RESEARCH ARTICLE

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The Role of Whole Body Volumetric ^{68}Ga-PSMA PET/CT Parameters in Prediction of Response to Abiraterone/Enzalutamide Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer

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Objective: To investigate the role of ^{68}Ga-PSMA PET/CT in predicting prostate specific antigen (PSA) response among castration-resistant metastatic prostate cancer patients receiving Abiraterone/ Enzalutamide treatment, based on the quantitative PET parameters such as SUVmax, SUVmean, highest SUVpeak, PSMA-TV and TL-PSMA, the biochemical parameters such as alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and the pathological parameters such as Gleason score.

Materials and Methods: A total of 45 patients initiating Abiraterone/Enzalutamide treatment after PSMA PET/CT in our clinic between January 2018 and January 2021 were included in this retrospective study. Data on whole body TL-PSMA, PSMA-TV, Highest SUVpeak (HPeak), Highest Background normalized SUVpeak (HBNSUVPeak), HSUVmax, HSUVmean, HBNSUVmax and HBNSUVmean values obtained by pre-treatment PSMA PET/CT imaging and pre- and post-treatment PSA values were recorded in each patient.

Results: ROC analysis revealed the cut-off values for predicting the progression to be ≥112.53 cm^3 for PSMA-TV (AUC: 0.930±0.37 p<0.001), ≥857.1 for TL-PSMA (AUC:0.916±0.44 p<0.001) and ≥16.36 g/ml for Hpeak (AUC: 0.721±071 p=0.075), and the area under the curve had statistically significant high sensitivity and specificity in prediction of the progression. While both PSMA-TV (≥112.53 cm^3) and TL-PSMA (≥857.1) values were associated with increased risk of progression in the univariate logistic regression analysis (OR and p values were OR: 29.7, p<0.001 and OR: 116, p<0.001, respectively), only the TL-PSMA value (≥857.1) was determined to be an independent prognostic factor in predicting progression (OR: 55.88, p:0.005) in the multivariate logistic regression analysis.

Conclusion: The TL-PSMA, as a parameter of ^{68}Ga-PSMA PET/CT and an independent prognostic factor in predicting the progression of the disease may contribute to the pre-treatment identification of patients who would not benefit from Abiraterone/Enzalutamide treatment and thus to provide timely guidance on use of alternative treatments.

Key Words: *Prostat adenokanser, PSA, ^{68}Ga-PSMA, PET/BT, abirateron, enzalutamide*

Abirateron/Enzalutamide Tedavisi Alan Metastatik Kastrasyona Dirençli Prostat Kanserli Hastalarda Tedavi Yanıtını Öngörmede Tüm Vücut Volümetrik ^{68}Ga-PSMA PET/BT Parametrelerinin Rolü

Amaç: Abirateron/Enzalutamide tedavisi altında kastrasyona dirençli metastatik prostat kanseri tanılı hastalarda SUVmax, SUVmean, Highest SUVpeak, PSMA-TV ve TL-PSMA gibi kantitatif PET parametreleri ile alkalen fosfataz (ALP), laktat dehidrogenez (LDH) gibi biyokimyasal parametreler ve Gleason skoru gibi patolojik bir parametre kullanarak prostat spesifik antijen (PSA) yanıtını öngörmede ^{68}Ga-PSMA PET/BT'nin rolünü incelemektir.

Gereç ve Yöntem: Retrospektif tasarlanan bu çalışmaya Ocak 2018-Ocak 2021 tarihleri arasında kliniğimizde PSMA PET/BT çekimi sonrası Abirateron/Enzalutamide tedavisi başlanan 45 hasta dahil edildi. Tüm hastalardan tedavi öncesi çekilen PSMA PET/BT den elde edilen tüm vücut TL-PSMA, PSMA-TV, Highest SUVpeak(HPeak), Highest Background normalised SUVpeak (HBNSUVPeak), HSUVmax, HSUVmean, HBNSUVmax, HBNSUVmean değerleri, tedavi öncesi ve sonrası PSA değerleri belirlenip kaydedildi.

Bulgular: ROC eğrileri ile progresyonu tahmin etmede cut-off değeri PSMA-TV için ≥112,53 cm^3 (AUC: 0,930±0,37 p<0.001), TL-PSMA için ≥857,1 (AUC: 0.16±0.44 p<0.001) ve Hpeak için ≥16.36 g/ml (AUC: 0,721±071 p=0.075) olarak bulunmuş olup eğri altında kalan alan progresyonu tahmin etmede yüksek hassasiyet ve özgüllük değerine sahip olup istatistiki olarak anlamlı bulunmuştur.

Univariant logistik regresyon analizinde PSMA-TV (≥112.53 cm^3) ve TL-PSMA (≥857.1) değerleri progresyonu tahmin etmede istatistiki anlamlı bulunurken (OR ve p değerleri sırasıyla OR:29.7 p<0.001 ve OR:116, p<0.001). Multivariant logistik regresyon analizde TL-PSMA (≥857.1) değeri progresyonu tahmin etmede bağımsız prognostik faktör olarak bulundu (OR: 55.88, p:0.005).

Sonuç: ^{68}Ga-PSMA PET/BT parametresi olan, TL-PSMA'nın hastalığın progresyonunu, tahmin etmede bağımsız prognostik faktör olduğu ve Abirateron/Enzalutamide tedavisinden fayda göremeyecek hastaların tedaviden önce belirlenerek farklı tedavi alternatiflerine yönlendirilmesinde katkı sağlayabileceğini düşündürtmektedir.

***Anahtar Kelimeler*:** *Prostat adenokanser, PSA, ^{68}Ga-PSMA, PET/BT, abirateron, enzalutamide*

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Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer and is known as the 5th most common cause of cancer-related death in men (1). Metastatic castration-resistant prostate cancer (mCRPCa) is the end stage PCa being associated with short survival and poor prognosis (2). Enzalutamide and abiraterone are new antiandrogen drugs (NADs) used in the treatment of mCRPCa (3). Abiraterone is a small molecule inhibitor of CYP17A1 enzyme. It prevents the synthesis of steroid precursors that can be converted to testosterone by cancer cells and is also a potent androgen receptor (AR) antagonist (4). Enzalutamide is a second generation AR inhibitor with 50 times greater AR binding capacity than Bicalutamide, and inhibits coactivator uptake, that impairs the binding of AR to DNA, and has DNA transcription (5). PSA (Prostate-specific antigen) is the most widely used biomarker in all stages of prostate cancer. However, it may sometimes (i.e. in some cases with neuroendocrine variants) fail to accurately predict the treatment response (6). Early PSA reductions among patients treated with abiraterone/enzalutamide are strongly associated with the outcomes (7). In patients with mCRPCa, the main goals are the selection of the right treatment, evaluation of the treatment response, and predicting the progression of the disease. However, biochemical markers and imaging modalities such as CT, magnetic resonance imaging (MRI), bone scintigraphy (BS) are not reliable enough to evaluate and predict the treatment response (8, 9).

Prostate specific membrane antigen (PSMA) is a type II transmembrane glycoprotein expressed primarily by prostate cancers and by prostate gland, salivary gland, renal proximal tubule and ileum (10). Gallium-68 (^{68}Ga)-PSMA positron emission tomography/computerised tomography (PET/CT) is the imaging modality reported to be better associated with outcomes in patients with recurrent PCa, even at low serum PSA levels (11). Maximum Standardized Uptake Value (SUVmax) in ^{68}Ga-PSMA PET/CT is a semi-quantitative parameter that is widely used as an imaging biomarker to evaluate the tumor burden of patients with PCa and to determine the stage of prostate cancer. Recent studies on ^{68}Ga-PSMA PET/CT suggest the use of volume-based parameters which more accurately reflect tumor burden of prostate cancer patients, such as PSMA-derived tumor volume (PSMA-TV) and total lesion PSMA (TL-PSMA) (12). Thus, a more effective route will be followed in evaluation of the prognosis and response to treatment in these patients (12). There is a recent study indicating that PSMA-based tumor burden may be useful in selecting mCRPCa patients who can benefit from Docetaxel therapy (13).

This study aimed to investigate the role of ^{68}Ga-PSMA PET/CT in prediction of PSA response in castration-resistant prostate cancer patients under abiraterone/enzalutamide treatment, based on the assessment of quantitative parameters such as SUVmax, SUVmean, Highest SUVpeak, PSMA-TV and TL-PSMA, biochemical parameters such as alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and a pathological parameter such as Gleason score.

Materials and Methods

Research and Publication Ethics: This study was conducted in accordance with the current legislations and good clinical practice guidelines and approved by the institutional ethics committee (approval no: 2021/835). Informed consent was obtained from the patients or their relatives.

Study Population: The patients initiating abiraterone/enzalutamide treatment after PSMA PET/CT imaging in our clinic between January 2018 and January 2021 were included in our retrospective study. Patients who progressed on completion of 6 cycles of docetaxel treatment before imaging, and those with a maximum of two weeks period between PET/CT and the initiation of treatment, regular use of abiraterone/enzalutamide treatment for 3 months and available data on pre-treatment and 3rd month PSA values as well as the digital data and images were included in the study. Patients who failed to complete docetaxel treatment or to continue abiraterone/enzalutamide treatment for 3 months, and those with lack of data on 3rd month PSA values were excluded from the study.

A total of 58 patients referred to ^{68}Ga-PSMA PET/CT scan were enrolled in this retrospective study. However, patients who did not complete 6 cycles of docetaxel treatment (5 patients), who did not receive regular enzalutamide treatment (3 patients), and who did not have a PSA value in the 3rd month after treatment (5 patients) were excluded from the study. All 45 selected patients comprising the final study population had a pre-treatment baseline PSA value and had a ^{68}Ga-PSMA PET/CT scan performed within 2 weeks prior to treatment initiation. The PSA values of all patients were measured at the third month after treatment. Before treatment, ALP values were available in 41 patients and LDH values in 24 patients.

PSMA PET/CT Imaging Protocol: The imaging was performed by Discovery IQ 4 ring 20 cm axial FOV PET/CT (GE Healthcare, Milwaukee, WI, USA). Whole body images were acquired in supine position from vertex to mid-thigh 60 min after the injection of 2 MBq/kg ^{68}Ga-PSMA-11. After CT images (CT parameters: 120 kV, 80 mAs/slice, 700 mm transaxial FOV, no gap, 64x0.625 mm collimation, pitch 1.4 µm, 0.5 s rotation time, 3.3 mm slice thickness, 512x512 matrix) bedside PET images in the same position and for the same regions [PET parameters: 3D FOV 20 cm, ordered subset expectation maximization algorithm (OSEM) 5 iterations/12 subset, full width at half maximum (FWHM) 3 mm] were obtained at 2.5 minutes. Intravenous non-ionic contrast of 1.5 mL/kg was injected to all patients who had no contraindications, before CT imaging at the 1st hour. Before all imaging, the patients were asked to drink water and urinate just before the imaging.

Imaging Analysis: All ^{68}Ga-PSMA-11 PET/CT images were examined in AW 4.7 (Advantage Workstation software version 4.7; GE Healthcare, Milwaukee, WI, ABD) and evaluated by two minimum 10 year PET/CT and seven year PSMA PET/CT experienced specialist. Except for the areas of physiological involvement and benign lesions, lesions that showed PSMA expression higher than the background activity and that were considered as malignant by both experts were considered as positive. Semiautomatic VOIs (volume of interest) were drawn from each of the metastatic areas in PET/CT, using 40% SUV threshold, in all three planes, with the lesion in the image area. Average SUV (SUVavg) values were obtained by drawing VOIs from the abdominal aorta at the level of L1 vertebra for each patient. Total PSMA tumor volume (PSMA-TV) value of all lesions, the highest SUVpeak (Hpeak) value, and the Highest background normalized SUVpeak (HBNSUVpeak) values obtained by ratio of Hpeak value to the SUVavg value of the aorta were given automatically by the device. Total lesion PSMA (TL-PSMA) value was obtained and recorded by summing the total lesion PSMA values (PSMA-TVxSUVmean) of all lesions. The highest SUVmax (HSUVmax), HSUVmean, HBNSUVmax, HBNSUVmean values in the patient were calculated and recorded (Figure 1).

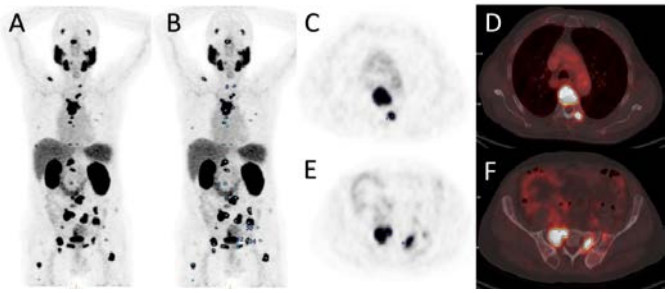

Figure 1: A 72-year-old male patient with prostate adenocarcinoma. GS: 4+4=8. Before abiraterone treatment PSA: 63.57 ng/ml, after 3 month therapy PSA: 183.5 ng/mL, PSMA-

TV: 389 cm^3, TL- PSMA: 2815.25 HPeak: 26.02 HSUVmax:42.82 HSUVmean: 12.55. MIP (A, B), PET (C, E) and Fusion images (D, F) with and without VOI are shown in the initial PET/CT.

Assessment of Treatment Response: Biochemical response; as described previously (8); Complete response (CR): PSA value 0ng/ml, partial response (PR): ∆PSA≤-50%, progressive disease (PD): ∆PSA≥+25% and between−49% and +24% was considered as stable diease (SD). The percentage change in PSA was calculated according the following formula by using pre-treatment (PSA1) and post-treatment (PSA2) PSA values:

∆PSA= (PSA2-PSA1)/ PSA1 x 100.

According to the PSA response, the patients with PD were determined as group 2 and the others as group 1.

Statistical Analysis: Statistical analysis was made using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). The normality of the distribution for univariate data was assessed using Kolmogorov-Smirnov test. The quantitative data of two independent groups were compared by using Mann-Whitney U test. The categorical variables were compared with Pearson Chi-Square exact test by using Fisher Exact results. The sensitivity and specificity ratios for the relation between the classification of the cut-off value calculated according to the group variables and the actual classification were analysed and presented by ROC (Receiver Operating Curve) curve analysis. Univariate and multivariate logistic regression analyses were used for analysing the association between predictive variables and PSA response to Abiraterone/Enzalutamide treatment. Quantitative variables are presented as mean±SD (standard deviation) and Median (Minimum/Maximum) and categorical variables were shown as n (%) in tables. Variables were analysed at 95% confidence level, and p value less than 0.05 was considered as significant. Power analysis of the study was performed using G power 3.1 software. Using a similar study in the literature, the effect size was calculated as 20. The Power (1-B) value of our sample number in the study was found to be 1.00.

Results

The mean age of the patients was 71.07±7.57 (51-91) years and the mean Gleason score was 8.1±0.98 (7-10). Radical prostatectomy was performed in 5 (11.1%) patients; 8 (17.7%) patients received radiotherapy; and orchiectomy was performed in 5 (11.1%) patients. Overall, 38 (84.44%) patients received enzalutamide and 7 (15.56%) patients received abiraterone treatment.

All patients had PSMA positive lesions on ^{68}Ga-PSMA PET/CT images. The involvement of the prostate gland was present in 37 (82.22%) patients. There were lymph node metastases in 26 (57.77%) patients, bone metastases in 35 (75.55%) patients, and visceral metastases in 3 (6.66%) patients. The mean HSUVmax, HSUVmean, HBNSUVmax, HBNSUVmean, Hpeak, PSMA-TV and TL-PMSA values on ^{68}Ga-PSMA PET/CT imaging were 28.32±29.15 (3.32-172.88), 15.33±16.88 (1.56-103.47), 19.94±24.01 (2.00-145.96), 9.70±10.93 (1.19-64.62), 20.72±24.32 (2.05-151.35), 161.80±296.97 (2.38-1793.69) and 1340.02± 2952.44 (22.48-18597.26), respectively (Table1).

Table 1. Descriptive parameters

	N	Mean	Std. Deviation	Median	Minimum	Maximum
AGE	45	71.07	7.57	72.00	51.0	91.00
PSA1	45	32.06	48.85	9.67	0.05	243.40
ΔPSA	45	5.77	144.79	-63.60	-99.29	579.31
PSA2	45	35.96	75.36	3.85	0.01	357.00
TLDH	24	275.54	247.22	217.00	140.0	1405.0
ALP	41	157.76	215.37	84.00	37.0	1262.0
GS	31	8.10	0.98	8.00	7.00	10.00
HSUVmax	45	28.32	29.15	22.85	3.32	172.88
HSUVmean	45	15.33	16.88	11.82	1.56	103.47
HBNmax	45	19.94	24.01	12.53	2.00	145.96
HBNmean	45	9.70	10.93	6.71	1.19	64.62
HPEAK	45	20.72	24.32	14.53	2.05	151.35
PSMA-TV	45	161.80	296.97	39.44	2.38	1793.69
TL-PMSA	45	1340.02	2952.44	356.17	22.48	18597.26

Table 2. Comparison of PSA values, PSMA PET/CT parameters and treatments in patients with and without progression

	Treatment Response								
	Stable Disease				Progressive Disease				P Value
THIRD MONTH RESPONSE/PRGS	N	Mean±Std.	Median	Min-Max	N	Mean± Std.	Median	Min-Max	
AGE	32	72.53±6.70	73.00	60.00-91.00	13	67.46±8.63	72.00	51.0-79.0	0.743^{t}
PSA1	32	34.54±55.86	8.56	0.05-243.40	13	25.97±25.14	15.92	4.16-88.00	.229u
ΔPSA	32	-70.38±32.32	-84.37	-99.29-15.81	13	193.23±143.67	158.76	-35.64-579.31	<0.001^{u}
PSA2	32	15.76±52.66	1.21	0.01-281.87	13	85.70±99.45	38.12	6.14-357.00	<0.001^{u}
LDH	16	219.56±60.92	209.50	140.00-352.00	8	387.50±413.98	252.00	165.00-1405.00	0.092^{u}
ALP	30	119.11±125.06	79.00	37.00-642.00	11	263.18±351.39	131.00	54.0-1262.0	0.027^{u}
GS	22	8.14±0.99	8.00	7.00-10.00	9	8.00±1.00	8.00	7.00-10.00	0.698^{u}
HSUVmax	32	27.49±32.94	19.96	3.32-172.88	13	30.37±17.53	25.20	10.73-72.30	0.146^{u}
HSUVmean	32	15.96±19.57	11.54	1.56-103.47	13	13.78±7.14	11.99	5.63-33.67	0.468^{u}
HBNmax	32	19.84±26.14	12.03	2.00-145.96	13	20.21±18.66	15.31	4.18-76.31	0.460^{u}
HBNmean	32	10.35±11.78	6.75	1.23-64.62	13	8.09±8.69	4.81	1.19-35.54	0.499^{u}
Hpeak	32	18.98±27.35	12.67	2.05-151.35	13	25.01±14.46	23.65	6.22-53.71	0.021^{u}
PSMA-TV	32	59.25±95.46	21.86	2.38-440.47	13	414.25±450.26	318.35	93.54-1793.69	<0.001^{u}
TL-PMSA	32	478.13±949.46	162.79	22.48-4288.15	13	3461.60±4772.43	1736.22	288.15-18597.26	<0.001^{u}
			N(%)				N(%)		
Abiraterone			4(8.8)				3(6.6)		0.394^{fe}
Enzalutamide			28(62.2)				10(22.2)		

T: independent t-test u: mann-Whitney U test, Fe: Fischer exact test GS: Gleason score

The PSA levels of all patients were measured before the treatment and the mean PSA1 value was found to be 32.06±48.85 (0.05-243.40), while the PSA levels measured after the treatment revealed that the mean PSA2 value was 35.96±75.36 (0.01-357). The ALP values of 41 patients were measured before the treatment and the mean value was found to be 157.76±215.37 (37-1262). LDH values of 24 patients were tested before the treatment, and the mean value was found to be 275.54±247.22 (140-1405) (Table 1). After treatment, 32 (71.1%) patients responded to therapy or remained stable (Group1), and progression was observed in 13 (28.9%) patients (Group 2).

In the comparison of group 1 and group 2 patients, the median Hpeak, PSMA-TV, TL-PSMA, PSA2 value, delta PSA value and pre-treatment ALP values of the group 2 patients were found to be significantly higher (p values were p=0.021, p<0.001, p<0.001, p<0.001, p<0.001 and p=0.027, respectively) (Table 2).

The ROC curves indicated predictive cut-off values in predicting group 2 to be ≥112.53 cm^3 for PSMA-TV (AUC: 0.930±0.37, p<0.001), ≥857.1 for TL-PSMA (AUC:0.916±0.44, p<0.001) and ≥16.36 g/mL (AUC:0.721±071, p=0.075) for Hpeak, and the area under the curve had statistically significant high sensitivity and specificity in predicting group 2 (Figure 2) (Table 3).

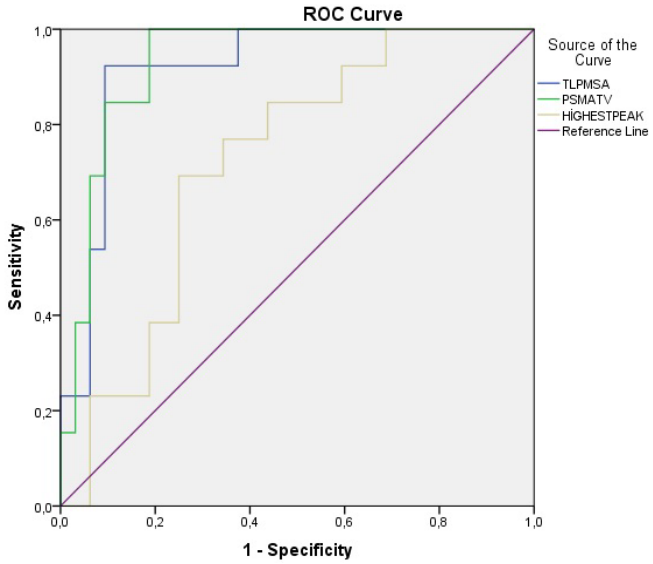

Figure 2. ROC curves for detecting progression

In univariate logistic regression analysis, PSMA-TV (≥112.53 cm^3) and TL-PSMA (≥857.1) values were statistically significant in predicting the progression (OR and p values were OR:29.7, p<0.001 and OR:116, p<0.001, respectively) (Table 4). In multivariate logistic regression analysis, TL-PSMA (≥857.1) value was found to be an independent prognostic factor in predicting the progression (OR:55.88, p:0.005) (Table 5).

Table 3. Cut-off, sensitivity and specificity values in predicting progression

Test Result Variable(s)	Area	Std. Error[a]	P	Asymptotic 95% Confidence Interval		Sensitivity (%)	Specificity (%)
				Lower Bound	Upper Bound		
TL-PMSA	0.916	0.044	<0.001	0.830	1.000	92.3	90.6
PSMA-TV	0.930	0.037	<0.001	0.857	1.000	84.6	84.4
HPEAK	0.721	0.077	0.021	0.569	0.873	69.2	68.7

Table 4. Univariate logistic regression analysis

	B	S.E.	Wald	df	Sig.	OR	95% C.I.for EXP(B)	
							Lower	Upper
PSA1	-.004	.008	.283	1	.595	.996	.981	1.011
ALP	.003	.002	2.255	1	.133	1.003	.999	1.007
LDH	.007	.008	.799	1	.371	1.007	.992	1.022
SUVmax	.003	.011	.091	1	.763	1.003	.982	1.025
SUVmean	-.009	.023	.154	1	.695	.991	.948	1.036
BNmax	.001	.014	.002	1	.962	1.001	.974	1.028
BNmean	-.024	.039	.384	1	.536	.976	.905	1.054
Hpeak	.009	.013	.534	1	.465	1.009	.984	1.035
HPEAK Categorical	1.329	.748	3.161	1	.075	3.778	.873	16.351
PSMA-TV Categorical	3.391	.910	13.890	1	.000	29.700	4.992	176.717
TL-PSMA Categorical	4.754	1.205	15.572	1	.000	116.000	10.941	1229.834
GS	-.150	.419	.128	1	.721	.861	.379	1.958

Table 5. Multivariate logistic regression analysis

	B	S.E.	Wald	df	Sig.	OR	95% C.I.for EXP(B)	
							Lower	Upper
TL-PSMA	4.023	1.437	7.834	1	.005	55.887	3.340	935.154
PSMA-TV	1.086	1.355	.643	1	.423	2.962	.208	42.136

Discussion

The prediction of the treatment response in diseases like mCRPCa with resistance to other treatments and increased likelihood of progression is of great importance in terms of guiding the treatment course. One of the most important milestones in determining whether PSMA imaging can be used to evaluate the efficacy of hormone therapy is to clarify the relation between PSMA expression and hormone therapy (NAD). In our study, we evaluated the PSA response predictability of ^{68}Ga-PSMA PET/CT-based parameters such as SUVmax, SUVmean, Highest Peak, PSMA–TV, TL-PSMA, biochemical markers such as ALP and LDH, and the Gleason score, which is a pathological marker, in patients with mCRPCa before abiraterone/enzalutamide treatment.

Unfortunately, it is still difficult to accurately predict treatment response in prostate cancer even with use of recommended screening methods including imaging tools (9). Serum PSA measurement is the most appropriate biomarker for treatment response. Many physicians use the change in PSA levels to evaluate the efficacy of treatment in patients with mCRPCa. In previous studies, a PSA reduction of more than 50% confirmed 4 weeks after the initiation of treatment is considered as the gold standard for an effective response (14, 15). The PSMA uptake in the tumor has been demonstrated to reliably reflect the number of viable tumor cells in preclinical studies (16). Total tumor volume obtained by ^{68}Ga-PSMA PET/CT in mCRPCa may be superior to total tumor volume derived from bone scintigraphy as it detects both bone and soft tissue metastases (17). In a study by Gupta et al. (18) in mCRPCa patients treated with ^{177}Lu-PSMA radio ligand, the authors reported the association of molecular vs. morphological criteria with a better performance in assessing the response via ^{68}Ga-PSMA 11-PET/CT.

Karyağar et al. showed that the PSMA-TV value on pre-treatment ^{68}Ga-PSMA PET/CT imaging and the post-treatment 12th week PSA value were able to predict the PSA response in 34 mCRPCa patients initiating enzalutamide treatment after docetaxel failure. Patients with a PSA response had significantly lower PSMA-TV values than the non-responders (78.37±80.99 cm^3 vs. 451.58±734.61 cm^3; p=0.028). At the 12th week of treatment, the mean serum PSA value was 9.35±17.54 ng/mL (0.53-61.4) in the responding group and 503.09±1028.16 ng/mL (8.60–4572) in the non-responder group (p<0.001) (19). In our study, the median Hpeak, PSMA-TV, TL-PSMA, 3rd month PSA value, delta PSA value and pre-treatment ALP values were significantly higher and able to predict the PSA response (p values were p=0.021, p<0.001, p<0.001, p<0.001, p<0.001 and p=0.027, respectively).

Plouznikoff et al. demonstrated that after a mean follow-up of 3 months, PSMA PET/CT is strongly associated with response to treatment in mCRPCa patients under NAD (enzalutamide or abiraterone) treatment. This strengthens the role of PSMA PET/CT in the follow-up of patients under NAD and confirms its usefulness as a modern PCa imaging technique. The authors also emphasized that while they did not find a PSMA-expressed flare phenomenon in their study, the likelihood of an early and limited flare phenomenon within the first 3 months of NAD cannot be excluded (20). In our study, we considered the 3rd month PSA values to determine the PSA response under treatment (8). The phenomenon of PSA flare during abiraterone therapy may occur up to 3 months after initiation of therapy in patients with mCRPCa (21). Although the emergence of the flare phenomenon does not affect PFS and OS, it may adversely affect the clinical decisions (22).

Karyağar et al. (19) found the cut-off value for PSMA-TV as >88.04 cm^3 (area under the curve 0.731, p=0.028) in predicting the PSA response, and the sensitivity and specificity of PSMA-TV were 68.2% and 83.3%. Has Şimşek et al. (13) reported the cut-off values in predicting the PSA response to be >107 cm^3 (p<0.001) for PSMA-TV and >1013 (p=0.001) for TL-PSMA, while the sensitivity and specificity values of PSMA-TV and TL-PSMA were reported as 75% and 80%. In our study, the cut-off value in predicting the response to PSA was ≥112.53 cm^3 (p<0.001) for PSMA-TV, ≥857.1 (p<0.001) for TL-PSMA, and ≥16.36 g/ml for Highest peak (p=0.075). The sensitivity and specificity values were 84.6% and 84.4% for PSMA-TV, 92.3% and 90.6% for TL-PSMA and 69.2% and 68.7% for Highest peak. This showed that PSMA-TV, TL-PSMA and highest peak were important predictive parameters in estimating the response to PSA. The PSMA-TV and TL-PSMA values were significantly higher in progressive patients. Has Şimşek et al. (13) showed that using PSMA-based tumor burden in mCRPCa patients can be a useful method in selecting the patients who will benefit from docetaxel therapy and that this therapy may fail in patients with high TV-PSMA.

Bone ALP changes, rather than PSA, may play a role in predicting tumor response when PSA levels cannot provide accurate information about the effect of treatment on the degree of metastatic skeletal involvement or bone disease progression (9). In the study of Has Şimşek et al. (13) in predicting the PSA response after docetaxel treatment in patients with prostate cancer reported that high ALP (>64 U/L) level before treatment was statistically insignificant, while high LDH level (>234) U/L was significant and it was one of the independent prognostic factors in predicting PSA response. In contrast we found that pre-treatment median ALP values were significantly higher in patients with PSA progression, however there was no statistically significant difference between LDH levels.

Bernhardh et al. (23), considering the potential applications of volumetric PSMA PET/CT imaging, demonstrated that intratumoral PSMA expression may be an option to predict treatment response, and the success of radionuclide therapy in patients with metastatic prostate cancer is dependent on tumor size and intratumoral activity concentration. Schmuck et al. (12) concluded that PSMA-TV and TL-PSMA could better assess tumor burden of metastatic lesions than

SUVmax in patients with biochemical recurrence after radical prostatectomy. They also stated that treatment response and failure were parallel to the coherent changes in both whole body PSMA-TV and whole-body TL-PSMA. Grubmüller et al. (24) proposed that parameters such as PSMA TTV, SUVmean, SUVmax and SUV-peak in PSMA 11-PET/CT may be appropriate to evaluate the treatment response in mCRPCa patients receiving systemic therapy. TL-PSMA may be a parameter that considers both lesion size and PSMA expression within the lesion in the prediction of metastatic disease. In the treatment of metastatic prostate cancer, treatment planning according to the size of the tumor burden has also gained importance (25, 26). In our study, PSMA-TV ($p<0.001$) and TL-PSMA ($p<0.001$) values were found to be statistically significant in prediction of the progression in univariate logistic regression analysis, while TL-PSMA ($p=0.005$) value in multivariate analysis was found to be an independent prognostic factor in predicting progression.

Limitations of our study; the retrospective design, lack of post-treatment images, short follow-up period, and small number of patients are considered to be limitations of our study, however most of the studies in the literature are retrospective and the number of patients is similar.

In conclusion, our findings revealed the likelihood of two ^{68}Ga-PSMA PET/CT parameters including PSMA–TV and TL-PSMA to predict the disease progression earlier than the PSA levels measured after treatment. Further prospective studies are needed to determine whether the combined use of ^{68}Ga-PSMA PET/CT imaging and other biomarkers can potentially contribute to the prediction of treatment response in mCRPCa patients.

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