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ORIGINAL ARTICLE

Role of baseline ^{68}Ga-PSMA PET/CT-derived whole-body volumetric parameters in predicting survival outcomes of metastatic castration-resistant prostate cancer patients receiving first-line treatment

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Abstract

Objective We aimed to evaluate whether baseline ^{68}Ga-PSMA PET/CT-derived whole-body volumetric parameters could be used as predictive biomarkers for survival in metastatic castration-resistant prostate cancer (mCRPC) patients receiving first-line treatment.

Materials and methods This retrospective study included 54 mCRPC patients, who underwent baseline ^{68}Ga-PSMA PET/CT imaging within 1 month before starting first-line treatment. Pre-treatment prostate-specific antigen (PSA) levels and treatments were recorded. SUVmax, SUVmean, whole-body PSMA-derived tumor volume (wbPSMA-TV), and whole-body total lesion PSMA (wbTL-PSMA) were calculated for all patients. PSA response was defined as a decline of ≥ 50% from pre-treatment value at 12 weeks. Overall survival (OS) was measured from the start of the first-line treatment for mCRPC.

Results Docetaxel and abiraterone/enzalutamide were administered to 32 and 22 patients in the first-line setting, respectively. wbPSMA-TV (rho = 0.582, $p = 0.004$) and wbTL-PSMA (rho = 0.564, $p = 0.007$) showed moderate positive correlations with PSA levels. Older age ($p = 0.02$), higher wbPSMA-TV ($p = 0.007$), higher PSA ($p = 0.01$), higher number of bone metastases ($p = 0.02$), and lack of PSA response ($p = 0.03$) were significantly associated with an increased risk of mortality. Multivariate analysis determined wbPSMA-TV (HR: 1.003, 95% CI 1.001–1.004, $p = 0.001$) and PSA response (HR: 2.241, 95% CI 1.189–4.222, $p = 0.01$) as independent predictors of OS.

Conclusion The wbPSMA-TV may be a useful tool to reflect tumor burden and predict survival outcomes in patients with mCRPC.

Keywords ^{68}Ga-PSMA PET/CT · Metastatic castration-resistant prostate cancer · Survival · Whole-body volumetric parameters

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Introduction

Prostate cancer (PC) is the second most common malignancy among men worldwide, with an estimated 1.4 million new diagnoses in 2020 [1]. Although 5-year survival rate for patients with localized disease is almost 100%, this figure dramatically drops to 30% in the metastatic setting [2]. Androgen deprivation therapy (ADT) has long been the mainstay of treatment, by decreasing endogenous androgen levels; however, vast majority of patients eventually progress on ADT and develop resistance despite low levels of serum testosterone. Thereby, the disease state changes

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to castration-resistant prostate cancer (CRPC), which ultimately reflects poor prognosis and survival [3].

Treatment of metastatic CRPC (mCRPC) has considerably evolved in the past few years with the approval of several novel agents based on the outcomes of large randomized clinical trials. Current standard therapy options in the first-line setting of patients with mCRPC apart from ADT include docetaxel [4, 5], abiraterone acetate [6, 7], and enzalutamide [8, 9]. Also, sipuleucel-T [10, 11] is recommended in the absence of visceral metastases, and radium-223 is approved for mCRPC patients with symptomatic bone metastases and no known visceral metastatic disease [12].

A wide range of available therapeutic options and highly variable disease course in patients with mCRPC make it challenging even for the most experienced oncologists to identify individuals who require therapy, to select the most effective management strategy, and evaluate treatment response. Functional status of patients, prostate-specific antigen (PSA) levels, and imaging findings appear to play a role in decision making at this point. In clinical practice, however, novel biomarkers are certainly required to provide a dynamic and powerful approach to disease management in patients with mCRPC.

Prostate specific membrane antigen (PSMA) is a membrane-bound glycoprotein that is abundantly expressed in PC cells; and its expression rises with tumor aggressiveness, androgen independency, recurrence, and metastatic disease [13]. As a result, PSMA has recently been the focus of interest as a molecular target for PC imaging and radionuclide therapy [14, 15]. The Gallium-68 (^{68}Ga)-PSMA positron emission tomography/computed tomography (PET/CT) is now a widely used imaging tool for tumor detection and staging of either primary or recurrent PC, as well as monitoring treatment response [16–18]. This modality has been shown to be particularly effective in the assessment of bone metastases, with strong evidence supporting its superiority over conventional methods [19]. Furthermore, ^{68}Ga-PSMA PET/CT enables a comprehensive assessment of whole-body tumor burden by volumetric parameters such as PSMA-derived tumor volume (PSMA-TV) and total lesion PSMA (TL-PSMA). These quantitative imaging biomarkers have broadly been investigated in initial staging [20, 21], biochemical recurrence [21–23], monitoring treatment response [23–26], and prognosis detection [25–27]. No clear consensus, however, has been reached thus far, due to conflicting results and inter-study differences in terms of patient characteristics, therapies administered, and primary outcomes.

In the current study, we aimed to investigate whether baseline ^{68}Ga-PSMA PET/CT-derived whole-body volumetric parameters could be used as predictive biomarkers for survival in mCRPC patients receiving first-line treatment. We also evaluated the correlation between PSA levels and volumetric parameters measured before first-line treatment. Lastly, volumetric parameters were compared between patients with and without PSA response to first-line treatment.

Materials and methods

Study design and patient selection

We retrospectively reviewed medical records of patients diagnosed with metastatic prostatic adenocarcinoma who were followed-up in the medical oncology department of our institute between 2015 and 2021. Patients who received first-line treatment after ADT failure, also known as CRPC, were eligible for the study, in case a ^{68}Ga-PSMA PET/CT scan was performed within 4 weeks before starting systemic treatment. Patients received either chemotherapy (docetaxel 75 mg/m^2) or second-generation antiandrogen treatment (abiraterone acetate 1000 mg with prednisone 5 mg 2×1 daily or enzalutamide 160 mg daily) in the first-line setting until disease progression, intolerable toxicity or death. ADT was continued with all three treatments during the refractory period. Patients had an available serum PSA measurement within 2 weeks before initiating treatment.

The exclusion criteria were pathological diagnosis other than prostate adenocarcinoma, absence of Gleason score or pre-treatment PSA value, castration-sensitive prostate cancer, no treatment with systemic chemotherapy or second-generation anti-androgens in the first-line setting of mCRPC, unavailability of ^{68}Ga-PSMA PET/CT scan within one month before treatment for the assessment of whole-body volumetric parameters, and lack of follow-up data.

PSA levels were measured once in every 3 and 4 weeks for patients treated with docetaxel and abiraterone/enzalutamide, respectively. PSA response was defined as a decline of $\geq 50\%$ from pre-treatment value at 12 weeks.

We collected data about demographic, clinicopathologic, and treatment-related factors that could affect prognosis. In this context, we recorded age, Eastern Cooperative Oncology Group (ECOG) performance status, Gleason score, history of primary surgery or radiotherapy, duration of ADT, metastatic sites, number of bone metastases and first-line treatment in the refractory period. Comorbidity was assessed using the Charlson Comorbidity Index (CCI) and patients were grouped based on the median CCI [28]. This study was approved by the institutional ethics committee (Date of approval: 24 July 2020, Protocol Code: 09.2020.888).

^{68}Ga-PSMA imaging procedure

All ^{68}Ga-PSMA PET/CT scans were acquired using a combined PET/CT scanner (Discovery-16 LS; GE Healthcare, Waukesha, Wisconsin, USA). All patients received diluted

iohexol (Omnipaque; GE Healthcare) as the oral contrast agent, and ^{68}Ga-PSMA-11 was administered intravenously according to 2 MBq/kg of body weight with an average dose of 150 MBq (IQR 104–206 MBq). Data acquisition consisted of two sets of PET/CT images. First, an early static image of the pelvis centered in the prostate bed was acquired in the prone position (one bed position, acquisition time: 3 min) starting within 5 min after the injection. Second, the whole-body images from the upper thigh to the skull base were taken in the supine position at approximately 1 h after the injection. A low-dose CT scan (parameters: 80 mA, 140 kV, table speed 27 mm/rotation, and slice width 5.0 mm) was performed to screen the body. Afterwards, a standard whole-body PET scan was conducted in 3D mode with an emission time of 3 min per bed position (six to eight bed positions) scanning the same area with the low-dose CT scan. All PET images were attenuation corrected and the acquired data were reconstructed using an iterative algorithm. Reconstruction was based on the ordered subsets expectation maximization (OSEM) algorithm with four iterations per eight subsets.

Image analysis

All ^{68}Ga-PSMA PET/CT images were reanalyzed using PET Volume Computerized Assisted Reporting (PET VCAR) software (Advantage Windows Workstation 4.5), which allowed the review of PET, CT, and fused images in axial, coronal, and sagittal slices. Two experienced nuclear medicine physicians re-evaluated the PET/CT images for local recurrence, malignant lymph node involvement, and distant metastasis. Any focal tracer uptake higher than surrounding background activity was considered as malignant based on the location, intensity, shape, and size [29]. Although typical pitfalls such as PSMA uptake in sacral and celiac ganglia or urinary uptake were often observed, they were not considered as pathological. All lesions suggestive of recurrent prostate cancer, their localizations as well as the number of detected metastases per patient were recorded. Volumetric PET parameters, the SUVmax and SUVmean were measured on attenuation-corrected images. A volume of interest (VOI) around the outline of a lesion was set and then VOI was automatically drawn along the margin of the tumor uptake using PET VCAR software. The SUVmax shows the highest ^{68}Ga-PSMA uptake in a VOI. SUVmean refers to the average SUV concentration in a VOI. Similar to the metabolic tumor volume (MTV), PSMA-derived tumor volume (PSMA-TV) represents the total volume of the tumor cells having PSMA uptake greater than a threshold of 45% of SUVmax in the VOI [23, 30, 31]. The SUVmax, SUVmean, and MTV were produced automatically from the VOIs by the workstation and then total lesion PSMA (TL-PSMA) was calculated by multiplying the SUVmean by the PSMA-TV of the lesions. The PSMA-TV of all lesions of a patient was summed as the whole-body PSMA-TV (wbPSMA-TV) and the TL-PSMA of all lesions of a patient was summed as the whole-body TL-PSMA (wbTL-PSMA).

Statistical analysis

Descriptive data were recorded as frequencies and percentages for categorical variables. Continuous variables were presented as median and ranges (minimum–maximum). The normality of data was tested by the Kolmogorov–Smirnov and Shapiro–Wilks test and the parameters did not show normal distribution. Continuous variables of two independent groups were compared with Mann–Whitney *U* test. Categorical variables were compared with Fisher's exact test. Correlation of whole-body volumetric parameters with PSA levels was investigated by Spearman's rank correlation test. Receiver operating characteristic (ROC) curve was plotted to estimate the optimal cut-off values of wbPSMA-TV, wbTL-PSMA, and PSA for predicting mortality. Survival was estimated with Kaplan–Meier method and log-rank test. Overall survival (OS) was defined as the interval from the start of first-line treatment in refractory period until death from any reason or last visit. Univariate and multivariate analyses were carried out using the Cox proportional hazard model to evaluate factors that predict OS. Confidence interval (CI) was selected as 95% and a two-sided *p* value of less than 0.05 was accepted as the level of significance. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinicopathologic and treatment characteristics of the study population

A total of 54 patients were included in this study. Clinicopathologic and treatment characteristics of the study population are presented in Table 1. Median age was 73 years (range 51–90). Most of the patients had an ECOG performance status of 0 (59.3%). More than half of the study cohort (55.6%) had at least one comorbidity. Median CCI was 6 (range 6–10). Gleason score of 8–10 was reported in 72.2% of the patients. Radical prostatectomy and primary radiotherapy were performed in 14.8% and 29.6% of the patients, respectively. Rest of the patients (55.6%) were diagnosed with metastatic disease. All patients received ADT before developing resistance; majority of patients (77.8%) were treated with ADT more than 12 months. The first-line treatments in the refractory setting were docetaxel and enzalutamide/abiraterone in 59.3% and 40.7% of the patients, respectively. Bone metastases were

Table 1 Clinicopathologic and treatment characteristics of the study population

Variables	All patients ($n=54$, %)
Median age, years (range)	73 (51–90)
ECOG performance status	
0	32 (59.3)
1–2	22 (40.7)
Charlson Comorbidity Index (median)	6 (6–10)
Gleason score	
<8	15 (27.8)
≥ 8	39 (72.2)
History of radical prostatectomy	
Yes	8 (14.8)
No	46 (85.2)
History of primary radiotherapy	
Yes	16 (29.6)
No	38 (70.4)
Metastatic disease at diagnosis	
Yes	30 (55.6)
No	24 (44.4)
Duration of ADT	
≤ 12 months	12 (22.2)
>12 months	42 (77.8)
Metastatic locations	
Local disease	35 (64.8)
Bone only	15 (27.7)
Lymph node only	5 (9.2)
Bone plus lymph node	32 (59.2)
Bone plus visceral	8 (14.8)
Number of bone metastases	
None	5 (9.3)
<5	18 (33.3)
5–10	9 (16.7)
≥ 10	22 (40.7)
First-line treatment in refractory period	
Docetaxel	32 (59.3)
Enzalutamide/Abiraterone	22 (40.7)

present in 90.7% of the patients, with the majority having more than ten metastases.

Correlation between ^{68}Ga-PSMA PET/CT-derived whole-body volumetric parameters and PSA levels

Both wbPSMA-TV (rho = 0.582, $p=0.004$) and wbTL-PSMA (rho = 0.564, $p=0.007$) showed moderate positive correlations with pre-treatment PSA levels.

Comparison of ^{68}Ga-PSMA PET/CT-derived volumetric parameters, PSA levels, and clinicopathologic factors between survivors and non-survivors

Older age ($p=0.02$), higher wbPSMA-TV ($p=0.007$), higher PSA ($p=0.01$), higher number of bone metastases ($p=0.02$), and lack of PSA response to first-line treatment ($p=0.03$) were significantly associated with an increased risk of mortality. Elevated wbTL-PSMA ($p=0.06$) showed tendency to enhance mortality risk with a borderline significance. CCI, ECOG-PS, duration of ADT, Gleason score, and treatment type did not have an impact on mortality risk. Table 2 demonstrates all comparisons of different parameters between survivors and non-survivors.

Comparison of ^{68}Ga-PSMA PET/CT-derived volumetric parameters, PSA levels and clinicopathologic factors between patients treated with docetaxel and abiraterone/enzalutamide

Patients receiving abiraterone/enzalutamide as first-line treatment had older age ($p<0.001$), worse ECOG-PS ($p<0.001$), higher wbPSMA-TV ($p=0.01$), and higher wbTL-PSMA ($p=0.01$). Duration of ADT was found significantly longer in patients treated with docetaxel ($p=0.01$). Supplementary Table S1 shows a detailed comparison of patients treated with docetaxel and abiraterone/enzalutamide.

Comparison of ^{68}Ga-PSMA PET/CT-derived volumetric parameters, PSA levels, and clinicopathologic factors between PSA responders and non-responders

PSA level measured before first-line treatment was significantly higher in PSA non-responder cohort ($p<0.001$). There was no statistical significant difference between groups in terms of wbPSMA-TV ($p=0.55$) and wbTL-PSMA ($p=0.38$). Mortality rate was higher in patients with no PSA response ($p=0.03$). Table 3 presents the comparison of patients based on PSA response to first-line treatment.

Survival outcomes, univariate, and multivariate analyses

Median follow-up time was 28 months (range 4–71 months). Among total study population, 77.7% (42/54) died during follow-up period. In the ROC analysis, the cut-off values for wbPSMA-TV, wbTL-PSMA and PSA to predict mortality were determined to be 40.1, 289.4 and 24.2, respectively (Supplementary Table S2, Fig. 1). Median OS was

Table 2 Comparison of ^{68}Ga-PSMA PET/CT-derived parameters, PSA levels, and clinicopathologic factors between survivors and non-survivors

		Exitus ($n=42$)	Alive ($n=12$)	p value
Age (years)	Median (range)	74.5 (52–90)	71 (51–73)	0.02*
Charlson Comorbidity Index	≤6	24	7	0.9*
	>6	18	5	
ECOG-PS	0	23	9	0.32^{+}
	1–2	19	3	
PSA	Median (range)	43.9 (2.1–1516)	19.6 (0.84–77)	0.01*
wbPSMA-TV	Median (range)	61.7 (1.45–841.8)	22.2 (9.5–72.5)	0.007*
wbTL-PSMA	Median (range)	455.1 (6.65–6559.7)	192.4 (105.9–1300)	0.06*
Number of bone metastases	Median (range)	9 (0–142)	3 (0–18)	0.02*
Duration of ADT (months)	Median (range)	26.5 (5–160)	18 (5–95)	0.15*
Gleason score	<8	10	5	0.22^{+}
	≥8	32	7	
Treatment	Docetaxel	23	9	0.32^{+}
	Enza/Abi	19	3	
PSA response	Responder	21	10	0.03^{+}
	Non-responder	21	2	

*Mann–Whitney U test

$^{+}$Fisher's exact test

Table 3 Comparison of patients based on PSA response to first-line treatment

		PSA response status		
		Responder ($n=31$)	Non-responder ($n=23$)	p value
Age (years)	Median (range)	72 (51–85)	75 (62–90)	0.05*
Charlson Comorbidity Index	≤6	20	11	0.27^{+}
	>6	11	12	
ECOG-PS	0	27	13	<0.72^{+}
	1–2	5	10	
PSA	Median (range)	32 (0.84–1516)	49 (2.1–525)	<0,001*
wbPSMA-TV	Median (range)	51.81 (4.3–841.8)	49.88 (1.45–657.1)	0.55*
wbTL-PSMA	Median (range)	371.7 (13.08–2824.7)	604.8 (6.65–6569.7)	0.38*
Number of bone metastases	Median (range)	4 (0–102)	9 (0–142)	0.2*
Duration of ADT (months)	Median (range)	26 (5–160)	24 (5–122)	0.75*
Gleason score	<8	11	4	0.14^{+}
	≥8	20	19	
Treatment type	Docetaxel	17	15	0.43^{+}
	Abiraterone/Enzalutamide	14	8	
Status	Alive	10	2	0.03^{+}
	Exitus	21	21	

*Mann–Whitney U test

$^{+}$Fisher's exact test

significantly longer in patients with wbPSMA-TV < 40.1 when compared to patients with wbPSMA-TV ≥ 40.1 (41 vs. 20 months, $p=0.02$). Likewise, higher wbTL-PSMA (≥ 289.4) and higher PSA (≥ 24.2) were significantly associated with worse OS ($p=0.01$ and $p=0.02$, respectively). Median OS was 29 months and 13 months in PSA-responder and non-responder groups, respectively. The difference in OS was statistically significant ($p=0.02$). Gleason score, number of bone metastases and treatment type did not affect OS outcomes (Supplementary Table S3, Fig. 2).

In univariate analysis, higher wbPSMA-TV ($p=0.004$), higher wbTL-PSMA ($p=0.01$), higher number of bone metastases ($p=0.04$), and lack of PSA response ($p=0.03$) were found to be significant poor prognostic factors for OS. Multivariate analysis determined wbPSMA-TV (HR: 1.003, 95% CI 1.001–1.004, $p=0.001$) and PSA response

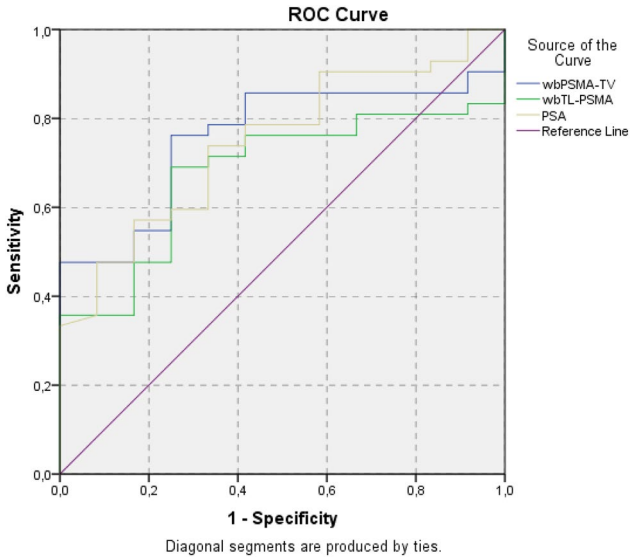


Fig. 1 Receiver operating characteristic (ROC) curve

(HR: 2.241, 95% CI 1.189–4.222, $p = 0.01$) as independent predictors of OS (Table 4).

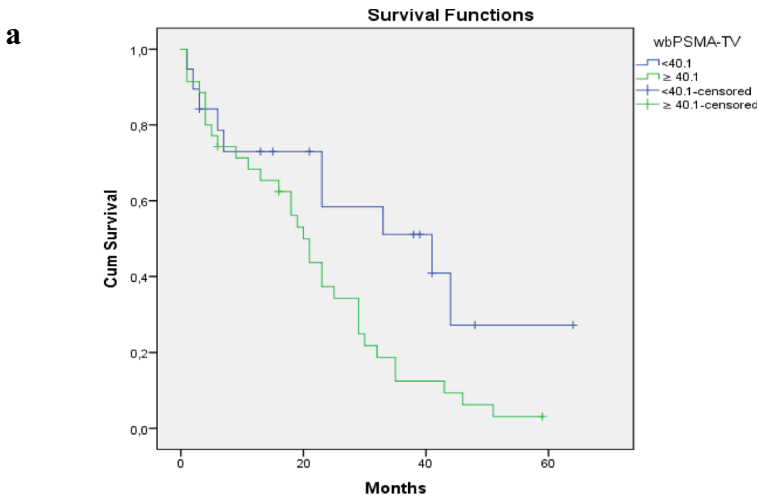
Discussion

The impact of tumor burden on cancer prognosis has been well documented, and volumetric parameters obtained from ^{18}F-FDG PET/CT such as metabolic tumor volume and total lesion glycolysis have been shown to reflect tumor load and found to be associated with prognosis in a variety of malignancies [32, 33]. As for PC, the CHAARTED trial effectively highlighted the importance of tumor burden by defining high and low volume disease based on the number and location of bone metastasis or visceral metastasis in a group of patients with metastatic castration-naive prostate cancer (mCNPC), and high volume disease was shown to be predictive of docetaxel benefit [34]. A similar definition of metastatic burden was also adopted in the LATITUDE and STAMPEDE trials, and abiraterone was approved for mCNPC after these randomized phase 3 clinical trials, regardless of disease burden [35, 36]. In patients with mCRPC, however, the concept of tumor burden did not receive much consideration when determining prognosis or treatment strategy. Furthermore, it is obvious that more quantitative descriptors of tumor burden are required in clinical practice and clinical trials, instead of considering only the number or location of lesions. Volume-based metabolic parameters generated from ^{68}Ga-PSMA PET/CT are some of those tools with very few studies in the literature. Therefore, we conducted the present study to investigate whether ^{68}Ga-PSMA PET/CT-derived volumetric parameters could predict survival outcomes in mCRPC patients receiving first-line treatment. According to our findings, wbPSMA-TV, wbTL-PSMA, PSA level, and PSA response were associated with OS. Among all those parameters, wbPSMA-TV was found to be an independent predictor of OS, along with PSA response irrespective of treatment type. We also investigated the correlation between PSA levels and volumetric parameters which were both measured before starting first-line treatment; a moderate positive correlation was found between PSA and both wbPSMA-TV and wbTL-PSMA.

The first evidence of ^{68}Ga-PSMA PET/CT-derived volumetric parameters as a quantitative imaging biomarker was provided by the study of Schmuck et al. [31]. This retrospective study included 101 patients who had elevated PSA levels after primary surgery and underwent a ^{68}Ga-PSMA PET/CT. Neither SUVmax nor SUVmean correlated significantly with PSA levels. PSMA-TV and TL-PSMA, on the other hand, were found to be significantly correlated with PSA levels, suggesting that these imaging parameters had the potential to reflect whole-body tumor burden. Furthermore, a significant concordance was observed between changes in PSMA-TV and TL-PSMA and changes in PSA levels, in a small group of patients ($n = 10$) who had a baseline and follow-up PET/CT scan.

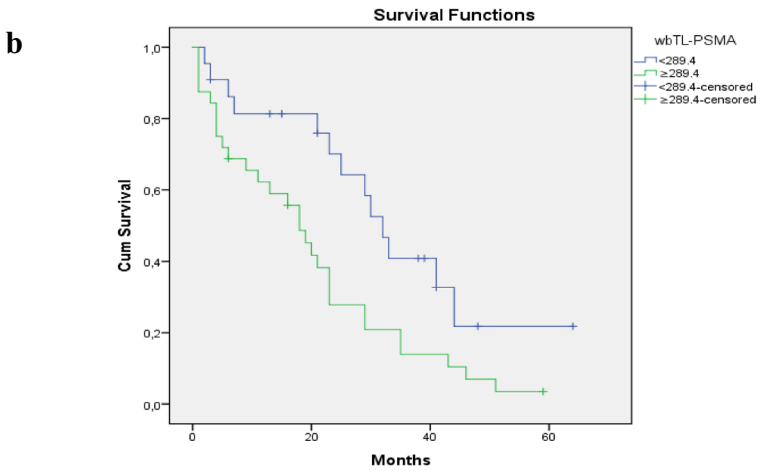
Brito et al. [22] and Schmidkonz et al. [23], respectively, published similar findings, focusing on the evaluation of whole-body tumor burden with ^{68}Ga-PSMA PET/CT. In the former study, a total of 100 PC patients who had a ^{68}Ga-PSMA PET/CT because of a biochemical recurrence, were included. The detection rate of malignant lesions with ^{68}Ga-PSMA PET/CT was 72%. Since PSMA-TV and TL-PSMA showed a strong correlation, they used only TL-PSMA in further analysis. A strong correlation was reported between TL-PSMA and PSA levels (rho = 0.73, $p < 0.0001$). The latter study, evaluated the role of ^{68}Ga-PSMA PET/CT in determining treatment response, as well as its ability to assess whole-body tumor burden. The study population was chosen similar to Brito el al. and 142 PC patients who underwent a ^{68}Ga-PSMA PET/CT due to biochemical recurrence were enrolled. Both PSMA-TV and TL-PSMA showed a significant correlation with PSA levels ($p < 0.0001$). Data of 23 patients who underwent a baseline and follow-up ^{68}Ga-PSMA PET/CT after external beam radiotherapy, ADT or chemotherapy were analyzed for therapeutic response evaluation. A higher rate of agreement (87%) was noted between biochemical response defined by changes in PSA levels and TL-PSMA (95% CI, 0.66–0.97; Cohen's $\kappa = 0.78$; $p < 0.01$), when compared to the rate of agreement (74%) for SUVmax, which was 74% (95% CI, 0.52–0.90; $\kappa = 0.55$; $p < 0.01$).

Consistent with the above-mentioned studies, our study identified a significant correlation between PSA levels and both volumetric parameters, demonstrating once again that PSA is a reliable predictor of tumor burden. However, we



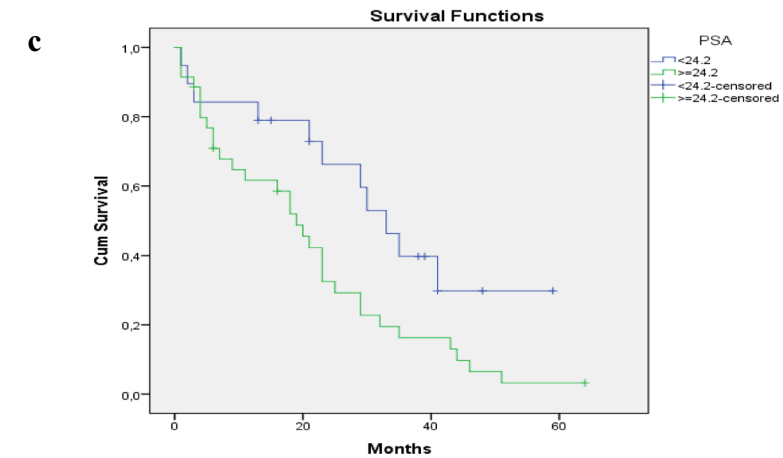
Number at risk

wbPSMA-TV <40.1	19	11	5	1
wbPSMA-TV≥ 40.1	35	17	4	0



Number at risk

wbTL-PSMA <289.4	22	15	5	1
wbTL-PSMA ≥289.4	32	13	4	0



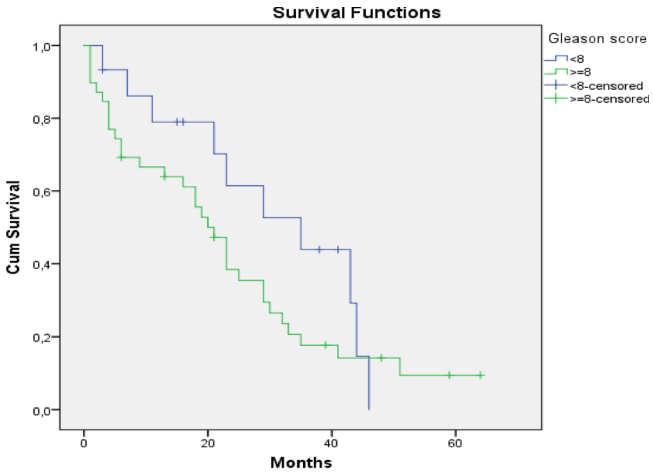
Number at risk

PSA <24.2 ng/ml	19	13	4	0
PSA ≥24.2 ng/ml	35	15	5	1

Fig. 2 Kaplan–Meier curves according to **a** wbPSMA-TV, **b** wbTL-PSMA, **c** PSA level, **d** Gleason score, **e** treatment type, and **f** PSA response

Fig. 2 (continued)

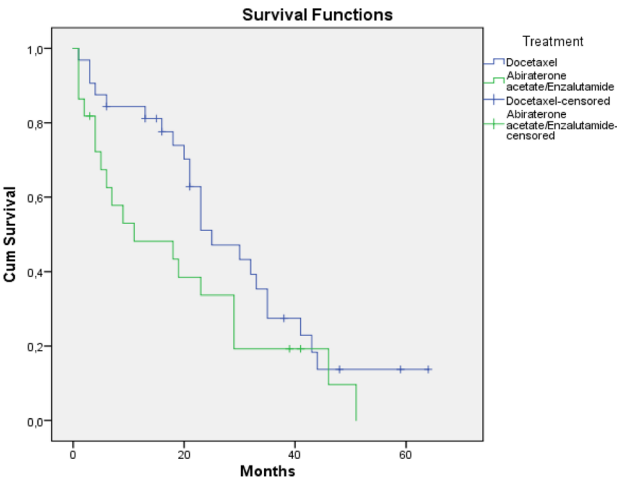
d



Number at risk

Gleason score <8	15	9	4	0
Gleason score ≥8	39	19	5	1

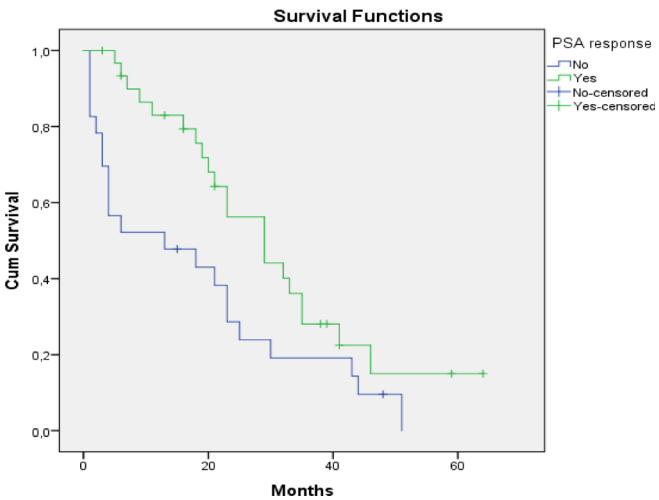
e



Number at risk

Docataxel	32	20	6	1
Abiraterone acetate /Enzalutamide	22	8	3	0

f



Number at risk

No	23	9	4	0
Yes	31	19	5	1

Table 4 Univariate and multivariate analyses of factors for predicting overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (year)	1.030 (0.996–1.066)	0.08	1.015 (0.979–1.051)	0.42
ECOG performance status	1.346 (0.729–2.484)	0.34		
Charlson Comorbidity Index	0.991 (0.536–1.831)	0.97		
Treatment	1.637 (0.889–3.013)	0.11		
Gleason score	1.161 (0.838–1.608)	0.36		
wbPSMA-TV	1.002 (1.001–1.004)	0.004*	1.003 (1.001–1.004)	0.001*
wbTL-PSMA	1.000 (1.000–1.001)	0.01*	1.000 (1.000–1.000)	0.98
PSA	1.000 (1.000–1.001)	0.25		
Number of bone metastases	1.008 (1.000–1.016)	0.04*	1.000 (0.989–1.011)	0.98
Duration of ADT	0.998 (0.990–1.007)	0.73		
PSA response	1.926 (1.046–3.545)	0.03*	2.241 (1.189–4.222)	0.01*

*Significant values ($p < 0.05$) are highlighted

could not assess treatment response using ^{68}Ga-PSMA PET/CT, since we did not adopt a follow-up ^{68}Ga-PSMA PET/CT in our clinical practice, particularly in case of decreasing PSA levels following treatment. Therefore, we decided to focus on the impact of volumetric parameters on survival outcomes instead.

To date, limited research has investigated the role of ^{68}Ga-PSMA PET/CT-derived volumetric parameters in predicting survival outcomes in metastatic setting. Two recently published studies addressed this issue in patients with mCRPC. Can et al. evaluated the predictive value of volumetric parameters in terms of survival, as well as their efficacy in monitoring treatment response [25]. This retrospective study included 151 mCRPC patients who were treated with docetaxel or abiraterone/enzalutamide and underwent ^{68}Ga-PSMA PET/CT before and after treatment. The findings of this study showed a correlation and concordance between both PSA response and PSMA-TV response (r: 0.66, $p < 0.01$ and k: 0.454, $p < 0.001$), and PSA response and TL-PSMA response (r: 0.71, $p < 0.001$ and k: 0.541, $p < 0.001$). The results were more significant when PSA levels were above 10 ng/mL. Pre-treatment PSMA-TV ($p = 0.003$) and PSMA-TV change ($p = 0.001$) were independent prognostic factors for mortality. In terms of treatment types, our study sample was similar to Can et al.'s, but we only included patients who received first-line treatment following ADT failure, which made our cohort more homogeneous and allowed for more reliable survival analyses. We also compared patients treated with docetaxel to those who received abiraterone/enzalutamide; not surprisingly, clinicians had tended to avoid providing chemotherapy to older patients with comorbidities. Despite the fact that pre-treatment PSMA-TV and TL-PSMA levels were higher in the abiraterone/enzalutamide group, there was no significant difference between groups in terms of PSA response or mortality, demonstrating that second-generation oral hormone treatments are also highly effective in the elderly. Second study from the same center included 44 mCRPC patients who were treated with abiraterone or enzalutamide and had two consecutive ^{68}Ga-PSMA PET/CT scans performed within 1 month before treatment and at least 3 months after treatment [26]. Pre-treatment PSA and PSMA-TV, as well as PSA change, were found to be independent prognostic factors associated with mortality. Recently, volumetric parameters were furthermore reported as negative prognostic factors of OS in patients receiving [177Lu]Lu-PSMA-617 radioligand therapy [27].

In the study of Karyağar et al. PSMA-TV was shown to predict PSA response in mCRPC patients treated with enzalutamide after docetaxel failure [24]. PSMA-TV was significantly higher in non-responder group ($p = 0.028$). Unlike this study, PSMA-TV and TL-PSMA were similar between PSA responders and non-responders in our study cohort. PSA levels, on the other hand, were significantly higher in non-responders ($p < 0.001$).

As ^{68}Ga-PSMA PET/CT becomes more widely used in different stages of prostate cancer, and up to one-third of patients referred for ^{68}Ga-PSMA PET/CT are already on some kind of ADT, it is of great importance to carefully consider the impact of ADT on PSMA expression and, as a result, imaging outcomes. A number of studies evaluated the ADT effect on PSMA expression with conflicting results [37]. Recently, the findings of a pilot prospective study evaluating the influence of short-term ADT (3 months) on ^{68}Ga-PSMA PET/CT parameters were published [38]. The study included clinical stage 3 or 4, untreated prostate cancer patients who underwent ^{68}Ga-PSMA PET/CT before and 10–14 weeks after ADT. Parameters including SUVmax, SUVmean, PSMA-TV and TL-PSMA were all shown to be significantly decreased after ADT in a total of 30 eligible patients.

Treatment-related neuroendocrine prostate cancer (t-NEPC) is a lethal variant of CRPC considered to be

caused by adenocarcinoma transition after ADT. The incidence of t-NEPC is substantially higher than that of de novo neuroendocrine prostate cancer (NEPC), and it has been increasing recently due to the widespread use of androgen receptor targeted therapies [39]. As a mechanism of treatment resistance, t-NEPC has been reported to develop in 10–20% of CRPC patients. De novo NEPC and t-NEPC have similar clinical features. Except in cases of mixed adenocarcinoma, NEPC is characterized by resistance to hormone therapy, poor prognosis due to rapid progression and low PSA levels relative to high tumor burden [40]. Cytotoxic chemotherapy is the primary treatment option for this group of patients. According to international guidelines, NEPC should be considered for patients who develop resistance to ADT and biopsy of accessible lesions for histologic confirmation is recommended [41]. Unfortunately, secondary biopsies were not routinely performed on our patient group, which could have resulted in missed diagnosis of t-NEPC. Since we included patients who were treated with both chemotherapy (docetaxel) and androgen receptor targeted therapies (abiraterone/enzalutamide) in the first-line setting, patients with a missed diagnosis of NEPC may actually have benefited more from chemotherapy. Additionally, both PSMA expression and PSA secretion are affected during the transition of PC to the neuroendocrine state. This aggressive subtype is typically characterized by low PSMA expression and increased glucose metabolism, which make lesions more detectable by ^{18}F-FDG PET/CT [42]. Due to this transition, the detection ability of ^{68}Ga-PSMA PET/CT may have diminished in some patients, making it possible that volumetric parameters could not adequately reflect the tumor burden. However, there are also some studies suggesting that NEPC can be delineated with ^{68}Ga-PSMA PET/CT or even that NEPC may benefit from PSMA-targeted therapy. This PSMA-positivity could be caused by the binding of PSMA radioligands to PSMA-like proteins expressed in NEPC tumors, which are normally PSMA-negative [43, 44].

The limitations of the present study are retrospective design in a single-center, relatively small sample size, absence of a secondary biopsy after progression on ADT and the lack of follow-up ^{68}Ga-PSMA PET/CT after first-line treatment.

Conclusion

Our findings suggest that ^{68}Ga-PSMA PET/CT-derived volumetric parameters, notably wbPSMA-TV, appear to be useful tools to assess tumor burden and predict long-term survival in patients with mCRPC. These quantitative instruments of disease burden correlated significantly with PSA levels. The wbPSMA-TV and PSA response were found to be independent prognostic factors for overall survival. With the increased use of ^{68}Ga-PSMA PET/CT in staging, biochemical recurrence and follow-up, volumetric parameters may become more applicable in clinical practice. Our results need to be further evaluated in prospective studies with larger populations.

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Declarations

Conflict of interest The authors declared no competing interest.

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