How reliable is the high-volume definition in prostate cancer patients: the potential game-changing role of PSMA
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Purpose To evaluate whether metabolic and volumetric data from 68Ga-PSMA PET/CT performed during staging of de-novo high-volume mCSPC patients who received docetaxel could be used to predict survival.

Methods Forty-two de-novo high-volume mCSPC patients, who received ADT + Docetaxel and underwent 68Ga-PSMA PET/CT for staging, were included in the study. The association between patients’ pathological data, all PSA measurements, treatments they received, the data obtained from 68Ga-PSMA PET/CT and progression-free and overall survival were examined.

Results In the multivariate analysis, PSMA-TV (primary) and PSMA-TV (WB) variables were shown to be independent negative predictors of overall survival. For the threshold value of 19.91 cm³ obtained for PSMA-TV (primary), HR was calculated as 6.31, the 95% confidence interval (CI): 1.01–39.18, P = 0.048. For the threshold value of 1226.5 cm³ obtained for PSMA-TV (WB) variable, HR was calculated as 58.62, the 95% CI: 2.55–1344.43, P = 0.037.

Conclusion Metabolic and volumetric data obtained from 68Ga-PSMA PET/CT can be used to predict survival in de-novo high-volume mCSPC. Our results show that in ADT + Docetaxel receiving patients, a subgroup with higher PSMA-TV (WB) values have a significantly worse prognosis. This situation suggests that the high-volume disease definition in the literature may be insufficient for this group, and that 68Ga-PSMA PET/CT can play an essential role in demonstrating the heterogeneity within the group. Nucl Med Commun 44: 816–824 Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction Prostate cancer (PCa), the second most common type of cancer in men [1], is metastatic in approximately 5% of the cases when diagnosed [2]. Although it seems like a small percentage, patients with de-novo metastatic PCa constitute a significant patient group when their prognostic characteristics and the overall incidence of PCa are considered. Prospective studies on these patients recently mainly divide the patient group into two major subgroups low volume (LV) and high volume (HV) [3–5]. This approach is based on the different prognostic characteristics of subgroups and the different levels of benefit they receive from the treatment approaches. While the combination of androgen deprivation therapy (ADT) with radiotherapy in the LV patient group is the current approach, it is known that Docetaxel (DTX) or second-generation anti-androgens provide higher benefits in the HV patient group [3]. The guideline of the European Urology Association (EUA) has also determined their treatment recommendations according to this approach [6].

Although the LV-HV classification is based on the extent of the disease rather than the volume, this classification provides important benefits. Nevertheless, current imaging modalities, may provide more accurate and detailed information. Especially for the HV group, this information may play a critical role in patient management. However, since the definition of HV disease is based on conventional imaging modalities, there isn’t enough information on the importance of the actual tumor volumes of patients receiving DTX therapy in this group.

Gallium-68 Prostate Specific Membrane Antigen - PET/Computed Tomography (68Ga-PSMA PET/CT) has been introduced and preferred as a reliable method in the staging phase of PCa in many centers, making it possible to evaluate metabolic disease volumes in this patient group [7]. PSMA, which is expressed at much higher rates in PCa cells than in normal prostate tissue, is used as a reliable agent in PCa imaging [8]. As stated in the EUA guideline, further studies are required to show how the high sensitivity provided by this imaging modality is effective in determining the treatment outcomes.
of patients [6]. In this study, we would like to seek an answer to whether the metabolic and volumetric data obtained from $^{68}$Ga-PSMA PET/CT, performed to staging, can be used to predict the survival of patients with de-novo high-volume metastatic castration-sensitive PCA (mCSPC) receiving DTX treatment.

**Materials and methods**

**Patient selection**

The files of patients who underwent $^{68}$Ga-PSMA PET/CT for the staging of PCA in the Nuclear Medicine Department of our hospital between September 2017 and December 2020 were browsed retrospectively. Out of a total of 862 patient files, 42 patients with no known secondary malignancy, diagnoses confirmed by biopsy, and high-volume de-novo metastatic castration-sensitive PCa followed by at least 6 cycles of DTX (75 mg/m$^2$ + prednisone 5 mg) treatment [6] were included in the study (Fig. 1). These patients had also received routine ADT (Leuprolide 22.5 mg SC every 3 months or Goserelin 10.8 mg SC every 3 months). All 42 patients underwent $^{68}$Ga-PSMA PET/CT before DTX and ADT treatment. Before the $^{68}$Ga-PSMA PET/CT, none of the patients had any treatment except focal palliative bone radiotherapy. Criteria defined in the ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) study were used to distinguish between HV and LV while including the patients in the study. Accordingly, the presence of 4 or more bone metastases, at least one of which is outside the vertebral column and pelvis, or visceral organ metastases were considered sufficient for the patients to be evaluated as having a high-volume disease [3].

**Study protocol**

In this retrospective study, the results of routine diagnostic procedures such as PSA tests, pathology results [International Society of Urological Pathology scores (ISUP)], and age data of eligible patients who were screened in our clinic were obtained from the hospital’s information management system. In addition, the information regarding whether the patients were alive or not and the date of death in case they were dead, was obtained from the Death Notification System.

As determined by the criteria of the Prostate Cancer Study Group 2 for the definition of progression, an increase in three consecutive PSA measurements and a PSA value above 2.0 ng/ml were adopted [9]. Since there was no progression detected by anatomical imaging without PSA progression in our study group, additional radiological progression criteria were not needed. This study was a graduation/specialization thesis and was carried out with the approval of the Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (protocol number 391). All patients signed a written informed consent form for the purposes of evaluation and publication of their data.

**Ga-68 PSMA PET-CT preparation, imaging, and evaluation**

Gallium-68 ($^{68}$Ga) radionuclide was obtained by eluting from a Germanium-68/Gallium-68 ($^{68}$Ge/$^{68}$Ga)
818 µg of PSMA I&T compound was labeled with 68Ga fully automated synthesis device (Scintomics, Germany), to exclude false positive (physiological and inflammatory uptakes were compared with the symmetrical area, surrounding area, and BT or MR images, with the intention to exclude false positive (physiological and inflammatory uptakes) areas.

$^{68}$Ga-PSMA PET/CT images were analyzed as MIP (maximum intensity projection) and cross-sectional imaging. All areas which visually exceed the normal background activity uptake in these images were evaluated as metastasis when they are outside the prostate and as primary tumors when in the prostate bed if they do not correspond to the known physiological uptake areas and if the described area does not correspond to any known non-malignant activity involvement (such as inflammation, urinary activity, etc.). Wherever possible, all those uptakes were compared with the symmetrical area, surrounding area, and BT or MR images, with the intention to exclude false positive (physiological and inflammatory uptakes) areas.

SUVmax, SUVmean, SUVpeak, and PSMA tumor volume (PSMA-TV) ($cm^3$) for each lesion were automatically generated from user-specified VOIs by the workstation. The borders of the target lesion within the VOI were automatically drawn with isocontour curves. Voxels greater than the 45% threshold of SUVmax in the VOI were defined as the lesion area to measure PSMA-TV and SUVmean [7,10]. In cases where the lesion area observed on CT and the VOI drawn were inconsistent, the threshold value was readjusted to cover the entire lesion and exclude the extralesional tissue. In cases where the borders of the primary tumor was determined as a lesion located in prostate tissue and shows $^{68}$Ga-PSMA uptake exceeding the normal background activity. For this primary tumor, total lesion PSMA, called TL-PSMA (primary), value was obtained by multiplying the SUVmean (primary) with the PSMA-TV (primary), namely tumor volume value, which were obtained in the determined VOI area. The whole-body PSMA-TV (WB) value of each patient was defined as the sum of the PSMA-TV of all lesions. Whole-body Total Lesion PSMA, namely TL-PSMA (WB), was obtained by multiplying the SUVmean determined in the volume selected with the isocontour and PSMA-TV (WB).

For each patient, SUVmax (primary), SUVmean (primary), SUVpeak (primary), TL-PSMA (primary) and SUVmax (WB), SUVmean (WB), SUVpeak (WB), PSMA-TV (WB), and TL-PSMA (WB) data were calculated on ADW 4.7 (GE Healthcare, Chicago, USA) consoles. Initial PSA before therapy, namely Basal PSA, and lowest PSA after treatment, called Nadir PSA, were incorporated to study as variables. In addition, the patients’ bone, visceral and intra-pelvic/extra-pelvic lymphatic metastases were also noted while the images were being evaluated.

**Statistical method**

SPSS 24.0 for Windows (IBM, New York, USA) package program was used to evaluate the data obtained in the study and the statistical significance limit was determined as $P < 0.05$. While descriptive statistics were presented as mean ± SD for normally distributed numerical variables, categorical, ordinal variables, and non-normally distributed numerical variables were presented as median (minimum, maximum).

Receiver operating characteristic (ROC) curves were plotted to determine the appropriate threshold value for continuous variables. This procedure was done separately for overall survival (OS) and progression-free survival (PFS) data for each variable. Threshold values were determined using the Youden index in the drawn ROC curves. After the threshold values of the continuous variables were determined, the survival graphs for the OS and PFS data separately for the variables and the appropriate area under the curve in the ROC curves were drawn using the Kaplan–Meier method. At this stage, univariate analyzes were performed using the log-rank method, and statistical significance was evaluated. Spearman’s correlation analysis was used to evaluate the probability of multicollinearity for the variables with univariate analysis $P < 0.25$. The Cox hazard ratio (HR) model was then
applied as a multivariate analysis to evaluate the potential independent effects of these variables on OS and PFS.

**Results**

**Patient characteristics**
The mean age of 42 patients with de-novo high-volume mCSPC included in the study was 63.52 ± 9.36, while basal PSA values were 77.75 (0.37–2314.64) ng/ml on average. Forty-one of the patients responded to 6 cycles of DTX treatment with PSA decrease, and only 1 patient had PSA progression despite treatment. 15 of the patients in the study group received palliative radiotherapy to the bones in the pre-chemotherapy period and 16 in the post-chemotherapy period. A total of 15 patients in our study group consisted of patients who received second-generation antiandrogen therapy in the post-chemotherapy period. The median follow-up period in our study group was 759 (196–1771) days. Age, ISUP scores, and other clinical characteristics of the patients are shared below (Table 1).

According to the data obtained from Kaplan-Meier graphs drawn to calculate the overall OS and PFS times of the study group, the median PFS was 296 days, and the 95% confidence interval (CI) was calculated as 149–442 days. The mean OS was calculated as 1217 ± 117 days in the study group, which did not reach the median duration in OS. In our study group, 1-year PFS was 46.1 ± 7.9%, while 4-year PFS was calculated as 20.5 ± 8.4%. The 1-year OS was 92.5 ± 4.2%, while the 4-year OS was 52.4 ± 10.5%.

**68Ga-PSMA PET-CT findings**
When the $^{68}$Ga-PSMA PET/CT images of the patients in the study group were examined, 38 (90.47%) lymphatic, 36 (85.71%) skeletal system, and 9 (21.42%) visceral organ metastases were detected.

A total of 10 different semi-quantitative parameters were calculated for each patient, 5 of which reflect the primary lesion and 5 reflect the whole-body data on $^{68}$Ga-PSMA PET/CT images. The median (minimum-maximum) values of the metabolic semi-quantitative data obtained throughout the study group are presented in Table 2.

**Univariate analysis**
A statistically significant difference was found in terms of PFS in the groups above and below the determined threshold values for Basal PSA, Nadir PSA, second-generation anti-androgens use, PSMA-TV (primary), TL-PSMA (primary), SUVmax (WB), PSMA-TV (WB), and TL-PSMA (WB) variables. In the analyses for OS, there was a statistically significant difference between the groups above and below the threshold values determined for Nadir PSA, PSMA-TV (primary), TL-PSMA (primary), PSMA-TV (WB), TL-PSMA (WB), and ECOG scores. The threshold values used in these analyses, their sensitivities, specificities, and all p values obtained are presented in Table 3.

**Multivariate analysis**
In the correlation analysis, no more than 60% correlation was found between the variables and it was accepted that there was no multicollinearity problem. Thereupon, Cox HR regression analysis was performed for PFS and OS in separate groups.

Among the variables included in the model studied for PFS, only the SUVmax(WB) variable was found to be statistically significant ($P = 0.037$). The HR calculated for the SUVmax (WB) variable was 16.24 and the 95% CI was found to be 1.18–22.76. (Fig. 2) According to this data obtained, the probability of progression in the group with SUVmax (WB) > 17.74 during the follow-up period in the study group was calculated as 16.24 times that of the group with SUVmax (WB) < 17.74 (Table 4).

Among the variables included in the studied model for OS, only PSMA-TV (primary) and PSMA-TV (WB) variables were found to be statistically significant (p values 0.048 and 0.011, respectively). HR, calculated for PSMA-TV (primary), which is one of the statistically

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Table 1  Demographic and clinical characteristics of the patients

| Age, mean ± SD (years) | 63.52 ± 9.36 |
|------------------------|-------------|
| Pre-DTX PSA level (ng/ml), median (range) | 77.75 (0.37–2314.64) |
| Nadir PSA value after DTX (ng/ml), median (range) | 0.76 (0.01–808.79) |
| Time interval between biopsy and PET-CT (days), mean ± SD | 20.12 ± 8.45 |
| Time interval between PET BT and DTX treatment (days), mean ± SD | 16.82 ± 6.46 |
| ECOG 0 | 15 (35.71%) |
| 1 | 27 (64.29%) |
| 2 | 0 (0%) |
| ISUP 3 | 3 (7.14%) |
| 4 | 13 (30.95%) |
| 5 | 26 (61.9%) |
| Other treatments |  |
| Palliative RT before DTX n(%) | 14 (33.3%) |
| Palliative RT after DTX n(%) | 16 (38.09%) |
| Second-generation anti-androgens after DTX, n (%) | 15 (35.71) |
| Progression, n (%) | 28 (66.6%) |
| Death, n (%) | 13 (30.95) |

Table 2  PET-BT-based variables (median, maximum, minimum)

| Variables                  | Median | Maximum | Minimum |
|---------------------------|--------|---------|---------|
| SUVmax (primary)          | 14.08  | 77.34   | 3.39    |
| SUVmean (primary)         | 6.71   | 26.53   | 1.76    |
| SUVpeak (primary)         | 10.52  | 55.95   | 2.96    |
| PSMA-TV (primary) (cm³)    | 16.35  | 421.00  | 5.33    |
| TL-PSMA (primary)         | 136.95 | 1371.31 | 16.24   |
| SUVmax (WB)               | 29.26  | 113.53  | 4.33    |
| SUVmean (WB)              | 7.01   | 20.66   | 1.46    |
| SUVpeak (WB)              | 20.30  | 88.91   | 5.19    |
| PSMA-TV (WB) (cm³)        | 243.20 | 2967.00 | 41.74   |
| TL-PSMA (WB)              | 1356.65| 26 020.59| 131.54  |
significant variables, was found to be 6.31, and the 95% CI was 1.01–39.18. (Fig. 3) According to this data, the probability of death in the group with PSMA-TV (primary) > 19.91 cm³ during the follow-up period in the study group was found to be 6.31 times that of the group with PSMA-TV (primary) < 19.91 cm³. HR, calculated for PSMA-TV (WB), which was another significant variable, was found as 58.62 and the 95% CI was 2.55–1344.43. (Fig. 4) According to the data obtained, the probability of death in the group with PSMA-TV (WB) > 1226.5 cm³ during the follow-up period in the study group was 58.26 times higher than in the group with PSMA-TV (WB) < 1226.5 cm³ (Table 5).

Among the variables evaluated in the study group, PSMA-TV (primary) and PSMA-TV (WB) variables stand out as independent negative predictors for OS and SUVmax (WB) variables for PFS. The survival times and p values calculated for the threshold values for these variables are presented in Table 6.

Discussion

Since the majority of PCa patients are not metastatic at the time of the first diagnosis, the treatment approach includes definitive treatments such as radiotherapy or surgery. However, the patient group that is metastatic at the time of diagnosis or later, requires a different approach in terms of treatment. The only data in the literature on OS obtained under ADT + DTX in the de-novo high-volume mCSPC group, on which was focused in our study, is presented in the article in which the long-term results of the prospective CHAARTED study were published. Based on the data in this article, OS achieved in the de-novo high-volume mCSPC group is 48 months [11]. The median OS of 1217 days (40.56 months) obtained in our study group is significantly lower than that was obtained in the literature. In our study, the median PSMA-TV (WB) value was found to be 243.2 cm³ and the difference between the literature and our study group is thought to be due to this high tumor burden.

Almost all studies in the literature on mCSPC patients focus on the efficacy of combined therapies, as well as the different levels of benefit that low-volume and high-volume patient groups from these treatments [3,4,12]. However, another crucial issue here is the different treatment responses of these groups within themselves. Our current study differs from the literature because it evaluates the high-volume group within itself and draws attention to this heterogeneity. In our study, the HR calculated in terms of OS between the groups above and below the threshold value of 1226.5 cm³ obtained in PSMA-TV (WB) value was found to be 58.62 and 95% CI 2.55–1344.43. This finding indicates that, within the broadly described high-volume disease group, a subgroup (the group with a total tumor volume in the body >1226.5 cm³) can be differentiated, with a worse prognosis than the general group despite standard treatment (Figs. 5 and 6).

Studies in the nuclear medicine literature generally focus on treatment response and the number of studies investigating OS and PFS are limited. In a study examining the response to DTX treatment and survival data in metastatic castration-resistant PCa (mCRPC) patients, it was found that high TV-PSMA (P = 0.024), high age (P = 0.016), and increased LDH (P < 0.001) values were negative predictors for OS [13]. This study differs from

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### Table 3 Results of univariant analysis

| Variable                        | PFS          | OS           |
|---------------------------------|--------------|--------------|
|                                | Sensitivity  | Specificity  |
| **Threshold Value**             | **P-value**  | **Threshold Value** | **P-value** |
| Age (years)                     | 78.6%        | 28.6%        | 58.5          | 0.803        | 61.5%        | 72.4%        | 65.5          | 0.228        |
| Basal PSA (ng/ml)               | 85.7%        | 50%          | 24.56         | 0.001<sup>a</sup> | 84.6%        | 31.2%        | 24.56         | 0.096        |
| Nadir PSA (ng/ml)               | 82.1%        | 64.3%        | 0.028         | 0.000<sup>b</sup> | 69.2%        | 69.1%        | 0.1           | 0.038<sup>b</sup> |
| Pre-Treatment RT                |              |              | 0.54          | No/Yes        |              |              | 0.350         |              |
| Post-Treatment RT               |              |              | Yes/No        | 0.32          |              |              | Yes/No        | 0.836        |
| Second-generation Anti-androgens|              |              | Yes/No        | 0.012<sup>b</sup> |              |              | Yes/No        | 0.786        |
| SUVmax(primary)                 | 67.9%        | 0%           | 10.52         | 0.817        | 100.0%       | 89.7%        | 5.42          | 0.454        |
| SUVmean(primary)                | 89.3%        | 35.7%        | 3.64          | 0.352        | 84.5%        | 24.1%        | 3.84          | 0.743        |
| SUVpeak(primary)                | 78.6%        | 42.9%        | 7.17          | 0.751        | 100.0%       | 9.6%         | 3.55          | 0.633        |
| PSMA-TV(primary) (cm³)          | 57.1%        | 92.9%        | 18.83         | 0.012<sup>b</sup> | 76.9%        | 79.3%        | 19.91         | 0.006<sup>b</sup> |
| TL-PSMA(primary)                | 82.1%        | 78.6%        | 91.75         | 0.005<sup>b</sup> | 92.3%        | 51.7%        | 91.75         | 0.007<sup>b</sup> |
| SUVmax(WB)                      | 89.3%        | 50%          | 17.74         | 0.019<sup>b</sup> | 84.5%        | 34.5%        | 20.21         | 0.413        |
| SUVmean(WB)                     | 64.3%        | 64.3%        | 6.75          | 0.274        | 61.5%        | 48.3%        | 6.75          | 0.921        |
| SUVpeak(WB)                     | 82.1%        | 50%          | 12.07         | 0.112        | 76.9%        | 37.9%        | 13.43         | 0.452        |
| PSMA-TV(WB) (cm³)               | 75%          | 71.4%        | 169.35        | 0.001<sup>b</sup> | 53.8%        | 89.7%        | 1226.5        | 0.008<sup>b</sup> |
| TL-PSMA(WB)                     | 71.4%        | 85.7%        | 1173.61       | 0.000<sup>b</sup> | 38.50%       | 93.1%        | 10.828.5      | 0.016<sup>b</sup> |
| Intra-pelvic Lymphatic Metastasis|              |              | Yes/No        | 0.639        |              |              | Yes/No        | 0.858        |
| Extra-pelvic Lymphatic Metastasis|              |              | Yes/No        | 0.148        |              |              | Yes/No        | 0.840        |
| Bone Metastasis                 |              |              | Yes/No        | 0.051        |              |              | Yes/No        | 0.235        |
| Visceral Metastasis             |              |              | Yes/No        | 0.483        |              |              | Yes/No        | 0.291        |
| ECOG                           |              |              | 0/1           | 0.185        |              |              | 0/1           | 0.006<sup>b</sup> |
| Progression Time (days)         |              |              |              | 100.0%       |              |              | 3.4%          | 0.364        |

<sup>a</sup>P < 0.05.

<sup>b</sup>Nominal variables.
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Ours by involving patients with mCRPC and not focusing on the distinction between LV and HV. The TV-PSMA variable (corresponding to the PSMA-TV (WB) variable in our study), which was found to be significant in terms of time to progression, was not found to be significant in terms of PFS in our study. In another study in the literature, Zou et al. found TL-PSMA (WB) and Gleason score as predictive variables for PFS [14]. However, when the composition of the study group is examined, it is seen that 29 of the 59 patients showed involvement only in the prostate. The difference between the patient groups in these cited studies and our study makes it difficult to compare the results obtained individually, and it is understood that prospective studies with larger series are needed in this area.

Although there is a consensus on the prognostic value of whole-body tumor volume, there is an ongoing debate on the predictive value of primary tumor volume. Studies have shown that primary tumor volume has no effect on survival in groups with low Gleason scores or does not show any correlation with survival data [15]. However, it has been demonstrated by studies on pathology preparations that, as the Gleason score of the disease increases, there appears a significant relationship between survival and tumor volume, especially in moderate and high-risk local diseases [16]. For instance, in a study by Knoedler et al., 13,687 patients were monitored for an average of 9.4 years and it was shown that primary tumor volume was associated with the risk of death (HR 1.29; \( P < 0.0001 \)) [17]. One of the crucial points here is how the tumor volume is measured. While the majority of studies in the literature reporting that primary tumor volume is not a predictor of survival data are based on the visual evaluation included in pathology reports [18], it is noticed that computer-based methods are generally used in studies that indicate a statistically significant relationship [16,17]. Therefore, it is necessary to be cautious about the studies performed with methods such as visual evaluation, which do not have sufficient accuracy in the evaluation of primary tumor volume. The problems encountered in the previous literature are not limited to our study because we used computer algorithms based on the focus with the highest PSMA uptake and calculating the PSMA uptake areas determined over these as independent voxels.

Table 4 Multivariate analysis (PFS)

| Variable                                      | P-value | HR     | 95% CI for HR     |
|-----------------------------------------------|---------|--------|-------------------|
| Basal PSA                                     | 0.244   | 2.604  | 0.520 13.035      |
| ECOG                                          | 0.355   | 0.606  | 0.210 17.53       |
| Nadir PSA                                     | 0.120   | 3.905  | 0.701 21.769      |
| Second-generation anti-androgens             | 0.268   | 2.695  | 0.812 8.946       |
| PSMA-TV (primary) (cm³)                       | 0.105   | 2.639  | 0.121 33.84       |
| TL-PSMA (primary)                             | 0.037   | 16.241 | 1.184 222.767     |
| SUVmax (WB)                                   | 0.055   | 0.102  | 0.010 10.53       |
| SUVpeak (WB)                                  | 0.777   | 0.747  | 0.100 5.607       |
| TL-PSMA (WB)                                  | 0.192   | 2.847  | 0.591 13.723      |
| Extra-pelvic lymphatic metastasis             | 0.148   | 23.424 | 0.740 74.13       |
| Bone metastasis                               | 0.145   | 63.90  | 0.527 77.505      |

Kaplan–Meier plot: SUVmax (WB) – time to progression.
It has long been known that there is an inverse relationship between tumor burden and survival of patients. The PSMA-TV (WB) parameter, which is used to calculate the whole-body tumor burden thanks to $^{68}$Ga-PSMA PET/CT, provided results that support and make usable our basic knowledge of tumor biology in this respect. Especially in staging patients who have not received treatment before, when homogenization is provided in terms of treatment, it is seen that the whole-body tumor burden at baseline is an independent predictor of OS. One of the striking findings in our study is that TL-PSMA was not found to be statistically significant, while the concomitant PSMA-TV value was significant. As can be seen in the literature, although not in terms...
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of survival, it is known that these variables correlate in clinical situations such as progression detection and treatment response failure [7,10,19–21]. In our study group, mild to moderate PSMA uptake was detected especially in patients with extensive bone metastases and we conclude that this might have affected the correlation between PSMA-TV and TL-PSMA values in the study.

When the median follow-up time of our study and the inaccessibility of median survival especially in low-volume groups are taken into account, it can be deduced that evaluations with longer follow-up results will be beneficial. Another one of our serious limitations is that our study group did not include many patients with the HV disease and a low tumor burden in volumetric calculations. Series with a more balanced volumetric distribution, including this subgroup, can provide more detailed data. The retrospective nature of our study was also one of our most important limitations. It is clear that this study, which was conducted with 42 patients, needs to be supported by prospective studies with larger series. Due to the threshold measurement being a data-dependent method, this kind of small group can increase

### Table 5  Multivariant analysis (OS)

|                          | P-value | HR       | 95% CI for HR Lower bound | Upper bound |
|--------------------------|---------|----------|--------------------------|-------------|
| Age                      | 0.162   | 1.084    | 0.968                    | 1.213       |
| Basal PSA                | 0.427   | 2.313    | 0.292                    | 18.339      |
| Nadir PSA                | 0.219   | 0.286    | 0.039                    | 2.093       |
| PSMA-TV (primary) (cm³)  | 0.048   | 63.18    | 10.19                    | 39.187      |
| TL-PSMA (primary)        | 0.767   | 1.427    | 0.136                    | 15.001      |
| PSMA-TV (WB) (cm³)       | 0.011   | 58.629   | 2557                     | 1344.439    |
| TL-PSMA (WB)             | 0.869   | 1237     | 0.099                    | 15.500      |
| Bone metastasis          | 0.984   | 3785.491 | 0.000                    | N/A         |
| ECOG                     | 0.936   | 1519.3972| 0.000                    | N/A         |

### Table 6  Variables that were significant at the end of the multivariate analysis and the survival times obtained

| Threshold               | OS                | P-value |
|-------------------------|-------------------|---------|
| PSMA-TV (primary)       |                   |         |
| >19.91 cm³              | 759 (641–876) days| 0.048   |
| <19.91 cm³              | 1299.55 ± 95.25 days|         |
| PSMA-TV (WB)            |                   |         |
| >1226.5 cm³             | 519 (61–398) days| 0.011   |
| <1226.5 cm³             | 1364.34 ± 135.91 days|         |
| Threshold SUVmax (WB)   |                   |         |
| >17.74                  | 263 (22–218) days| 0.037   |
| <17.74                  | 490 ± 19.15 days  |         |

*Survival statistics are given as mean ± SD instead of the median (range) in subgroups whose median survival time could not be reached.
the risk of bias. This must also consider an important limitation.

In our study, in which metabolic data obtained from $^{68}$Ga-PSMA PET/CT imaging were examined, it was found that SUVmax (WB) in terms of PFS and PSMA-TV (primary) and PSMA-TV (WB) variables in terms of OS had negative predictive values. Our study makes us think that de-novo high-volume mCSPC patients can be a heterogeneous group within themselves. In terms of treatment response, namely OS, this group can be divided into subcategories on the basis of metabolic volumes.

In this context, LV–HV disease definitions based on assessment of the extent of the disease in the body with conventional methods are insufficient when classifying the patient group. Cutting-edge diagnostic tools like $^{68}$Ga-PSMA PET/CT stands out as an important potential that can fill the gap in this area.

PCa is a popular topic in medical oncology and nuclear medicine. Understanding that a part of the high-volume group, which was thought to benefit from chemotherapy in the classical approach, did not benefit at the expected level may bring up new approaches to those patients. From a nuclear medicine perspective, this group of patients can be considered as a significant potential in the of beta and alpha therapies. While we hope that our study may be inspirational in this respect, we anticipate that this subject will be investigated in further studies.

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Conflicts of interest

There are no conflicts of interest.

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