

Relationship Between SUVmax and ADC Values of Metastatic Lymph Nodes Detected by Ga-68 PSMA PET/MR in Prostate Cancer Patients

Prostat Kanseri Hastalarında Ga-68 PET/MR ile Saptanan Metastatik Lenf Nodlarına Ait SUVmaks ve ADC Değerleri Arasındaki İlişki

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Abstract

Objective: Our aim is to assess if there is a relationship between maximum standardized uptake (SUVmax) and apparent diffusion coefficient (ADC) values of reactive and metastatic lymph nodes, also to compare ADC values of reactive and metastatic lymph nodes in prostate cancer patients.

Materials and Methods: We have retrospectively investigated 20 patients diagnosed with prostate cancer who underwent Ga-68 PSMA PET/MR imaging. Three metastatic and three reactive lymph nodes classified according to PSMA Ga-68 uptake in PET/MR were chosen for each patient. SUVmax and ADCmean values were calculated for each lymph node separately. SPSS version 22 was used for statistical analysis.

Results: A total of 120 lymph nodes in 20 prostate cancer patients were assessed. There was a weak negative correlation between SUVmax values and ADCmean values of metastatic lymph nodes ($p=0.009$, $r=-0.333$). However, there was no significant correlation between SUVmax values and ADCmean values of reactive lymph nodes ($p=0.271$, $r=-0.144$). ADCmean values of metastatic lymph nodes were significantly lower than those of reactive lymph nodes ($p=0.0001$).

Conclusion: PET/MR, which combines both advantages of PET and MRI, is an important tool for the diagnosis and management of prostate cancer. We have found that SUVmax values of metastatic lymph nodes were inversely correlated with ADCmean values and combination of both parameters may increase the diagnostic accuracy of Ga-68 PSMA PET/MR in the detection of lymph node metastasis.

Keywords: prostate cancer, lymph node metastasis, Ga-68 PSMA, positron emission tomography

Öz

Amaç: Amacımız, prostat kanserli hastalarda reaktif ve metastatik lenf nodlarının maksimum standardize uptake değeri (SUVmaks) ile görünür difüzyon katsayısı (ADC) değerleri arasında bir ilişki olup olmadığını değerlendirmek, ayrıca reaktif ve metastatik lenf nodlarının ADC değerlerini karşılaştırmaktır.

Gereçler ve Yöntemler: Ga-68 PSMA PET/MR görüntüleme yapılmış prostat kanseri tanılı 20 hastanın görüntüleri retrospektif olarak incelendi. Her hasta için PSMA PET tutulumuna göre sınıflandırılan üç metastatik ve üç reaktif lenf nodu seçildi. SUVmax ve ADCortalama değerleri her bir lenf nodu için ayrı ayrı hesaplandı. İstatistiksel analiz için SPSS versiyon 22 kullanıldı.

Bulgular: Yirmi prostat kanserli hastada toplam 120 lenf nodu değerlendirildi. SUVmaks değerleri ile metastatik lenf nodu ADCortalama değerleri arasında düşük düzeyde negatif korelasyon vardı ($p=0,009$, $r=-0,333$). Ancak SUVmaks değerleri ile reaktif lenf nodlarının ADCortalama değerleri arasında anlamlı bir ilişki yoktu ($p=0,271$, $r=-0,144$). Metastatik lenf nodlarının ADCortalama değerleri, reaktif lenf nodlarından anlamlı derecede düşüktü ($p=0,0001$).

Sonuç: PET ve MR'in avantajlarını bir araya getiren PET/MR, prostat kanseri teşhisi ve tedavisi için önemli bir araçtır. Metastatik lenf nodlarının SUVmaks değerlerinin ADCortalama değerleri ile ters orantılı olduğunu ve her iki parametrenin kombinasyonunun lenf nodu metastazının saptanmasında Ga-68 PSMA PET/MR'in tanısal doğruluğunu artırabileceğini bulduk.

Anahtar kelimeler: prostat kanseri, lenf nodu metastazı, Ga-68 PSMA, positron emisyon tomografisi

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Introduction

According to American Cancer Society, prostate cancer is the second most common cancer among men after skin cancer and also the second most common cause of cancer related mortality among men. Early detection and treatment is crucial. Prostate specific membrane antigen (PSMA) is a type 2 integral membrane protein which is shown to be overexpressed in prostate cancer cells [1, 2]. Expression of PSMA increases with the grade of cellular dysplasia [3]. As the grade of prostate cancer increases PSMA expression also increases [4]. For imaging and therapeutic use, PSMA is radiolabeled with different radionuclides and to date Gallium-68 labeled PSMA (Ga-68 PSMA) is the most commonly used PSMA-targeted radiopharmaceutical for imaging.

Standardized uptake value (SUV) is a measure which shows uptake level in PET scan. Higher SUV values mean higher radiotracer uptake within that lesion. Apparent diffusion coefficient (ADC) is a measure of the diffusion of water molecules within tissue which is calculated for magnetic resonance imaging (MRI) lesions. Ga-68 PSMA positron emission tomography (PET) is a useful tool for the staging and follow-up of the primary disease as it shows increased uptake in PSMA- positive lesions of prostate cancer [5]. The development of integrated positron emission tomography/magnetic resonance imaging (PET/MR) devices enables simultaneous acquisition of PET and MRI, which increases the accuracy of PET imaging in prostatic as well as other soft tissue lesions [6]. Prostate cancer frequently metastasizes to regional lymph nodes and Ga-68 PSMA PET is a highly sensitive and specific imaging modality for the detection of metastatic lymph nodes [7]. Patients with higher Gleason scores show higher radiotracer uptake [8]. Maximum SUV (SUVmax) of primary prostate lesions acquired by Ga-68 PSMA PET have been shown to have positive correlation with Gleason scores [9]. Conversely, ADC values of prostate lesions, acquired from MRI images have been negatively correlated with Gleason scores [10]. Also, an inverse correlation between SUVmax and ADCmean of primary prostate lesions have been recorded and the prognostic importance of both of them for the detection of the status of lymph node metastases has been shown [11]. Similar to prostate lesions, ADC values of metastatic lymph nodes are expected to be lower than those of reactive lymph nodes [12]. In this study, we have aimed to evaluate the ADC values of metastatic and reactive lymph nodes in prostate cancer patients and to assess the relationship between ADC and PSMA SUV values, if any.

Materials and Methods

Study Population

This study was approved by the institutional Clinical Research Ethics Committee of Cerrahpasa Medical Faculty (2019/6927). Our study was conducted between 02/2017, and 04/2018. Twenty patients diagnosed with prostate cancer who underwent Ga-68 PSMA PET/MRI imaging were retrospectively included in our analysis. Mean age of the patients was $68,2 \pm 7,4$ (range: 58-82 years). All patients had verified prostate biopsy results. Gleason scores of patients are given in **Table 1**. Patients with prostate cancer diagnosis, who underwent PSMA PET imaging, and had more than three metastatic and reactive lymph nodes were included in our study. Prostate cancer patients having less than three metastatic/reactive lymph nodes were not enrolled in the study.

Imaging

Patients were imaged after intravenous injection of mean activity of $6,3 \pm 1,73$ mCi Ga-68 PSMA HBED-CC. Radiolabeling procedure was performed using a fully automated radiopharmaceutical synthesis device (Eckert & Ziegler Eurotope, Berlin, Germany). All PET/MRI images were acquired using an integrated 3 Tesla- PET/MRI scanner (GE Signa PET/MRI, GE Healthcare, Waukesha, Wisconsin, USA). Patients underwent whole body PET/MRI imaging at an average of $67,16 \pm 18,8$ minutes after injection. Sequences obtained by PET/MRI consisted of an initial localizer scan, a 3D dual-echo fast spoiled gradient recalled echo liver-accelerated volume acquisition sequence (LAVA-FLEX) for MRI based attenuation correction (MRAC), followed by a high-resolution axial T1-weighted (T1W) 3D LAVA-FLEX sequence, diffusion-weighted imaging (DWI) with b values: 50 and 1000 s/mm^2 and corresponding ADC mapping.

Image Analysis

Ga-68 PSMA PET/MRI images of 20 patients were retrospectively reviewed and analyzed using GE AW Volume Share 7 workstation (GE Medical Systems, Buc, France). Three metastatic and three reactive lymph nodes were chosen for each patient according to PSMA PET findings. Lymph nodes which showed markedly increased Ga-68 PSMA uptake compared to background activity were considered as metastatic (**Figure 1**). Inguinal lymph nodes without significant PSMA uptake or any morphological appearance suspicious for metastasis (including

Table 1. Gleason scores and PSA values of the patients

Gleason score	Number of patients (median PSA values ng/ml)
3+3	1 (628.0)
3+4	4 (42.0; range: 0.2- 81.4)
4+3	5 (13.2; range: 1.1- 21.6)
4+4	3 (22.2; range: 8.5- 84.3)
4+5	3 (119.3; range: 52.1-155.2)
5+4	3 (207.1; range: 58.3- 934.4)
5+5	1 (18.8)

PSA: prostate specific antigen

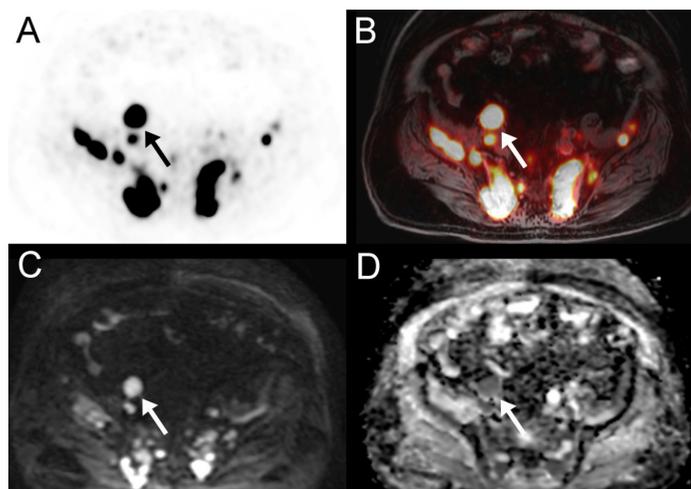


Figure 1. A 79-year-old patient with Gleason score 5+5 prostate cancer. Metastatic common iliac lymph node is shown with arrow (SUVmax 37,5 gr/ml; ADCmean 0,000812 mm²/s). A: PET image; B: PET/MR fusion; C: DWI (b:1000); D: ADC

abnormal size, shape and cortical thickness) were regarded as reactive lymph nodes (**Figure 2**). SUVmax and ADCmean values were calculated for each lymph node separately by drawing a region of interest (ROI) within each lymph node.

Statistical Analysis

SPSS software version 22 (IBM Corp., Armonk, New York, USA) was used for statistical analysis. P<0.05 was accepted as the level of statistical significance. Normal distribution of the values in the population was confirmed by both the Kolmogorov-Smirnov test and the histogram curves. Linear regression analysis was performed to determine the relationship between SUVmax and ADCmean values, and Spearman correlation analysis to determine the significance of this relationship. Student T-test was performed to analyze the relationship between ADC values. ROC analysis for ADC values was also made.

Results

A total of 120 lymph nodes in 20 prostate cancer patients with Gleason scores of 3+3 (n=1), 3+4 (n=4), 4+3 (n=5), 4+4 (n=3), 4+5 (n=3), 5+4 (n=3), and 5+5 (n=1) were assessed (**Table 1**). SUVmax and ADCmean values of the lymph nodes are given in **Table 2**. SUVmax values of metastatic and reactive lymph nodes were between 5.57-62.53 and 0.20-2.51, respectively. Mean (±SD) SUVmax and SUVmean values for metastatic lymph nodes were 19.17 (±13.60) and 12.63 (±7.78), respectively. Mean (±SD) ADC values for metastatic and reactive lymph nodes were 9.78 (±2.71) and 13.3 (±4.52), respectively (**Figure 3**).

ADCmean values of metastatic lymph nodes were significantly lower than those of reactive lymph nodes (p=0.0001). Cut-off value for ADC was calculated as 0,001595 (sensitivity: 30%, specificity: 98%). There was a weak negative correlation between SUVmax values and ADCmean values of metastatic lymph nodes (p=0.009, r=-0.3) (**Figure 4a**). However, there was no significant correlation between SUVmax values and ADCmean values of reactive lymph nodes (p=0.271, r=-0.2) (**Figure 4b**).

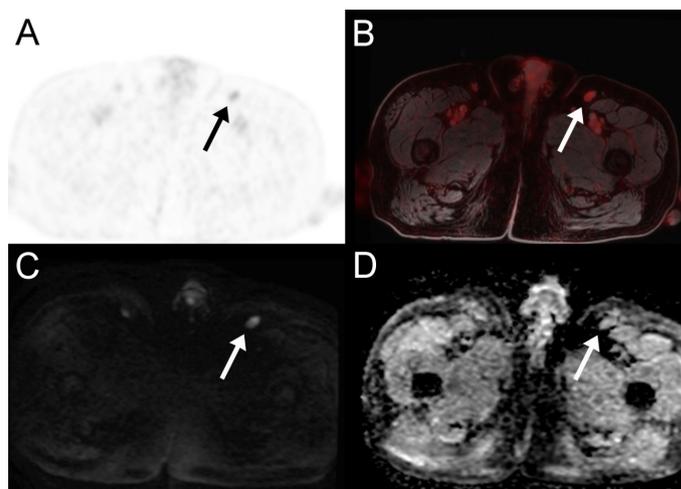


Figure 2. A 53-year-old patient with Gleason score 4+3 prostate cancer. Lower SUVmax and higher ADCmean values for reactive left inguinal lymph node is shown with arrow (SUVmax 2,51 gr/ml; ADCmean 0,00170 mm²/s). A: PET image; B: PET/MR fusion; C: DWI (b:1000); D: ADC

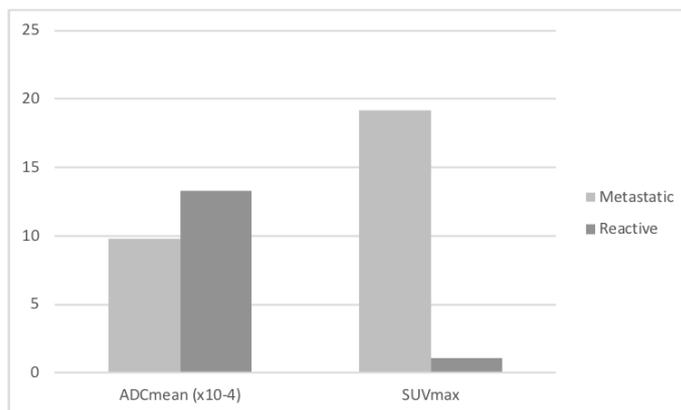


Figure 3. Comparison of ADCmean and SUVmax values of metastatic and reactive lymph nodes. Metastatic lymph nodes have lower ADCmean values and higher SUVmax values

Discussion

PSMA PET is a relatively new diagnostic imaging tool for the detection of prostate cancer, however its demand for it increases rapidly. It shows higher radiotracer uptake in patients with higher Gleason scores [8], and also higher diagnostic sensitivity and specificity for lymph node metastasis [13]. PSMA PET changes prostate cancer management decisions for many patients [14, 15].

DWI is based upon the random Brownian motion of water molecules within the tissue and gives microstructural information about the tumor tissue. Normal or reactive lymph nodes also show a relatively restricted diffusion due to high cellular density. However, metastatic lymph nodes have higher cellular density, which further restricts diffusion compared to normal or reactive lymph nodes [16]. The resulting signal changes in restricted diffusion in MRI are high-signal intensity on DWI with corresponding reduced apparent diffusion coefficient (ADC) values. In our study we found lower ADC values in metastatic lymph nodes compared to reactive lymph nodes consistent with the current literature data.

Ga-68 PSMA PET targets PSMA, which is a membrane

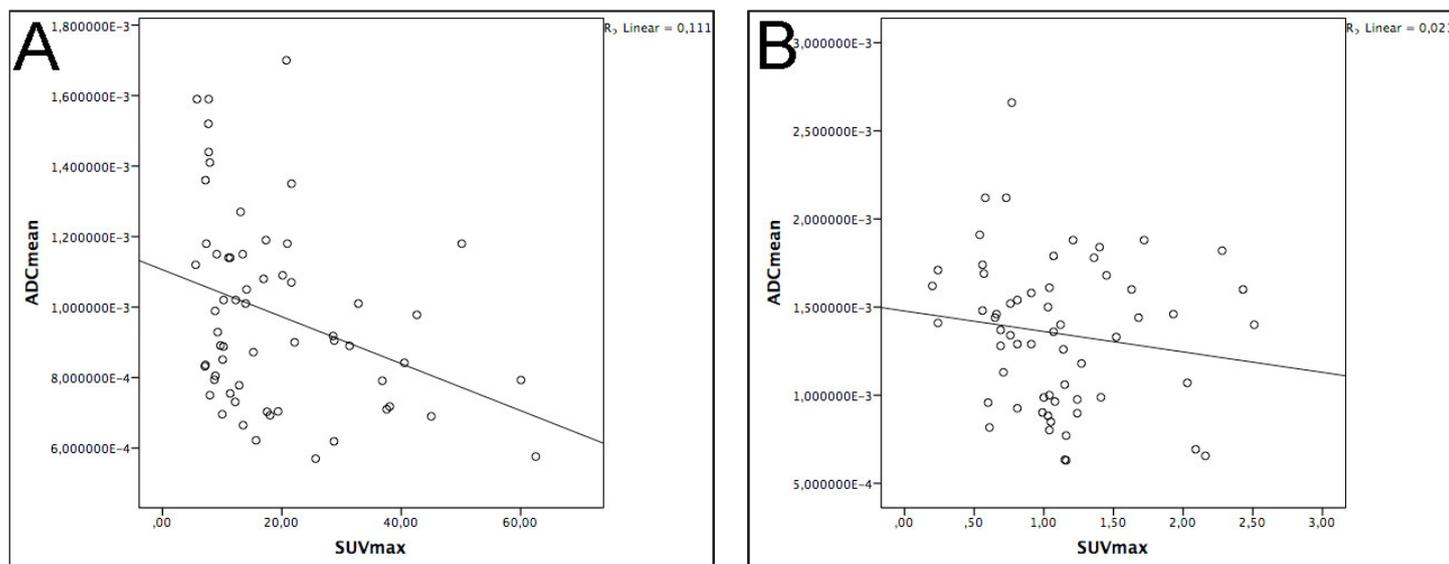


Figure 4. Correlation of ADCmean and SUVmax values. Metastatic lymph nodes have weak inverse correlation (A), whereas reactive lymph nodes do not have significant correlation (B)

Table 2. SUV and ADC values of lymph nodes

	Mean±Standard deviation	Range
Metastatic lymph nodes		
SUVmax (g/ml)	19.17±13.60	5.57-62.53
SUVmean (g/ml)	12.63±7.78	4.17-41.65
ADCmean (x10 ⁻⁴) (mm ² /s)	9.78±2.71	5.70-17.0
Reactive lymph nodes		
SUVmax (g/ml)	1.10±0.53	0.20-2.51
SUVmean (g/ml)	0.79±0.32	0.11-1.49
ADCmean (x10 ⁻⁴) (mm ² /s)	13.30±4.52	1.29-26.60

SUVmax: maximum standardized uptake value; SUVmean: mean standardized uptake value; ADCmean: mean apparent diffusion coefficient

protein expressed 100-1000-fold higher in prostate cancer cells than in normal tissues and provides metabolic information about prostate cancer cells [17]. SUV is a semi-quantitative parameter reflecting PSMA uptake of tissues. PSMA PET was shown to have positive correlation with Gleason scores [18]. Also, ADC values were shown to be inversely correlated with Gleason scores [19]. We found a weak inverse correlation between SUVmax values and ADCmean values in metastatic lymph nodes. Inverse correlation was also reported previously for bone lesions and primary prostate lesions in prostate cancer [20, 21]. Wetter et al found moderately significant inverse correlation between SUVmax and ADC values of metastatic bone lesions of prostate cancer [22]. Also, Uslu-Besli et al found an inverse relationship between SUVmax and ADC values of primary prostate lesions detected by PSMA PET/MRI [11]. Wang et al showed that ADC values had significant negative correlation with Gleason score and SUVmax in primary prostate lesions [23]. Wu et al found that minimum ADC values inversely correlated with the Gleason score in prostate lesions [24].

Most scientific articles compared SUVmax values obtained by PET/CT with MRI ADC values, however in our study we used

hybrid PET/MR machine for determining SUVmax and ADC values. Contrary to sequential PET/CT imaging, hybrid PET/MR involves simultaneous acquisition of PET and MRI images which enables excellent PET and MRI fusion, reducing the fusion-related artifacts. Also, as MRI has better soft-tissue resolution compared to CT, detection and characterization of lymph nodes is better with PET/MR compared to PET/CT.

The main limitation of our study is its small sample size. We have evaluated 120 lymph nodes in 20 patients. Lack of histopathological diagnosis of lymph nodes is another limitation of our study.

Conclusion

PET/MR, which combines both advantages of PET and MRI, is an important tool for prostate cancer diagnosis and management. ADCmean values of metastatic lymph nodes were found to be significantly lower than those of reactive lymph nodes. Also, SUVmax values and ADCmean values of metastatic lymph nodes were found to be inversely correlated. Combination of both SUVmax values and ADCmean values may reinforce each other

and increase the diagnostic accuracy of Ga-68 PSMA PET/MR in the detection of lymph node metastases.

Ethics Committee Approval: This study was approved by Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (Approval number, and registration number: 01/14/2019-6927).

Informed Consent: An informed consent was obtained from all the patients.

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – F.A., A.K., R.L.U.B.; Design – F.A., A.K., R.L.U.B.; Supervision – F.A., K.S.; Resources – M.S.S., H.B.S.; Materials – M.S.S., H.B.S.; Data Collection and/or Processing – R.L.U.B., M.S.S., H.B.S.; Analysis and/or Interpretation – F.A., R.L.U.B., K.S.; Literature Search – M.S.S., H.B.S.; Writing Manuscript – F.A., A.K., R.L.U.B.; Critical Review – F.A., K.S.

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