Original Article

Mol Imaging Radionucl Ther 2025;34:1-9 *DOI:10.4274/mirt.galenos.2025.16023*

Improved Accuracy and Reliability of PRIMARY Scoring Using Delayed [^{68}Ga] Ga-PSMA PET/CT Imaging

Geç [^{68}Ga] Ga-PSMA PET/BT Görüntüleme Yöntemi İle PRIMARY Derecelendirmesinin Doğruluğunun ve Güvenilirliğinin Artırılması

Kaan Akçay[1], Gamze Beydağı[1], Onur Erdem Şahin[2], Reşit Akyel[3], Elife Akgün[4], Özgül Ekmekçioğlu[5], Nalan Alan Selçuk[1], Türkay Toklu[1], Asiye Işın Doğan Ekici[6], Kayra Kapran[1], Levent Kabasakal[1,2]

[1]*Yeditepe University Faculty of Medicine, Department of Nuclear Medicine, İstanbul, Türkiye*
[2]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Nuclear Medicine, İstanbul, Türkiye*
[3]*Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, Clinic of Nuclear Medicine, İstanbul, Türkiye*
[4]*University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Nuclear Medicine, İstanbul, Türkiye*
[5]*University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Nuclear Medicine, İstanbul, Türkiye*
[6]*Acıbadem University Faculty of Medicine, Department of Pathology, İstanbul, Türkiye*

Abstract

Objectives: Delayed [^{68}Ga]Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) images show reduced PSMA uptake in benign lesions and increased PSMA uptake in malignant lesions. This study investigated the efficacy of PRIMARY scoring on [^{68}Ga]Ga-PSMA PET/CT images at standard versus delayed time points and assessed the potential added value of delayed imaging in PRIMARY scoring.

Methods: A total of 140 patients with biopsy results of International Society of Urological Pathology grade groups (ISUP) 1-2 who had standard (median 60 min) and delayed images (median 138 min) with [^{68}Ga]Ga-PSMA PET/CT before radical prostatectomy were included. Results were confirmed in pathological reports. For diagnostic parameters, two experienced nuclear medicine physicians, who were blinded to clinical data, independently reviewed the images, and a third physician provided consensus in cases of disagreement. PRIMARY scoring was also conducted by four nuclear medicine physicians on both images, with a 1-month interval between assessments for intraobserver agreement analyses.

Results: The percentage of lesions scored as 1-2 in PRIMARY scoring decreased from 29% to 10% in delayed images compared with standard images, whereas lesions scored as 3-5 increased from 71% to 90%. Additionally, agreement between two experienced nuclear medicine physicians regarding scoring was 66% for standard imaging and 77% for delayed imaging. The number of patients with PRIMARY score 5 increased from 31 to 46 in delayed imaging. All patients were confirmed to have clinically significant prostate cancer (csPCa). Furthermore, no csPCa of ISUP grade 3 or higher was detected in patients with a delayed PRIMARY score (dPRIMARY). The sensitivity of standard PRIMARY scoring was 71%, which increased to 92% with dPRIMARY scoring, with a consistent positive predictive value of 87% for both. Intraobserver agreement Cohen's kappa values for all observers were higher for delayed images than for standard images. Inter-observer agreement, assessed by Fleiss kappa, was 0.47 and 0.52 for standard images in rounds 1 and 2, respectively, and 0.61 and 0.72 for delayed images, respectively.

Conclusion: Decreased background activity and increased primary tumor uptake in delayed images improved differentiation between primary tumors and benign lesions, leading to better primary tumor identification. Enhanced reliability was also observed in both intraobserver and interobserver assessments of delayed images.

Keywords: Prostate-specific membrane antigen, prostate cancer, clinically significant prostate cancer, active surveillance, primary staging, prostate biopsy

Address for Correspondence: Levent Kabasakal, Yeditepe University Faculty of Medicine; İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Nuclear Medicine, İstanbul, Türkiye
E-mail: lkabasakal@tsnm.org **ORCID ID:** orcid.org/0000-0002-4050-1972
Received: 26.08.2024 **Accepted:** 23.12.2024 **Epub:** 31.01.2025 **Publication Date:** 07.02.2025

Cite this article as: Akçay K, Beydağı G, Şahin OE, Akyel R, Akgün E, Ekmekçioğlu Ö, Alan Selçuk N, Toklu T, Doğan Ekici AI, Kapran K, Kabasakal L. Improved accuracy and reliability of PRIMARY scoring using delayed [^{68}Ga] Ga-PSMA PET/CT imaging. Mol Imaging Radionucl Ther. 2025;34:1-9.

Öz

Amaç: Yapılan çalışmalarda malign lezyonların prostat-spesifik membran antijeni (PSMA) tutulumunun geç [^{68}Ga]Ga-PSMA Pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) görüntülemede belirginleştiği bildirilmiştir. Bu çalışmanın amacı [^{68}Ga]Ga-PSMA PET/BT'nin PRIMARY derecelendirmesinde etkinliğini araştırmak ve PRIMARY derecelendirmesinde geç görüntülemenin olası katkısını değerlendirmektedir.

Yöntem: Radikal prostatektomi öncesi standart (ortalama 60 dakika) ve geç (ortalama 138 dakika) [^{68}Ga]Ga-PSMA PET/BT görüntüleri olan biyopsi sonucuna göre Uluslararası Ürolojik Patoloji Derneği Derece Grupları (ISUP) 1-2 (bISUP 1-2) prostat kanseri tanılı 140 hasta çalışmaya dahil edilmiştir. Sonuçlar radikal prostatektomi sonrası patoloji raporları ile doğrulanmıştır. Tanısal parametreler için klinik verilerden habersiz iki deneyimli nükleer tıp uzmanı görüntüleri bağımsız olarak incelemiş, anlaşmazlık durumunda üçüncü bir uzman ile uzlaşma sağlanmıştır. PRIMARY derecelendirmesinin gözlemci içi uyum analizleri dört nükleer tıp uzmanı tarafından, bir ay arayla ile standart ve geç görüntüler üzerinden gerçekleştirilmiştir.

Bulgular: PRIMARY derecelendirmesi sonuçlarına göre, geç görüntülerde PRIMARY 1-2 olarak derecelendirilen lezyonların yüzdesi standart görüntülerle karşılaştırıldığında %29'dan %10'a düşerken, 3-5 olarak derecelendirilen lezyonlar %71'den %90'a yükselmiştir. Ayrıca, iki deneyimli nükleer tıp uzmanı arasındaki derecelendirme uyumu, standart görüntülemede %66 iken, geç görüntülemede %77'ye çıkmıştır. Geç görüntülemede PRIMARY 5 olan hasta sayısı 31'den 46'ya yükselmiş ve tamamının klinik önemi olan prostat kanseri (csPCa) olduğu doğrulanmıştır. Ayrıca, geç görüntülerde PRIMARY derecelendirmesi 1-2 olan hastalarda ISUP 3 veya daha yüksek derecede csPCa tespit edilmemiştir. Standart görüntülerdeki PRIMARY derecelendirmesinin duyarlılığı %71 iken, geç görüntülerde bu oran %92'ye çıkmış, her ikisi için de pozitif öngörü değeri %87 olarak sabit kalmıştır. Gözlemci-içi uyumu için Cohen's kappa değerleri, geç görüntülerde standart görüntülere göre daha yüksek bulunmuştur. Gözlemciler-arası uyumu ise Fleiss kappa ile değerlendirilmiş, 1. ve 2. değerlendirme turunda sırasıyla standart görüntüler için 0,47 ve 0,52, geç görüntüler için ise 0,61 ve 0,72 olarak bulunmuştur.

Sonuç: Geç görüntülerde arka plan aktivitesindeki azalmanın ve primer tümör tutulumundaki artışın, primer tümörün daha net bir şekilde tanımlanmasına olanak sağladığı gözlemlenmiştir. Ayrıca, bu görüntülerde hem gözlemci içi uyumun hem de gözlemciler arası uyumun güvenilirliğinin belirgin şekilde arttığı tespit edilmiştir.

Anahtar kelimeler: Prostat-spesifik membran antijeni, prostat kanseri, klinik anlamlı prostat kanseri, aktif izlem, PRIMARY derecelendirme, prostat biyopsisi

Introduction

Positron emission tomography/computed tomography (PET/CT) with [^{68}Ga]-labeled prostate-specific membrane antigen (PSMA) inhibitors ([^{68}Ga]Ga-PSMA-11 PET/CT) has emerged as a valuable modality for both staging and restaging of clinically significant prostaate cancer (csPCa) (1,2,3). However, recent studies have suggested its potential utility in the primary diagnosis of csPCa, particularly in distinguishing clinically significant csPCa from indolent forms (4,5). Notably, PSMA expression correlates positively with csPCa grade, with higher expression associated with increased disease severity and poorer prognosis (6). Molecular imaging with [^{68}Ga]Ga-PSMA PET/CT provides insights into disease at the molecular level, with PSMA uptake reflecting PSMA expression levels. Studies have indicated a direct association between maximum standardized uptake value (SUV_{max}) on [^{68}Ga]Ga-PSMA PET/CT and PSMA expression, with SUV_{max} escalating alongside higher-grade groups of csPCa (7). The PRIMARY trial was undertaken to evaluate the diagnostic roles of [^{68}Ga]Ga-PSMA PET/CT and multi-parametric magnetic resonance imaging (mpMRI) in discerning csPCa (8). Notably, the PRIMARY trial revealed a higher sensitivity [^{68}Ga]Ga-PSMA PET/CT than mpMRI, with a marked improvement observed when both modalities were combined.

The introduction of the PRIMARY score signifies a remarkable advancement in csPCa diagnosis. Incorporating factors such as the uptake pattern within the prostate gland, location within the peripheral zone, and intensity of PSMA uptake, the PRIMARY score aims to enhance diagnostic accuracy (4). Reproducibility studies have demonstrated comparable reliability to that of MRI, suggesting the potential for predicting csPCa (9). Although the PRIMARY score has been reported to achieve successful results in the diagnosis of csPCa in a selected group of patients with low-grade csPCa (10), its applicability in patients with low-grade disease remains uncertain and requires further refinement (11).

PSMA uptake varies in benign prostate lesions and in normal prostate tissue on [^{68}Ga]Ga-PSMA PET/CT. Within the PRIMARY scoring system, the first three scores are primarily aimed at differentiating benign pathologies from csPCa, with a focus on lesions predominantly located in the peripheral zone (4). It has been postulated that increased PSMA uptake outside the peripheral zone predominantly indicates benign conditions. Early studies using [^{68}Ga]Ga-PSMA PET/CT demonstrated a reduction in PSMA uptake in benign lesions and background activity on delayed images obtained 2-3 hours after injection (12,13,14,15). In contrast, PSMA uptake was observed to be constant or increased in malignant lesions. Therefore, delayed imaging may allow for a more accurate classification of benign prostate lesions, potentially improving the efficacy of the PRIMARY scoring system.

This study aimed to investigate the comparative efficacy of PRIMARY scoring on [^{68}Ga]Ga-PSMA PET/CT images acquired at standard versus delayed time points and to ascertain the potential incremental value of delayed imaging in PRIMARY scoring assessment.

Materials and Methods

Patient Population and Study Protocol

We assessed 140 treatment-naive patient records diagnosed with International Society of Urological Pathology grade groups (ISUP) 1 and 2 PCa by biopsy (bISUP) and who underwent radical prostatectomy (RP) in different hospitals. The indications for RP were patient preference, physician preference, and high D'Amico risk. The final pathology results were compared with preoperative [^{68}Ga]Ga-PSMA PET/CT imaging PRIMARY scoring data. [^{68}Ga]Ga-PSMA PET/CT imaging was performed within 3 months before RP. The initial informed consent form also included consent for future retrospective analysis. The study was approved by the Yeditepe University Rectorate Non-Interventional Clinical Research Ethics Committee (number: E.83321821-805.02.03-377, date: 15.03.2024) and was carried out in accordance with the Declaration of Helsinki.

Imaging Protocol

Preoperative [^{68}Ga]Ga-PSMA PET/CT imaging was performed with a mean dose of 240.5±67.16 MBq of [^{68}Ga]Ga-PSMA-11. The mean start time of scanning after injection was 59.5±15.8 min (median 60.0 min). Whole-body [^{68}Ga]Ga-PSMA PET/CT imaging was performed using a GE Discovery 710 PET/CT scanner with 64 CT slices from the vertex to the mid-thigh. Additional delayed pelvic imaging, which is routine in our clinic, was also acquired using 3-bed pelvic imaging at a mean of 139.1±21.3 min (median 138.0 min) after injection. Standard and delayed imaging was performed with an acquisition time of 3 min per bed position (Figure 1). Low-dose CT images were obtained for anatomical localization and attenuation correction. [^{68}Ga]Ga-PSMA PET/CT images were analyzed using the Advanced Workstation (v4.7) (GE Healthcare, WI, USA). The prostate region of interest was manually delineated for SUV_{max} measurement. The standard uptake value (SUV) calibration of the scanner was performed every 3 months as recommended by the manufacturer. The other quality control checks were regularly performed according to the recommendations of the European Association of Nuclear Medicine Guidelines (16).

PRIMARY Scoring

[^{68}Ga]Ga-PSMA PET/CT images were independently assessed by two experienced nuclear medicine physicians to determine the PRIMARY scores of both standard (sPRIMARY score) and delayed imaging (dPRIMARY score). To ensure an unbiased assessment, these physicians were blinded to the patients' clinical and pathologic data. In case of disagreement in the assignment of PRIMARY scores, a third nuclear medicine physician was consulted to reach a consensus. To assess inter- and intra-observer reproducibility, initial scoring was performed on standard imaging by four distinct nuclear medicine specialists who were blinded to both each other and the patient's clinical information. Subsequently, the same specialists repeated the procedure using only delayed [^{68}Ga]Ga-PSMA PET/CT images, while remaining blinded to the standard [^{68}Ga]Ga-PSMA PET/CT images and initial scores. Intra-observer agreement analysis involved the specialists re-assessing all images after a 1-month interval, following the same protocol as described above. In the PRIMARY scoring system used, score 2 was not divided into two subgroups;

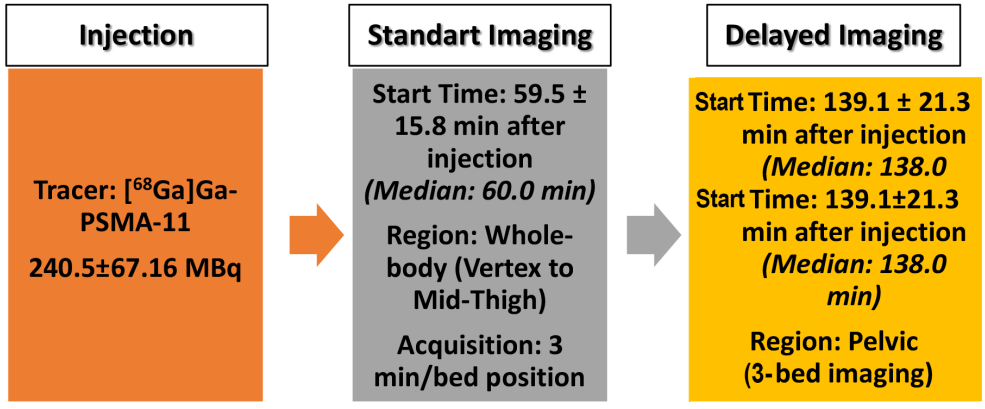

Figure 1. The imaging protocol for standard and delayed [^{68}Ga]Ga-PSMA PET/CT
PSMA: Prostate-specific membrane antigen, Min: Minimum, PET: Positron emission tomography, CT: Computed tomography

instead, both subgroups A and B were considered as group 2. Patients with a final pathological report indicating ISUP 2 or higher were diagnosed with csPCa.

Statistical Analysis

The descriptive data were used to calculate the median and mean values and the corresponding standard deviations(±). The values were analyzed using the Statistical Package for the Social Sciences, version 25.0 (IBM Corporation in Chicago, Illinois, USA). Sensitivity and specificity values for PRIMARY scoring were determined using pathologic ISUP results as a standard reference. Differences in diagnostic parameters between the sPRIMARY and dPRIMARY scores were assessed using the MedCalc proportional comparison calculator, which can be accessed at the following URL: https://www.medcalc.org. The relationship between ISUP and both sPRIMARY or dPRIMARY scores was analyzed using the Spearman correlation test. Cohen's kappa and Fleiss kappa were determined as 5 categories of the PRIMARY scoring for both imaging. Receiver operating characteristic (ROC) curves were also calculated for 5-level sPRIMARY and dPRIMARY scores. The paired samples t-test was used to compare the SUV_{max} of standard and delayed images. The Related-Samples Wilcoxon signed-rank test and McNemar's test were used to perform a comparative analysis between the sPRIMARY and dPRIMARY scores. Statistical significance was attributed to the values with a $p<0.05$ (two-sided).

Results

The mean age of the 140 men included in the study was 62.6±7.6 years (range, 43-80 years). The mean prostate-specific antigen (PSA) level was 8.5±7.2 ng/mL, with values ranging from 1.8 to 67.0 ng/mL. Regarding the preoperative biopsy results, 51 patients (36%) had bISUP 1, while 89 patients (64%) had bISUP 1 and 2, respectively. After RP, a 69% and 20% upgrade was observed in patients initially classified as bISUP 1 and a 20% upgrade in patients initially classified as bISUP 2. There was a 38% increase in bISUP in all patients to a higher value (Table 1).

Among the 140 patients, csPCa was detected in 34 (24%) patients with sPRIMARY scores 1-2 and in 86 (61%) patients with sPRIMARY scores 3-5 after RP (Tables 2,3). The sensitivity and specificity of sPRIMARY scoring in identifying csPCa were calculated to be 71% and 35%, respectively (Table 4). The positive predictive value (PPV) and negative predictive value were calculated to be 87% and 17%, respectively. The sensitivity of dPRIMARY scoring increased from 71% [confidence interval (CI): 63%-80%] to 92% (CI: 85%-96%) ($p<0.0001$) without any change in PPV. It is noteworthy that the number of patients with sPRIMARY score 5 increased from 31 to 46 with dPRIMARY score 5, all of whom were confirmed to have csPCa. Additionally, no csPCa of ISUP grade 3 or higher was detected in any of the patients with a dPRIMARY score of 1-2. The area under curves (AUCs) of sPRIMARY and dPRIMARY in the receiver operating characteristic curves (ROC) analysis were 0.616 and 0.721, respectively. The sPRIMARY and dPRIMARY scores were moderately correlated with ISUP, with Spearman-Rho values of 0.302 and 0.389, respectively.

The percentage of lesions scored as 1-2 in the PRIMARY scoring decreased from 29% in standard images to 10% in delayed images, whereas the percentage of lesions scored as 3-5 increased from 71% in standard images to 90% in delayed images ($p<0.001$ Table 2). In addition, the percentage of giving the same PRIMARY score by two experienced nuclear medicine physicians in standard imaging was 66%, which increased to 77% in delayed imaging ($p<0.05$). According to the results of Cohen's kappa analysis at standard imaging, intra-observer agreement was 0.536, 0.798, 0.593, and 0.638 for observers 1, 2, 3, and 4, respectively. The delayed images showed higher Cohen's

Table 1. Patient characteristics, biopsy findings, and histopathological findings

	Mean ± SD		**Median (range)**
Age (n=140)	62.6±7.6		63 (43-80)
PSA (n=138) (ng/mL)	8.5±7.2		6.9 (1.8-67.0)
	bISUP 1 (n=51)	bISUP 2 (n=89)	bISUP 1-2 (n=140)
ISUP 1	16 (31%)	4 (5%)	20 (14%)
ISUP 2	29 (57%)	67 (75%)	96 (67%)
ISUP 3	4 (8%)	15 (17%)	19 (14%)
ISUP 4	2 (4%)	1 (1%)	3 (2%)
ISUP 5	-	2 (2%)	2 (1%)
Upgrade	35 (69%)	18 (20%)	53 (38%)

ISUP: International Society of Urological Pathology Grade Groups, SD: Standard deviation, PSA: Prostate-specific antigen

Kappa coefficients of 0.697, 0.839, 0.769, and 0.740 for all observers, respectively, compared with the standard images, indicating better intraobserver reproducibility for delayed images (Figure 2). In the first assessment for PRIMARY scoring, the inter-observer Fleiss kappa coefficient was 0.47 for standard images and 0.61 for delayed images. In the second assessment, these coefficients increased to 0.52 for standard images and 0.72 for delayed images (Figure 3). Fleiss kappa coefficients were better for delayed images than for standard images in both sessions.

Table 2. Scanning time intervals of [^{68}Ga]Ga-PSMA PET/CT imaging and the results of the PRIMARY scoring obtained from standard and delayed imaging

	Standard imaging (n=140)	Delayed imaging (n=140)	Significance
Mean scan time ± SD (min)	59.5±15.8	139.1±21.3	
Median scan time (min)	60.0	138.0	
Mean SUV_{max}±SD	9.3±6.1	11.4±7.8	p<0.001*
PRIMARY score 1-2	**41 (29%)**	**14 (10%)**	**p<0.001****
ciPCa	7 (5%)	4 (3%)	
csPCa	34 (24%)	10 (7%)	
PRIMARY score 3-5	**99 (71%)**	**126 (90%)**	
ciPCa	13 (9%)	16 (11%)	
csPCa	86 (62%)	110 (79%)	

SD: Standard deviation, ciPCa: Clinically insignificant prostate cancer, csPCa: Clinically significant prostate cancer, PRIMARY: PRIMARY scoring system, SUV_{max}: Maximum standardized uptake value, *Paired-samples t-test **Related samples Wilcoxon signed-rank test for standard and delayed imaging PRIMARY scores

Table 3. ISUP grade groups of patients according to PRIMARY scores in patients diagnosed with bISUP 1 and 2

	PRIMARY Score	ISUP 1	ISUP 2	ISUP 3	ISUP 4	ISUP 5
Standard imaging (bISUP 1 and 2), n=140 (Spearmen Rho: 0.302)	**1**	2	19	2	-	-
	2	5	13	-	-	-
	3	2	3	-	-	-
	4	11	42	8	1	1
	5	-	19	9	2	1
Delayed imaging (bISUP 1 and 2), n=140 (Spearmen Rho: 0.389	**1**	3	8	-	-	-
	2	1	2	-	-	-
	3	1	1	-	-	-
	4	15	54	7	1	1
	5	-	31	12	2	1

ISUP: International Society of Urological Pathology Grade Group obtained after radical prostatectomy; bISUP: ISUP GG obtained after biopsy; PRIMARY: PRIMARY scoring system

Table 4. Diagnostic parameters for detecting csPCa from PRIMARY scoring in patients diagnosed as bISUP 1 and 2 (n=140) in both standard and delayed imaging

	Sensitivity	Specificity	PPV	NPV
	(95% CI)			
sPRIMARY score	71% (63%-80%)	35% (15%-59%)	87% (82%-90%)	17% (9%-29%)
dPRIMARY score	92% (85%-96%)	20% (6%-44%)	87% (85%-90%)	29% (12%-54%)
Significance*	**p<0.0001**	**p<0.05**	p>0.05	**p<0.05**

csPCa: Clinically significant prostate cancer, ISUP: International Society of Urological Pathology grade group obtained after radical prostatectomy, bISUP: ISUP GG obtained after biopsy, sPRIMARY: PRIMARY scoring for standard imaging, dPRIMARY: PRIMARY scoring for delayed imaging, NPV: Negative predictive value, PPV: Positive predictive value, CI: Confidence interval, *Statistically significant values are given bold

Additionally, inter-observer Fleiss kappa coefficients were higher in the second assessment evaluation than in the first assessment evaluation for standard and delayed images.

The mean SUV_{max} of the focal lesion, regarded as the primary tumor in the prostate gland, was 9.3±6.1 (Table 2) using standard images. The SUV_{max} significantly increased to a mean value of 11.4±7 in delayed images. The SUV_{max} was significantly higher in delayed images than in standard images ($p<0.001$, Figure 4).

Discussion

The introduction of the PRIMARY score represents a remarkable advance in the initial diagnosis of PCa using [^{68}Ga]Ga-PSMA PET/CT (4). The incorporation of the PRIMARY risk classification scheme has the potential to standardize the interpretation of lesions and allow for clearer and more objective communication between nuclear medicine physicians and clinicians (5). Nevertheless, further refinement of the PRIMARY score is required, particularly in cases of low-risk PCa (11). The purpose of PRIMARY scoring was to identify PCa in the prostate gland. However, PSMA uptake can be high under benign conditions. In such cases, PRIMARY scoring can be challenging because it is difficult to distinguish between csPCa with low PSMA expression and benign lesions with high uptake (4).

Initial studies reported that the normal prostate gland showed heterogeneous PSMA uptake and that even patients without a diagnosis of csPCa could show PSMA uptake as high as an SUV_{max} of 8.3 (17). High uptake within the prostate gland may make it difficult to distinguish csPCa with low PSMA expression. However, both early and recent studies have shown that background activity decreases in [^{68}Ga]Ga-PSMA PET/CT images taken after 2-3 hours and higher tumor/background ratios are obtained in delayed images compared with standard images (12,13,14,15). These findings may allow for better classification of benign prostate lesions and more accurate detection of masked malignant lesions. Accordingly, studies have shown that

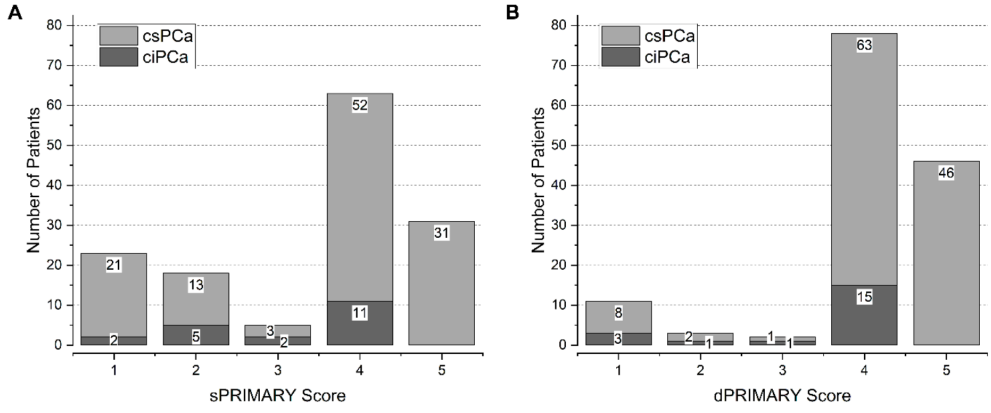

Figure 2. Distribution of ISUP groups according to primary scores obtained from standard and delayed [^{68}Ga]Ga-PSMA PET/CT
PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography, CT: Computed tomography, ISUP: International Society of Urological Pathology grade group obtained after radical prostatectomy, ciPCa: Clinically insignificant prostate cancer, csPCa: Clinically significant prostate cancer

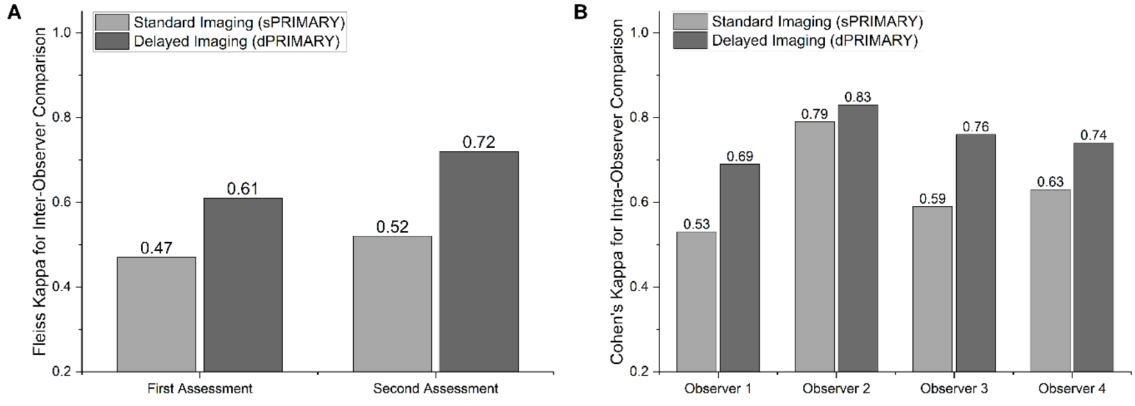

Figure 3. Intraobserver and interobserver Flesiss and Cohen's kappa analysis obtained from standard and delayed images

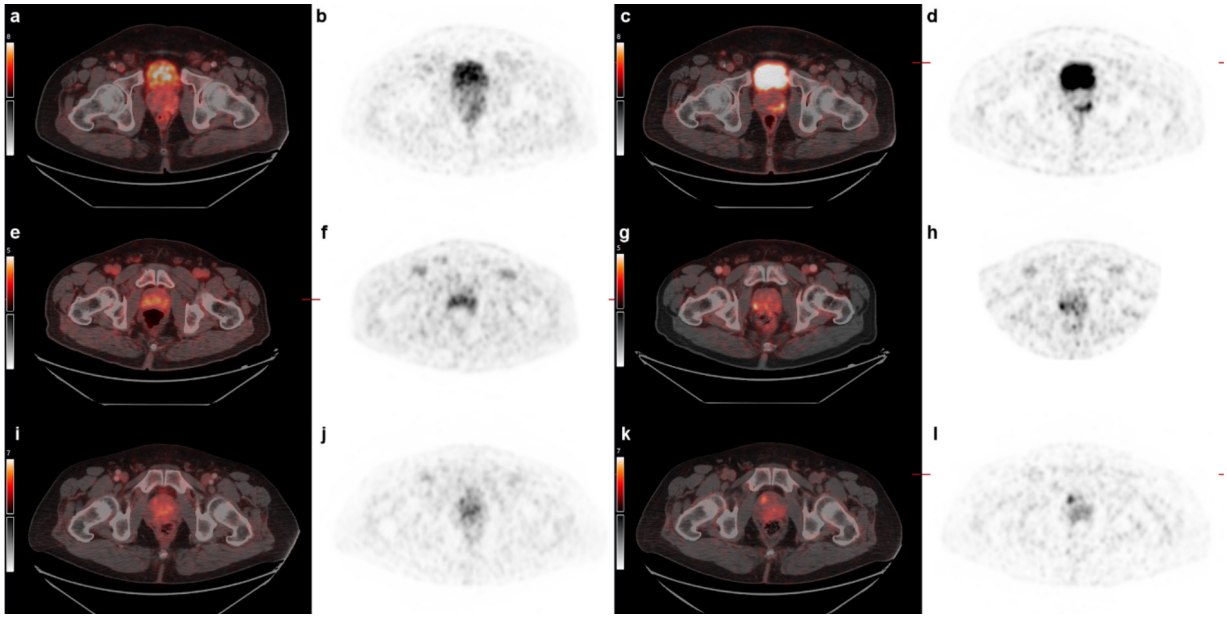

Figure 4. Standard and delayed imaging with fusion and PET/CT images of the cases. Images from different patients are presented in each line. Panels a and b display the fusion and PET images obtained during standard imaging, respectively, while panels c and d present the fusion and PET images acquired during delayed imaging. a, e, i) axial fusion images on standard images. b, f, j) axial PET images on standard images. c, g, k) axial fusion images on delayed images. d, h, l) axial PET images of delayed images.
PET/CT: Positron emission tomography/computed tomography

additional lesions that can change the stage of the disease and treatment management can be detected in up to 25% of patients in delayed images due to the higher tumor/background ratios. In our study, we observed a significant decrease in the frequency of the first two scores (from 29% to 10%) in the PRIMARY scoring on delayed images, which reflects the washout of PSMA uptake from benign lesions in delayed images ($p<0.001$). In addition, the agreement rate between two experienced nuclear medicine physicians in assigning identical PRIMARY scores during standard imaging was 66%, a rate that increased to 77% during delayed imaging ($p<0.05$).

In the aforementioned studies, it was noted that not only does the background uptake decrease in delayed images, but also the PSMA uptake of the tumor increases, resulting in enhanced visibility of the tumor (12,13,14,15). Consistent with this observation, a significant increase in SUV_{max} of the focal lesion, which is considered the primary tumor in the prostate gland, was observed in delayed [^{68}Ga]Ga-PSMA PET/CT images compared with standard [^{68}Ga]Ga-PSMA PET/CT images in our study. Decreased background activity and increased primary tumor uptake have contributed to a clearer distinction between primary tumors and benign lesions, leading to an improved identification of the primary tumor and a better assessment of its location in the peripheral zone of the prostate gland (Figure 4). Consequently, our diagnostic parameters exhibited statistically significant improvement for delayed images compared with standard images. The sensitivity of dPRIMARY scoring increased significantly from 71% to 92% compared with sPRIMARY scoring ($p<0.0001$). When comparing the AUCs of the sPRIMARY and dPRIMARY scoring in the ROC analysis, the higher AUC of the dPRIMARY score indicated superior diagnostic parameters.

For all sPRIMARY scores, Fleiss's kappa values of inter-observer reproducibility were found to be 0.47 for the first-assessment and 0.52 for the second assessment. Emmett et al. (9) found Cohen's kappa values for inter-observer reproducibility to be 0.65 for the entire sPRIMARY scoring scale. Inter-observer Fleiss's kappa values in standard images in our study were found to be lower compared to that of study by Emmett et al. (9) This difference may be explained by the presence of patients with bISUP 2 in their patient cohort and the kappa analysis with two observers instead of four. In our study, unlike the study conducted by Emmett et al. (9), PRIMARY scoring was also evaluated in delayed images. For the dPRIMARY scoring, the Fleiss's kappa coefficients were 0.61 for the first assessment and increased to 0.72 in the second assessment. The decrease in PSMA uptake in benign lesions and the increase in PSMA uptake in the primary tumor over time improved

both intra-observer and inter-observer consistency in dPRIMARY scoring. Higher consistency rates in late images were also observed for all four observers. In addition, it was consistently observed that the second assessment was better than the first assessment for both standard and delayed images. This result was considered to be related to the learning process. Even though the observers in this study were experienced in reading [^{68}Ga]Ga-PSMA PET/CT, they had not learned PRIMARY scoring before. The importance of the learning process was already emphasized by Emmett et al. (9).

In this study, as in previous studies, csPCa was detected in all patients with a PRIMARY score of 5 (4,10). Moreover, no ISUP 3-5 was detected in any of the patients with a dPRIMARY score of 1-2 after RP. This approach could have significant clinical implications and could help identify patients who should not be placed under active surveillance. he majority of patients with ISUP 1 exhibit PSMA expression and corresponding PSMA uptake; however, a subset of ISUP 2 patients lack PSMA expression and therefore show no PSMA uptake. This observation underscores the heterogeneity in prognosis among patients with ISUP 1 and 2, reflecting potential biological variability within these groups. Previously, it has been reported that the prognosis of the majority of patients with ISUP 1 is very good, 11% experience biochemical recurrence or progression, and 65% of patients with ISUP 2 do not experience recurrence (18). Additionally, it has been shown that high levels of PSMA expression may be present in some patients with ISUP 1-2 (19). The increased PSMA expression observed in patients with ISUP 1-2 may indicate poor clinical outcomes (6). Further studies on clinical outcomes are needed to clarify whether such a relationship exists or not.

The interpretation of the findings of this study requires caution due to the inherent limitations associated with retrospective studies. The patient cohort for RP introduces potential selection bias, as evidenced by the 86% incidence of csPCa, highlighting the need for careful evaluation of diagnostic parameters. However, the study focused on assessing the effectiveness of the PRIMARY SCORE in both standard and delayed images. Furthermore, the relatively elevated rate of upstaging from the bISUP might be attributable to the absence of a screening setting in the study.

Conclusion

In conclusion, when comparing standard and delayed images, a notable improvement in reliability was observed in both intra-observer and inter-observer assessments of delayed images. Furthermore, delayed images facilitated enhanced detection of csPCA patients with bISUP 1-2 that had been previously overlooked. Consequently, it can be used to distinguish individuals suitable for active surveillance in routine clinical practice.

Ethics

Ethics Committee Approval: The study was approved by the Yeditepe University Rectorate Non-Interventional Clinical Research Ethics Committee (number: E.83321821-805.02.03-377, date: 15.03.2024) and was carried out in accordance with the Declaration of Helsinki.

Informed Consent: The initial informed consent form also included consent for future retrospective analysis.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.E.Ş., R.A., E.A., Ö.E., N.A.S., A.I.D.E., Concept: L.K., Design: N.A.S., T.T., L.K., Data Collection or Processing: K.A., O.E.Ş., R.A., E.A., Ö.E., N.A.S., K.K., Analysis or Interpretation: K.A., G.B., N.A.S., L.K., Literature Search: K.A., G.B., L.K., Writing: K.A., G.B., N.A.S., T.T., L.K.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, Rutherford N, Martin JM, Frydenberg M, Shakher R, Wong LM, Taubman K, Ting Lee S, Hsiao E, Roach P, Nottage M, Kirkwood I, Hayne D, Link E, Marusic P, Matera A, Herschtal A, Iravani A, Hicks RJ, Williams S, Murphy DG; proPSMA Study Group Collaborators. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet. 2020;395:1208-1216.
2. Gultekin MH, Demirci E, Turegun FA, Kabasakal L, Sahin OE, Ocak M, Onal B, Erozenci A. The role of 68GA-PSMA PET/CT scan in patients with prostate adenocarcinoma who underwent radical prostatectomy. Urol J. 2020;18:58-65.
3. Kabasakal L, Demirci E, Nematyazar J, Akyel R, Razavi B, Ocak M, Aygun A, Obek C, Kural AR. The role of PSMA PET/CT imaging in restaging of prostate cancer patients with low prostate-specific antigen. Nucl Med Commun. 2017;38:149-155.
4. Emmett L, Papa N, Buteau J, Ho B, Liu V, Roberts M, Thompson J, Moon D, Sheehan-Dare G, Alghazo O, Agrawal S, Murphy D, Stricker P, Hope TA, Hofman MS. The PRIMARY score: using intraprostatic 68Ga-PSMA PET/CT patterns to optimize prostate cancer diagnosis. J Nucl Med. 2022;63:1644-1650.
5. Kabasakal L, Turkay R, Onal B. Incorporating the [68Ga]Ga-PSMA PET/CT PRIMARY score into the selection criteria for prostate cancer patients eligible for active surveillance. Eur J Nucl Med Mol Imaging. 2024;51:1464-1466.
6. Hupe MC, Philippi C, Roth D, Kümpers C, Ribbat-Idel J, Becker F, Joerg V, Duensing S, Lubczyk VH, Kirfel J, Sailer V, Kuefer R, Merseburger

AS, Perner S, Offermann A. Expression of prostate-specific membrane antigen (PSMA) on biopsies is an independent risk stratifier of prostate cancer patients at time of initial diagnosis. Front Oncol. 2018;8:623.

7. Demirci E, Kabasakal L, Şahin OE, Akgün E, Gültekin MH, Doğanca T, Tuna MB, Öbek C, Kiliç M, Esen T, Kural AR. Can SUVmax values of Ga-68-PSMA PET/CT scan predict the clinically significant prostate cancer? Nucl Med Commun. 2019;40:86-91.
8. Emmett L, Buteau J, Papa N, Moon D, Thompson J, Roberts MJ, Rasiah K, Pattison DA, Yaxley J, Thomas P, Hutton AC, Agrawal S, Amin A, Blazevski A, Chalasani V, Ho B, Nguyen A, Liu V, Lee J, Sheehan-Dare G, Kooner R, Coughlin G, Chan L, Cusick T, Namdarian B, Kapoor J, Alghazo O, Woo HH, Lawrentschuk N, Murphy D, Hofman MS, Stricker P. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. Eur Urol. 2021;80:682-689.
9. Emmett L, Papa N, Counter W, Calais J, Barbato F, Burger I, Eiber M, Roberts MJ, Agrawal S, Franklin A, Xue A, Rasiah K, John N, Moon D, Frydenberg M, Yaxley J, Stricker P, Wong K, Coughlin G, Gianduzzo T, Kua B, Ho B, Nguyen A, Liu V, Lee J, Hsiao E, Sutherland T, Perry E, Fendler WP, Hope TA. Reproducibility and accuracy of the PRIMARY score on PSMA PET and of PI-RADS on multiparametric MRI for prostate cancer diagnosis within a real-world database. J Nucl Med. 2024;65:94-99.
10. Akcay K, Kibar A, Sahin OE, Demirbilek M, Beydagi G, Asa S, Aghazada F, Toklu T, Selcuk NA, Onal B, Kabasakal L. Prediction of clinically significant prostate cancer by [68 Ga]Ga-PSMA-11 PET/CT: a potential tool for selecting patients for active surveillance. Eur J Nucl Med Mol Imaging. 2024;51:1467-1475.
11. Zhang J, Kang F, Gao J, Jiao J, Quan Z, Ma S, Li Y, Guo S, Li Z, Jing Y, Zhang K, Yang F, Han D, Wen W, Zhang J, Ren J, Wang J, Guo H, Qin W. A prostate-specific membrane antigen PET-based approach for improved diagnosis of prostate cancer in Gleason grade group 1: a multicenter retrospective study. J Nucl Med. 2023;64:1750-1757.
12. Afshar-Oromieh A, Sattler LP, Mier W, Hadaschik BA, Debus J, Holland-Letz T, Kopka K, Haberkorn U. The clinical impact of additional late PET/CT imaging with 68Ga-PSMA-11 (HBED-CC) in the diagnosis of prostate cancer. J Nucl Med. 2017;58:750-755.
13. Herrmann K, Bluemel C, Weineisen M, Schottelius M, Wester HJ, Czernin J, Eberlein U, Beykan S, Lapa C, Riedmiller H, Krebs M, Kropf S, Schirbel A, Buck AK, Lassmann M. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. J Nucl Med. 2015;56:855-861.
14. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, Holland-Letz T, Giesel FL, Kratochwil C, Haufe S, Haberkorn U, Zechmann CM. PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging. 2013;40:486-495.
15. Yu X, Xu L, Huang G, Liu J, Chen R, Chen Y. The image quality and feasibility of solitary delayed [68 Ga]Ga-PSMA-11 PET/CT using long field-of-view scanning in patients with prostate cancer. EJNMMI Res. 2024;14:14.
16. Koole M, Armstrong I, Krizsan AK, Stromvall A, Visvikis D, Sattler B, Nekolla SG, Dickson J; EANM Physics committee. EANM guidelines for PET-CT and PET-MR routine quality control. Z Med Phys. 2023;33:103-113.
17. Demirci E, Sahin OE, Ocak M, Akovali B, Nematyazar J, Kabasakal L. Normal distribution pattern and physiological variants of 68Ga-PSMA-11 PET/CT imaging. Nucl Med Commun. 2016;37:1169-1179.
18. Offermann A, Hohensteiner S, Kuempers C, Ribbat-Idel J, Schneider F, Becker F, Hupe MC, Duensing S, Merseburger AS, Kirfel J, Reischl M, Lubczyk V, Kuefer R, Perner S. Prognostic Value of the New Prostate Cancer International Society of Urological Pathology Grade Groups. Front Med (Lausanne). 2017;29:4:157.
19. Bravaccini S, Puccetti M, Bocchini M, Ravaioli S, Celli M, Scarpi E, De Giorgi U, Tumedei MM, Raulli G, Cardinale L, Paganelli G. PSMA expression: a potential ally for the pathologist in prostate cancer diagnosis. Sci Rep. 2018;8:4254.