Original Article

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Performance of ^{68}Ga-PSMA PET/CT in Metastatic Prostate Cancers at the Time of Diagnosis and Correlation with Obesity

Tanı Anında Metastatik Prostat Kanserlerinde ^{68}Ga- PSMA PET/BT'nin Performansı ve Obezite ile Korelasyonu

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Abstract

Objective: The aim of this study was to evaluate the relationship between Galium-68 prostate-specific membrane antigen positron emission tomography combined with computed tomography (^{68}Ga-PSMA PET/CT) quantitative parameters and patient obesity, prostate-specific antigen (PSA) levels, and metastasis type in prostate cancer.

Methods: In the present study, we included 112 patients diagnosed with prostate cancer between 2020 and 2024. These patients underwent ^{68}Ga-PSMA PET/CT imaging for staging purposes, with locoregional or distant metastasis detected in the imaging results.

Results: No significant correlation was observed between body mass index (BMI) classification and prostate gland maximum standard uptake values (SUV_{max}), metabolic tumor volume (MTV), total lesion glycolysis (TLG), standardized uptake value lean (SUL), or SUV_{mean} values. A weak inverse correlation was found between BMI and PSA levels (p=0.08, r=-0.248), with PSA values decreasing as patient weight increased. The presence of locoregional disease or distant metastasis was not significantly associated with prostate gland SUV_{max}, MTV, TLG, SUV_{mean}, or SUL values (p=0.25; 0.667; 0.667; 0.244; 0.126, respectively). However, a significant association was detected between PSA levels and distant metastases or locoregional disease (p=0.02), with higher PSA values observed in patients with distant metastases compared to those with locoregional disease. Additionally, significant correlations were found between the D'Amico risk classification and the prostate gland SUV_{max}, TLG, SUL, and SUV_{mean} values (p=0.035, 0.037, 0.012, 0.028, respectively).

Conclusion: PSA levels may assist in estimating whether metastases are local or distant. However, due to the weak inverse correlation between BMI and PSA, it is important that low PSA levels may not necessarily indicate localized disease during clinical evaluation.

Keywords: Prostate cancer, ^{68}Ga-PSMA PET/CT, PSA, BMI, D'Amico risk classification

Öz

Amaç: Bu çalışmanın amacı prostat kanserlerinde Gallium-68 prostat spesifik membran antijeni pozitron emisyon tomografisi/bilgisayarlı tomografi (^{68}Ga-PSMA PET/BT) kantitatif değerleri ile, hastanın obezitesi, prostat spesifik antijen (PSA) değerleri ve metastaz tipi ilişkisini değerlendirmekti.

Yöntem: Bu çalışmaya 2020-2024 tarihleri arasında prostat kanseri tanısı almış ve evreleme amacıyla ^{68}Ga-PSMA PET/BT görüntülemesi yapılan ve görüntülemede lokorejyonel veya uzak metastaz tespit edilen 112 hasta dahil edildi.

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Öz

Bulgular: Hastaların beden kitle indeks sınıflaması ile prostat bezimaksimum standart tutulum değeri (SUV_{max}), metabolik tümör hacmi (MTV), toplam lezyon glikolizi (TLG), standardize edilmiş alım değeri (SUL) ve SUV_{mean} değerleri arasında anlamlı ilişki bulunamadı. Hastaların vücut kitle indeksi (VKİ) indeksi ile PSA değeri arasında VKİ vardı (p=0,08, r=-0,248). Hastalarda kilo arttıkça PSA değerlerinde azalma tespit edildi. Hastaların lokorejyonel hastalığı ya da uzak metastazı olmasının, prostat bezi SUV_{max}, MTV, TLG, SUV_{mean} ve SUL değerleri ile anlamlı bir ilişkisi bulunamadı (p=0,25, p=0,667, p=0,244 p=0,126, p=0,057). Bununla birlikte, hastaların uzak metastaz olması veya lokorejyonel hastalığı olması ile PSA değerleri arasında anlamlı bir ilişki vardı (p=0,02). Uzak metastazı olan hastada lokorejyonel hastalığa göre PSA değerleri daha yüksek bulundu. D'Amico risk sınıflaması ile, prostat bezi SUV_{max}, TLG, SUL ve SUV_{mean} arasında da anlamlı ilişki vardı (p=0,035, p=0,037, p=0,12, p=0,028).

Sonuç: PSA değerleri metastazların lokal mi yoksa uzak mı olduğunu tahmin etmemize yardımcı olabilir. Ancak VKİ ile PSA üzerinde düşük düzeyde ters korelasyon olması sebebiyle, düşük PSA düzeylerinin obez hastalarda lokal hastalık ile sınır olmayabileceği klinik değerlendirmede mutlaka göz önünde bulundurmalıyız.

Anahtar Kelimeler: Prostat kanseri, ^{68}Ga-PSMA PET/BT, PSA, BMI, D'Amico risk sınıflaması

Introduction

Prostate cancer is the second most common cancer among men and the second leading cause of cancer-related mortality (1). Although it is often curable, the presence of metastasis at the time of diagnosis or during the course of treatment significantly worsens both treatment response and prognosis (2). Consequently, the identification of metastasis at diagnosis and staging has become a critical factor in determining treatment strategies for prostate cancer. Transrectal ultrasound, thoracoabdominal computed tomography (CT), multiparametric magnetic resonance imaging, and bone scintigraphy are commonly employed for initial clinical staging. The primary aim of clinical staging in prostate cancer is to assess the disease burden and to guide the selection of the most appropriate treatment plan for each patient.

For many years, clinical staging systems based on prostate-specific antigen (PSA) levels, Gleason score, and radiological imaging systems have been used to guide treatment planning. However, Gallium-68 (^{68}Ga) prostate specific membrane antigen (PSMA) positron emission tomography/CT (PET/CT) has emerged as the most reliable method for staging, particularly in detecting distant metastases. This nuclear medicine imaging modality is especially recommended for patients with intermediate- to high-risk prostate cancer. PSMA is a transmembrane protein consisting of 750 amino acids, significantly expressed in prostate cancer and metastases (3). As a result, it is frequently utilized in imaging for the detection of both primary tumors and metastatic lesions in prostate cancer.

This study aimed to evaluate the effectiveness of ^{68}Ga-PSMA PET/CT in detecting primary tumors and metastatic lesions in patients with metastatic prostate cancer and to investigate its correlation with obesity.

Materials and Methods

In this study, 112 patients diagnosed with prostate cancer between 2020 and 2024 who underwent ^{68}Ga-PSMA PET/CT imaging for staging purposes and in whom locoregional or distant metastasis was detected on imaging were included. Patients with no metastasis detected on ^{68}Ga-PSMA PET/CT were excluded from the study. All patients underwent biopsy from all quadrants of the prostate gland, and patients who had not received any treatment (hormonotherapy, radiotherapy, chemotherapy) or surgery were included in the imaging study. PSA values in the last month were recorded.

^{68}Ga-PSMA PET/CT images were evaluated by 2 experienced nuclear medicine specialists and ^{68}Ga-PSMA PET/CT data were recorded. Informed consent forms were obtained from the patients.

The Faculty of Medicine Dean's Office at Tokat Gaziosmanpaşa University and The University's Ethics Committee approved our study on (number: 831116987-522, date: 12.09.2024).

^{68}Ga-PSMA PET/CT Imaging Protocol

During the ^{68}Ga-PSMA PET/CT examinations, patients were administered an average of 111-185 Megabecquerel (3-5 mCi) of ^{68}Ga-PSMA. The examination included a low-dose CT scan, followed by a PET scan conducted 45-60 minutes after the injection, taking about 10 minutes in total. The CT data were used for anatomical correlation and attenuation correction, while the PET scans were employed to compute the maximum standardized uptake values (SUV_{max}).

The SUV_{max} was calculated by drawing regions of interest from the whole prostate tissue and metastatic tissue, which were considered to have the highest PSMA expression, and this value was recorded. Semi-automatic volumetric quantification of individual lesions and each patient was performed using a volume measurement software named

positron emission tomography volume computer assisted reading, which can measure metabolic tumor volume (MTV) as well as the SUV_{max} or SUV_{mean}. Total lesion glycolysis (TLG) is a quantitative value obtained from the product of SUV_{max} and MTV.

The images were evaluated by two experienced nuclear medicine specialists.

Statistical Analysis

SPSS version 24 software was used for statistical analysis. The median value was used to express descriptive quantitative data, while percentages were used to express qualitative data. Fisher's exact test and chi-square test were used to compare variables. Analytical techniques (Kolmogorov-Smirnov/Shapiro-Wilk tests) and visual methods (histograms and probability graphs) were used to assess whether the variables showed a normal distribution. Descriptive analyses were performed using the median and interquartile range for non-normally distributed variables. When analyzing data that was not normally distributed, the Mann-Whitney U test was employed. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman's correlation coefficient test. A p-value of less than 0.05 was considered to indicate a statistically significant result.

Prostate Biopsy Protocol

All patients were started on antibiotics for prophylaxis one day before the procedure. On the day before the biopsy, 500 mg of ciprofloxacin was administered orally in the morning and evening. Antibiotics were continued in the morning and evening for 3 days after the procedure. The day before the biopsy, rectal cleansing was achieved using an enema. A 12-quadrant biopsy was taken from the prostate gland. The biopsy needle and automatic biopsy gun used were Angiotech Tru-Core I (Florida, USA).

Results

The study included 112 patients, with a mean age of 70.5 years (range: 31-85 years). The mean PSA level was 46.35 ng/dL, which ranged from 2.15 to 5000 ng/dL. Among the patients, 13 (11.6%) had a Gleason score of 6, 27 (24.1%) of 7, 32 (28.6%) of 8, 25 (22.3%) of 9, and 15 (13.4%) of 10. For ISUP scoring, 13 patients (11.6%) had a score of 6, 6 patients (5.4%) hadscore of 7 (3+4), 22 patients (19.6%) had score of 7 (4+3), 31 patients (27.7%) had score of 8, and 40 patients (35.7%) had a score of 9-10.

According to the D'Amico risk classification, the number of low-risk patients was 3 (2.7%) medium-risk patients was 6 (5.4%) high-risk patients was 103 (92%).

According to body mass index (BMI), 1 patient (0.9%) was underweight, 35 patients (31.3%) were normal-weight, 49 patients (43.8%) were overweight, 22 patients (19.6%) were obese, and 5 patients (4.5%) were severely obese. The PSA value of the only underweight patient was 149 ng/dL. The mean PSA value of 35 normal-weight patients was 100 ng/dl. 49 overweight patients had a mean PSA value of 45.9 ng/mL. The 22 obese patients had a mean PSA value of 19.93 ng/dL, and 5 extremely obese patients had a mean PSA value of 82.6 ng/dL. A low correlation was observed between PSA values and BMI in the patients (p=0.08, r=-0.248).

The SUV_{max} for the prostate gland was 38.9 in the only underweight patient. Among 35 normal-weight patients, the median SUV_{max} value was 16.2 (ranging from 3.9 to 55.8). For the 49 overweight patients, the median SUV_{max} was 15.4 (with a range of 1 to 123).

The 22 obese patients exhibited a median SUV_{max} value of 12.75 (ranging from 3.9 to 40.5), while the 5 extremely obese patients had a median SUV_{max} value of 40.2 (ranging from 8.7 to 55.6). No significant correlation was observed between the SUV_{max} value of the prostate gland and BMI (p=0.128) (Table 1). There was also no significant correlation between prostate gland MTV, TLG, SUL, and SUV_{mean} (p=0.363, p=0.558, p=0.247, p=0.085).

Table 1. Relationship between BMI and prostate gland SUV_{max} and PSA value

	BMI					p-value
	Underweight <18.5	Normal 18.5-24.9	Overweight 25- 29.9	Obese 30- 34.9	Extremely obese 35- 39.9	
Prostate gland SUV_{max} (median) (min-max)	38.9	16.2 (3.9-55.8)	15.4 (1-123)	12.75 (3.9-40.5)	40.2 (8.7-55.6)	p=0.128
PSA value ng/dL	149 ng/dL	100 ng/dL	45.9 ng/dL	19.93 ng/dL	82.6 ng/dL	p=0.008 r=-0.248

*: p<0.05, significant, BMI: Body mass index, SUV_{max}: Maximum standard uptake values, PSA: Prostate-specific antigen

There was no correlation between BMI and D'Amico classification. Of the 3 low-risk patients, 1 (33.3%) was obese and 2 (66.7%) were overweight. Of the 6 patients with medium risk, 2 (33.3%) were normal weight, 2 (33.3%) were overweight, and 2 (33.3%) were obese. Of 103 high-risk patients, 1 (1%) was underweight, 33 (32%) were normal weight, 45 (43.7%) were overweight, 19 (18.4%) were obese, and 5 (4.9%) were extremely obese (p=0.467) (Table 2).

A correlation was observed between D'Amico risk groups and prostate SUV_{max} values (p=0.035). In the low-risk group, the median SUV_{max} value of the prostate gland was 6.8 (ranging from 6.4 to 8.7), while in the medium-risk group, it was 6.2 (ranging from 3.9 to 34.8), and in the high-risk group, it was 16.6 (ranging from 1 to 123). The SUV_{max} values of the prostate gland were elevated in the high-risk group. There were also significant associations between D'Amico risk classification and prostate gland TLG, SUL and SUV_{mean} (p=0.037, p=0.012, p=0.028). However, there was no significant association between prostate gland MTV value and D'Amico classification (p=0.366).

Seventy-six patients with distant metastases had a mean PSA level of 63 ng/dL (range: 2.15-5000 ng/dL). No significant correlation was observed between PSA value and prostate gland SUV_{max}, MTV, TLG, SUL, and SUV_{mean} (p=0.881, p=0.602, p=0.630, p=0.995, p=0.875). Thirty-six patients with locoregional metastases had a mean PSA value of 31.15 ng/mL (range: 3-495 ng/mL). The PSA value was significantly higher for patients with distant metastasis compared to patients with locoregional metastasis only (p=0.02).

Thirty-six patients (32.1%) had locoregional metastases while 76 patients (67.9%) had distant metastases. Thirty-eight patients (33.9%) had only bone metastases. Fourteen patients (12.5%) had bone and distant lymph node metastases. There were 4 patients (3.6%) with solid organ metastases only. There were 6 patients (5.4%) with both bone and solid organ metastases. One patient (0.9% of the cohort) had solid organ and distant lymph node metastasis. Six patients (5.4%) had only distant metastasis to lymph nodes. Five patients (4.5%) had bone, distant lymph node, and solid organ metastases.

According to D'Amico's classification, 31 out of 36 patients (86.1%) with locoregional disease were classified as high-risk, 2 patients (5.6%), were classified as low-risk, and 3 patients (8.3%), were categorized as intermediate-risk. Among the 76 patients with distant metastasis, 72 patients (94.8%) were classified as high-risk, 3 patients (3.9%) as intermediate-risk, and 1 patient (1.3%) as low-risk. Of the 38 patients with only bone metastases, 37 patients (97.4%) were in the high-risk group, and 1 patient (2.6%) was in the low-risk group. No patients were classified within the intermediate-risk group. All 14 patients with both bone and distant lymph node metastases were classified as high-risk, as were all 4 patients with only solid organ metastases. Among the 6 patients with both bone and solid organ metastases, 5 patients (83.3%) were in the high-risk group, 1 patient (16.7%) was in the intermediate-risk group, and none were classified as low-risk. Only 1 patient with both solid organ and distant lymph node metastasis was classified as high-risk. Of the 8 patients with only distant lymph node metastasis, 6 (75%) were in the high-risk group, and 2 (25%) were in the intermediate-risk group. No significant correlation was observed between D'Amico risk groups and metastasis localization (p=0.452).

Furthermore, no significant correlation was observed between D'Amico classification and the presence of distant metastasis or locoregional disease (p=0.257). The presence of locoregional disease or distant metastasis was not significantly associated with prostate gland SUV_{max}, MTV, TLG, SUVmean and SUL values (p=0.25, p=0.667, p=0.667, p=0.244, p=0.126, p=0.057). However, a significant correlation was observed between the presence of distant metastasis or locoregional disease and PSA levels (p=0.02). The average PSA value for the 76 patients with distant metastasis was 63 ng/mL (range: 2.15-5000 ng/mL), whereas the average PSA value for the 36 patients with locoregional disease was 31.15 ng/mL (range: 3-495 ng/mL).

Table 2. Relationship between BMI and D'Amico risk classifications

	BMI					**p-value**
D'Amico risk classifications	Underweight <18.5	Normal 18.5-24.9	Overweight 25-29.9	Obese 30-34.9	Extremely obese 35-39.9	
Low-risk	0 (0%)	0 (0%)	2 (66.7%)	1 (33.3%)	0 (0%)	p=0.467
Medium-risk	0 (0%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	0 (0%)	
High-risk	1 (1%)	33 (32%)	45 (43.7%)	19 (18.4%)	5 (4.9%)	

BMI: Body mass index

Discussion

The D'Amico classification is the most widely used system for assessing metastatic risk in prostate cancer. ^{68}Ga-PSMA PET/CT is the most sensitive imaging modality for staging prostate cancer, especially in patients classified as intermediate to high risk. The majority of our patients were classified as high-risk all of whom exhibited metastases on ^{68}Ga-PSMA PET/CT. Although not statistically significant, metastases were detected in 3 patients classified as the low-risk group and 6 patients in the intermediate-risk group; however, not all patients in these groups were metastatic. No significant correlation was observed between metastasis location and the D'Amico risk classification. However, a significant correlation was observed between D'Amico risk classification and the SUV_{max} values of the prostate gland. Significant associations were also observed between the D'Amico risk classification and TLG, SUV_{mean}, and SUL values. As the risk classification increased, PSMA uptake in the prostate gland correspondingly increased. Our literature review revealed that similar studies investigating the relationship between the D'Amico risk classification and prostate gland SUV_{max} values in prostate cancer patients have likewise reported significant findings. Significant associations were also observed between the D'Amico risk classification and TLG, SUV_{mean}, and SUL values. In the same study, a significant relationship was reported between the D'Amico risk classification and both SUV_{max} and MTV. However, in our study, no significant correlation was found between the D'Amico classification and MTV (4).

For instance, Koerber et al. (5), in a study involving 104 patients, demonstrated that PSMA uptake levels increased with higher D'Amico risk classifications. Similarly, Ekmekçioğlu et al. (6) and Liu et al. (7) reported findings consistent with ours, showing increased PSMA uptake levels in the prostate gland in patients in the high-risk group.

No significant correlation was observed between PSA values and quantitative PET/CT measurements of the prostate gland in our study. However, Jafari et al. (8) reported a significant correlation between PSA levels and all PET/CT parameters. This discrepancy may be attributed to all patients in our study having metastatic disease.

No significant correlation was observed between the presence of distant metastasis or locoregional disease and prostate gland SUV_{max} values. However, the general trend of higher SUV_{max} values in high-risk patients suggests that an increased SUV_{max} may be associated with a greater likelihood of metastasis. However, no significant correlation was found between SUV_{max} values and the presence of local versus distant metastases. Similarly, no significant associations were observed between other PET/CT parameters and either local or distant metastasis. Our literature review did not reveal any previous studies specifically addressing this topic. Therefore, we believe that the findings of our study provide valuable and novel insights.

However, we observed a significant association between PSA levels and the presence of distant metastasis or locoregional disease. Blackwell et al. (9) demonstrated that preoperative serum PSA values had predictive value for determining tumour burden and stage. Another study reported that the probability of lymph node involvement is less than 1% n patients with PSA levels below 20 ng/mL, suggesting that radiological imaging for staging could be minimized in this group (10). In our study, all patients were metastatic, with a median PSA level of 31.15 ng/dL in patients with locoregional metastasis and 63 ng/dL in those with distant metastasis.

The majority of our patients being overweight and obese suggested that obesity was associated with prostate cancer. However, no significant correlation was observed between BMI and prostate gland PET/CT values. According to a meta-analysis study, obesity was associated with an increased risk of prostate cancer in Europe (11). Several large cohort studies also observed a stronger association between increasing BMI and prostate cancer risk (12,13,14). However, some studies did not find an association between BMI and certain health outcomes related to obesity (15,16). Considering these contradictory results, a recent meta-analysis revealed that prostate cancer was weakly associated with an increased risk related to obesity (11). In addition, since our study included patients with locally advanced and distant metastases, and the majority of them were overweight, we think that obesity may contribute to the aggressiveness of prostate cancer. The mechanisms showing that obesity causes aggressive prostate cancer were described in Allot et al.'s (17). They suggested that low PSA levels, resulting from hemodilution due to increased blood volume in obese men, may delay or prevent prostate biopsy, potentially leading to the diagnosis of more aggressive prostate cancer (18). Additionally, the difficulty of performing digital rectal examination and the increased prostate volume in obese men may contribute to delayed cancer detection during biopsy (19,20).

Obese men had significantly lower PSA values compared to lean, and normal-weight men. Consistent with our findings, Vidal et al. (21) also reported lower PSA levels in obese and overweight patients compared with normal-weight patients. Other studies have indicated that obesity

is associated with reduced PSA levels, which may in turn decrease the rate of cancer detection (22,23). Further research is warranted to better understand this relationship.

Study Limitation

The limited number of patients and the retrospective nature of the study are among the limitations of our study. In addition, not all metastases could be confirmed histopathologically.

Conclusion

There are numerous treatment options for prostate cancer, with staging being the most critical factor in determining effective management. Consequently, the detection and localization of metastases are of paramount importance. In our study, we would like to emphasize that metastasis is present in a large proportion of patients in the high-risk class in the D'Amico risk classification. However, considering the possibility of distant metastasis in the low- and intermediate-risk class, ^{68}Ga-PSMA PET/CT may also be recommended in the staging of these patients. We would like to emphasize that although PSA values carry important information about the stage of the disease, they may not reflect the reality in overweight or obese patients and should be taken into consideration in clinical evaluation.

Ethics

Ethics Committee Approval: The Faculty of Medicine Dean's Office at Tokat Gaziosmanpaşa University and The University's Ethics Committee approved our study on (number: 831116987-522, date: 12.09.2024).

Informed Consent: Our study was retrospective, and informed consent was obtained from the patients.

Footnotes

Authorship Contributions

Concept: Z.H., Design: Z.H., Data Collection or Processing: O.U., Analysis or Interpretation: Z.H., Literature Search: O.U., Z.H., Writing: O.U., Z.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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