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A Comprehensive Analysis of Volumetric ^{68}Ga-PSMA PET/CT Parameters, Clinical and Histopathologic Features: Evaluation of the Predictive Role

Volümetrik ^{68}Ga-PSMA PET/BT Parametreleri, Klinik ve Histopatolojik Özelliklerin Kapsamlı Bir Analizi: Prediktif Rolün Değerlendirilmesi

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Abstract

Objectives: To evaluate the relationships between volumetric ^{68}Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) parameters, Gleason score (GS), prostate-specific antigen (PSA) levels, histopathological data, and metastatic status in newly diagnosed prostate cancer (PCa) patients and to assess the predictive factors for progression despite treatment.

Methods: A total of 78 newly diagnosed patients with PCa who had ^{68}Ga-PSMA PET/CT scans were included. Clinical parameters, histopathological data, and metastatic status were documented, and volumetric parameters of primary prostate lesions were measured. All obtained data were compared statistically.

Results: Primary prostate tumor maximum standardized uptake value (SUV_{max}) and GS were significantly related to serum PSA levels ($p<0.05$). PSA levels and SUV_{max} values were significantly higher in patients with lymph node metastases than in those without. GS was found to be significantly increased in metastatic patients. PSMA-derived tumor volume (PSMA-TV) and total lesion PSMA of the primary lesion had a significant relationship with PSA value, GS, and regional lymph node metastases. Receiver operating characteristic analysis, conducted in patients with metastatic and localized disease, identified the cutoff value for SUV_{max} as 10.85. According to the results of the logistic regression analysis, PSMA-TV was found to be a predictive factor for progression despite treatment.

Conclusion: ^{68}Ga-PSMA PET/CT remains an invaluable imaging modality that should be considered first in PCa staging because of its superior compatibility with clinical and histopathologic data. The importance of this method goes beyond diagnostic accuracy; it also extends into the predictive domain, where the PSMA-TV value of primary prostate lesions is a potential predictor of treatment efficacy. This information is valuable for personalizing patient treatment, improving prognostic accuracy, and predicting clinical outcomes.

Keywords: ^{68}Ga-PSMA PET/CT, prostate cancer, volumetric parameters

Öz

Amaç: Bu çalışmanın amacı yeni tanı konmuş prostat kanseri (PKa) hastalarında volümetrik ^{68}Ga-prostat-spesifik membran antijeni (PSMA) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) parametreleri, Gleason skoru (GS), prostat-spesifik antijeni (PSA) düzeyleri, histopatolojik veriler ve metastatik durum arasındaki ilişkileri ve prediktif faktörleri değerlendirmektir.

Yöntem: ^{68}Ga-PSMA PET/BT taramaları yapılmış toplam 78 yeni tanı PKa hastası çalışmaya dahil edildi. Klinik parametreler, histopatolojik veriler ve metastatik durum belgelendi ve prostat bezindeki primer tümörden elde edilen volümetrik parametreler ölçüldü. Elde edilen tüm veriler istatistiksel olarak karşılaştırıldı.

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Bulgular: GS ve primer prostat tümöründen elde edilen maksimum standardize tutulum değeri (SUV_{maks}), serum PSA düzeyleri ile anlamlı olarak ilişkiliydi (p<0,05). PSA düzeyleri ve SUV_{maks} değerleri lenf nodu metastazı olan hastalarda olmayanlara göre anlamlı olarak daha yüksekti. GS metastatik hastalarda anlamlı olarak yüksek bulundu. Primer lezyonun PSMA-tümör volümü (PSMA-TV) ve total lezyon-PSMA değerlerinin PSA değeri, GS ve bölgesel lenf nodu metastazları ile anlamlı ilişkisi vardı. Metastatik ve lokalize hastalığı olan hastalarda yapılan alıcı işletim karakteristik analizi, SUV_{maks} için kesim değerini 10,85 olarak belirlemiştir. Lojistik regresyon analizi sonuçlarına göre, PSMA-TV progresyon için prediktif bir faktör olarak bulunmuştur.

Sonuç: ^{68}Ga-PSMA PET/BT, klinik ve histopatolojik verilerle üstün uyumluluğu nedeniyle PKa evrelemesinde ilk olarak düşünülmesi gereken çok değerli bir görüntüleme yöntemi olmaya devam etmektedir. ^{68}Ga-PSMA PET/BT'nin klinik yeri ve önemi, sadece tanısal doğruluğu ile sınırlı değildir. ^{68}Ga-PSMA PET/BT'den elde edilen primer prostat lezyonunun PSMA-TV değeri tedavi başarısını öngörebilecek potansiyel bir gösterge olarak önem taşımaktadır. Bu bilgi, hasta tedavisini kişiselleştirmek, prognostik doğruluğu artırmak ve klinik sonuçları tahmin etmek için değerlidir.

Anahtar kelimeler: ^{68}Ga-PSMA PET/BT, prostat kanseri, volümetrik parametreler

Introduction

Prostate cancer (PCa) is the most common cancer in men in the United States and the second most common cancer in men worldwide (1,2). Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein with overexpression in most PCa cells and is of increasing interest as a target molecule for imaging and treatment (3). Gallium-68-PSMA (^{68}Ga-PSMA) [Glu-NH-CONH-Lys-(Ahx)-[Ga-68(HBED-CC)] positron emission tomography/computed tomography (PET/CT) scan is an advanced and promising imaging method having high sensitivity in determining lesions of PCa with a high tumor-to-background ratio (4). ^{68}Ga-PSMA PET/CT has been used with increasing frequency in recent years for staging, restaging, and treatment response evaluation in patients with PCa. ^{68}Ga-PSMA PET/CT shows higher diagnostic accuracy for restaging during biochemical recurrence and is superior to conventional imaging modalities in the preoperative staging of PCa (5). Classifying patients with PCa according to their risk status affects treatment management and makes an important contribution to predicting the response to treatment. Gleason score (GS) and serum prostate-specific antigen (PSA) levels are accepted as strong predictors of prognosis in patients with PCa and play an important role in clinical treatment (6). PCa risk classification criteria are generally based on clinical stage, GS, and pretreatment PSA levels. A detailed risk classification has been published by D'Amico et al. (7) low-risk group (PSA ≤10 ng/mL and GS ≤6 and T1-T2a), intermediate-risk group (PSA 10-20 ng/mL or GS 7 or T2b), and high-risk group (PSA >20 ng/mL or GS ≥8 or ≥T2c). With the widespread use of ^{68}Ga-PSMA PET/CT, studies have shown that increased PSMA expression is correlated with GS and the development of metastatic disease (8,9). The maximum standardized uptake value (SUV_{max}) is the most commonly used semi-quantitative parameter in PET/CT to assess tumor burden. However, SUV_{max} is not the only volumetric parameter obtainable in ^{68}Ga-PSMA PET/CT. PSMA-derived tumor volume (PSMA-TV) and total lesion PSMA (TL-PSMA) can also be calculated. There are clinical studies stating that ^{68}Ga-PSMA PET/CT results are highly predictive of treatment response (10,11). Volumetric analysis of ^{68}Ga-PSMA PET/CT in newly diagnosed PCa patients can provide comprehensive insights into tumor characteristics, aid in treatment planning, and predict clinical outcomes. This information is invaluable for personalizing patient care and improving prognostic accuracy (12,13).

In this study, we aimed to measure primary lesion SUV_{max}, PSMA-TV, and TL-PSMA; and to evaluate the relationships among volumetric parameters, GS, PSA levels, histopathological data, and metastases status in newly diagnosed PCa patients. Another endpoint of our study was the evaluation of the possible predictive role of volumetric ^{68}Ga-PSMA PET/CT parameters for clinical, radiological, or biochemical progression.

Materials and Methods

We retrospectively evaluated 78 patients with PCa who underwent ^{68}Ga-PSMA PET/CT for staging. All patients had a diagnosis of prostate adenocarcinoma by 10-12 core transrectal ultrasonography (TRUS)-guided prostate biopsy (bx) before imaging. All patients had PSA levels measured at most 3 weeks before the ^{68}Ga-PSMA PET/CT scan. Patients with missing laboratory or pathological data, treated for PCa, and in whom the primary tumor was indistinguishable from the surrounding prostate tissue were not included. This study protocol was reviewed and approved by the Manisa Celal Bayar University Health Sciences Ethics Committee (decision no: 20.478.486/506, date: 19.08.2020). Informed consent was obtained from all subjects when they were enrolled.

Preparation of the PSMA-targeting Ligand

^{68}Ga-PSMA I&T was synthesized by a fully automated, good manufacturing practice-a compliant procedure using a good radiopharmaceutical practice module (ITG iQS-TS)

connected to a 68Ge/68Ga generator (1.11-GBq, ITM) and equipped with a disposable single-use cassette kit. A standardized labeling sequence with 25 µg of unlabeled PSMA I&T was used. The synthesis of the ^{68}Ga peptides was performed using a cationic purification method with 25 µg of peptide used for the reaction. The labeling efficiency and radiochemical purity (≥95%) were determined using radio-high-performance liquid chromatography.

Image Acquisition and Reconstruction

Patient preparation, acquisition protocols, and reconstruction parameters were standardized for all patients. Sixty minutes after the intravenous injection of 2.2-2.5 MBq/kg ^{68}Ga-PSMA, the patients were scanned from the vertex to the proximal thigh, and low-dose CT (120 kVp and 80 mAs) and PET [Philips TrueFlight Select model, lutetium yttrium orthosilicate crystals; 3-dimensional acquisition; 180 s per bed position (s/bp); 5-6 bed positions] images were obtained. CT was obtained for attenuation correction. The ordered subset expectation maximization reconstruction algorithm was used with reconstruction parameters of three iterations and 33 subsets.

Image Analysis

Images were evaluated by two experienced nuclear medicine physicians blinded to the pathological and laboratory results. Any disagreement was resolved by consensus. Focal or diffuse ^{68}Ga-PSMA uptake in the prostate gland was identified as the primary lesion. Lesions with a ^{68}Ga-PSMA uptake higher than that in the blood pool and discordant with the physiological distribution were considered metastases. Regional lymph node (RLN), extra-regional lymph node (ERLN), bone, and visceral organ metastases were determined. Using a three-dimensional segmentation method, an isodontous volume of interest was created around the prostate gland, avoiding bladder activity, to calculate the volumetric parameters (Figure 1). Primary tumor TL-PSMA was calculated by multiplying PSMA-TV by the mean standardized uptake value (SUV_{mean}).

Statistical Analysis

The data obtained were entered into SPSS version 23.0 (IBM, Türkiye), and a p-value of 0.05 was considered statistically significant. Quantitative variables were described using means, standard deviations, and ranges. Mean comparisons between the groups were performed using one-way ANOVA for the quantitative variable. The relationships between the D'Amico risk groups and metastatic status were analyzed using the chi-square test. Correlations between different parameters were analyzed using the Pearson correlation test. Receiver operating characteristic (ROC) analysis was used to determine the cut-off values of SUV_{max}, PSMA-TV, and TL-PSMA for metastatic and non-metastatic patients. Possible predictive factors for clinical and biochemical recurrence were evaluated using logistic regression analysis.

Results

Patients were classified according to the D'Amico risk stratification system. The majority of patients (n=51) (65.4%) in our study were in the high-risk group. Nineteen patients (24.3%) were in the intermediate-risk group and eight patients (10.3%) were in the low-risk group. ^{68}Ga-PSMA PET/CT and PSA tests were performed within 3 weeks. The mean PSA level was 45.2 ng/mL. Descriptive characteristics are presented in Table 1. We observed

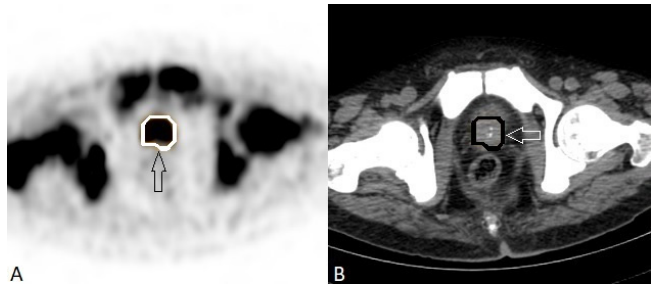

Figure 1. ^{68}Ga-PSMA PET/CT axial PET (A) and axial CT (B) images. A volume of interest was drawn around the prostate lesion (arrow)
^{68}Ga-PSMA: ^{68}Ga-prostate-specific membrane antigen, PET/CT: Positron emission tomography/computed tomography

Table 1. Distribution of descriptive characteristics

Parameter	Value
Patients (n)	78
Age	
Mean ± SD	68.5±7.3 years
Range	49-87 years
PSA	
Range	3.3-277 ng/mL
Gleason score (GS)	
GS6	10 (12.8%)
GS7	26 (33.3%)
GS8	12 (15.4%)
GS9	23 (29.5%)
GS10	7 (9%)
D'Amico risk stratification	
High-risk	51 (65.4%)
Intermediate-risk	19 (24.3%)
Low-risk	8 (10.3%)

SD: Standard deviation, PSA: Prostate-specific antigen

significant relationships between GS, SUV_{max}, and PSA levels ($p<0.05$). Of the patients included in the study, 29 (37.2%) had bone metastases (BM), and most of the ^{68}Ga-PSMA uptake observed in the bones was sclerotic on CT (Figure 2). However, pathological ^{68}Ga-PSMA accumulations that could not be detected on CT were also observed. These patients were considered highly suspicious of metastases. Magnetic resonance imaging (MRI) correlation was performed for these patients, and bone marrow infiltration on MRI was considered positive for BM. Visceral organ involvement was detected only in the lungs and was observed in 7 (9.0%) patients. Five of these seven patients had concomitant BM. When patients with and without BM were compared, differences were significant between the two groups in terms of PSA, SUV_{max}, and SUV_{mean} ($p=0.000$, $p=0.008$, and $p=0.003$, respectively). When patients with and without lung metastases (LM) were compared, a significant difference was detected only in PSA values ($p=0.002$). However, no statistically significant difference was detected between LM and SUV_{max}. We believe that this result is due to the small number of patients with LM in our study group. Isolated RLN metastases were observed in 42 of 78 (53.8%) patients. ERLN metastases were observed in 23 (29.5%) patients, and all were accompanied by RLN metastases. When the presence of ERLN and RLN metastases were compared with the SUV_{max} of the primary lesion, significant relationships were found ($p<0.05$). The mean PSA value was significantly higher in patients with RLN metastases (63.6±66.6) compared to those without lymph node metastases (23.65±32.3, $p=0.002$), and similarly, patients with ERLN metastases showed a significantly higher mean PSA value (82.9±69.2) than those without ERLN metastases (29.37±42.5, $p<0.05$). When the relationships between GS and the presence of lymph node, bone, and visceral organ metastases were examined, the sum of GS was statistically significantly increased in patients with positive metastases ($p<0.05$). We also analyzed the risk groups of patients with metastases and observed that the majority were in the high-risk group, which was an expected finding. This analysis revealed statistically significant differences between the presence of pelvic, extrapelvic, and BM and risk groups ($p=0.001$, $p=0.001$, $p=0.002$, respectively). Primary lesion PSMA-TV and TL-PSMA were compared with PSA, LM, BM, GS, and lymph node metastases. Significant relationships were observed when the PSA and GS levels of the patients were compared with PSMA-TV and TL-PSMA ($p<0.05$). When PSMA-TV and TL-PSMA were compared with the presence of bone, lung, and ERLN metastases, the relationships were not statistically significant ($p\geq0.05$). Considering the metastatic status, a significant relationship was found between the parameters defined only with RLN metastases ($p<0.05$). The mean values of PSA, SUV_{max}, and SUV_{mean} according to metastasis status are summarized in Table 2. Statistical comparisons were made according to the histopathological data such as extraprostatic extension (EPE), lymphovascular invasion (LVI), and perineural invasion (PNI) reported in the TRUS-bx results. When PSA level, SUV_{max}, SUV_{mean}, PSMA-TV, and TL-PSMA were compared with histopathological data, significant relationships were observed between all except PNI and TL-PSMA (Table 3). The SUV_{max}, PSMA-TV, and TL-PSMA cut-off values of 37 metastatic (ERLN, bone, or LM) patients were determined by ROC analysis. Area under the curve (AUC) was significant at 0.770 [95% confidence interval (CI): 0.66-0.87, $p\leq0.001$], and the SUV_{max} cut-off value was 10.85, yielding a sensitivity of 83.8% and a specificity of 63.4%. Furthermore, ROC analysis was performed for PSMA-TV and TL-PSMA, and statistically significant results were found (PSMA-TV cut-off: 33.05, AUC=0.796, 95% CI: 0.69-0.89, $p\leq0.001$, sensitivity 73%, specificity 75.6%) (TL-PSMA cut-off: 136.65, AUC=0.820, 95% CI: 0.72-0.91, $p\leq0.001$, sensitivity 75.7%, specificity 75.6%). In addition, we calculated correlation coefficients (r) for the variables we controlled. According to Table 4, the most correlated variables are observed as such; RLN-LVI (r: 0.658; $p<0.01$), ERLN-LVI (r: 0.566; $p<0.01$), and SUV_{max}-LVI (r: 0.543; $p<0.01$). The median follow-up time after ^{68}Ga-PSMA PET/CT was 45 months (interquartile range 34-52 months). The treatments that the patients received after staging are detailed in Table 5. There was no clinical, radiological, or biochemical evidence of progression in 46

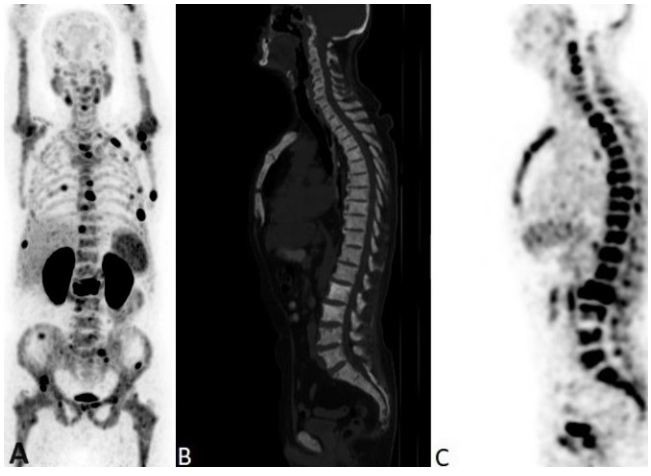

Figure 2. ^{68}Ga-PSMA PET/CT with maximum-intensity projection (A), sagittal CT (B), and sagittal PET (C) images of a 75-year-old patient with PCa (GS 5+5) with a PSA level of 64.0 ng/mL. ^{68}Ga-PSMA PET/CT images showed multiple sclerotic bone metastases

^{68}Ga-PSMA: ^{68}Ga-prostate-specific membrane antigen, PET/CT: Positron emission tomography/computed tomography, PCa: Prostate cancer, PSA: Prostate-specific antigen

Table 2. Mean values of PSA, SUV_{max}, and SUV_{mean} according to metastasis status

	Non-metastatic	Regional lymph node metastases	Extra-regional lymph node metastases	Lung metastases	Bone metastases	Total
PSA (mean ± SD)	19.3±31.8	63.6±66.6	82.9±69.3	101.9±93.4	77.2±72.8	45.2±56.9
SUV_{max} (mean ± SD)	11.3±7.4	28.2±19.5	32.3±17.9	21.6±16.2	27.2±20.5	20.5±17.2
SUV_{mean} (mean ± SD)	4.3±1.5	8.4±4.9	9.5±4.4	7.9±4.3	8.4±5.3	6.6±4.2
N (number)	29	42	23	7	29	78

PSA: Prostate-specific antigen, SUV_{max}: Maximum standardized uptake value, SUV_{mean}: Mean standardized uptake value

Table 3. Statistical results for PSA, SUV_{max}, SUV_{mean}, PSMA-TV, TL-PSMA, and histopathological features

	PSA	SUV_{max}	SUV_{mean}	PSMA-TV	TL-PSMA
EPE	p=0.003	p=0.000	p=0.000	p=0.005	p=0.028
LVI	p=0.000	p=0.000	p=0.000	p=0.004	p=0.021
PNI	p=0.002	p=0.000	p=0.000	p=0.018	**p=0.076***

PSA: Prostate-specific antigen, PSMA-TV: PSMA-derived tumor volume, TL-PSMA: Total lesion PSMA, EPE: Extraprostatic extension, LVI: Lymphovascular invasion, PNI: Perineural invasion
*p≥0.05

Table 4. Correlation coefficients of the study variables

Variables	PSA	SUV_{max}	PSMA-TV	TL-PSMA	RLN	ERLN	EPE	LVI	PNI
1. PSA	-	0.387 (0.00**)	0.408 (0.00**)	0.344 (0.00**)	0.352 (0.00**)	0.431 (0.00**)	0.393 (0.00**)	0.452 (0.00**)	0.345 (0.00**)
2. SUV_{max}	-	-	0.700 (0.00**)	0.630 (0.00**)	0.487 (0.00**)	0.448 (0.00**)	0.497 (0.00**)	0.543 (0.00**)	0.420 (0.00**)
3. PSMA-TV	-	-	-	0.962 (0.00**)	0.292 (0.01**)	0.192 (0.09)	0.322 (0.00**)	0.330 (0.00**)	0.271 (0.02*)
4. TL-PSMA	-	-	-	-	0.222 (0.05)	0.097 (0.39)	0.251 (0.03*)	0.264 (0.02*)	0.206 (0.07)
5. RLN	-	-	-	-	-	0.599 (0.00**)	0.525 (0.00**)	0.658 (0.00**)	0.404 (0.00**)
6. ERLN	-	-	-	-	-	-	0.434 (0.00**)	0.566 (0.00**)	0.440 (0.00**)
7. EPE	-	-	-	-	-	-	-	0.403 (0.00**)	0.303 (0.00**)
8. LVI	-	-	-	-	-	-	-	-	0.439 (0.00**)
9. PNI	-	-	-	-	-	-	-	-	-

*Denotes p<0.05 and **denotes p<0.01 significance levels. PSA: Prostate-specific antigen, SUV_{max}: Maximum standardized uptake value, PSMA-TV: PSMA-derived tumor volume, TL-PSMA: Total lesion PSMA, RLN: Regional lymph node, ERLN: Extra-regional lymph node, EPE: Extraprostatic extension, LVI: Lymphovascular invasion, PNI: Perineural invasion

Table 5. Initial treatments of the study group	
Initial management	**Number of patients**
RP (+/- lymph node dissection)	6
ADT + EBRT	20
EBRT	6
RP (+/- lymph node dissection) + EBRT	11
ADT	17
RP (+/- lymph node dissection) + EBRT + ADT	5
RP (+/- lymph node dissection) + ADT	8
ADT + chemotherapy	5

RP: Radical prostatectomy, EBRT: External beam radiotherapy, ADT: Androgen deprivation therapy

(59%) participants. Thirty-two (41%) patients progressed despite treatment, and four of these died during follow-up. Lesion SUV_{max}, PSMA-TV, TL-PSMA, and histopathological parameters were evaluated as predictive factors for progression. According to the logistic regression analysis results, PSMA-TV was determined to be a significant predictive factor for clinical, radiological, or biochemical progression ($p<0.05$). When histopathological parameters were evaluated, the coexistence of positive PNI and EPE was statistically predictive of progression.

Discussion

Numerous studies have highlighted the critical role of ^{68}Ga-PSMA PET/CT in restaging patients with biochemical recurrence. However, accurate initial staging is critical to improve prognosis and treatment strategies. Studies indicate that ^{68}Ga-PSMA PET/CT is superior to conventional imaging modalities in initial staging and altering the disease stage (14-17). The consensus from these investigations suggests adopting PSMA-PET as the primary modality for initially staging intermediate-high-risk PCa (18).

GS, PSA levels, and ^{68}Ga-PSMA PET/CT parameters are used to determine the risk status of newly diagnosed PCa patients (19). The combined evaluation of clinical and ^{68}Ga-PSMA PET/CT-derived parameters during initial staging would be more valuable in predicting risk status. Despite TRUS-bx being the standard method for obtaining pre-treatment GS, it potentially underestimates the true GS because of sample under-representation. However, our findings indicate a significant relationship between GS, PSA levels, and prostate lesion SUV_{max}. We also found significant relationships between the presence of lymph node metastases and SUV_{max} and PSA levels. In addition, SUV_{max} and PSA levels were significantly higher in patients with BM than in those without metastases. We also investigated the association between GS and the presence of lymph node, bone, and visceral organ metastases. The sum of GS was significantly increased in patients with metastases ($p<0.05$). Researchers assessed the correlations between SUV_{max}, GS, and PSA levels in newly diagnosed PCa patients, and similar to our results, they revealed significant relationships between PSA values, SUV_{max}, and GS (6,20). Uprimny et al. (6) also found that the PSA level and prostate lesion SUV_{max} of patients with lymph node metastases were statistically higher than those without lymph node metastases; however, they stated that, unlike the PSA level, SUV_{max} and the presence of BM were not statistically related. We believe that this is primarily due to the small number of patients with BM in their study.

PET/CT volumetric parameters have gained importance in predicting the prognosis and response to treatment in oncological patients in recent years. Investigations have shown that PSMA-TV and TL-PSMA demonstrated significant correlations with GS and PSA levels. They considered that PSMA-derived volumetric parameters could be better quantitative imaging biomarkers for whole-body tumor burden (12,13). In our study, we investigated volumetric measurements of primary prostate lesions regardless of metastatic status and found significant relationships between SUV_{max}, PSMA-TV, and TL-PSMA with PSA and GS. Karyagar et al. (21) found that metastatic patients had significantly higher primary prostate lesion PSMA-TV and TL-PSMA than the non-metastatic group. In our study, we categorized the metastatic status as RLN metastases, ERLN metastases, LM, and BM. We observed significant associations between prostate lesion SUV_{max} and all metastatic conditions, except LM. In addition, PSMA-TV and TL-PSMA of prostate lesions were statistically higher in patients with RLN metastases than in those without ($p<0.05$). The cut-off SUV_{max} value for prostate lesions in terms of the metastatic or high-risk patient group has also been the subject of investigations. Two studies investigating SUV_{max} cut-off values for high-risk patients identified these as 9.1 and 10.55, respectively (8,22). In our study, in 37 metastatic patients, ROC curve analysis was performed to identify the cut-off values for SUV_{max}, PSMA-TV, and TL-PSMA, which were determined to be 10.85, 33.05, and 136.65, respectively. Additionally, we compared the volumetric parameters and clinical data of the patients with pathological features (EPE, LVI, and PNI) in the TRUS-bx results. PSA, SUV_{max}, PSMA-TV, and TL-PSMA were compared with histopathological data, and significant correlations were observed between all except PNI and TL-PSMA. PNI and TL-PSMA discordance are not clinically relevant or important to consider as our main findings. Based on the correlation coefficients, the high

correlation between SUV_{max} and LVI stands out as one of the meaningful and valuable outcomes of our study.

Clinicians face the challenge of delaying PCa progression while avoiding overtreatment. Therefore, the predictive value of volumetric parameters in newly diagnosed PCa is of great interest. While existing studies predominantly focus on whole-body volumetric parameters, our research investigates whether primary prostate lesion volumetric parameters can predict treatment response. Retrospective analyses suggest ^{68}Ga-PSMA PET/CT as a valuable tool for assessing therapy response in metastatic PCa, highlighting changes in quantitative volumetric tumor parameters, particularly PSMA-TV, as potential predictive and prognostic indicators for overall survival, thereby aiding in personalized treatment approaches (23-25). The patients included in our study were followed up with different treatment protocols. As a result of the analysis on whether volumetric parameters (SUV_{max}, PSMA-TV, TL-PSMA) obtained from pretreatment ^{68}Ga-PSMA PET/CT can predict progression, we concluded that only PSMA-TV has a place in predicting progression. Similarly, Karyağar et al. (26) conducted a study to ascertain whether pretreatment ^{68}Ga-PSMA PET/CT parameters could serve as indicators for predicting PSA response in metastatic castration-resistant prostate cancer patients undergoing enzalutamide treatment. Their findings indicated that PSMA-TV values are predictive of PSA response. In addition to volumetric parameters, we evaluated whether any of the histopathological parameters detected at biopsy (EPE, LVI, and PNI) played a role in predicting treatment failure. We concluded that none of these parameters alone had a predictive value, but the coexistence of positive PNI and EPE was predictive of progression. In other words, the simultaneous presence of these two conditions (PNI and EPE) was considered a strong predictor of treatment failure. Studies have been conducted on the predictive roles of histopathologic features in PCa treatment success and prognosis. In these studies, EPE has been acknowledged as a negative prognostic indicator that impacts both cancer progression and patient survival (27). However, research on the prognostic value of PNI has yielded conflicting results. PNI is a commonly observed pathway for tumor spread and is significant in the clinical management of PCa. PNI refers to the process by which cancer cells spread along nerve pathways. This method of tumor dissemination is frequently observed in patients with PCa and holds significant importance in its clinical management. Several studies have suggested that the presence of PNI should not automatically lead to more aggressive treatment strategies, but it could be an indicator of a higher risk of progression (28). Some researchers have mentioned that PNI is a predictive factor for disease progression, whereas others have emphasized that it plays no such role (27). The studies mentioned that the prognostic value of PNI is more important in biopsy specimens as it could affect treatment management decisions and surgical techniques. Moreira et al. (29) found that PNI in biopsies was associated with an increased risk of progression. However, Lee et al. (30) reported that PNI in a prostatectomy specimen was significantly related to biologically aggressive tumor patterns but was not a prognostic factor for PSA recurrence or cancer-specific survival in patients with PCa.

Study Limitations

Our study has several limitations. First, the pathologic data were exclusively derived from TRUS-bx, which may limit the generalizability of our findings. Second, the retrospective nature of our analysis. Third, the study was conducted in a single center with a relatively small patient cohort. To overcome these limitations and enhance the robustness of our conclusions, future research should conduct prospective, multicenter studies involving larger patient populations in this field.

Conclusion

PCa is the second most common cancer in men globally, making research in this field crucial. All clinical, histopathological, and imaging-based parameters and their relations with each other should be clarified, and the effect of these parameters on the course of the disease should be well known. Because of its high diagnostic accuracy and superiority over conventional imaging methods, ^{68}Ga-PSMA PET/CT has become a milestone in the diagnosis and follow-up of PCa. Our research specifically targets the volumetric parameters of primary prostate lesions, thus addressing a gap in the existing literature. The relationships emphasized in our study underscore the potential of these parameters to synergistically contribute to a more comprehensive understanding of disease severity and progression. In conclusion, this retrospective analysis showed that ^{68}Ga-PSMA PET/CT retains its place as an invaluable imaging modality that should be considered first in PCa staging because of its superior compatibility with clinical and histopathological data. Our results indicate that the PSMA-TV value of a primary prostate lesion can predict treatment failure. This information is valuable for personalizing patient treatment, improving prognostic accuracy, and predicting clinical outcomes; therefore, we anticipate that ^{68}Ga-PSMA PET/CT will become a risk stratification tool in the management of this disease.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by the Manisa Celal Bayar University Health Sciences Ethics Committee (decision no: 20.478.486/506, date: 19.08.2020). Informed consent was obtained from all subjects when they were enrolled.

Informed Consent: Written informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: G.M., C.S.A., Concept: G.M., Y.P., C.S.A., Design: G.M., E.S., Data Collection or Processing: G.M., Y.P., C.S.A., G.G., Analysis or Interpretation: G.M., Y.P., E.S., Literature Search: G.M., G.G., Writing: G.M., E.S.

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