Prostatic Specific Membrane Antigen Reporting and Data System (PSMA-RADS) Version 1.0: A Prospective Validation and Comparison to Updated Version (v2.0)

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Introduction

In recent years, positron emission tomography (PET) imaging with radiotracers targeting the prostate-specific membrane antigen (PSMA) has emerged as a promising tool for detecting and staging prostate cancer (PCa) [1-3]. Several PSMA-targeted PET radiotracers, such as ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, have demonstrated superior diagnostic performance compared to conventional imaging modalities [4-9]. However, the interpretation of PSMA-PET imaging can be subjective and prone to variability among readers, hindering its widespread clinical adoption [10-13]. To address this challenge, different standardized framework systems have been developed for interpreting PSMA-PET imaging, such as the PROstate cancer Molecular Imaging Standardization Evaluation (PROMISE) [14, 15] and the standardized reporting guidelines endorsed by the European Association of Nuclear Medicine (E-PSMA) [16]. While these systems aim to improve consistency and accuracy in interpretation, they are specific to certain imaging agents, requiring interpreting specialists to become familiar with multiple non-overlapping standardization frameworks [13].

In light of this, Rowe et al. proposed a Reporting and Data System (RADS) specifically for PSMA-PET/CT imaging, called PSMA-RADS version 1.0 [17, 18]. Like other RADS, the PSMA-RADS aims to reduce interpretation variability, standardize the reporting and interpretation of PSMA-PET findings, facilitate effective communication among healthcare professionals, and provide clear guidelines for clinical decision-making [13]. PSMA-RADS categorizes PSMA-PET scans and individual findings on these images into categories that reflect the likelihood of the presence of PCa. PSMA-RADS version 1.0 is organized around a 5-point scale, with higher numbers indicating a greater probability of PCa. PSMA-RADS-1 (certainly benign) indicates an absence of PCa. PSMA-RADS-2 (likely benign) suggests a low probability of PCa. PSMA-RADS-

3 (equivocal) indicates a moderate probability of PCa. PSMA-RADS-4 (highly likely malignant) suggests a high probability of PCa. PSMA-RADS-5 (almost certainly malignant) indicates the presence of PCa [17, 18].

Since its first publication in 2018, numerous studies [19-35] have been conducted to investigate the potential of PSMA-RADS v1.0 to improve diagnostic accuracy and inter-reader agreement in PSMA-PET imaging. These studies consistently demonstrated the excellent diagnostic accuracy and reliability of PSMA-RADS v1.0. However, most of these studies were retrospective or limited to case reports, highlighting the need for further research to establish the clinical utility and performance characteristics of PSMA-RADS. In 2023, an updated version of PSMA-RADS (v2.0) was developed. This version updated the PSMA-RADS framework to include a refined set of categories for optimizing lesion-level characterization, addressing deficiencies, and aiding clinical decision-making [36]. In this prospective multicenter study, we aimed to evaluate the diagnostic accuracy and reliability of PSMA-RADS v1.0 in evaluating PCa using ^{68}Ga-PSMA-11 and to compare its performance with the updated version (v2.0).

Patients and Methods

Ethical Considerations

This prospective study was conducted in accordance with international guidelines approved by the Institutional Review Board (approval number: ZU-10490). Informed consent was obtained from all patients prior to their participation in the study. Our study adhered to the ethical principles outlined in the Declaration of Helsinki.

Study Population

Between January 2023 and March 2024, a total of 208 consecutive patients were recruited from three institutions. The study cohort included patients with newly diagnosed Pca and patients with biochemical recurrence (BCR). Patients were excluded based on the following criteria: inability to undergo PET/CT scan due to weight (e.g.,>180 kg) (n= 5), claustrophobia or inability to lie still throughout the scanning duration (n= 3), allergy to contrast media (n= 2), hepatic impairment (n= 5), renal failure (n= 2), and patients lost during follow-up (n= 7). This resulted in a final cohort of 186 patients (52 with a new diagnosis and 134 with biochemical recurrence). The flowchart of the study is illustrated in Fig. 1. Once enrolled, all patients underwent a ^{68}Ga-PSMA-11 PET/CT scan. For each patient, we determined the prostate-specific antigen (PSA) value, Gleason score (GS), and disease stage according to the TNM classification (molecular imaging TM (miTNM)), as proposed by PROMISE criteria [37].

^{68}Ga-PSMA-11 PET/CT Imaging Protocol

All ^{68}Ga-PSMA PET/CT images were performed using two integrated PET/CT scanners (Ingenuity TF 128; Philips Healthcare, Cleveland, OH, USA). All patients were instructed to fast and rest for at least 6 hours before the examination. Activities, including talking, chewing, and walking, were restricted. In addition, all patients were instructed to void preceding the

examination. The patients were in a supine position with their arms above their heads. An average of 4.0 mCi ^{68}Ga-PSMA was administered intravenously (IV) according to the body weight, and the image started after almost 60 min. A low dose non-contrast CT for attenuation correction and anatomic localization from the skull vault to the mid-thigh were obtained (tube rotation time of 1 sec per revolution; 120 kV; 60 mA; 7.5 mm per rotation; and an acquisition time of 60.9 sec for a scan length of 867 mm). Immediately after CT scanning, seven or eight frames (3 min/frame) of emission PET data were obtained in the three-dimensional mode. Images of CT and corresponding functional PET images are taken in axial, coronal and sagittal planes. Diagnostic contrast-enhanced CT (CECT) scans of the thorax, abdomen, and pelvis were acquired in all patients after IV administration of 60-120 ml of non-ionic contrast agent (Ultravist 370, Bayer Schering Pharma AG, Berlin, Germany) depending on patient body weight. The CECT parameters were: 120 kV, 250 mAs, 128x0.625 collimation, 5.0 mm slice thickness and interval, 0.993 pitch, 42 cm2 field of view, 512×512 matrix, and 330 ms gantry rotation.

Image Analysis and PSMA-RADS Evaluation

All CT, attenuation-corrected PET, and fused PET/CT images were anonymized and transmitted for central review on an interactive workstation (IntelliSpace Portal V4.0; Philips Healthcare, Cleveland, Ohio, USA). Three nuclear medicine radiologists with over five years of experience independently evaluated all PET/CT images in random presentations during separate reading sessions. Before the study commenced, the radiologists underwent five hours of lecture-based and practical training, which provided detailed explanations of the PSMA-RADS classification. They were blinded to clinical data and biopsy reports. For each patient, the PET/CT scan was divided into four regions: prostate/prostate bed, regional lymph nodes (LNs), bone structures, and soft tissue (visceral structures and non-pelvic LNs). Each region was individually

evaluated for (i) the presence and intensity of uptake (none, equivocal, or intense), (ii) the relevance of the sites (typical or atypical for PCa metastases), and (iii) the clarity of the lesions on corresponding CT images (defined or not defined). The disease activity in each region was determined through qualitative and quantitative methods. The qualitative analysis was based on identifying focal ^{68}Ga-PSMA-11 uptake that exceeded background levels and was distinct from known physiological tracer uptake areas. The quantitative analysis involved measuring the maximum standardized uptake value (SUV_{max}). Subsequently, each radiologist independently assigned a PSMA-RADS category to each region and an overall PSMA-RADS score to each patient using the PSMA-RADS v1.0 criteria [14, 15]. Since the updated PSMA-RADS v2.0 was published in July 2023 during this study, the same three nuclear medicine radiologists retrospectively and independently re-reviewed the images for all patients. Using the updated PSMA-RADS v2.0 criteria [16], they independently reassigned PSMA-RADS categories to each patient. Any disagreement between the three radiologists was discussed until a consensus was reached.

Reference Standard

The primary endpoint was diagnostic accuracy on a per-patient basis. For newly diagnosed patients, the definitive diagnosis was validated by histopathological results after biopsy. Biopsies were obtained through a transrectal ultrasound (TRUS) guided procedure within two weeks before ^{68}Ga-PSMA-11 PET/CT imaging. For patients with biochemical recurrence, the final diagnosis was confirmed based on the following: (i) Histopathological findings after biopsy (n= 151 patients (55 locoregional, 96 lymph nodes, 45 bone lesions, and 42 visceral soft tissue lesions)). Biopsies were taken by ultrasound-guided (n=78) or CT-guided (n=73) procedure within two weeks before ^{68}Ga-PSMA-11 PET/CT imaging. Two experienced pathologists evaluated all

specimens, and the results were obtained by consensus. In patients with multiple lesions, the biopsy result of one lesion was considered representative of all lesions. Biopsies were performed to determine the lesion type as per the doctor's request. (ii) One year of clinical and imaging follow-up (n= 37). Follow-up imaging was completed every six months via ^{68}Ga-PSMA PET/CT analysis. It was interpreted by a panel of expert readers who were informed of the locations of the lesions described by the blinded readers at initial imaging.

Statistical Analysis

Statistical analysis was performed using MedCalc version 20.022 (Ltd., Ostend, Belgium) and SPSS version 26 (IBM, Armonk, NY). Continuous variables were presented as means and standard deviations, while categorical variables were presented as numbers and percentages. To compare categorical variables, we used the chi-square test; for continuous variables, we used the one-way ANOVA test. The receiver operating characteristic (ROC) curve was utilized to identify the best cut-off value and the area under the curve (AUC) for detecting PCa. To evaluate the diagnostic accuracy of both PSMA-RADS versions in categorizing PCa, we employed a four-fold table test with histopathology and follow-up as the reference standards. We used Fleiss kappa (κ) statistics to assess the inter-rater agreement (IRA) of PSMA-RADS scoring results in detecting PCa. The κ values were interpreted as follows: 0.01–0.20= poor agreement, 0.21–0.40= fair agreement, 0.41–0.60= moderate agreement, 0.61–0.80= good agreement, and 0.81–1.0= perfect agreement. Statistical significance was set at $P \leq 0.05$.

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