Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2026;51(1):254-261
DOI: 10.17826/cumj.1858822

RESEARCH

Assessment of changes in physiologic distribution of 68Ga-PSMA in normal tissues relative to tumor burden in patients undergoing PET/CT for prostate cancer

Prostat kanseri için PET/CT uygulanan hastalarda tümör yüküne göre normal dokularda 68Ga-PSMA'nın fizyolojik dağılımındaki değişikliklerin değerlendirilmesi

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Abstract

Purpose: This study aimed to evaluate changes in 68Ga-PSMA (Prostate-specific membrane antigen) uptake in normal tissues according to prostate cancer (PC) tumor burden, as assessed by PET/CT.

Materials and Methods: This retrospective study included 213 consecutive patients with histologically confirmed PC who underwent 68Ga-PSMA PET/CT imaging. Based on PET/CT findings, patients were categorized into three groups according to 68Ga-PSMA expression: 1) PSMA-negative prostate cancer; 2) local disease: PSMA uptake limited to the prostate gland and/or pelvic region; 3) metastatic disease: presence of extrapelvic and/or distant PSMA-avid lesions.

Results: Among the 213 patients, 68Ga-PSMA PET/CT imaging revealed normal PSMA distribution in 57 patients (26.8%), localized disease in 88 patients (41.3%), and metastatic involvement in 68 patients (31.9%). In the metastatic disease group, the mean SUVmax values were significantly lower in the lacrimal, parotid, and submandibular glands, as well as in the spleen, kidneys, and bowel, compared to the PSMA-negative prostate cancer and local disease groups. In contrast, prostate SUVmax was markedly higher in the metastatic group.

Conclusion: This study demonstrates that 68Ga-PSMA uptake in normal tissues decreases with increasing metastatic tumor burden, particularly in salivary glands, kidneys, and lacrimal glands.

Keywords:. Prostate-specific membrane antigen; prostate cancer; 68Ga-PSMA PET/CT.

Öz

Amaç: Bu çalışma, prostat kanseri (PK) tümör yüküne göre normal dokulardaki 68Ga-PSMA (Prostat spesifik membran antijeni) tutulumundaki değişiklikleri PET/BT ile değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya, histolojik olarak doğrulanmış PK tanısı konmuş ve 68Ga-PSMA PET/BT görüntülemesi yapılmış ardışık 213 hasta dahil edildi. PET/BT bulgularına dayanarak, hastalar 68Ga-PSMA ekspresyonuna göre üç gruba ayrıldı: 1) PSMA negatif prostat kanseri; 2) lokal hastalık: PSMA tutulumu prostat bezi ve/veya pelvik bölge ile sınırlı; 3) metastatik hastalık: pelvik dışı ve/veya uzak PSMA tutulumlu lezyonların varlığı.

Bulgular: Toplam 213 hastanın 57'sinde (%26,8) normal PSMA dağılımı, 88'inde (%41,3) lokal hastalık ve 68'inde (%31,9) metastatik tutulum saptandı. Metastatik hastalık grubunda ortalama SUVmax değerleri lakrimal, parotis ve submandibular bezler ile dalak, böbrekler ve bağırsaklarda PSMA-negative prostate kanseri ve lokal hastalık gruplarına kıyasla anlamlı derecede daha düşüktü. Buna karşılık, prostat SUVmax değeri metastatik grupta belirgin şekilde daha yüksekti.

Sonuç: Bu çalışma, metastatik tümör yükü arttıkça normal dokulardaki ^{68}Ga-PSMA tutulumunun azaldığını; özellikle tükürük bezleri, böbrekler ve lakrimal bezlerde belirgin düşüş olduğunu göstermektedir.

Anahtar kelimeler: Prostat spesifik membran antijeni; prostat kanseri; 68Ga-PSMA PET/BT.

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Received: 08.01.2026 Accepted: 23.02.2026

INTRODUCTION

Prostate cancer (PC) remains one of the most frequently diagnosed malignancies among men worldwide and continues to represent a significant cause of cancer-related morbidity and mortality[1-3]. Accurate assessment of disease extent at initial diagnosis is essential for risk stratification, treatment selection, and prognostic evaluation. In recent years, positron emission tomography/computed tomography (PET/CT) using prostate-specific membrane antigen (PSMA) ligands has transformed the imaging landscape of PC, demonstrating superior sensitivity and specificity compared with conventional imaging modalities, particularly in high-risk and recurrent disease[1,3,4]. In this context, positron emission tomography/computed tomography (PET/CT) using prostate-specific membrane antigen (PSMA) ligands has emerged as a highly sensitive and specific imaging modality for staging and restaging PC[3-5].

Prostate-specific membrane antigen is a type II transmembrane glycoprotein that is significantly overexpressed in PC cells, especially in high-grade and metastatic lesions. Upon ligand binding, PSMA is internalized, making it an ideal theranostic target for both diagnostic and therapeutic applications[4,6]. However, PSMA is also physiologically expressed in various normal tissues, notably the salivary and lacrimal glands, kidneys, small intestines, and liver, leading to non-specific uptake in these organs[7-9]. The unintended uptake in these organs presents a challenge during PSMA-targeted therapies, potentially resulting in irreversible toxicity[4,8,10].

The clinical relevance of this physiological uptake has become increasingly apparent in the era of PSMA-targeted radioligand therapy (PRLT). Salivary gland toxicity, particularly xerostomia, remains one of the most common dose-limiting adverse effects of 177Lu-PSMA and 225Ac-PSMA treatments[10-11]. Similarly, renal radiation exposure requires careful dosimetric consideration given tubular PSMA expression and tracer excretion pathways[10-11]. Hence, understanding the biodistribution of PSMA ligands in normal tissues is critical for optimizing therapeutic index, minimizing toxicity, and refining patient selection strategies[11].

Several studies have demonstrated the "tumor sink effect," a phenomenon in which increasing metastatic tumor burden is associated with reduced PSMA ligand uptake in normal tissues[5,8,11-14]. This is hypothesized to result from competitive binding and preferential redistribution of the radiotracer toward tumor sites with high PSMA expression, thereby limiting tracer availability for physiological uptake.

Moreover, PSMA uptake in cases of metastatic disease can alter the distribution of these ligands in non-tumor tissues, with radionuclide uptake in normal organs often dependent on tumor burden. Previous studies have reported reductions of up to 58–64% in PSMA uptake in normal organs, particularly the salivary glands and kidneys, among patients with high tumor burden [5,8,11]. However, most prior studies focused on visual assessment or small cohorts, with limited organ-specific quantitative data.

We hypothesized that a higher metastatic tumor burden would be associated with decreased radiopharmaceutical uptake in normal PSMA-expressing tissues, consistent with a clinically measurable tumor sink effect.

Therefore, the aim of this study was to systematically assess organ-specific changes in 68Ga-PSMA biodistribution in normal tissues according to tumor burden in patients undergoing PET/CT for prostate cancer, using standardized SUV-based quantitative analysis.

MATERIALS AND METHODS

Study design and sample

This retrospective observational study included 213 consecutive male patients with histopathologically confirmed PC who underwent initial staging with ^{68}Ga-PSMA PET/CT at the Prof. Dr. Cemil Taşçıoğlu City Hospital Nuclear Medicine Clinic. The mean patient age was 70.39 ± 8.14 years (range: 45–88 years). Only treatment-naïve patients referred for primary staging and imaged at our institution were eligible for inclusion. Patients were excluded if they had received any prior local or systemic therapy for prostate cancer (including prostate surgery, radiotherapy, androgen deprivation therapy, or chemotherapy), had a concomitant second primary malignancy at the time of imaging, demonstrated radiotracer extravasation at the injection site, or had an inappropriate injection-to-imaging interval that could affect quantitative assessment.

Based on PET/CT findings, patients were categorized into three groups according to 68Ga-

PSMA expression: 1) PSMA-negative prostate cancer; 2) local disease: uptake limited to the prostate gland and/or pelvic region; 3) metastatic disease: presence of extrapelvic and/or distant PSMA-avid lesions.

Procedure

The study protocol was reviewed and approved by the Ministry of Health of Türkiye and the Local Ethics Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (approval date: 22 May 2018; Decision No: 2018/913). Written informed consent was obtained from all participants. All procedures were conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines.

Radiolabelling of 68Ga-imaging and image acquisition

The PSMA-targeting ligand 68Ga-PSMA I&T was synthesized using a fully automated, Good Manufacturing Practice-compliant procedure with a GRP synthesis module (SCINTOMICS GmbH, Germany) connected to a $^{68}Ge/^{68}Ga$ generator (iThemba Labs, South Africa) and equipped with a disposable single-use cassette kit (ABX, Radeberg, Germany). Radiochemical purity and labeling efficiency were assessed using radiothin-layer chromatography and radiohigh-performance liquid chromatography (HPLC). Only preparations with ≥95% radiochemical purity were used. Each patient received 65–178 MBq (mean ± SD, 113.3 ± 21.2 MBq) of 68Ga-PSMA I&T intravenously. PET/CT imaging was performed approximately 60 minutes post-injection. Patients were encouraged to hydrate well and void before imaging to reduce urinary activity.

Whole-body PET/CT scans were acquired using a Siemens Biograph 6 full-ring HI-REZ LSO PET/CT scanner (Chicago, IL, USA) with a six-slice CT system. First, a low-dose, non-contrast-enhanced CT was performed (parameters: 40–60 mAs, 140 kV, 5 mm slice thickness) for attenuation correction and anatomical localization. Subsequently, PET imaging was conducted in the caudocranial direction, with 3 minutes of acquisition per bed position. All PET images were reconstructed using an iterative algorithm.

Image analysis and quantification

Quantitative image analysis was performed on attenuation-corrected PET images. Circular regions of interest (ROIs) were drawn on attenuation-corrected transaxial PET images in the following normal tissues: lacrimal gland, parotid gland, submandibular gland, mediastinal blood pool, liver, spleen, kidneys, intestines, bone marrow, urinary bladder, and prostate gland. For each region, the maximum standardized uptake value (SUVmax) was recorded to quantify radiotracer accumulation.

SUVmax measurements were performed using standardized circular regions of interest (ROIs). For bilateral organs (parotid, submandibular, lacrimal glands), measurements were obtained from the visually unaffected side or averaged if symmetrical. Liver measurements were obtained from a 3-cm spherical ROI placed in the right hepatic lobe, avoiding focal lesions. In patients with hepatic metastases, ROIs were positioned in tumor-free parenchyma. The mediastinal blood pool was measured at the level of the ascending aorta. Intestinal uptake was measured from a visually stable segment without focal pathological uptake. Bone marrow activity was assessed from the L3 vertebral body. Bladder activity was not used for comparative analysis due to variability in urinary excretion and catheterization status.

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Normality of the data distribution was assessed using the Shapiro–Wilk test. Continuous variables with normal distribution were compared among the three groups using one-way analysis of variance (ANOVA). Post-hoc comparisons were conducted with Tukey's HSD or Tamhane's T2 test, depending on variance homogeneity. For pairwise comparisons, independent-samples t-tests were applied, while paired-samples t-tests were used for bilateral organ analyses. Effect sizes were calculated using eta squared (η^2) for ANOVA and Cohen's d for pairwise comparisons. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal SUVmax cut-off values for predicting metastatic disease; the area under the curve (AUC) with 95% confidence intervals (CI) was calculated, and optimal cut-off values were determined using the Youden index (J = sensitivity + specificity − 1). A p-value < 0.05 was considered statistically significant. An a priori power analysis was conducted using G*Power software (Version 3.1.9.7; Heinrich Heine University, Düsseldorf, Germany),

assuming a medium-to-large effect size (Cohen's f = 0.30), α = 0.05, and power (1–β) = 0.80, which indicated a minimum required sample size of 111 patients; given the inclusion of 188 patients, the study was considered adequately powered. A two-tailed p-value < 0.05 was regarded as statistically significant.

RESULTS

A total of 213 patients with histologically confirmed PC were included in the study. The mean age was 70.3 ± 8.4 years, and the average administered activity of 68Ga-PSMA was 150.2 ± 39.6 MBq. Based on PET/CT findings, patients were categorized into three groups: 57 (26.8%) had no PSMA expression (PSMA-negative prostate cancer patients' group), 88 (41.3%) had disease confined to the prostate and/or pelvic region (Local disease group), and 68 (31.9%) showed extrapelvic or distant metastases (Metastatic group).

The mean c of the PSMA-negative patients' group in the lacrimal gland, parotid gland, submandibular gland, mediastinal blood pool, liver, spleen, kidneys, urinary bladder, intestine, bone marrow, and prostate gland was 11.7, 21.5, 20.8, 3.5, 8.1, 9.4,57.1, 22.9, 11.4,3.5, and 4.4, respectively. The mean SUVmax of the local disease group in the lacrimal gland, parotid gland, submandibular gland, mediastinal blood pool, liver, spleen, kidneys, urinary bladder, intestine, bone marrow, and prostate gland was 11.2, 20.05, 20.4, 3.79, 8.3, 9.45, 59.7, 17.9, 13.6, 2.9, and 15,7, respectively. The mean SUVmax of the metastatic disease group in the lacrimal gland, parotid gland, submandibular gland, mediastinal blood pool, liver, spleen, kidneys, urinary bladder, intestine, bone marrow, and prostate gland was 9.8, 16.7, 16.4, 3.5, 7.5, 8.5, 48.4, 20.6, 10.8, 2.7, 16.2, and 17.7, respectively.

SUVmax comparisons across groups are presented in Table 1. The metastatic group had statistically significantly lower SUVmax values for parotid gland (p: 0.000), submandibular gland (p: 0.000), liver (p: 0.043), spleen (p: 0.019), kidney (p: 0.000), and intestine (p: 0.005) compared to the PSMA-negative prostate cancer patients and Local disease groups ($p<0.05$). Overall, the SUVmax value was significantly lower in the PSMA-positive metastatic group than in the PSMA-negative group.

Table 1. SUVmax values were significantly reduced in the metastatic group compared to the normal and local groups in the following tissues

Tissue	Normal (Mean SUVmax)	Local	Metastatic	p-value
Lacrimal gland	11.7	11.2	9.8	0.026
Parotid gland	21.5	20.05	16.7	<0.001
Submandibular gland	20.8	20.4	16.4	0.001
Spleen	9.4	9.45	8.5	0.035
Kidneys	57.1	59.7	48.4	<0.001
Intestine	11.4	13.6	10.8	0.005
Prostate gland	4.4	15.7	17.7	<0.001

The maximum standardized uptake value: SUVmax

Table 2. ROC analysis table for detection of metastatic disease

Organ	AUC	Cut-off	Sensitivity (%)	Specificity (%)
Lacrimal gland	0.612	≤8.8	55.9	62.8
Parotid gland	0.699	≤14.0	55.9	86.2
Submandibular gland	0.698	≤16.9	66.2	68.9
Liver	0.64	≤4.6	26.5	95.2
Spleen	0.666	≤6.02	48.5	86.6
Kidneys	0.685	≤53.4	73.5	57.9
Intestine	0.676	≤9.0	67.6	64.1
Prostate gland	0.61	>16.1	50.9	73.5

Receiver operating characteristic curve: ROC

There were no significant intergroup differences in SUVmax for the mediastinal blood pool, urinary bladder, or vertebral bone marrow ($p > 0.05$). In contrast, the SUVmax value for the prostate gland was significantly higher in the metastatic group (p: 0.023; $p < 0.05$). The diagnostic performance of SUVmax values for distinguishing metastatic from non-metastatic PC was assessed using receiver operating characteristic (ROC) curve analysis across multiple PSMA-avid organs. The lacrimal gland demonstrated an area under the curve (AUC) of 0.612 (standard error [SE] = 0.04, $p = 0.007$), with an optimal cut-off value of ≤8.8, yielding a sensitivity of 55.9% and a specificity of 62.8% (Table 2).

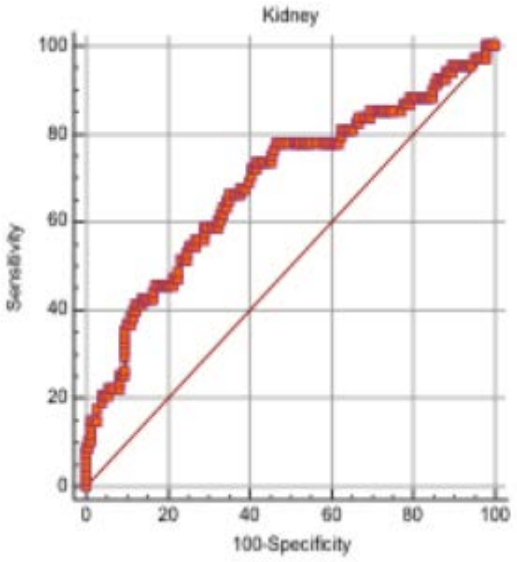

Figure 1. ROC curve for the kidney in the presence of metastasis.

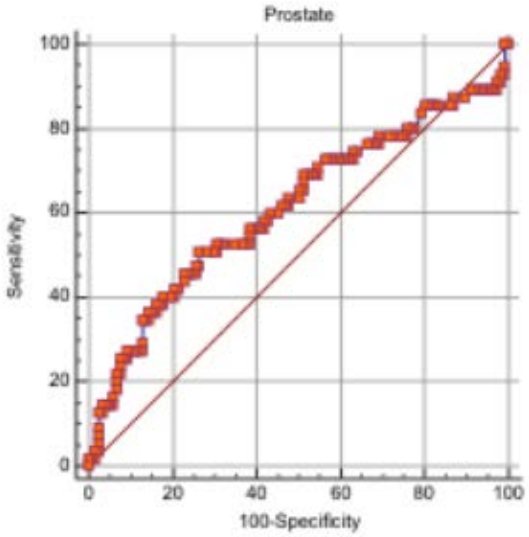

Figure 2. ROC curve for prostate in the presence of metastasis.

Among the salivary glands, the parotid gland showed an AUC of 0.699 ($p < 0.001$), with a cut-off value of ≤14.0 providing 55.9% sensitivity and 86.2% specificity. Similarly, the submandibular gland yielded an AUC of 0.698 ($p < 0.001$), with a cut-off of ≤16.9, sensitivity of 66.2%, and specificity of 68.9%.

The liver demonstrated an AUC of 0.640 ($p = 0.001$), though with relatively low sensitivity (26.5%) but high specificity (95.2%) at a cut-off of ≤4.6. The spleen showed moderate discriminatory power with an AUC of 0.666 ($p < 0.001$), a cut-off of ≤6.02, a sensitivity of 48.5%, and a specificity of 86.6%.

The kidneys had an AUC of 0.685 ($p < 0.001$), with a cut-off of ≤53.4, providing 73.5% sensitivity and 57.9% specificity. In contrast, the intestine had an AUC of 0.676 ($p < 0.001$) with a cut-off of ≤9.0, yielding 67.6% sensitivity and 64.1% specificity (Figure 1).

Finally, for the prostate gland, the AUC was 0.610 ($p = 0.026$), and a cutoff value >16.1 was associated with 50.9% sensitivity and 73.5% specificity, indicating elevated PSMA uptake in the context of metastasis (Figure 2).

DISCUSSION

This study investigated the impact of metastatic tumor burden on the physiological biodistribution of 68Ga-PSMA using PET/CT in patients with PC. Previous studies, similar to our research, have highlighted non-prostate physiological uptake of PSMA ligands, particularly in organs such as the salivary glands and kidneys[4,7,8,12,14]. This off-target uptake has raised concerns about potential toxicity in PSMA-targeted radioligand therapies, in which the salivary glands and kidneys are particularly considered dose-limiting organs[8,10]. Our findings revealed a significant reduction in SUVmax values in several PSMA-avid normal tissues, especially the salivary and lacrimal glands, kidneys, spleen, and intestines, in patients with metastatic disease.

These observations support the tumor "sink effect" hypothesis, whereby high tumor burden leads to increased PSMA ligand accumulation in metastatic lesions, thereby reducing radiotracer availability for normal tissues [8,10,11]. Gaertner et al. previously quantified this effect, reporting up to a 58% reduction in PSMA uptake in non-tumoral organs among patients with extensive metastatic spread [8]. Our findings agree, and more recent research has further validated the physiological plausibility of this competitive tracer redistribution[9,12,14].

Other studies have also shown that high tumor burden can significantly reduce PSMA uptake in normal tissues[5,8,12,14]. In our study, as in other studies, we observed a significant inverse correlation between metastatic disease spread and SUVmax values in various tumor-free, PSMA-sensitive organs, primarily the lacrimal glands, parotid and submandibular glands, kidneys, and intestines. These findings are consistent with prior studies by Demirci et al., Einspieler et al., and Zamanian et al., reinforcing the reproducibility of the tumor sink effect across different cohorts and PSMA tracers[8,9,12,14].

Clinically, this redistribution effect may be beneficial during PSMA-targeted therapies, such as 177Lu-PSMA treatment. Reduced uptake in dose-limiting organs could result in lower absorbed radiation doses, thereby decreasing adverse events such as xerostomia and nephrotoxicity [2,10,11]. Our data support the hypothesis that patients with higher tumor burden may experience lower radiotracer uptake and, consequently, potentially lower radiation dose to these critical organs, potentially allowing increased therapeutic dosing with improved safety profiles [2,15]. However, patient-specific organ dosimetry was not performed in this study, which is an important limitation given its retrospective design. The main limitations of this study are its retrospective design and the lack of volumetric tumor burden measurement.

Additional limitations include the absence of standardized pre-imaging bladder preparation and the inherent variability of SUVmax-based measurements, which may be influenced by physiological and technical factors. Incorporating quantitative metrics such as total tumor volume or PSMA expression load could enhance understanding of radiotracer distribution and refine predictive modeling of organ-specific uptake.

Prospective studies incorporating individualized dosimetric assessment and volumetric tumor quantification are warranted to clarify the true clinical impact of tumor-mediated tracer redistribution.

This potential reduction in off-target radiation exposure during therapy could optimize the therapeutic index of PRLT and help guide patient-specific treatment planning. Studies modeling peptide mass, tumor-to-organ affinity, and internalization kinetics have similarly suggested that receptor saturation and sink effects are critical considerations in optimizing dosing strategies [16-18].

Notably, in our study, the prostate gland SUVmax values were significantly higher in both the local and metastatic groups, consistent with PSMA overexpression in malignant prostate epithelium [4,6]. In contrast, no significant differences were observed in the mediastinal blood pool, urinary bladder, or bone marrow across groups, likely due to minimal PSMA expression or confounding physiological factors such as excretion kinetics and blood flow[19-21].

Furthermore, studies by Hofman et al. and Perera et al. have emphasized the diagnostic utility and sensitivity of 68Ga-PSMA PET/CT in staging high-risk PC[1,3]. Our findings suggest that organ-specific PSMA uptake patterns, modulated by tumor burden, may further enhance diagnostic interpretation and therapy planning, particularly when combined with volumetric assessments or total-lesion PSMA metrics[5,14].

This study demonstrates that the physiological uptake of 68Ga-PSMA in normal organs, particularly the salivary and lacrimal glands, kidneys, and intestines, significantly decreases in the presence of metastatic disease, supporting the tumor sink effect. These findings have clinical relevance for PSMA-targeted radioligand therapy, suggesting that higher treatment doses may be administered more safely in patients with high tumor burden due to reduced off-target uptake. Furthermore, understanding these distribution dynamics is essential for optimizing individualized imaging protocols, dosimetry, and therapeutic strategies. Future studies integrating volumetric tumor assessment and dosimetric analysis are warranted to further refine these applications and improve patient outcomes.

Author Contributions: Concept/Design : MÖT, RE; Data acquisition: RE, ÖVT; Data analysis and interpretation: HÖ, MÖT; Drafting manuscript: HÖ; Critical revision of manuscript: HÖ; Final approval

and accountability: HÖ, MÖT, RE, ÖVT; Technical or material support: RE, ÖVT; Supervision: NÖM; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained from the Ethics Committee of Okmeydanı Education and Research Hospital with the decision dated 22.05.2018 and numbered 913.
The institutional review board approved this retrospective study, and informed consent was waived.
Peer-review: Externally peer-reviewed.
Conflict of Interest: The authors declare no conflict of interest.
Financial Disclosure: No funding was received for this study.
Acknowledgement: We would like to thank all nuclear medicine physicians, nurses, and technicians at the Department of Nuclear Medicine at Prof. Dr. Cemil Taşcıoğlu City Hospital for their support.

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