received therapies were grouped as antiandrogenic (first-line hormone, enzalutamide, abiraterone), chemotherapeutic (docetaxel, cabazitaxel) and radionuclide ([^{177}Lu]Lu-PSMA-617), statistically significant difference was not found between concordant and discordant results as well ($p > 0.05$) (Table 5) (Fig. 2).

At the time of response evaluation, when the correlation between rate of changes of serum PSA and SUV values on target lesion sites were examined, statistically significant correlation was found in all. This correlation was low in SUVmax and SUVmean of prostate gland, modarate in SUVmax of lymph node and bone lesions (Table 6).

Table 1 Clinical and pathological features of patient group

Feature			Total
Gleason score	7	7 (26.9%)	26 (100%)
	8	9 (34.6%)	
	9	8 (30.8%)	
	10	2 (7.7%)	
ISUP score	1	0	26 (100%)
	2	2 (7.7%)	
	3	5 (19.2%)	
	4	9 (34.6%)	
	5	10 (38.5%)	
Risk classification	High risk	29 (90.6%)	31 (100%)
	Intermediate risk	2 (9.4%)	
	Low risk	0	
Definitive therapy to prostate gland	None	41 (87.2%)	47 (100%)
	Total prostatectomy	3 (6.4%)	
	Radiotherapy	3 (6.4%)	
Serum PSA value at diagnosis	Mean ± standart deviation (minimum–maximum)	510.72 ± 1127.49 (0.22–5476)	

Table 2 Features of the patients before the second [^{68} Ga] Ga-PSMA-11 PET/CT images

Feature			Total
Castration resistance	Sensitive	20 (40%)	50 (100%)
	Resistant	30 (60%)	
Received treatment	First-line hormone therapy	17 (34%)	50 (100%)
	Docetaxel	21 (42%)	
	Cabazitaxel	3 (6%)	
	Enzalutamide	3 (6%)	
	Abiraterone	3 (6%)	
	[^{177}Lu]Lu-PSMA-617	3 (6%)	
Treatment group	Antiandrogenic	23 (46%)	50 (100%)
	Chemotherapeutic	24 (48%)	
	Radionuclide	3 (6%)	

Discussion

Up to 1000-fold increased expression of PSMA in prostate cancer cells [9], has increased the use of PSMA-targeted imaging methods and made it an essential part of prostate cancer management in the recent 10 years. PSMA PET/CT is advantageous tool due to its on-site production and providing high quality imaging with low radiation dose thanks to its high emission rate. The diagnostic power of [^{68}Ga]Ga-PSMA PET/CT agents in primary diagnosis, staging and biochemical recurrence of prostate adenocarcinoma was investigated by a lot of center and it was found superior to conventional imaging modalities with up to 90% of diagnostic rates [14]. However, limited data exist about the role of PSMA PET/CT in systemic therapy response assessment in the literature. It is still not clearly figured out that how androgen supressor agents and taxan-based chemotherapeuticals effect PSMA expression and uptake of [^{68}Ga]Ga-PSMA agents in target cells and as a result how the changes of uptakes in target cells should be interpreted. PERCIST 1.0 criteria [15] which was published for therapy response of 2-fluorodeoxyglucose (2-[^{18}F]FDG) PET/CT in 2009, is not entirely appropriate for PSMA PET/CT due to different uptake mechanisms and metabolic pathways of radiopharmaceuticals.

On February 2020, a panel was recruited by EAU and EANM with joining of intenational experts of prostate carcinoma in the fields of nuclear medicine, radiology and urology to make clear the utility, best timing for performing, criteria for treatment response, benefit to the patients and use of radiolabeled PSMA PET tracers [12]. According to the consensus criteria, PSMA PET/CT should be used prior and after all local/systemic treatments in metastatic disease to evaluate response. Besides, due to potential flare phenomenon of ADT and possibility of misinterpretation in early stage of therapy, the PSMA PET/CT should not be performed earlier than 3 months after initiation of ADT. The panelists also declared that the patients should be divided as responders to treatment (complete response, partial response and stable disease) and not responders (progressive disease). In responders to therapy, complete response can be considered as absence of PSMA uptake in target foci, more than 30% decrease in uptake and tumor volume in target foci can be considered as

Table 3 Comparison of the results of serum PSA and [^{68}Ga]Ga-PSMA-11 PET/CT after therapy

			[^{68}Ga]Ga-PSMA-11 PET/CT				Total
			Progression	Stable	Partial regression	Complete regression	
Serum PSA	Progression	No	19	2	0	0	21
		% within PSA	90.5%	9.5%	0%	0%	100%
		% within PET/CT	76%	40%	0%	0%	40%
	Stable	No	2	3	3	0	8
		% within PSA	25%	37.5%	37.5%	0%	100%
		% within PET/CT	8%	60%	15%	0%	18%
	Regression	No	4	0	17	0	21
		% within PSA	19%	0%	81%	0%	100%
		% within PET/CT	16%	0%	85%	0%	42%
Total		No	25	5	20	0	50
		% within PSA	50%	10%	40%	0%	100%
		% within PET/CT	100%	100%	100%	0%	

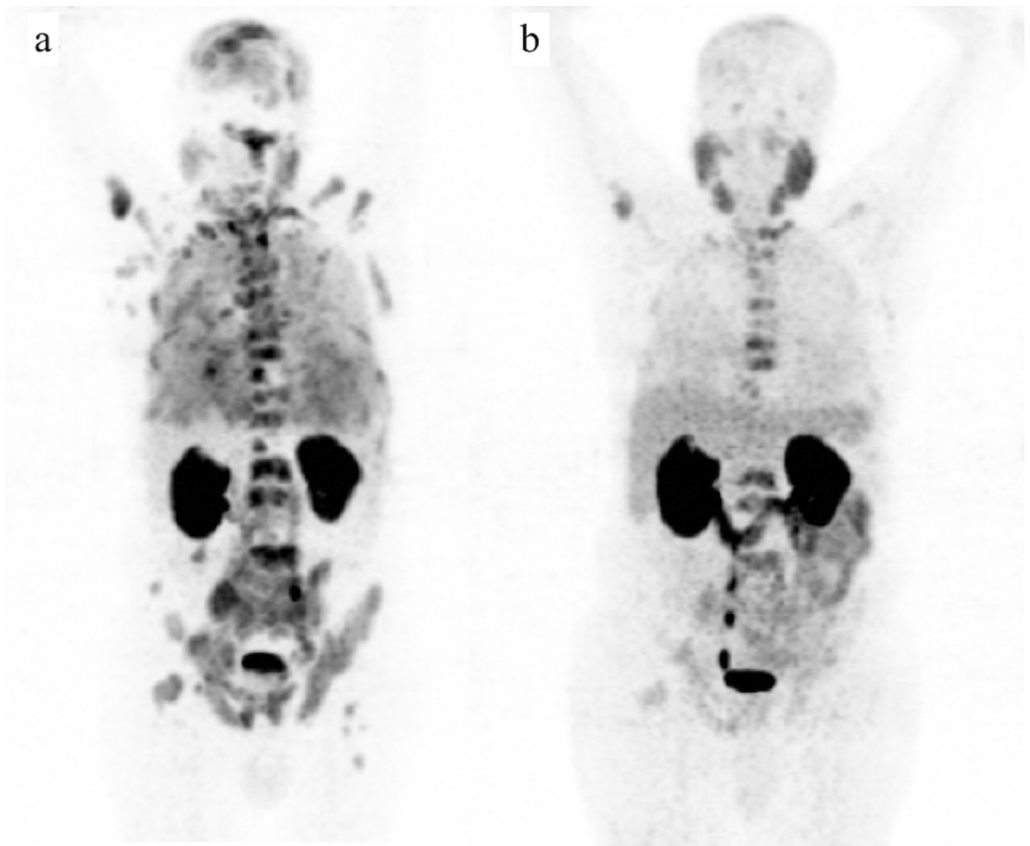

Fig. 1 Serum PSA value of a 78 years old patient with prostate adenocarcinoma falled to 0.33 ng/ml from 5476 ng/ml (**a)** after leuprolide + docetaxel therapy regimen. A significant regression in the lesions of prostate gland, bilateral lungs, lymph nodes and bones is seen after on [^{68}Ga]Ga-PSMA-11 PET/CT images following therapy (**b**)

Table 4 The distrubution of received therapies in concordant and discordant results

		Result of [^{68}Ga]Ga-PSMA-11 and serum PSA		Total
		Concordant	Discordant	
Received Treatment	First-line hormone therapy	14	3	17
		82.4%	17.6%	100%
	Docetaxel	17	4	21
		81%	19%	100%
	Abiraterone	2	1	3
		66.7%	33.3%	100%
	Enzalutamide	2	1	3
		66.7%	33.3%	100%
	Cabazitaxel	1	2	3
		33.3%	66.7%	100%
	[^{177}Lu]Lu-PSMA-617	3	0	3
		100%	0%	100%
	Total	39	11	50
		78%	22%	100%

Table 5 The distribution of received therapies in terms of effect mechanism in concordant and discordant results

		Result of [^{68}Ga]Ga-PSMA-11 and serum PSA		Total
		Concordant	Discordant	
Recieved treatment group	Antiandrogenic	18	5	23
		78.3%	21.7%	100%
	Chemotherapeutic	18	6	24
		75%	25%	100%
	Radionuclide	3	0	3
		100%	0%	100%
Total		39	11	50
		78%	22%	100%

partial response and less than 30% decrease or increase in uptake and tumor volume in target foci can be considered as stable disease. Otherwise, more than 30% increase in uptake and/or ≥ 2 new lesion represents progression. Nevertheless, it is indicated that due to lack of sufficient data about PSMA behavior after therapy, the suspicion remains in therapy response assessment except in patients with complete response and obvious progression. Although the 30% of threshold value was determined for 2-[^{18}F]FDG, due to not being a proved threshold value for PSMA and for the purpose of determining baseline value to further studies, 30% threshold value was chosen for PSMA as well. In this study, we evaluated comparatively 100 [^{68}Ga]Ga-PSMA-11 PET/CT images of 50 patients in light of these response criteria. Then, the results of [^{68}Ga]Ga-PSMA-11 PET/CT images were compared with serum PSA response. High concordance was found between PSMA PET/CT and serum PSA responses (Gamma coefficient: 0.84). In a study by Schmidkonz et al. [^{68}Ga]Ga-PSMA-11 PET/CT that performed for biochemical recurrence and serum PSA values were compared and near to high concordance was found between total PSMA amount which equals the multiplication of total PSMA volume and SUVmean of each lesion and serum PSA changes (Cohen's Kappa coefficient: 0.78) [16]. This value is similar to ours but in that study total PSMA amount was used for comparison with serum PSA values. Whereas we evaluated the therapy response categorically as progression, stable disease, partial or complete response.

In a study which has similar patient number and methodology to ours, Kuten et al. found a concordance between [^{68}Ga]Ga-PSMA-11 PET/CT and serum PSA response with the rate of 65.4% which is close to ours (78%) [17]. Besides, the authors detected that most

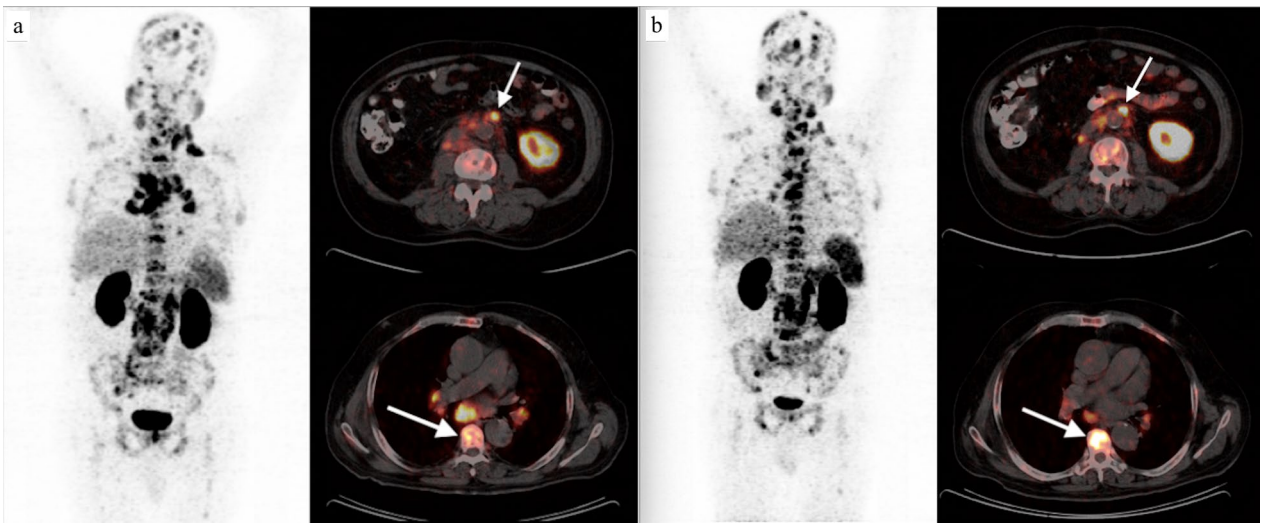

Fig. 2 The [^{68}Ga]Ga-PSMA-11 PET/CT images of a 63 years old patient who received cabazitaxel following goserelin and docetaxel before (**a**) and after (**b**) therapy. Despite decreasing of serum PSA from 382 ng/ml to 236 ng/dl and considering the patient in biochemically stable group, new metastatic abdominal paraaortic lymph nodes and bone lesions were detected and [^{68} Ga]Ga-PSMA-11 uptakes of those were increased significantly (arrows)

Table 6 The correlations between alteration percantages of serum PSA and SUV values

		Spearman correlation coefficient	*p*
Δ Serum PSA %	Δ Prostate SUVmax %	0.457	0.003
	Δ Prostate SUVmean %	0.449	0.003
	Δ Lymph nodes SUVmax %	0.657	< 0.001
	Δ Bone SUVmax %	0.707	< 0.001

discordance occured in biochemical stable status (90.9%). In our study, five of 11 discordant situation were seen in biochemical stable patients. Serum PSA and PSMA PET/CT results of three of these patients whose further follow-up data could be obtained, became concordant at progressive status after a while. Because while serum PSA value represents cumulative active tumor cell amount of the body, the PSMA PET/CT results are obtained with lesion-based comparison in light of criteria. For instance, two new lymph node lesion in PSMA PET/CT is thought progression after therapy, but there may not be a significant difference in the number of active tumor cells between two assessment. On contrary, despite increasing number of active tumor cells with increased serum PSA, PSMA PET/CT may not be able to represent progressive results according to the criteria. It is possible to detect more clear relationships at following response assessments especially when they were evaluated with former PET/CT images and serum PSA values. That's why serum PSA and PSMA PET/CT should be correlated during response assessment and therapy management process. Pathological studies and prospective randomized clinical trials are necessary to overcome that unclear situation.

Gupta et al. compared the molecular (EORTC and PERCIST) and morphological (RECIST and MDA) response criteria on biochemical progression and they found superior the molecular response criterias to morphologicals significantly [18]. They also pointed out that molecular criteria is more useful especially in bone lesions which are not easily diagnosed as sclerotic lesion or metastasis with morphological modalities. In our study, of the 19 patients whose PET/CT and PSA results are concordant as progression, 13 had progression due to sclerotic bone metastasis. It is very crucial to use molecular response criteria instead of morphological criteria especially in terms of bone metastases at follow-ups.

Despite wide use of PSMA PET/CT around the world, the question that how systemic antiandrogenic therapies effect PSMA expression still remains. It is known that antiandrogenic therapies increase PSMA expression of target cells via FOLH1 gene by suppressing androgen releasing hormones and androgen receptors [19, 20]. Increased PSMA expression in advanced stage and castration-resistant prostate carcinoma is also showed [21, 22]. In a study performed with cell culture that contains enzalutamide and abiraterone by Murga et al., it is showed that PSMA expression of target cells increases with antiandrogenic therapy and drops back to basal

levels following cessation of therapy. Moreover, in the castration-sensitive cells, antiproliferative effect was seen in addition to increased PSMA expression while antiproliferative effect diminishes in the castration-resistant cells despite persisting increased PSMA expression [23]. Some clinical trials also showed that PSMA expression increases in early periods of ADT (< 6 weeks) and decreases at the later periods (> 3 months) [22, 24–27]. In a study which investigates the long period effects of ADT to PSMA expression by Afshar-Oromieh et al. ADT was initated to the patients and [^{68}Ga]Ga-PSMA-11 PET/CT was performed after mean 229 ± 89 days to evaluate therapy response and changes in SUV values [26]. In the second PET/CT, 45% of lesions remain visible and SUVmean and SUVmax values decreased in 71% and 74.2% of lesions, respectively. Total lesion number, SUVmax and SUVmean values, tumor volume, SUV values/tumor volume and serum PSA values were also found statistically significantly lower at second PET/CT images. The authors concluded that the proportional decreasing of SUV values and tumor volume may be explained as that long-term ADT use causes decreased tumor cell clones following apoptosis. They also hypothesized that increase in SUVmean and SUVmax in the 12.9% and 19.4% of lesions could be compatible with the cell clones becoming resistant to castration. Due to presence of median 151 days between PET/CT images in our study, we assume that we are not be able to observe long-term effects of ADT. However, of the 17 patients who received ADT therapy, 14 (82.5%) had concordant results in PSMA PET/CT and serum PSA. There is a high concordance even it is not statistically significant. In a study which consists of non-metastatic 108 patients who received ADT median 2.9 months by Onal et al. a low but significant correlation was found between the changes of prostate gland SUVmax and serum PSA (Spearman coefficient: 0,367, $p < 0,05$) [28]. We found a low correlation between SUVmax and SUVmean of prostate gland and serum PSA changes (Spearman coefficient for SUVmax and SUVmean: 0.457 and 0.449, respectively) similar to that study. However, less patients with different received therapy agents exist in our study (50 vs. 108). We also compared the changes of serum PSA and SUVmax of lymph nodes and bones and significant correlation was found between them (Spearman coefficient for lymph nodes and bone: 0.657 and 0.707, respectively). When the results of Schmidkonz et al. which shows high concordance between total PSMA and serum PSA changes were taken under consideration [16], it may be concluded that serum PSA has higher concordance with PSMA PET/CT results in showing therapy response especially in metastatic patients according to the criteria.

A statistically significant difference was not found between patients with concordant and discordant results in terms of received therapies in our study. A study which is similar to ours in point of evaluating different therapy regimens was conducted with 43 patients who received 67 systemic therapies by Grubmüller et al. Serum PSA changes after therapy shows significant but low correlation both with changes of all PET parameters and response according to RECIST (Cohen's Kappa: 0.2–0.3, $p < 0.05$) [29]. In our study, we found high concordance in PET/CT and serum PSA results regardless of received theapies (Gamma coefficient: 0.84). Gamma coefficent was used because it is more suitable for consecutive categorical data comparison.

Increased PSMA expression in the castration-resistant prostate cells was shown in the literature [21]. However, there is not a study which investigates the efficiacy of the hormone resistance status to response assessment to the best of our knowledge. When our patient group was divided as hormone sensitive and resistant, there was not a significant difference in terms of concordance between PSMA PET/CT and serum PSA results. Therefore, in our opinion, castration resistance status does not a restrictive factor in response assessment. The serum PSA and PSMA PET/CT findings should be evaluated together regardless whether the patient is castration sensitive or not.

There are some limitations of the study. First, limited number of patients who received different kinds of therapy were included. More homogenous patient groups in which patients who are at similar stage of disease and received same therapy agent were included, have to be created to get more accurate data about therapy response. Secondly, the long-term results of patients do not exist. The behavior of PSMA in target cells can be observed better at long-term results with correlation of PET/CT and serum PSA values. Thirdly, the study is retrospective. Multi-centered prospective studies with contribution of histopathological studies should be performed from the initiation of therapy so that the changes of PSMA uptake in target cells can be detected more clear.

Conclusions

As a result, the systemic therapy response evaluation with [^{68}Ga]Ga-PSMA-11 PET/CT by using published criteria from EAU and EANM is useful for now especially when correlated with the serum PSA response. Moreover, the concordance of PSMA PET/CT and serum PSA responses is not affected by castration resistance and received therapies and also is improved when evaluated together with the former results. There is still need of proving PSMA response of target cells with larger series

to configure more accurate therapy response evaluation criteria for PSMA PET/CT.

Abbreviations
^{177}Lu: Lutetium-177; ^{223}Ra: Radium-223; ^{68} Ga: Gallium-68; ADT: Androgen deprivation therapy; EANM: European Association of Nuclear Medicine; EAU: European Association of Urology; EORTC: European Organization for Research and Treatment of Cancer; IQR: Interquartile range; ISUP: International Society of Urological Pathology; kg: Kilogram; MBq: Megabecquerel; mCRPC: Metastatic castration-resistant prostate cancer; mCSPC: Metastatic castration-sensitive prostate cancer; MDA: MD Anderson criteria; PERCIST: Positron emission tomography response criteria in solid tumors; PET/CT: Positron emission tomography/computed tomography; PSA: Prostate spesific antigen; PSMA: Prostat spesific membrane antigen; RECIST: Response evaluation criteria in solid tumors; SUVmax: Maximum standardized uptake value; SUVmean: Mean standardized uptake value.

Acknowledgments
Assoc. Prof. Ilker Unal from Biostatistics Department of Cukurova University. Faculty of Medicine performed all the statistical tests and calculations.

Author contributions
KAK and ZY designed the study concept and collected the materials; KAK, ZY and IBG evaluated and analyzed the patient data; SP was consultant of patient management and provided some patient data; KAK and ZY were the major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was given by Cukurova University Non-Interventional Research Ethic Committee with the number of 21.01.2021/107. The informed consent was obtained from all the participants.

Consent for publication
Consent for publication was taken for published images from participants.

Competing interests
The authors declare that they have no competing interests.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424
2. SEER Cancer Stat Facts: Prostate Cancer. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/prost.html
3. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA et al (1998) Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 280:969–974
4. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative Intent. Eur Urol 71:618–629
5. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 71:630–642
6. Wallis CJD, Klaassen Z, Bhindi B, Goldberg H, Chandrasekar T, Farrell AM et al (2018) Comparison of abiraterone acetate and docetaxel with androgen deprivation therapy in high-risk and metastatic hormone-naïve prostate cancer: a systematic review and network meta-analysis. Eur Urol 73:834–844
7. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC et al (2021) [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet 397:797–804
8. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K et al (2021) Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 385(12):1091–1103
9. Maurer T, Eiber M, Schwaiger M, Gschwend JE (2016) Current use of PSMA-PET in prostate cancer management. Nat Rev Urol 13:226–235
10. Hope TA, Goodman JZ, Allen IE, Calais J, Fendler WP, Carroll PR (2019) Metaanalysis of ^{68}Ga-PSMA-11 PET accuracy for the detection of prostate cancer validated by histopathology. J Nucl Med 60:786–793
11. Fanti S, Goffin K, Hadaschik BA, Herrmann K, Maurer T, MacLennan S et al (2021) Consensus statements on PSMA PET/CT response assessment criteria in prostate cancer. Eur J Nucl Med Mol Imaging 48:469–476
12. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K et al (2016) Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. J Clin Oncol 34:1402–1418
13. IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, IBM Corp
14. Matushita CS, da Silva AMM, Schuck PN, Bardisserotto M, Piant DB, Pereira JL et al (2021) 68Ga-Prostate-specific membrane antigen (psma) positron emission tomography (pet) in prostate cancer: a systematic review and meta-analysis. Int Braz J Urol 47:705–729
15. Wahl RL, Jacene H, Kasamon Y, Lodge MA (2009) From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med 50:122S-S150
16. Schmidkonz C, Cordes M, Schmidt D, Bäuerle T, Goetz TI, Beck M, Prante O, Cavallaro A, Uder M, Wullich B, Goebell P, Kuwert T, Ritt P (2018) ^{68}Ga-PSMA-11 PET/CT-derived metabolic parameters for determination of whole-body tumor burden and treatment response in prostate cancer. Eur J Nucl Med Mol Imaging 45:1862–1872
17. Kuten J, Sarid D, Yossepowitch O, Mabjeesh NJ, Even-Sapir E (2019) [^{68}Ga] Ga-PSMA-11 PET/CT for monitoring response to treatment in metastatic prostate cancer: is there any added value over standard follow-up? EJNMMI Res 9:84
18. Gupta M, Choudhury PS, Rawal S, Goel HC, Rao SA (2018) Evaluation of RECIST, PERCIST, EORTC, and MDA Criteria for assessing treatment response with Ga68-PSMA PET-CT in metastatic prostate cancer patient with biochemical progression: a comparative study. Nucl Med Mol Imaging 52:420–429
19. Hope TA, Truillet C, Ehman EC, Afshar-Oromieh A, Aggarwal R, Ryan CJ et al (2017) 68Ga-PSMA-11 PET imaging of response to androgen receptor inhibition: first human experience. J Nucl Med 58:81–84
20. Vaz S, Hadaschik B, Gabriel M, Herrmann K, Eiber M, Costa D (2020) Influence of androgen deprivation therapy on PSMA expression and PSMA-ligand PET imaging of prostate cancer patients. Eur J Nucl Med Mol Imaging 47:9–15
21. Paschalis A, Sheehan B, Riisnaes R, Rodrigues DN, Gurel B, Bertan C et al (2019) Prostate-specific membrane antigen heterogeneity and DNA repair defects in prostate cancer. Eur Urol 76:469–478
22. Emmett L, Yin C, Crumbaker M, Hruby G, Kneebone A, Epstein R et al (2019) Rapid modulation of PSMA expression by androgen deprivation: serial ^{68}Ga-PSMA-11 PET in men with hormone-sensitive and

castrate-resistant prostate cancer commencing androgen blockade. J Nucl Med 60:950–954
23. Murga JD, Moorji SM, Han AQ, Magargal WW, DiPippo VA, Olson WC (2015) Synergistic co-targeting of prostate-specific membrane antigen and androgen receptor in prostate cancer. Prostate 75:242–254
24. Aggarwal R, Wei X, Kim W, Small EJ, Ryan CJ, Carroll P et al (2018) Heterogeneous flare in prostate-specific membrane antigen positron emission tomography tracer uptake with initiation of androgen pathway blockade in metastatic prostate cancer. Eur Urol Oncol 1:78–82
25. Leitsmann C, Thelen P, Schmid M, Meller J, Sahlmann CO, Meller B et al (2019) Enhancing PSMA-uptake with androgen deprivation therapy - a new way to detect prostate cancer metastases? Int Braz J Urol 45:459–467
26. Afshar-Oromieh A, Debus N, Uhrig M, Hope TA, Evans MJ, Holland-Letz T et al (2018) Impact of long-term androgen deprivation therapy on PSMA ligand PET/CT in patients with castration-sensitive prostate cancer. Eur J Nucl Med Mol Imaging 45:2045–2054
27. Zacho HD, Petersen LJ (2018) Bone flare to androgen deprivation therapy in metastatic, hormone-sensitive prostate cancer on 68Ga-prostate-specific membrane antigen PET/CT. Clin Nucl Med 43:e404–e406
28. Onal C, Guler OC, Torun N, Reyhan M, Yapar AF (2020) The effect of androgen deprivation therapy on ^{68}Ga-PSMA tracer uptake in non-metastatic prostate cancer patients. Eur J Nucl Med Mol Imaging 47:632–641
29. Grubmüller B, Rasul S, Baltzer P, Fajkovic H, D'Andrea D, Berndl F, Maj-Hes A, Grubmüller KH, Mitterhauser M, Wadsak W, Pfaff S, Shariat SF, Hacker M et al (2020) Response assessment using [^{68}Ga]Ga-PSMA ligand PET in patients undergoing systemic therapy for metastatic castration-resistant prostate cancer. Prostate 80:74–82

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