Original Article

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The Significance of Ga-68 PSMA PET SUV_{max} Value in Distinguishing Multimetastatic from Oligometastatic and High-risk from Intermediate Risk Prostate Cancer

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Abstract

Objective: This study aims to identify the maximum standardized uptake value (SUV_{max}) value that predicts the presence of oligometastatic and high-risk prostate cancer and forecasts disease behavior.
Materials and Methods: In this retrospective analysis, patients who underwent 12-quadrant transrectal prostate biopsy in our clinic were evaluated in the study. D'Amico risk scoring was performed. Data of non-metastasis, oligometastatic and multimetastatic patients were recorded using imaging methods. Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) SUV_{max} values, prostate-specific antigen (PSA) and pathology parameters were recorded. PSA and SUV_{max} values were compared between oligometastatic/multimetastatic and D'Amico risk groups. By performing receiver operating characteristic analyses, SUV_{max} values in predicting oligometastatic and high-risk disease were tried to be predicted.
Results: According to the D'Amico risk scoring, there was no significant difference in SUV_{max} values between the low-risk group and the intermediate-risk group (p=0.18). However, a significant difference was observed between the intermediate-risk group and the high-risk group (p=0.006). According to the D'Amico risk classification, the best SUV_{max} cut-off value that distinguishes medium risk from high risk was 7.95, and the sensitivity for this value was found to be 73% and the specificity was 86%. The cut-off SUV_{max} value in distinguishing between oligometastatic and multimetastasis was found to be 12.65, and its sensitivity was 77% and specificity was 68%. The area under the curve was found to be 0.735.
Conclusion: PSMA-PET should be considered as a factor guiding treatment in prostate cancer. The SUV_{max} value of 7.95 in the distinction of high-risk prostate cancer and the SUV_{max} value of 12.65 in the distinction of multimetastatic prostate cancer are safe parameters that can be used in daily practice. It will achieve more successful results with more standardized studies conducted on larger populations and will be used in a more standardized way in planning treatment.
Keywords: Prostatic neoplasms, metastasis, SUV_{max}, Ga-68 PSMA PET/CT

Introduction

Prostate cancer ranks as the most frequently diagnosed cancer in men (21%) (1). While the 5-year survival rate for prostate cancer is around 100% in localized disease, it drops to 31% in metastatic disease (2). Although the treatment varies depending on the risk group and degree of the disease, follow-up, surgical treatment, hormonal therapy, radiotherapy and their combinations are decided according to the spread of the disease and its aggressiveness. Perhaps the most accurate approach for prostate cancer, which is discussed today at what stage treatment is required, is to determine the risk of the severity of the disease. By performing a digital rectal examination, tests such as prostate specific antigen, imaging such as magnetic resonance, bone scintigraphy, prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) and using the Gleason scoring system, the potential of the disease is interpreted and treatment is planned at the beginning.

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The purpose of clinical staging in prostate cancer is to determine the burden of the disease and to treat the patient with the most appropriate treatment plan by estimating the prognosis through pre-treatment clinical parameters. The procedures to be chosen for staging are determined according to risk classification. The D'Amico risk classification is the most frequently utilized system for grouping prostate cancer risk (3).

Oligometastatic disease can be defined as an intermediate stage between local advanced disease and widespread metastasis. Especially with the development of diagnostic and staging methods such as functional imaging, oligometastatic disease is diagnosed more frequently than before. Our knowledge of oligometastatic disease has matured over the past two decades (4). Clinical studies play a crucial role in closely observing patients, enabling the detection of even the smallest masses through advanced imaging techniques, and uncovering treatments that extend the survival of individuals affected by the disease (5). Due to the lack of consensus on the definition of oligometastatic prostate cancer, the criteria frequently referenced are based on the CHAARTED and LATITUDE trials (6). Prostate cancer with a limited number of metastases, typically fewer than five lesions, is defined as oligometastatic. This form of the disease involves lesions contained within the axial versus the appendicular skeleton (7). This definition of oligometastasis has also been included in the European Urology Guidelines (8,9).

Surgical procedures or stereotactic radiotherapy may serve as appropriate alternatives for a limited number of metastatic lesions categorized as oligometastatic (10). Several studies have reported that radical treatment approaches—such as radical prostatectomy or radiotherapy—when applied in addition to hormonotherapy, improve overall survival in patients with oligometastatic prostate cancer. In metastatic prostate cancer, it is essential to determine the tumor burden in order to achieve satisfactory treatment outcomes (11). Therefore, it is important to distinguish oligometastatic disease from multimetastatic disease in the initial staging. Prostate cancer cells display high levels of Type II transmembrane glycoprotein antigen (PSMA) on their surface. As the tumor grade increases, Ga-68 PSMA uptake and maximum standardized uptake value (SUV_{max}) increase (12). In this way, malignant lesions can be distinguished from benign lesions, and metastases of prostate cancer and even recurrences after treatment can be detected.

In this study, we aim to determine the relationship between SUV_{max} value of prostate cancer primary lesion in Ga-68 PSMA scan and the D'Amico risk score, ISUP grade, lymph node involvement, oligometastasis and neurovascular invasion.

Materials and Methods

The data of patients who underwent 12-quadrant transrectal ultrasound-guided prostate biopsy for the purpose of investigating prostate cancer were evaluated retrospectively. ISUP grade scores of the patients were recorded using Gleason parameters according to the conditions implemented by the International Society of Urological Pathology in 2014 (13). D'Amico risk groups were evaluated according to prostate biopsy material. Categorized as mentioned in the European Urology Guidelines (9). Prostate-specific antigen (PSA) (total) values of the patients measured before treatment were recorded. It was ensured that no more than 45 days elapsed between the PSMA PET and PSA measurement period. Ga-68 PSMA PET/CT results of the patients were evaluated. Metastases were recorded. Neurovascular invasion and lymph node metastasis parameters were recorded according to prostate biopsy and PSMA PET data. Metastases were defined based on PSMA PET/CT findings. In this study, metastatic lesions were evaluated radiologically without histopathological confirmation and were defined as nuclear medicine imaging foci showing PSMA uptake consistent with metastasis

In our study, we adopted the definition of oligometastasis consistent with previous studies and those accepted in the European Urology Guidelines (7,8). Oligometastasis was defined as the presence of five or fewer metastatic lesions.

The study was initiated by obtaining approval numbered 2023-11/06, dated: 16.11.2023, from the Scientific Research Ethics Committee of Sivas Cumhuriyet University. All evaluations in our study were made in accordance with the ethical rules of the 1964 Declaration of Helsinki. Since our study was retrospective, consent was not obtained from the included patients.

Patients who had previously undergone transurethral prostate resection, radical prostatectomy, pelvic radiotherapy, or hormonotherapy were excluded from the study.

Ga-68 PSMA PET Imaging Technique and SUV_{max} Measurement

Patients were administered of 2 MBq/kg of Ga-68 PSMA 45 to 60 minutes prior to imaging. All patients underwent imaging (GE Medical Systems,LLC, 3000 N.,WI., U.S.A.). Firstly, CT imaging was performed. PET imaging was performed in three dimensions, including cranium and feet, for approximately 3 minutes in each bed position. CT and PET images were matched and fused. Subsequently, visual and semi-quantitative analyses were performed by a single nuclear medicine specialist (ZH). The highest measured SUV_{max} value in the prostate was recorded. The regions of bone, lymph nodes, and visceral organs exhibiting PSMA expression were recorded as a result of the whole-body scan.

Statistical Analysis

SPSS 20.0 software was used for statistical analysis (IBM Inc., Chicago, IL, USA). Descriptive statistics were utilized to assess numerical variables. The normality of the PSA and SUV_{max} values was evaluated (Kolmogorov-Smirnov test), which indicated that both variables were non-parametric. Consequently, comparisons were made using the Mann-Whitney U test and the Kruskal-Wallis test. Significant results of the post-hoc analysis are indicated in the tables with superscript letters, and the Dunn post-hoc test was applied for pairwise comparisons following the Kruskal-Wallis test. Receiver operating characteristic (ROC) analysis was used to determine the SUV_{max} value that best predicts multimetastatic and high-risk prostate cancer, and the area under the curve (AUC) values were presented with their 95% confidence intervals (CI). All tests were two-sided, with 95% CIs and p-values reported ($p<0.05$).

Results

The data of 81 patients between 2018 and 2024 were retrospectively examined, but 5 patients were not included in the study because all data could not be accessed, 2 patients transurethral surgery was performed. A total of 74 patients were included in the study, with a median age of 69.40 years (range: 52-84 years). When divided into categories, patients under the age of 65 constituted 35% of the patients and patients over the age of 65 constituted 65%. Thirty-eight of 74 patients (51%) were locally and locally advanced (non-metastatic), 36 (49%) were metastatic. Twenty-nine of them (38%) were oligometastatic and 7 were multi-metastatic (9%). Of the 74 patients, 35 (47%) had lymph node metastasis, 29 (39%) had bone metastasis, and 7 (9%) had visceral metastasis. Of the 35 patients with lymph node metastases, 12 had only pelvic lymph nodes, 23 had pelvic and extra-pelvic lymph node metastases. Of patients, 12 (16%), 13 (18%), 12 (16%), 23 (31%), and 14 (19%) were reported as ISUP grade groups 1, 2, 3, 4, and 5 respectively. According to D'Amico risk classification, there were 4 patients with low risk (5%), 11 patients with medium risk (15%), and 24 patients with high risk (32%). According to the biopsy material results the number of patients with positive neurovascular invasion was 39 (53%) (Table 1).

Prostatic primary tumor SUV_{max} and PSA values were significantly different between the metastatic and non-metastatic groups. The p-values were 0.025 and 0.007 respectively. When the groups were evaluated as no metastasis, oligometastasis and multiple metastasis, PSA and SUV_{max} values showed significant differences between the groups. P-values were 0.00 and 0.01, respectively. According to D'Amico risk grouping, PSA and SUV_{max}values were found to be different between intermediate risk and high risk groups. P-values were found to be 0.003 and 0.006, respectively. PSA and SUV_{max} values were not significantly different between groups with and without visceral metastasis (Table 2). When the lymph node metastasis groups were evaluated as no lymph node, pelvic and extrapelvic metastasis, here was a significant difference between the groups in terms of PSA and SUV_{max}values. The p-values were 0.035 and 0.010, respectively.

According to the D'Amico risk scoring, there was no significant difference in SUV_{max}values between the low-risk group and the intermediate-risk group (p=0.18). However, a significant difference was observed between the intermediate-risk group and the high-risk group (p=0.006). Box plot graph is shown in Figure 1.

According to the D'Amico risk classification, the best SUV_{max} cut-off value that distinguishes low and medium risk from high risk was 7.95, and the sensitivity for this value was found to be 73% and the specificity was 86%. When the ROC curve was evaluated, the AUC was found to be 0.829 (95% CI: 0.72-0.94). The ROC curve is shown in Figure 2.

The cut-off SUV_{max} value in distinguishing between oligometastatic and multimetastasis was found to be 12.65, and its sensitivity was 77% and specificity was 68%. The AUC was found to be 0.735 (95% CI: 0.61-0.86). The ROC curve is shown in Figure 3.

Discussion

One of the things that is as important as the stage of the cancer in choosing treatment for prostate cancer is the tumor burden and behavior of the cancer (14,15). In our study, the prostatic SUV_{max} value of metastatic prostate cancer and the PSA and SUV_{max} values of non-metastatic prostatic cancer were found to be statistically different. Likewise, in the D'Amico risk grouping, which determines the risk of the disease, a significant difference was found between the intermediate and the high-risk group. There were also differences between oligometastatic and multimetastatic groups, which is important in treatment management. These differences give us valuable information at the initial evaluation stage of the disease. Especially in the D'Amico risk grouping, while there is no difference between the

Table 1. The statistical results of the groups, PSA and SUV_{max} values

		n (%)	PSA		SUV_{max}	
			Mean ± standard error	**p-value**	**Mean ± standard error**	**p-value**
ISUP grade	1	12 (16%)	23.56±6.26	0.270	6.03±0.76	**0.046***
	2	13 (18%)	115.44 ±87.92		8.95±2.85	
	3	12 (16%)	374.46±269.57		17.07±3.36	
	4	23 (31%)	240.64±151.83		15.97±2.99	
	5	14 (19%)	688.23±367.58		15.55±2.60	
D'Amico	Intermediate risk	11 (15%)	5.36±1.54	**0.003***	5.05±0.85	**0.006***
	High-risk	24 (32%)	24.53±5.11		13.66±2.76	
Neurovascular invasion	None	35 (47%)	385.22±141.01	0.173	11.84± 1.52	**0.046***
	Exist	39 (53%)	204.21±133.48		14.47±2.51	
Lymph node	None	39 (53%)	118.25±84.32	**0.035***	11.34±1.64	**0.010***
	Pelvic	12 (16%)	496.96±192.8		11.23± 4.18	
	Extrapelvic	23 (31%)	472.94±118.34		17.45±2.44	

*: Statistically significant (p<0.05), ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen; SUV_{max}: Maximum standardized uptake value

Table 2. Results of PSA and SUV_{max} according to metastasis groups

		n (%)	PSA		SUV_{max}	
			Mean ± standard error	p-value	Mean ± standard error	p-value
Metastasis	None	38 (51%)	25.33±3.66	**0.007***	10.28±1.81	**0.025***
	Exist	36 (49%)	569.02± 189.37		16.33±1.90	
Bone metastasis	None	45 (61%)	35.49±5.46	**0.009***	12.08±1.85	**0.042***
	Exist	29 (39%)	684.48±230.61		14.73±1.91	
Visceral Metastasis	None	67 (91%)	287.40±105.90	0.744	13.05±1.45	0.089
	Exist	7 (9%)	313.04±159.91		14.74±3.38	
Metastasis	None-metastasis	38 (51%)	25.33±3.66	**0.00***	10.28±1.81	**0.01***
	Oligo	29 (39%)	125.00±23.63		11.29±1.71	
	Multiple	7 (10%)	865.27±96.81		19.94±3.88	

*: Statistically significant (p<0.05), PSA: Prostate-specific antigen, SUV_{max}: Maximum standardized uptake value

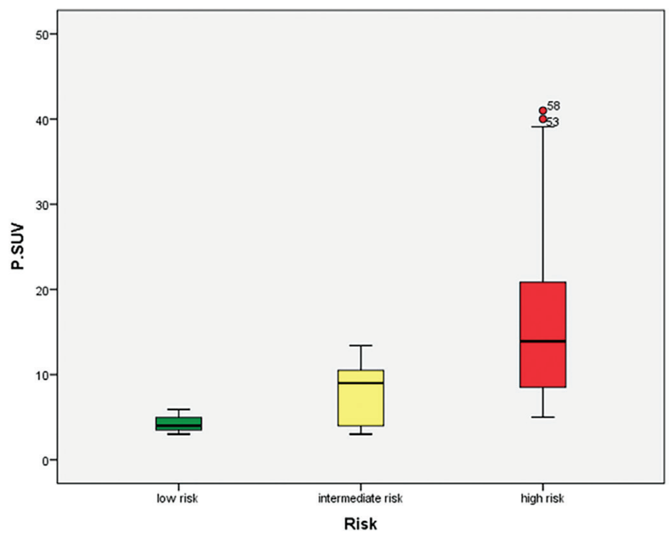

Figure 1. Box plot of SUV_{max} values by D'Amico risk groups

X-axis: Risk groups, Y-axis: Primary tumor, SUV_{max}: Medians and outliers are shown

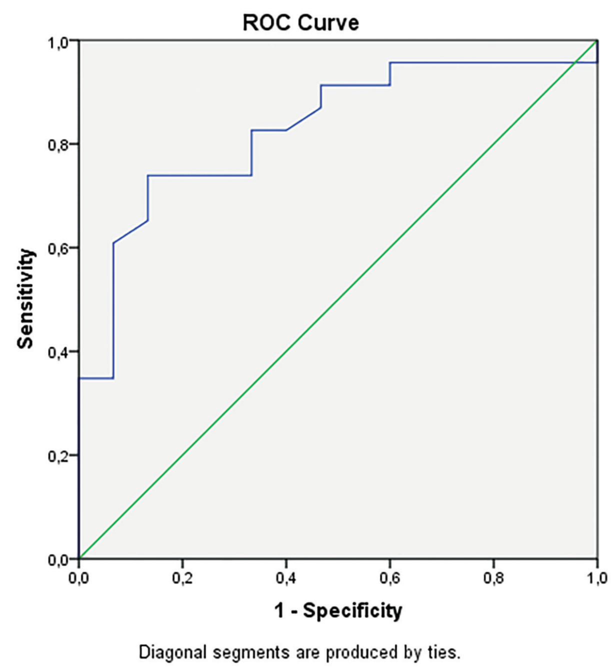

Figure 2. ROC curve for SUV_{max} distinguishing low-intermediate vs. high D'Amico risk

X-axis: 1-Specificity, Y-axis: Sensitivity, ROC: Receiver operating characteristic

low and medium risk groups, the fact that there is a significant difference in the high risk group shows that it provides valuable information in predicting the risk. The difference in SUV_{max} values in the ISUP rating system shows that the SUV_{max} value can be used in scientific studies in this direction in the future. For example, an upgrade rate of 38-72% is observed after radical prostatectomy (16,17). Various nomograms have been produced using Gleason score and clinical stages to predict this upgrade (18). SUV_{max} value can also be used as a predictor in this regard and this issue should be investigated with new studies.

We see that PSMA PET is of increasing importance in determining metastasis and lymph node involvement before surgery. In the study conducted by Meijer et al. (19), it was observed that adding PSMA PET data to nomograms increased the success of predicting lymph node involvement. However, in a study conducted by Klingenberg et al. (20), a result was obtained that did not fully support other studies. Although the SUV_{max} value increased with increasing ISUP value in the cohort consisting only of the high-risk patient population, the fact that even the lowest SUV_{max} values coincided with high ISUP values was found to be a reason that questions its applicability.

Due to the widespread use of PET/CT, many scientific articles have been written so far on the diagnosis and treatment processes of prostate cancer. In Pepe et al.'s (21) manuscript, they found the best cut-off value of SUV_{max} value that can be

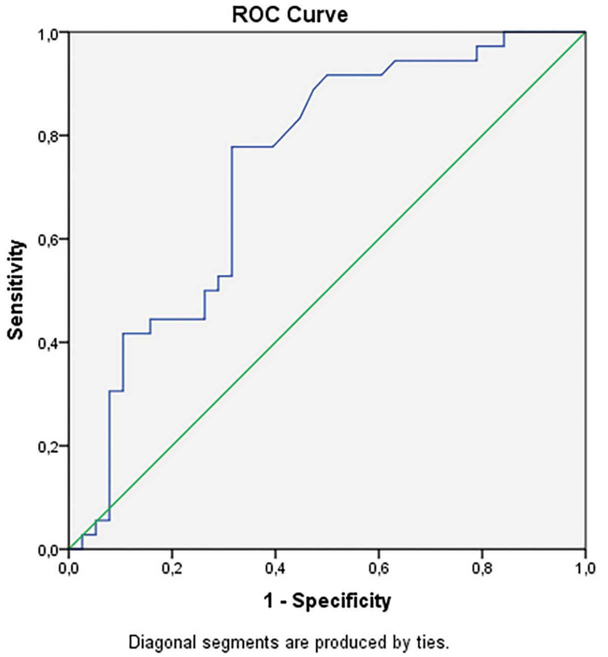

Figure 3. ROC curve for SUV_{max} distinguishing oligometastatic vs. multimetastatic disease

X-axis: 1-Specificity, Y-axis: Sensitivity, ROC: Receiver operating characteristic

used in the diagnosis of prostate cancer to be 8.0. For this value, the presence of ISUP grade group 1 was found with 87.7% accuracy, the presence of grade group 2 was found with 89.3% accuracy, and the presence of Grade group 3 and above was found with 100% accuracy (21). In the article of Demirci et al. (22), written on the same subject, they found a significant difference between SUV_{max}values and risk groups, and the cut-off value in detecting high-risk disease was found to be 9.1, and 78% sensitivity and 81% specificity were determined for this value. These differences in cut-off values across studies may be attributed to variations in patient selection criteria, imaging intervals between biopsy and PET/CT, and methods used for determining the optimal threshold. In a study conducted by Yi et al. (23) with 147 patients, the cut-off SUV_{max}value of the intermediate and high risk prostate cancer group was found to be 10.12. In our case series of 74 patients, we found this value to be 7.95.

There are many articles aimed at detecting oligometastatic prostate cancer, which guides prostate cancer treatment and has become increasingly important over the last 20 years. In the study conducted by Erdoğan et al. (24), they found a cut-off SUV_{max}value of 7.96 in the distinction between oligometastatic and metastatic prostate cancers. For this value, 68% sensitivity and 86% specificity were determined (24). In our study, this value was 12.65, and the reason for this difference may be due to the absence of a visceral metastatic patient group in Erdoğan et al.'s (24) study or may be related to the excess of extreme values in our study. There are many other studies on this subject, and although most of them have similar aims and results, the numbers and statistics do not completely match each other. The reasons for these are that no studies have been conducted on large and standardized sample groups and the times between prostate biopsy and PSMA PET/CT are different in the studies. Due to different clinics, there are many factors affecting the results such as scintigraphy evaluation and interpretation standardizations and pathologist differences. Based on all these evaluations, it is concluded that standardized and organized randomized controlled studies with larger samples are needed.

Study Limitations

A limitation of our diagnostic approach is the lack of histopathological confirmation of metastatic lesions. Since metastases were identified solely based on nuclear imaging findings, differences in sensitivity and specificity compared with surgically or pathologically confirmed diagnoses should be considered. This limitation may have influenced the detection rates and SUV_{max} threshold values in our study.The other limitation of our study can be stated as being retrospective and the study sample consisting of a low number of patients.

Conclusion

As a result, not only the pathological diagnosis but also the risk and severity are important in prostate cancer. PSMA-PET should be considered as a factor guiding treatment in prostate cancer. The SUV_{max}value of 7.95 (sensitivity 73%, specificity 86%) in the distinction of high-risk prostate cancer and the SUV_{max}value of 12.65 (sensitivity 77%, specificity 68%) in the distinction of multimetastatic prostate cancer are safe parameters that can be used in daily practice. It will achieve more successful results with more standardized studies conducted on larger populations and will be used in a more standardized way in planning treatment.

Ethics

Ethics Committee Approval: The study was initiated by obtaining approval numbered 2023-11/06, dated: 16.11.2023, from the Scientific Research Ethics Committee of Sivas Cumhuriyet University.

Informed Consent: Since our study was retrospective, consent was not obtained from the included patients.

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Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Ö., A.A., H.S., E.K., Concept: İ.E.E., A.A., H.S., Design: A.Ö., Data Collection or Processing: A.Ö., A.A., Analysis or Interpretation: İ.E.E., A.Ö., Literature Search: İ.E.E., Z.H., E.K., Writing: İ.E.E., A.Ö.

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