^{18}F-PSMA 1007 PET/CT Metrics for Assessment of Whole-Body Tumor Burden in Patients with Metastatic Prostate Cancer

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Abstract:

Background: Conventional assessment based solely on standardized uptake values (SUVs) of individual lesions may inadequately reflect the total tumor burden in patients suffering from metastatic prostate cancer (PCa). Prostate-specific membrane antigen (PSMA)-targeted PET/CT imaging enables the derivation of quantitative volumetric biomarkers that simultaneously reflect lesion volume, number, and metabolic activity.

Objective: Our objective was to validate PSMA-total volume (PSMA-TV) and -total lesion (PSMA-TL) as quantitative volumetric biomarkers for whole-body tumor burden in metastatic PCa and assess their relation to PSA and Gleason score (GS) to enhance risk stratification and disease monitoring.

Patients and Methods: Thirty-nine individuals with PSMA-positive metastatic PCa were included. Quantitative PET/CT parameters were computed from all probable pathological lesions, encompassing SUVmean, SUVmax, and PSMA-TV/PSMA-TL. Correlations among imaging biomarkers, PSA levels, and GS were examined.

Results: Whole-body PSMA parameters exhibited significant moderate relationships with PSA levels (SUVmax: $r = 0.55$, $p = 0.001$; SUVmean: $r = 0.60$, $p < 0.001$; PSMA-TL: $r = 0.60$, $p < 0.001$). Nonetheless, there was a weak association with PSMA-TV: $r = 0.31$, $p = 0.05$. Furthermore, PSMA-derived metrics exhibited significant moderate correlations with GS (SUVmax: $r = 0.40$, $p = 0.03$; PSMA-TV: $r = 0.40$, $p = 0.02$; PSMA-TL: $r = 0.40$, $p = 0.006$), whereas a weak correlation with SUVmean: $r = 0.30$, $p = 0.046$;

Conclusion: Both PSMA-TV/PSMA-TL serve as potential quantitative imaging biomarkers for the volumetric evaluation of tumor burden in metastatic PCa. These measures offer significant insight into intra-lesional PSMA expression and systemic disease activity.

Keywords: PSMA PET/CT; Tumor burden; Volumetric biomarkers; Metastatic prostate cancer

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Introduction:

Prostate cancer (PCa) represents a prevalent malignancy in males globally and remains a significant factor in cancer-related morbidity and mortality [1]. Timely identification, precise staging, and thorough tumor characterization are essential for informing therapy choices and enhancing patient outcomes [2]. Molecular imaging, specifically positron-emission tomography/computed tomography (PET/CT), has become an indispensable diagnostic instrument and is now included in the European Association of Urology guidelines for PCa care [3].

Metastatic dissemination in PCa generally affects lymph nodes and bone, but visceral metastases, including those in the liver and lungs, commonly manifest in advanced stages of the illness [4]. Conventional imaging techniques: Computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy are utilized for disease evaluation [5]. Nonetheless, these approaches possess significant limitations. The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) are inadequate for assessing osteoblastic bone metastases, which are frequently non-measurable, whereas bone scans predominantly identify osteoblastic reactions instead of live tumor load [6]. Likewise, serum prostate-specific antigen (PSA), despite its prevalent usage as a biomarker, exhibits inconsistent production among tumor cells and does not

reliably relate to tumor size, grade, or disease activity [7].

Prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein predominantly expressed in PCa cells, constitutes a molecular target for diagnostic imaging and treatment [8]. PSMA PET/CT displays enhanced sensitivity and specificity, even at minimal tumor volumes, in comparison to traditional methods [9]. However, individual lesion standardized uptake values (SUVs) obtained from PSMA PET/CT may insufficiently reflect the total disease burden, hence constraining their utility in therapeutic monitoring and patient stratification [10].

Recent research has concentrated on quantitative imaging biomarkers to overcome these constraints, which may quantify the entire tumor burden by incorporating lesion size, quantity, and metabolic activity [11]. Volumetric metrics generated from PSMA, specifically PSMA-total volume (PSMA-TV) and -total lesion (PSMA-TL), present a promising methodology [12]. These measures integrate volumetric and functional data, facilitating a more accurate evaluation of illness degree and providing a uniform criterion for assessing therapy response [13]. Initial research indicates that these criteria could enhance patient classification, especially for oligometastatic or limited metastatic disease, thus facilitating individualized treatment approaches [14, 15].

This study aims to test PSMA-TV and PSMA-TL as quantitative imaging indicators for the volumetric evaluation of total tumor burden in patients with metastatic PCa and their roles in patient stratification. We posited that these metrics would exhibit a substantial correlation with existing clinical indicators, such as PSA levels and Gleason score (GS), hence improving patient classification and disease monitoring.

Patients and Methods:

Study Design and Ethical Approval

This is retrospective observational study performed at the Faculty of Medicine, Assiut University. The Institutional Review Board (IRB) of Assiut University authorized the study protocol (Approval No. 04-2024-300426). All procedures followed the Declaration of Helsinki and institutional ethical standards, and all participants signed informed consent.

Participants

Herein, 39 male patients with histologically verified metastatic PCa were included. Eligibility criteria necessitated the identification of PSMA-avid metastatic lesions observed on ^{18}F-PSMA-1007 PET/CT imaging. Patients with incomplete clinical records, non-PSMA-avid lesions, or previous imaging artifacts that could compromise interpretation were excluded.

Radiotracer Preparation

The radiotracer ^{18}F-PSMA-1007 was delivered intravenously at 0.05- 0.1 mCi/kg of body weight. Standardized safety and quality control protocols were adhered to during preparation and injection.

PET/CT Acquisition and Reconstruction

Imaging was conducted with a specialized PET/CT scanner (Siemens, Germany), featuring a 16-slice spiral CT system and a full-ring, high-resolution, extended field-of-view (FOV) lutetium orthosilicate PET component. Whole-body PET/CT images were obtained 60–90 min post-radiotracer administration, encompassing the area from the skull base to the proximal thigh. Images were acquired at three minutes per bed position. Low-dose CT, with or without intravenous contrast, voltage 120 kVp, CARE Dose 4 D, reference 100 mAs, was employed for attenuation correction and anatomical correlation.

Image Analysis

PSMA PET/CT scans were examined for pathological PSMA-avid metastatic lesions, characterized by uptake equivalent to or above blood pool activity. For each lesion, quantitative parameters such as SUVmean, SUVmax, and PSMA-TV were ascertained via volumes of interest (VOIs) defined by isocontours at 40% of the maximum uptake. The PSMA-TL was calculated by multiplying PSMA-TV by the SUVmean. Six anatomical areas were analyzed for each patient: prostate, lymph nodes, bone, liver, lung, and other visceral regions. Figure 1 depicts the procedure of whole-body quantification, encompassing VOI determination and the extraction of SUV and volumetric data. High-volume disease was characterized according to CHAARTED criteria, which stipulate the existence of visceral metastases or four or more bone metastases, with at least one located outside the vertebral bodies or pelvis.

Statistical Analysis

Statistical analyses were carried out utilizing SPSS software (v26.0; IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), contingent upon distribution. The Shapiro–Wilk test was employed to determine data normality.

Comparisons for normally distributed variables were applied using the independent t-test with 95% confidence interval (95% CIs). The Mann–Whitney U test was utilized for variables that are not regularly distributed. Pearson correlation analysis was employed to evaluate the relationships between PET/CT parameters and serum PSA levels. Where the correlation degree was considered negligible (0.00-0.10), weak (0.10-0.39), moderate (0.40-0.69), strong (0.70-0.89), or very strong (0.9-1.00) [16]. Correlations between GS and volumetric PET/CT parameters were analyzed utilizing one-way ANOVA accompanied by Tukey's post hoc multiple-comparison test. A stepwise multiple regression analysis was conducted to ascertain independent determinants of PSMA-TV/PSMA-TL. ROC curve analysis was deployed to assess the sensitivity and specificity of quantitative PET/CT parameters in diagnosing high-risk PCa. The ideal cutoff values were established utilizing the Youden J index. $P < 0.05$ indicated significance for all analyses.

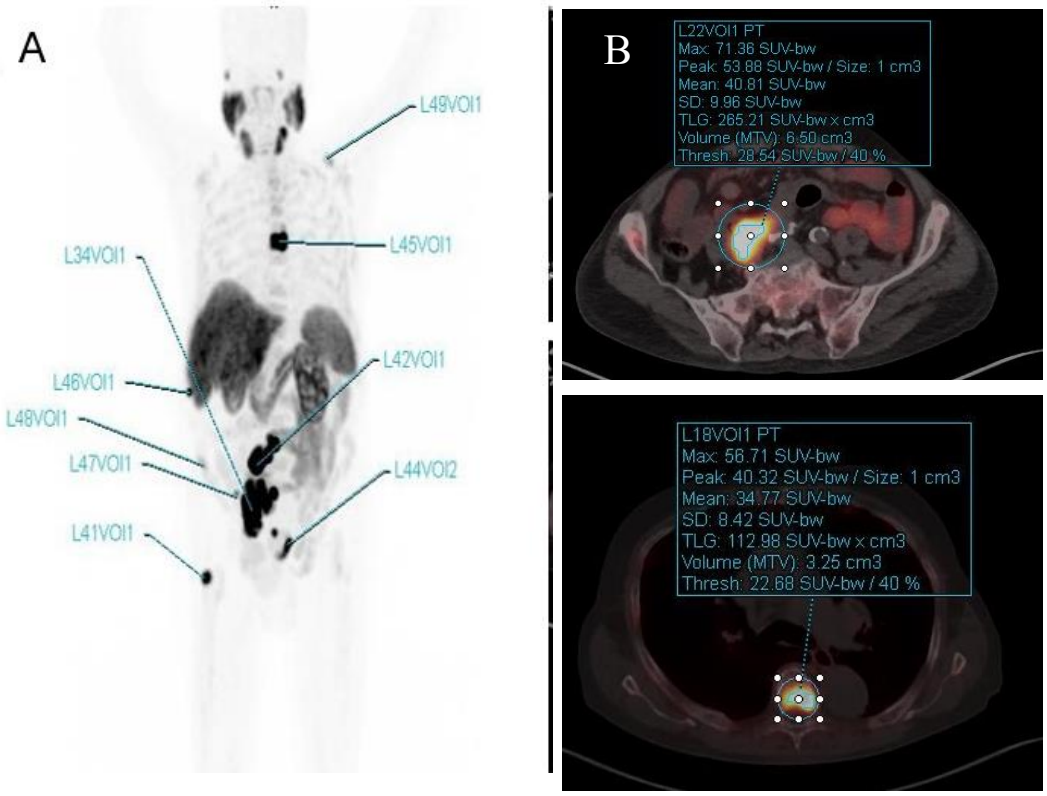

Figure 1. Example of whole-body PSMA quantification. (A) Maximum intensity projection (MIP) image displaying volumes of interest (VOIs) of metastatic lesions; VOIs not meeting selection criteria were excluded after careful evaluation. (B) Fused PET/CT images illustrating VOI data generated by the software, including SUVmax, SUVmean, TV, and TL values.

Results:

Patient Characteristics

This study includes 39 male patients diagnosed with metastatic PCa. The median age was 68 years (range: 53–86 years). Most patients exhibited a GS of ≥ 8 (59%), which aligned with grade group 5 in 46.2% of instances. The majority (59%) were classified as high or very high risk, while 17.9% were categorized as low risk. The average PSA level was 397.3 ± 1619.8 ng/mL, with a range of 0.05 to 10,000 ng/mL (Table 1).

Correlations with Whole Body, PSA, GS, and Risk Groups

In terms of the mean for the whole body, the PSMA-derived values were as follows: PSMA-TL 969.5 ± 1288.9, PSMA-TV 120.25 ± 163.2, and SUVmax 132.3 ± 155.6. We found significant relationships between PSA levels and all PSMA-derived metrics in the Pearson correlation analysis. These include moderate relationship with SUVmax ($r = 0.55$, $p = 0.001$), SUVmean ($r = 0.60$, $p < 0.001$), and PSMA-TL ($r = 0.60$, $p < 0.001$), Nonetheless, there was a weak association with PSMA-TV ($r = 0.31$, $p = 0.05$), In a similar vein, the GS was significantly correlated moderately with SUVmax ($r = 0.40$, $p = 0.03$), PSMA-TV ($r = 0.40$, $p = 0.02$), and PSMA-TL ($r = 0.40$, $p = 0.006$) whereas a weak correlation with SUVmean ($r = 0.30$, $p = 0.046$). There was no significant difference between SUVmax and SUVmean ($p = 0.2$), with significant connections detected for PSMA-TV ($p = 0.03$) and PSMA-TL ($p = 0.04$) when evaluated across risk groups (Table 2).

ROC Analysis for Risk Stratification

ROC curve analysis was applied to ascertain the predictive efficacy of prostatic PSMA-derived characteristics in differentiating high-risk patients from those with low or intermediate risk. Statistically significant cutoff values were determined for SUVmax (14.7, AUC = 0.88, $p < 0.001$), SUVmean (11.81, AUC = 0.87, $p < 0.001$), and PSMA-TL (118.2, AUC = 0.79, $p = 0.006$). Conversely, PSMA-TV exhibited minimal discriminatory capability (AUC = 0.42, $p = 0.4$; Table 3; Figure 2).

Association with CHAARTED High-Volume Disease

Significant variations were detected across all PSMA-derived measures when patients were classified based on CHAARTED high- and low-volume disease criteria. Patients with high-volume disease exhibited

significantly elevated total SUVmax (175.9 ± 30.6 vs. 15.1 ± 4.6, p < 0.001), SUVmean (156.5 ± 39.6 vs. 15.2 ± 4.8, p = 0.002), PSMA-TV (108.9 ± 17.8 vs. 10.8 ± 2.5, p < 0.001), and PSMA-TL (1231.9 ± 283.4 vs. 71.1 ± 29.0, p < 0.001) compared to patients with low-volume disease (Table 4).

ROC Analysis for High-Volume Disease

Subsequent ROC analysis revealed the superior diagnostic efficacy of whole-body PSMA measures in forecasting high-volume illness. Significant cutoff values were identified as 34.7 for total SUVmax (AUC = 0.92, p < 0.001), 20.85 for total SUVmean (AUC = 0.93, p < 0.001), 28.3 for PSMA-TV (AUC = 0.95, p < 0.001), and 213.8 for PSMA-TL (AUC = 0.97, p < 0.001). The sensitivity and specificity for these parameters were 79%–92% and 80%–87%, respectively (Table 5, Figure 3).

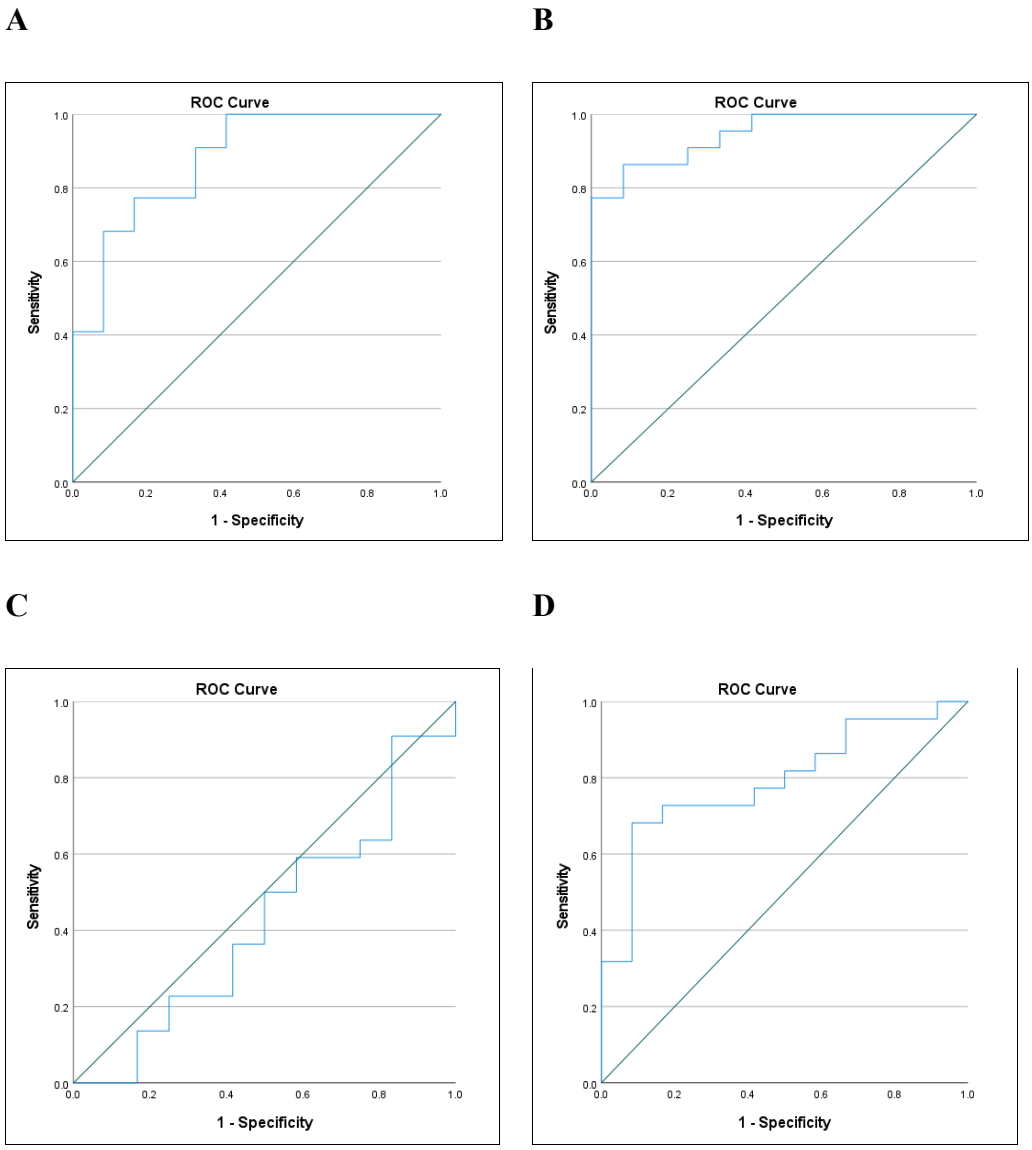

Figure 2. Representative ROC curves of prostatic PSMA-derived characteristics. ROC curve for detecting the cutpoint of prostatic **(A)** SUVmean, **(B)** SUVmax, **(C)** PSMA-TV, and **(D)** PSMA-TL.

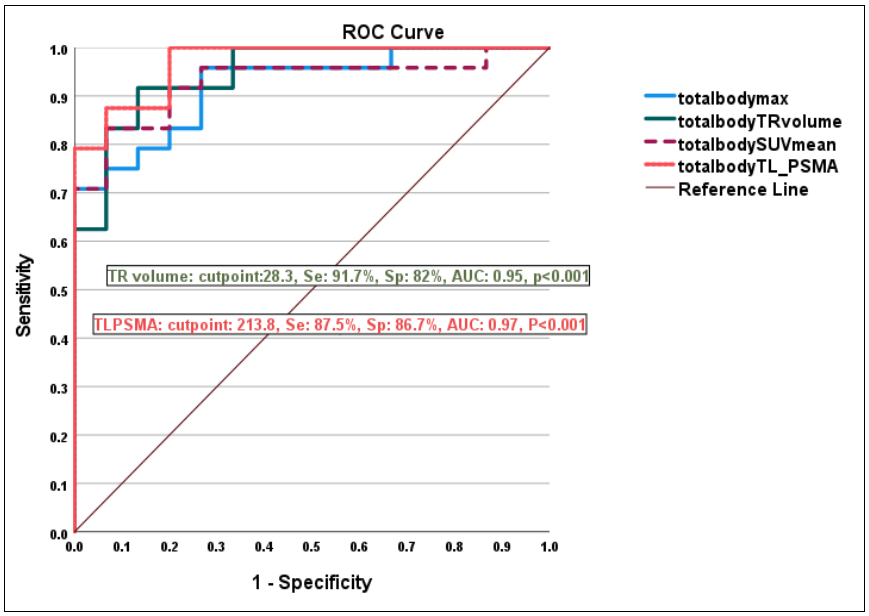

Figure 3. ROC curve of different total body metrics to categorize patients as high-burden diseases

Table 1. Clinical characteristics of enrolled patients

Characteristics	Descriptives
Age median (range)	68 (53-86)
Gleason Score	
GS ≤ 6	7 (17.9%)
GS = 7	9 (23.1%)
GS ≥ 8	23 (59%)
Grades	
1 (GS ≤ 6)	7 (17.9%)
2 (GS 7 = 3 + 4)	5 (12.8%)
3 (GS 7 = 4 + 3)	4 (10.3%)
4 (GS = 8)	5 (12.8%)
5 (GS = 9 - 10)	18 (46.2%)
Risk groups	
Low risk	7 (17.9%)
Intermediate risk (favorable/unfavorable)	9 (23.1%)
High and very high risk	23 (59%)
PSA (ng/ml)	
mean ± SD	397.3 ± 1619.8
Range	0.05-10000

Table 2. Correlation between clinicopathological features and whole body PSMA-derived parameters in PCa patients

	Total SUVmax (132.3± 155.6)		Total SUVmean (81.6± 92.2)		PSMA-TV (120.25±163.2)		PSMA-TL (969.5± 1288.9)	
PSA	r=0.55, p=0.001**		r=0.6, p=<0.001***		r=0.31, p=0.05*		r=0.6, p<0.001***	
GS	r=0.4, p=0.03*		r=0.3, p=0.046*		r=0.4, p=0.02*		r=0.4, p=0.006*	
Risk group	mean± SD	P	mean± SD	P	mean± SD	P	mean± SD	p
Low risk	70.5± 88.9	0.2	45.2± 64.6	0.2	60.0±47.5	0.03*	398.7±428.7	0.04*
Intermediate	80.8± 96.0		55.7± 54.3		45.2± 33.2		404.6± 391.9	
High risk	171.2± 180.0		102.8±106.3		168.0±197.8		1364.2±1538.3	

Table 3. ROC parameters determining high-risk group patients

Parameter	High-risk group						
	AUC±SE	p-value	95% CI	Cut point	sensitivity	specificity	Youden index
Prostatic SUVmax	0.88±0.1	<0.001	0.761-0.996	14.7	83%	80%	0.618
Prostatic SUVmean	0.87±0.1	<0.001	0.753-1.000	11.81	77.3%	81%	0.583
Prostatic PSMA-TV	0.424±0.11	0.4	0.22-0.63	11.1	60%	42%	0.02
Prostatic PSMA-TL	0.792±0.08	0.006	0.637-0.946	118.2	72%	80%	0.52

Table 4. Significance of PSMA metrics to predict high-volume disease

Parameters	Low-volume disease (n= 15)	High-volume disease (n=24)	p-value
Total body SUVmax	15.1±4.6	175.9±30.6	<0.001
Total body SUVmean	15.2±4.8	156.5±39.6	0.002
Total body PSMA-TV	10.8±2.5	108.9±17.8	<0.001
Total body PSMA-TL	71.1±29.0	1231.9±283.4	<0.001

Data Interpretation: mean ± SE; Mann-Whitney test.

Table 5. Determination of cut points of different body PSMA metrics to predict high-volume disease

Parameter	High-volume disease						
	Cut point	AUC±SE	95% CI	p-value	sensitivity	specificity	Youden
T. body SUVmax	34.7	0.92±0.04	0.841-1.0	<0.001	79.2%	87%	0.662
T. body SUVmean	20.85	0.93±0.043	0.844-1.0	<0.001	83.3	80%	0.633
T. body PSMA-TV	28.3	0.95±0.03	0.882-1.0	<0.001	91.7	82%	0.737
T. body PSMA-TL	213.8	0.97±0.023	0.925-1.0	<0.001	87.5%	86.7%	0.742

Discussion:

PSMA PET has substantially revolutionized the imaging paradigm in PCa by providing enhanced sensitivity and specificity for identifying primary, recurring, and metastatic disease relative to traditional imaging techniques [17]. In addition to detection, PSMA PET/CT has proven its clinical significance in staging, directing personalized treatment approaches, and functioning as a therapeutic target, hence solidifying its role as an essential instrument in modern PCa care [18, 19].

PET-derived quantitative measurements have garnered heightened acknowledgment as surrogate indicators for objective response evaluation. Their predictive and prognostic significance continues to develop, especially in risk identification and treatment stratification from the point of initial assessment [20]. These measurements are anticipated to assume an increasingly pivotal role in customizing therapeutic strategies to specific patient profiles.

SUV-based metrics, including SUVmax and SUVmean, are recognized predictors of tumor aggressiveness [21]. The present investigation revealed significant relationships between SUVmax and SUVmean with PSA levels and GSs, yielding p-values of 0.03 and 0.046, respectively. Although SUVs offer significant insights into tumor biology, they predominantly reflect metabolic activity within a confined area of interest [22]. In contrast, volumetric PET/CT measurements, including total body PSMA-TV/PSMA-TL, provide a more thorough evaluation of tumor burden [23]. PSMA-TV indicates the total volume of PSMA-avid disease, while PSMA-TL amalgamates volumetric and metabolic activity, thus combining lesion extent with intralesional PSMA expression [24]. Our investigation demonstrated a moderate relation between PSMA-TL and PSA, yielding $p < 0.001$. Nonetheless, there was a weak correlation with PSMA-TV, yielding p-values of 0.05, as well as a moderate correlation between PSMA-TL/PSMA-TV with GS yielding p value of 0.006 and 0.02, respectively thus affirming their efficacy as quantitative indicators of disease aggressiveness.

Risk classification is fundamental in PCa care, directing treatment choices and informing prognosis [25]. Established classification approaches, like the D'Amico and NCCN risk categories, incorporate clinical and pathological markers: PSA, GS, and clinical T stage [26]. In our cohort, PSMA-derived volumetric measures (PSMA-TV/PSMA-TL) exhibited a significant relation to NCCN risk categories ($p = 0.03$ and 0.04, respectively), although SUVmax and SUVmean did not ($p = 0.2$). ROC curve analysis further determined cutoff values that effectively differentiate high-risk from low- and intermediate-risk groups, revealing significant thresholds for SUVmax (14.7), SUVmean (11.81), and PSMA-TL (118.2), with $p < 0.001$, < 0.001, and 0.006, respectively.

Regarding metastasis, categorizing disease into low- versus high-volume classifications has significant therapeutic consequences, as evidenced by the CHAARTED study, which showed that patients with high-volume disease experienced larger advantages from early docetaxel combined with androgen deprivation therapy (ADT) [27]. The current investigation revealed that individuals with high-volume metastatic disease demonstrated significantly elevated whole-body SUVmax, SUVmean, and PSMA-TV/PSMA-TL in comparison to those with low-volume disease ($p < 0.05$). ROC analyses showcased significant cutoff values for forecasting high-volume disease: 34.7 for SUVmax, 20.85 for SUVmean, 28.3 for PSMA-TV, and 213.8 for PSMA-TL (all $p < 0.001$). This highlights the potential of PSMA PET/CT characteristics to function as imaging biomarkers for disease volume stratification, which may enhance or refine current clinical classifications.

Our findings are partially aligned with previous investigations. Santos et al. [28] identified strong relationships among PSMA-TL, PSA, and GS in patients with biochemical recurrence, but not during primary staging. Similarly, Schmuck et al. [29] identified robust connections among whole-body PSMA-TV/PSMA-TL and PSA levels; however, our analysis further revealed associations for SUVmax and SUVmean. Discrepancies may be ascribed to

methodological discrepancies, especially in lesion selection and patient populations. Schmidkonz et al. [30] discovered that PSMA-TL, unlike SUV or PSMA-TV, had a strong correlation with the primary GS, whereas we identified relationships across several metrics. Our findings corroborate those of Schmidkonz et al. [31], who documented favorable relationships between SUVmean, SUVmax, and PSMA-TV/PSMA-TL with elevated GSs. Additionally, Chandekar et al. [32] reported moderate-to-strong relationships among PSMA-TV/PSMA-TL and GS, corroborating our findings. In contrast, Soeterik et al. [33] identified correlations between SUVmax and PSMA-total with ISUP grade groups, but not with PSMA-TV, which differs from our results. These variations presumably indicate variability in patient demographics, disease progression, treatment conditions, and sample sizes.

Francesco et al. [34] proposed a PSMA-based limit for high-volume illness of approximately 40 cm^3, which contrasts with our ROC-derived findings. This gap may be attributed to the smaller sample size of our cohort relative to their larger research group of 105 patients. Notwithstanding these disparities, our research endorses the idea that volumetric PSMA measurements are promising for enhancing definitions of disease burden and advancing patient categorization.

Strengths and Limitations

This study demonstrates several key strengths that enhance the clinical relevance and methodological robustness of its findings. It is among the first to validate PSMA-TV/PSMA-TL volumetric parameters derived from ^{18}F-PSMA-1007 PET/CT against both serum PSA levels and GS in patients with metastatic PCa, revealing significant correlations that support their biological and clinical validity. The derivation of clinically actionable cutoff values via ROC analysis for both risk stratification (NCCN categories) and disease volume classification (CHAARTED criteria) enhances their utility in real-world decision-making. The use of a standardized, whole-body quantification approach based on 40% isocontour volumes of interest promotes reproducibility and scalability across imaging centers. Importantly, PSMA-TL integrates both metabolic activity and lesion volume, offering a more comprehensive biomarker of tumor burden than SUV-based metrics alone. The findings provide a strong foundation for incorporating these metrics into precision oncology workflows to guide therapy selection, monitor treatment response, and improve patient stratification in metastatic PCa.

This research possesses multiple limitations. The limited sample size may constrain the generalizability of the results and diminish statistical power. The possible impact of continued androgen deprivation therapy on PSMA expression and tracer uptake was not assessed, which may have influenced volumetric evaluations. Furthermore, histological validation of the distinction of metastatic lesions was lacking, as the assessment depended on the primary GS, which may not accurately represent the biology of metastatic deposits. Furthermore, volumetric measures were obtained by manual techniques, hence adding the potential for interobserver heterogeneity. Future research should address these concerns using bigger, prospectively validated cohorts and standardized imaging procedures.

Clinical Implications

Our findings underscore the significant clinical applicability of ^{18}F-PSMA-1007 PET/CT-derived volumetric metrics, particularly PSMA-TV/PSMA-TL, that reflect both the spatial extent and metabolic intensity of metastatic PCa, offering a more comprehensive assessment of tumor burden than traditional SUV-based measures, PSA levels, or GS alone. These metrics demonstrate strong correlations with established clinical indicators and provide validated cutoffs (e.g., TL-PSMA > 118.2 for high-risk disease; PSMA-TV > 28.3 for high-volume disease per CHAARTED criteria) that can enhance risk stratification, refine patient selection for intensified systemic therapies (such as early docetaxel or ARSIs), and guide personalized treatment approaches, including metastasis-directed therapy or PSMA-targeted radioligand therapy. Moreover, PSMA-TV/PSMA-TL hold promise as objective, reproducible tools for monitoring treatment response over time, overcoming the limitations of RECIST 1.1 in bone-predominant disease and the unreliability of PSA as a surrogate marker. As PSMA PET/CT becomes routine in PCa care, adopting PSMA-TV/PSMA-TL into clinical workflows can enable more precise, biologically informed, and individualized management of metastatic disease, ultimately improving prognostication, therapeutic selection, and patient outcomes.

Conclusion:

PSMA-derived volumetric measures, including PSMA-TV/PSMA-TL, serve as promising quantitative imaging indicators for evaluating disease burden and aggressiveness in PCa. These measurements offer significant insights that extend beyond traditional SUV-based evaluations by incorporating lesion size, quantity, and metabolic activity. Notably, PSMA-TV/PSMA-TL exhibited substantial relationships with PSA levels, GSs, and NCCN risk classifications, and they proficiently differentiated between low- and high-volume metastatic illness. Collectively, PSMA PET/CT parameters may enhance or redefine existing clinical risk classification models. The future amalgamation of PSMA PET measures with recognized clinical and molecular indicators may refine precision in patient categorization, therapy selection, and monitoring, hence enhancing management and outcomes in metastatic PCa.

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