Role of ^{68}Ga-PSMA PET/CT parameters in treatment evaluation and survival prediction in prostate cancer patients compared with biochemical response assessment

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Abstract

Objective: In this study, we aimed to evaluate the concordance of biochemical treatment response with gallium-68-prostate specific membrane antigen (^{68}Ga-PSMA) positron emission tomography/computed tomography (PET/CT) treatment response in prostate cancer (PCa) and investigate their prognostic effects on survival. **Materials and Methods:** One hundred and fifty-one patients with PCa, who underwent ^{68}Ga-PSMA PET/CT imaging in our clinic between May 2016 and December 2019, were on treatment, and had pre-treatment and post-treatment imaging studies were included in our study. The treatment patients received and prostate-specific antigen (PSA) levels at the time of PET/CT imaging were recorded. Pre- and post-treatment whole-body metabolic tumor volume (MTVw), whole-body total lesion PSMA (TLPw), percent change in PSA (ΔPSA), ΔMTV, and ΔTLP values were calculated in all patients. Survival time of all patients was measured from the time of initial PET imaging. **Results:** Median age of patients included in our study was 71 years (range: 51-88). When ΔPSA response and ΔTLP response were evaluated together (r:0.71, P<0.001 and k:0.541, P<0.001), statistically significance strong correlation and moderate concordance was observed. ΔPSA response and ΔMTV treatment response had statistically significant moderate correlation and moderate concordance (r: 0.66, P<0.01 and k: 0.454, P<0.001, significantly). Between ΔPSA response and ΔTLP and ΔMTV response had stronger correlation and higher concordance when PSA levels were above 10. Multivariate analyses using multiple Cox regression analysis revealed MTVw1 and ΔMTV parameters to be independent prognostic factors for mortality (P:0.003 and P:0.001, respectively). **Conclusion:** We observed that biochemical response and whole-body volumetric ^{68}Ga-PSMA PET/CT parameter response showed correlation and concordance in all groups with PCa, which was more significant when PSA level was ≥10ng/mL. MTVw1 and ΔMTV parameters obtained via ^{68}Ga-PSMA PET/CT were independent prognostic factors for mortality in Pca. Gallium-68-PSMA PET/CT is a valuable imaging technique for diagnostic purposes as well as follow-up and prognostic evaluation.

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Introduction

Prostate cancer (PCa) is the second most common malignancy in men after lung cancer and is the fifth leading cause of malignancy-related deaths in men [1]. Androgen deprivation therapy (ADT) has become the standard of care in metastatic PCa in the last decades. After rapid resistance to castration, novel therapies including taxane-based chemotherapeutics (docetaxel, cabazitaxel) and new generation antiandrogenic agents (abiraterone, enzalutamide) have become available, increasing survival [2]. Due to treatment failure, resistance to treatment, and rapid disease progression, response evaluation criteria are required to determine treatment response and implement treatment changes as soon as possible. Serial prostate specific antigen (PSA) testing is the most frequently used parameter in evaluating treatment response and follow-up. However, it is not specific enough to accurately predict treatment response [3].

Prostate specific membrane antigen (PSMA) is a glycoprotein that is bound to type II cell surfaces which is highly expressed by prostate tissue, but its role in the PCa cell is not fully known. In PCa cells an overexpression of PSMA is observed compared to normal prostate tissue [4]. Gallium-68 (^{68}Ga)-PSMA positron emission tomography/computed tomography (PET/CT) is routinely used for tumor detection, staging, treatment planning, treatment response and biochemical recurrence in PCa [5-7]. Recently, there are studies reporting that the parameters of whole-body metabolic tumor volume (MTVw) and whole-body total lesion PSMA (TLPw) obtained from ^{68}Ga-PSMA PET/CT can be used in treatment planning and determining prognosis by showing the whole-body

tumor burden [8,9]. Whole-body metabolic (SUVmax, SUVmean and SUVpeak) and volumetric (MTV and TLP) parameters obtained from ^{68}Ga-PSMA PET/CT have been found to be effective in demonstrating treatment response in patients receiving different treatments, including docetaxel, abiraterone/enzalutamide, and lutetium-177 (^{177}Lu)-PSMA [10-13]. There are studies reporting that whole-body volumetric parameters obtained from ^{68}Ga-PSMA PET/CT are prognostic factors on survival [14,15].

In this study, we aimed to evaluate the concordance of biochemical treatment response with metabolic and volumetric whole-body PSMA PET/CT treatment response in PCa and investigate their prognostic effects on survival.

Materials and Methods

One hundred and fifty-one patients with PCa, who underwent ^{68}Ga-PSMA PET/CT imaging in our clinic between May 2016 and December 2019, were on treatment, and had pre- and post-treatment imaging studies were included in this retrospective study. Patients received at least one of the docetaxel andabiraterone/enzalutamide, therapies following castration resistance. Prostate specific antigen levels were measured simultaneously (at the same week) with the PET/CT imaging. Initial ^{68}Ga-PSMA PET/CT imaging was performed at most 3 weeks before treatment. On the other hand, a ^{68}Ga-PSMA PET/CT imaging study was performed to evaluate the treatment response 6 weeks after the last chemotherapy in patients receiving docetaxel. In those receiving abiraterone/enzalutamide therapy, imaging was performed to confirm the clinician's suspected biochemical response or progression.

Patients who did not have both ^{68}Ga-PSMA PET/CT images or a PSA level simultaneous with the ^{68}Ga-PSMA PET/CT studies were excluded. Percent change in PSA (ΔPSA) was calculated in all patients using pre-treatment (PSA1) and post-treatment (PSA2) PSA levels with the formula below:

$$\Delta PSA = (PSA2-PSA1)/ PSA1 \times 100$$

Survival times of patients were measured from the date of initial PET/CT to the date of death in non-survivors or the date of last follow-up in survivors. This study was conducted in concordance with the current law, Good Clinical Practice guidelines, and the ethical principles of Declaration of Helsinki. Approval of the institutional review board was also obtained (Approval no: 2020/595). Informed consent for retrospective research was obtained from patients or their relatives during their examination without personal identification information.

^{68}Ga-PSMA PET/CT imaging protocol

All imaging studies were performed using Discovery IQ 4 ring 20cm axial FOV PET/CT (GE Healthcare, Milwaukee, WI, USA). Sixty minutes after 2MBq/kg of ^{68}Ga-PSMA injection, whole-body images were obtained in the supine position from the vertex to mid-femur. After CT images (CT parameters: 120kV, 80mAs/slice, 700mm transaxial FOV, no gap, 64x0.625mm collimation, pitch 1.4. 0.5s rotation time, 3.3mm slice thickness, 512x512 matrix), PET images were obtained in the same position and including the same regions at 2.5 minutes per bed position (PET parameters: 3D, FOV 20cm, ordered subset expectation maximization algorithm [OSEM] 5 iterations/12 subset, full width at half maximum [FWHM] 3mm). IV nonionic contrast medium was administered to all patients before CT imaging unless there was a contraindication.

Evaluation of images

All pre- and post-treatment ^{68}Ga-PSMA PET/CT images were evaluated at the AW 4.7(Advantage Workstation software version 4.7; GE Healthcare, Milwaukee, WI, ABD) workstation by two nuclear medicine attending physicians with at least 6 years of experience in ^{68}Ga-PSMA PET/CT. Excluding areas of physiological uptake and benign lesions, lesions that show higher PSMA expression than the background activity and were recognized as malignant by both physicians were considered positive. Semi-automatic volumes of interest (VOI) were drawn from the primary lesion, local relapse, and all metastatic lesions (lymph node, bone, and visceral) in both PET/CT images as to include the lesions in the imaging field at all three planes using 40% SUV threshold. Average SUV (SUVavg) was obtained by drawing VOI from the abdominal aorta in all patients. Whole-body total lesion PSMA (TLPw) value, which is obtained from the total of lesions in the whole-body, highest SUVpeak (Hpeak) value, and highest background normalized SUVpeak (HBNpeak) values, which is Hpeak divided by SUVavg of aorta, were automatically generated by the device. Metabolic tumor volumes (MTV) obtained from all lesions were summed to achieve whole-body MTV (MTVw). Values of the initial PET/CT (TLPw1, MTVw1, Hpeak1, HBNpeak1) and the second PET/CT (TLPw2, MTVw2, Hpeak2, HBNpeak2) were recorded. ΔMTV, ΔTLP, ΔHpeak, and ΔHBNpeak parameters were calculated using the formula below.

$$\Delta MTV = (MTVw2-MTVw1)/ MTVw1 \times 100$$

Evaluation of treatment response

As for ^{68}Ga-PSMA PET/CT response, no pathological lesion with ^{68}Ga-PSMA uptake in PET/CT was considered as complete remission (CR). ΔHpeak, ΔHBNpeak, ΔMTV and ΔTLP being ≤-30% as partial remission (PR), ≥30% as progressive disease (PD), and values between -29% and +29% were considered as stable disease (SD), as described in the literature [13,16].

As for biochemical response, CR was defined as PSA level=0ng/mL, PR as ΔPSA-50, PD as ΔPSA≥25%, and SD as ΔPSA between -49% and +24%, as described in the literature [12, 16].

Statistical analysis

Statistical analyses were performed using SPSS 25.0 (IBM Corporation, Armonk, New York, United States). Normality of distribution of single-variable parameters was assessed with Kolmogorov-Smirnov test. Mann-Whitney U test was preferred for the comparison of two independent groups in terms of quantitative parameters. Pearson chi-squared test was employed to compare categorical variable using the outcomes of Fisher's

exact test. Cohen's kappa test was used to evaluate the concordance of biochemical response and ^{68}Ga-PSMA PET/CT treatment response and Spearman's rho test was used to evaluate the correlation between these parameters. In addition, patients were divided into two groups as PSA1< 10ng/mL and PSA1≥10ng/mL, concordance and correlations of biochemical treatment response and ^{68}Ga-PSMA PET/CT treatment response in both groups were evaluated separately. The impacts of variables on mortality and survival were evaluated with Kaplan-Meier (product limit method) and Log Rank (Mantel-Cox) analyses. Multivariate Cox regression analysis was used to assess the impact of prognostic variables on survival based on the main factor. Sensitivity and specificity for the relation between the actual classification and the classification based on the estimated cut-off values for variables were assessed and expressed using ROC (receiver operating curve) analysis. Quantitative variables were described as mean±SD (standard deviation) or median (minimum-maximum), while categorical variables were described as n (%). All variables were evaluated within 95% confidence interval and P<0.05 was considered significant.

Results

Patient characteristics

Median age of the patients included in our study was 71 (51-88). Median Gleason score (GS) was 8 (7-10). Twenty-two (14.6%) patients underwent radical prostatectomy and 15 (9.9%) patients received definitive radiation therapy. Median initial PSA level was 12.59ng/mL (0.01-2381). Pre-treatment ^{68}Ga-PSMA PET/CT revealed prostate uptake (primary/relapse) in96 (63.6%) patients, lymph node metastases in 86 (56.9%), skeletal metastases in 121 (80.1%), and visceral metastases in 8 (5.3%) patients. After initial PET/CT imaging, 67 (44.4%) patients received docetaxel and 84 (55.6%) received abiraterone/enzalutamide treatments. Patient characteristics are presented in detail in Table 1.

Comparison of treatment response

The evaluation of biochemical and ^{68}Ga-PSMA PET/CT responses of all patients using Cohen's kappa and Spearman's correlation tests are summarized in Table 2. Evaluation of ΔPSA response together with ΔTLP response yielded statistically significant strong correlation and moderate concordance (r: 0.71, P<0.001 and k: 0.541, P<0.001) (Figure 1). There were statistically significant moderate correlation and moderate concordance between the ΔPSA response and ΔMTV treatment response (r: 0.66, P<0.01 and k: 0.454, P< 0.001 respectively). ΔPSA response had a significantly weak correlation and weak concordance with ΔHpeak and ΔHBNpeak responses (r: 0.49, P<0.001; k: 0.371, P<0.001 and r: 0.337 P<0.001; k: 0.235, P<0.001 respectively).

Patients were divided into two groups according to their PSA levels at the time of initial PET imaging as PSA1<10 and PSA1≥10. Among patients with PSA1≥10, stronger correlation and higher concordance were observed between ΔPSA response and ΔMTV and ΔTLP response (Table 3). When grouped according to the treatments received, it was observed that those who received docetaxel in terms of ΔPSA-ΔTLP response had a relatively higher correlation and a relatively higher concordance value than those who received abiraterone/enzalutamide. However, the correlation and agreement values of the other parameters were similar in both treatment groups (Table 3).

Comparison of volumetric ^{68}Ga-PSMA PET/CT parameters, PSA, and other parameters in terms of mortality

Median MTVw1, TLPw1, ΔPSA, ΔMTV, and ΔTLP values were significantly higher in non-survivors than survivors (P< 0.001, P: 0.012, P: 0.041, P<0.001 and P:0.003, respectively). There was no statistically significant difference between survivors and non-survivors in terms of GS, treatments received, age, and other parameters (P>0.05) (Table 4).

Receiver operating characteristic (ROC) curves analyses revealed that cut-off values for MTVw1 (cut-off 116.88), TLPw1 (cut-off 1022.06), PSA1 (cut-off 12.88), ΔPSA (cut-off 17.79), ΔMTV (cut-off 8.41), and ΔTLP (cut-off 12.13) were significant in predicting mortality. Results of the ROC curves are presented in detail in Table 5 (Figure 2).

Association of volumetric PSMA PET parameters and PSA levels with mortality

Sixty-four patients were deceased during the follow-up period. Median overall survival (OS) of non-survivors was 14 (3-43) months, while median OS of all patients was 17 (3-53) months.

Univariate analyses revealed that patients with MTVw1< 116.88, TLPw1<1022.06, ΔPSA<17.79, ΔTLP<12.13 and ΔMTV<8.41 had better OS (Figure 3). Multivariate analyses with multiple Cox regression analysis showed that MTVw1 and ΔMTV parameters were independent prognostic factors for mortality (P: 0.003 and P: 0.001, respectively) (Table 6).

Discussion

In this study, we found a correlation and concordance between PET parameters and biochemical monitoring with PSA in patients with PCa, who were castration-resistant, received different treatment protocols, and were evaluated with PSA and ^{68}Ga-PSMA PET/CT during this treatment process. This correlation and concordance were significantly stronger in patients with PSA 10ng/mL. Gallium-68-PSMA PET/CT findings predicted mortality, overall survival, and survival for 1-3 years in univariate analyses, while multivariate analyses revealed MTVw1 and ΔMTV to be independent prognostic factors for mortality. We also observed a strong correlation and moderate concordance between ΔPSA and ΔTLP responses in the entire patient group. Barbarosa et al. (2020) emphasized that ^{68}Ga-PSMA PET/CT imaging modality has the potential to fill the gaps that may be created with follow-up using conventional imaging techniques and biochemical monitoring with PSA in metastatic Pca [10]. In their study, Onal et al. (2020) showed that primary tumor and lymph node SUV decreases along with PSA in locoregional disease after ADT and patients with high grade tumors exhibit the

Table 1. Patient characteristics.

		n	%
Primary radiation therapy			
	Present	15	9.9
Prior RP			
	Present	22	14.6%
Sites of metastasis			
	Local	96	63.6%
	Lymph node	86	56.9%
	Bone	121	80.1%
	Visceral	8	5.3%
Treatments received			
	Docetaxel	67	44.4%
	Abiraterone/Enzalutamide	84	55.6%
Mortality			
	Alive	87	57.6%
	Exitus	64	42.3%
		Mean±SD	**Median (Min/Max)**
Age (y)		70.61±8.34	71 (51/88)
Time between two imagings (months)		5.3±2.2	5(2-12)
PSA1		130.65±309.2	12.6 (0.01/2381)
MTVw1		262.15±371.79	101.99 (3.12/1814.97)
TLPw1		2547.45±3715.22	906.0(8.1/ 22852.76)
Hpeak1		23.65±19.16	19.76 (2.65/151.3)
HBNpeak		17.30±14.78	13.77 (1.13/93.63)
PSA2		177.76±615.61	9.3 (0.01/5286)
MTVw2		503.82±2287.4	95.09(0/27295.76)
TLPw2		4026.59±14477.92	877.66(0/168813.78)
Hpeak2		22.89±21.77	16.70(0/190.55)
HBNpeak2		19.36±19.27	13.52(0/116.71)
ΔPSA		4613.25±40722.5	7.76 (-99.98/484349)
ΔMTV		332.07±2647.73	5.49 (-100.0/32455)
ΔTLP		273.4±1359.2	11.41 (-100/-15547.9)
ΔHpeak		17.48±88.48	-3.95 (-100/519)
ΔHBNpeak		68.9±288.6	3.2 (-100/2732.9)
Overall survival (m)		18.85±9.55	17 (3/53)

RP: radical prostatectomy. SD: Standard Deviation. Min: Minimum. Max: Maximum

Table 2. *Kappa analysis and correlation of PSA levels, volume-based PET parameters and treatment response.*

		ΔPSA response			Total	Spearman's Correlation		Cohen's kappa	
		PR	**SD**	**PD**		**r**	**P**	**k**	**P**
ΔTLP response	CR	2	0	1	3				
	PR	42	10	6	58				
						0.71	<0.001	0.541	<0.001
	SD	6	10	9	25				
	PD	2	8	55	65				
Total		**52**	**28**	**71**	**151**				
ΔMTV response	CR	2	0	1	3				
	PR	38	11	5	54				
						0.660	<0.001	0.454	<0.001
	SD	8	9	14	31				
	PD	4	8	51	63				
Total		**53**	**30**	**75**	**151**				
ΔHpeak response	CR	2	0	1	3				
	PR	30	7	12	49				
						0.49	<0.001	0.371	<0.001
	SD	14	15	15	44				
	PD	6	6	43	55				
Total		**52**	**28**	**71**	**151**				
ΔHBNpeak response	CR	2	0	1	3				
	PR	25	7	14	46				
						0.337	<0.001	0.235	<0.001
	SD	15	11	18	44				
	PD	10	10	48	68				
Total		**52**	**28**	**71**	**151**				

Spearman's correlation, Cohen's kappa test

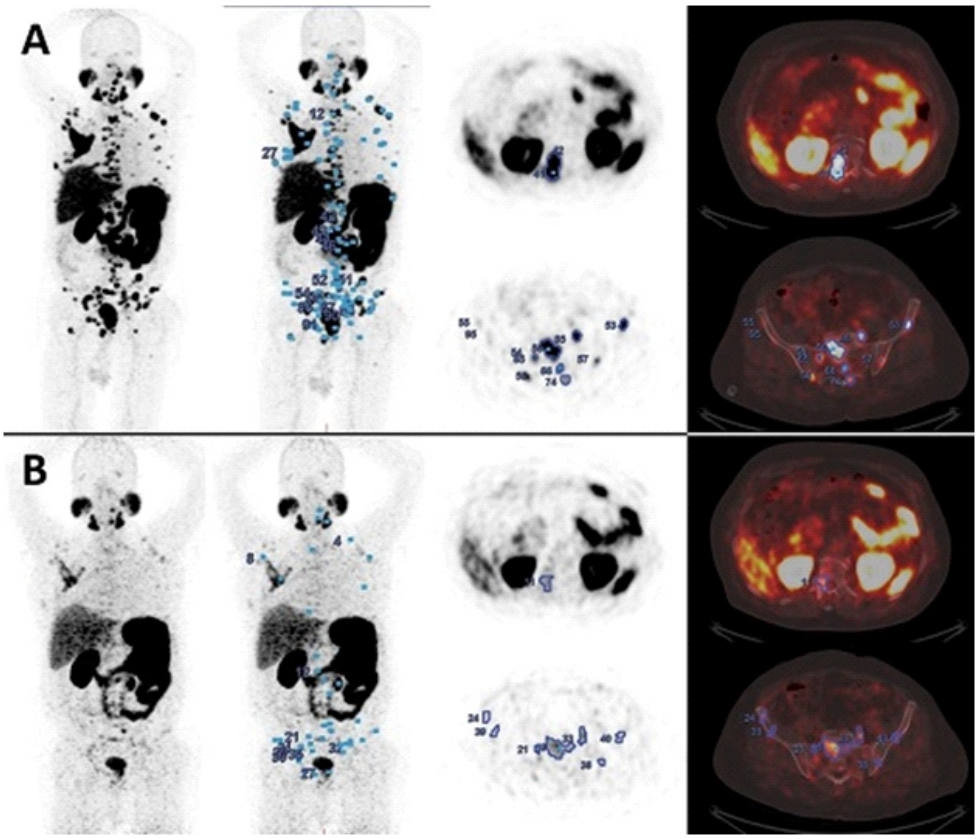

Figure 1. A 73-years old male patient was diagnosed with prostate cancer. His Gleason score was 4+5=9, and initial PSA level was 145ng/mL. Initial ^{68}Ga-PSMA PET/CT showed (A: MIP, PET,and fusion images) MTVw1:208, TLPw1:4842, Hpeak1:43.19, and HBNpeak1:19.63. After docetaxel therapy, his PSA level regressed to 14.8ng/mL. Post-treatment ^{68}Ga-PSMA PET/CT (B: MIP, PET,and fusion images) revealed MTVw2:95, TLPw2:1139, Hpeak2:26.7, HBNpeak2:16.3, indicating both partial biochemical response (ΔPSA: -89.7%) and partial PET/CT response (ΔMTV: -54.4%, ΔTLP: -76.5%).

Table 3. *Correlation and Cohen's kappa concordance test results of treatment response comparisons according to treatments received and PSA levels.*

	ΔPSA-ΔTLP		ΔPSA-ΔMTV		ΔPSA-ΔHpeak		ΔPSA-ΔHBNPeak	
	r	k	r	k	r	k	r	k
	P	P	P	P	P	P	P	P
Docetaxel	0.757	0.655	0.673	0.489	0.464	0.375	0.361	0.260
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.003	0.002
Abiraterone-Enzalutamide	0.674	0.448	0.656	0.416	0.518	0.366	0.357	0.209
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	0.004
PSA1<10	0.589	0.352	0.573	0.290	0.515	0.357	0.343	0.204
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.004	0.005
PSA1≥10	0.830	0.652	0.761	0.554	0.433	0.332	0.344	0.228
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002

Spearman's correlation, Cohen's kappa test.

Table 4. *Comparison of Gleason score. PSA levels and PET parameters between survivors and non-survivors.*

		Mortality		
		Alive	Exitus	P
		(n=87) Median (Min / Max)	(n=64) Median (Min / Max)	
Age		71(51/88)	70(53/ 88)	0.118[u]
PSA1		9.3 (0.02/4775)	21.9 (0.01/2388)	0.037[u]
MTVw1		55.2 (3.23/1814.9)	207.6 (3.12/1763.68)	**<0.001**[u]
TLPw1		616.5(9.74/22852.7)	1761.9(8.1/21385.7)	**0.012**[u]
Hpeak1		30.0 (2.65/151.3)	17.93 (2.67/72.43)	0.478[u]
HBNpeak1		15.7(0.83/111.71)	15.02 (1.36/50.62)	0.502[u]
∆PSA		-18.97(100/13163.9)	50.2(-99.9/484349)	0.041[u]
∆TLP		-24.89(-100/1906)	62.1(-100/1547.8)	**0.003**[u]
∆MTV		-19.12(-100/812.4)	65.22(-100/32455.5)	**<0.001**[u]
∆Hpeak		-11.5(-100/518.9)	21.58(-100/375.7)	**0.229**[u]
∆HBNpeak		-4.1(-100/800.8)	20.6(-100/2732.8)	**0.376**[u]
Overall survival (m)		21 (7/53)	14 (3/43)	**<0.001**[u]
		n (%)	**n (%)**	
GS				
	7	17 (11.2)	19 (12.5)	0.205[p]
	8	20 (13.2)	20 (13.2)	
	9	14 (8.9)	29 (19.2)	
	10	5 (3.3)	10 (6.6)	
Treatments received				
	Docetaxel	37 (24.5)	30 (19.8)	0.369[p]
	Abiraterone/ Enzalutamide	50 (33.1)	34 (22.5)	

Mann Whitney U Test (Monte Carlo), p Pearson Chi Square test, Min: Minimum, Max: Maximum, GS: Gleason score

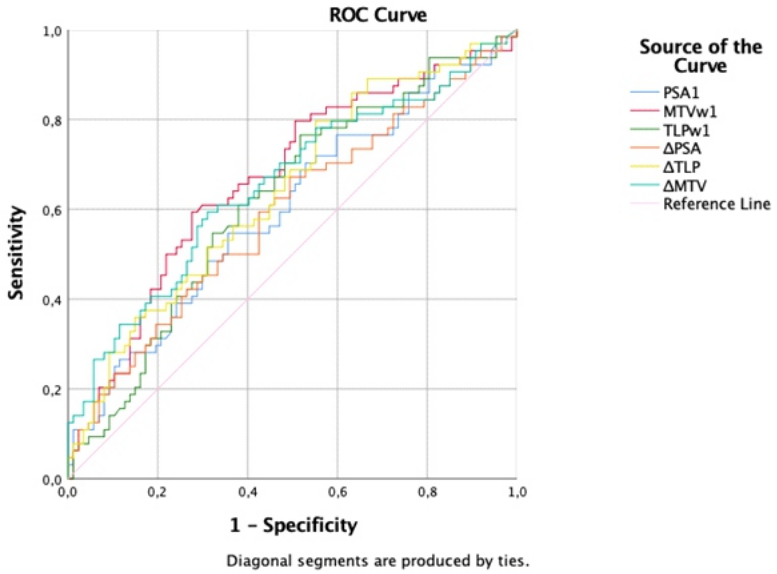

Figure 2. Receiver operating characteristics (ROC) analysis forthe prediction mortality.

Table 5. *ROC curve cut-off, sensitivity, and specificity values in predicting mortality.*

Classification variable	Variable	Cut-off	Sensitivity	Specificity	AUC±SE	P value
	MTVw1	≥116.88	62.3%	61.8%	0.668 ± 0.044	**<0.001**
	TLPw1	≥1022.06	59.4%	59.6%	0.617±0.045	**0.012**
	PSA1	≥12.88	54.7%	55.2%	0.599 ± 0.047	**0.037**
	ΔPSA	≥17. 79	58.0%	57.0%	0.595± 0.046	0.041
	ΔMTV	≥8.41	60.9%	60.7%	0.652±0.044	**0.001**
	ΔTLP	≥12.13	56.5%	56.2%	0.638±0.044	**0.003**

ROC (Receiver Operating Curve) Analysis (Honley&Mc Nell - Youden index J). AUC: Area under the ROC curve SE: Standard Error

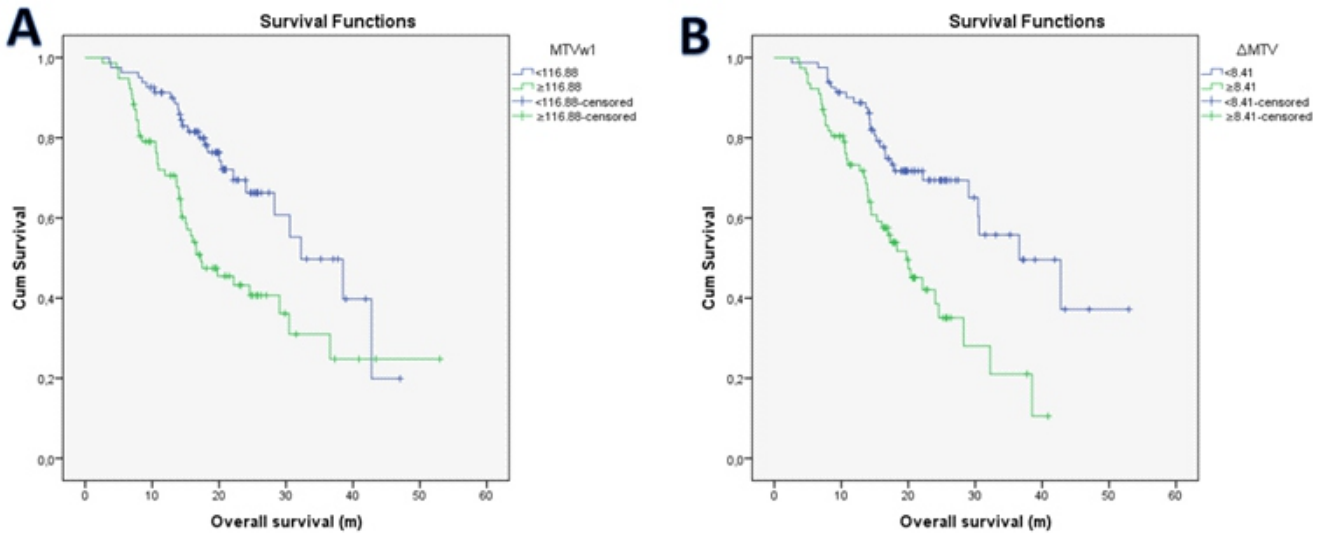

Figure 3. Kaplan-Meier curves of overall survival according to MTVw1 (A) andΔMTV (B).

		Dead	Alive	Estimated survival (m)	Estimated Proportion Surviving at 1st/3rd Year	P Value
		n	n	Median ± SE		
MTVw1						
	<116.88	23	54	38.5±5.92	92.2/53.9	**<0.001***
	≥116.88	41	33	17.46±3.4	70.9/31.8	
TLPw1						
	<1022.06	25	52	38.5±5.8	90.7/52.2	**0.006***
	≥1022.06	39	35	19.73±4.5	72.4/32.3	
ΔPSA						
	<17.79	27	50	36.57±4.82	88.1/50.2	0.033*
	≥17.79	37	37	20.33±3.98	75.2/34.2	
ΔMTV						
	<8.41	25	54	42.76±8.43	89.7/57.3	**<0.001**
	≥8.41	39	33	18.3±2.1	72.9/23.4	
ΔTLP						
	<12.13	27	49	36.56±6.2	89.2/55	**0.017***
	≥12.13	37	38	24.57±3.93	74.3/27.7	
PSA1						
	<12.88	29	48	30.56±2.04	88.2/42.7	0.109*
	≥12.88	35	39	22.16±6.48	75.0/46.1	
Overall		64	87	30.46±3.2	82.2/49	

	Multiple Cox Regression			
		95% CI for Odds Ratio		
	Odds Ratio	Lower Bound	Upper Bound	P
Mortality-Overall Survival				
MTVw1	3.237	1.495	7.012	**0.003****
TLPw1	1.223	0.583	2.566	0.595**
ΔPSA	0.998	0.498	2.000	0.994**
ΔMTV	4.032	1.762	9.227	**0.001****
ΔTLP	1.042	0.438	2.478	0.925**

*Kaplan Meier Test *Log Rank (Mantel-Cox). SE: Standard Error. **Cox Regression-Enter Method. CI: Confidence interval.*

the lowest response. The researchers argued that ^{68}Ga-PSMA PET/CT is a good quantitative diagnostic tool for evaluating response to castration in hormone-naïve patients [17]. A recent analysis arrived at a consensus that PSMA PET/CT can be used in patients with metastatic disease to evaluate treatment response before or after any local or systemic treatment. Patient-based assessment was recommended for specific clinical scenarios including oligometastatic and polymetastatic disease [13].

In our study, ΔPSA-ΔTLP and ΔPSA-ΔMTV treatment responses were observed to have stronger correlation and higher concordance in patients with PSA1≥10ng/mL than PSA1<10ng/mL. Uprimny et al. (2017) also highlighted the 10ng/mL PSA cut-off for ^{68}Ga-PSMA PET/CT results and showed that ^{68}Ga-PSMA PET/CT uptake was significantly lower in patients with PSA<10ng/mL [18]. In concordance with the current study, Ergül et al. (2018) also stratified patients according to the 10ng/mL PSA cut-off and found that the lesion detection rate was significantly higher in the group with PSA>10ng/mL [19]. As these studies underline, 10 ng/m LPSA cut-off is a critical threshold for biochemical disease burden. Our study supports the hypothesis that the concordance between biochemical and radiological disease burden increases along with the disease burden, as we found that correlation and concordance was stronger in patients above this threshold. However, it should be remembered that PSMA PET/CT can yield false negative results because PSMA expression may be dedifferentiated in high tumor volumes. Dedifferentiated tumors will also have lower PSA secretion and might require evaluation with ^{18}F-FDG PET/CT [20]. However, we found that high tumor volume was correlated with elevated PSA levels.

In our study, patients who received docetaxel treatment showed relatively higher ΔPSA-ΔTLP response concordance compared to those who received in abiraterone-enzalutamide treatment, which may be a result of the preference of docetaxel more commonly for castration resistance compared to other agents. We do not have a statistical evaluation in this context. Because of the health insurance policies in our country, patients received abiraterone and enzalutamide therapies more frequently as second line or higher treatments. This may have resulted in weaker biochemical response concordance. In the earlier treatment steps, a higher PSMA uptake regression in the initial PSMA response is an expected result from the nature of the disease [17]. Further studies aiming this as the primary endpoint may help elucidate this context. A study that evaluated ^{68}Ga-PSMA PET/CT treatment response correlation in 43 patients showed that MTVw, SUVmean, SUVmax and SUVpeak parameters assessed regardless of the treatment subtypes had significant concordance with PSA response rates, and this concordance persisted in analyses with RECIST criteria [16]. In a retrospective study, PSMA expression alterations in PET/CT were strongly correlated with treatment response in patients under enzalutamide or abiraterone for a mean of 3 months follow-up [21]. In our study, the highest concordance with ΔPSA response was found with ΔTLP followed by ΔMTV, while concordance with ΔHpeak and ΔHBNpeak were found to be lower. Grubmüller et al. (2020) reported ΔPSA to have more concordance with ΔHpeak compared to ΔMTV [16]. Even though in our study ΔPSA-ΔHpeak kappa values were moderately higher, ΔPSA-ΔMTV kappa values were much higher in comparison with the study of Grubmüller et al. (2020) while SUVpeak only represents values in a 1cm^3 area, MTVw and TLPw values represent tumor burden of the whole-body. Therefore, it is within reason to expect a greater concordance between ΔTLP and ΔMTV than ΔHpeak and ΔHBNpeak which only represents changes in a 1cm^3 area of a single lesion.

In our study, median MTVw1, TLPw1, PSA1, ΔPSA, ΔMTV and ΔTLP values were significantly higher in non-survivors than survivors. Univariate analyses revealed groups below the cut-off values had longer survival than groups above the cut-offs, and 1- and 3-year survival rates were significantly higher for MTVw1, TLPw1, ΔPSA, ΔMTV, and ΔTLP parameters. Multivariate Cox regression analysis showed that MTVw1 and ΔMTV were independent prognostic factors for mortality. While cut-off value for ΔMTV was 8.41, which is generally considered as stable disease, an increase above this level may require a greater vigilance for worse prognosis according to our results. Rapid and strong PSA response (faster than 4 weeks and more than 50%) to post-docetaxel abiraterone acetate is associated with improved survival [22]. Atakan et al. (2020) found that 30% and higher PSA response was associated with longer progression-free survival (PFS) [23]. Another study that aimed to predict prognosis in localized disease showed that intraprostatic ^{68}Ga-PSMA-11 uptake may be prognostic and, considering the initial approach of active surveillance or focal treatment, may serve as a valuable novel biomarker in men with biopsy-proved, GS 3+4, localized PCa [24]. The number of studies in the literature that evaluate the prognostic role of ^{68}Ga-PSMA PET/CT in predicting survival in metastatic disease is limited. One of the very first studies on the subject was conducted by our teamand showed that SUV cut-offs for ^{68}Ga-PSMA PET/CT may have potential benefit in predicting survival in prostate cancer patients with metastatic disease [25]. Acar et al. (2019) found that among individuals receiving ^{177}Lu-PSMA treatment, patients who demonstrated a post-treatment decrease in MTVw and TLPw had improved survival [26]. On the contrary, Grubmüller et al. (2019) failed to demonstrate an association between volume based PSMA PET parameters and survivals in PCa patients receiving systemic therapy [12].

The major limitation of our study is its retrospective nature. However, most of the studies in the literature on the subject matter are also designed retrospectively. Second limitation of our study is treatments were not all given at the same step and additional analysis for same-step treatments is lacking. Third limitation may be that survival was measured from the date of initial PET/CT imaging rather than the date of diagnosis or hormone refractoriness. However, because prognostic factors in PET/CT were assessed, we measured survival from the date of initial PET/CT imaging and performed analyses accordingly.

In conclusion, we observed that biochemical response and whole-body volumetric ^{68}Ga-PSMA PET/CT parameter response showed correlation and concordance in all groups with PCa, which were more significant when PSA level was ≥10ng/mL. MTVw1 and ΔMTV parameters obtained via ^{68}Ga-PSMA PET/CT were independent prognostic factors for mor-

tality in PCa. Gallium-68-PSMA PET/CT is a valuable imaging technique for diagnostic purposes as well as follow-up and prognostic evaluation.

The authors declare that they have no conflicts of interest.

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