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Professional Paper



# CURRENT STATE OF EVIDENCE AND PRACTICE OF PROSTATE-SPECIFIC MEMBRANE ANTIGEN (PSMA) IMAGING ACROSS THE PROSTATE CANCER CLINICAL LANDSCAPE – ONCOLOGIST PERSPECTIVE

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SUMMARY – Prostate cancer (PC) is the most widespread malignancy in men worldwide and the third leading cause of cancer-related death. Accurate diagnostic and staging procedures are key for therapy success and personalized treatment in all stages of PC. Prostate cancer-specific positron emission tomography-computed tomography (PET/CT) is able to detect disease sites in both localized and recurrent PC, at serum levels of prostate specific antigen (PSA) that are lower compared with those detected by conventional imaging. Currently, the backbone of nuclear medicine staging in PC is based on prostate-specific membrane antigen (PSMA) PET/CT, given the numerous advantages of PSMA over other tracers used for PC molecular imaging. In this free-style narrative review, the historic perspective, literature, clinical utility, and practice patterns of PSMA PET/CT in PC are discussed and key points summarized for busy oncologists with an interest in PC.

Key words: *PSMA; staging; restaging; biochemical failure; theranostics; PET/CT; new generation imaging; prostate cancer*

## Introduction

Conventional imaging of metastatic prostate cancer (PC) has long been unable to reliably determine the prevalence of the disease. The potential role of prostate-specific membrane antigen (PSMA) as a target for effective imaging or targeted cytotoxic therapy has been recognized for several decades. The history of PSMA dates back to 1987, when Gerald Murphy, Julius Horoszewicz, and their colleagues developed a monoclonal antibody called 7E11-C5 from mice immunized with the human prostate cancer cell line LNCaP[1,2]. This antibody recognized an antigen found on normal and malignant prostate epithelium[1,2].

Subsequently, in 1993, Warren Heston and William Fair cloned the PSMA gene using the 7E11-C5 monoclonal antibody[2,3], and this gene has been mapped to chromosome11q14[4].

PSMA is an integral type II membrane glycoprotein expressed throughout the disease process. PSMA

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is also expressed in the tumor neovasculature of a broad spectrum of malignancies[5]. PSMA has known enzymatic activities and acts as a carboxypeptidase, preferentially binding glutamate. It is also well-known that PSMA levels can change in androgen deficiency[6].

## History

The development of small molecules with a particular urea core represents a significant advancement in PSMA positron emission tomography (PET) imaging. These tiny compounds specifically target the outer domain of PSMA.

These small urea-based compounds have a long history that dates back several decades. In 1996, Jackson et al. described high-affinity drugs that target NAALADase, an enzyme that breaks down N-acetylaspartylglutamic acid into glutamate and N-acetylacetoacetic acid. These drugs were supposed to be therapeutically useful since they were more potent than earlier inhibitors[7].

Using the data from that study, Martin Pomper, a neuroradiologist at Johns Hopkins University, proposed that these substances might be utilized for brain PET imaging. Although the chemicals at issue were chemically unsuitable for brain imaging[8], Pomper redirected his attention to the investigation of prostate cancer because NAALADase and PSMA are chemically similar.

At Georgetown University, a group under the direction of Koziwotsky created inhibitors of glutamate carboxypeptidase II (GCP-II, NAALADse), a neurotransmitter regulator[9,10]. These inhibitors are urea-based (glutamate-urea-lysine) and bind strongly to the extracellular domain of GCP-II. They were initially developed because of their potential use as a neuroprotective agent. However, Pomper identified the possibility of turning Kozikowski's inhibitors into PSMA-targeted agents that could be radiolabeled for molecular imaging or therapy[2].

The Pomper lab then produced a number of pre-clinical pharmacological candidates, which culminated in the first usable human PSMA PET agent, 18F-DCFBC, which was reported in 2008[11].

The investigation continued and led to the development of the second generation of $^{18}$F-labeled PSMA agents, $^{18}$F-DCFPyL, in 2011[12] and the first $^{68}$Ga-labeled PSMA-targeted ligands in 2010[13].

In 2012, Matthias Eder and a team of researchers from Heidelberg reported the syntheses and biodistribution data of the radiogallium-labelled PSMA inhibitor Glu-NH-CO-NH-Lys(Ahx) with the highly potent acyclic Ga(III) chelator N,N′-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine,N′-diacetinic acid (HBED-CC), also known as PSMA 11[8,14]. This agent quickly entered clinical use in Germany, and from there the use of $^{68}$Ga-labelled PSMA agents spread worldwide[8].

## Clinical studies

With two medicines already approved by the Food and Drug Administration (FDA), PSMA PET is a very sensitive and focused imaging method for prostate cancer.

PSMA PET is superior to standard imaging (bone scan and computerized tomography) in all aspects of prostate cancer imaging. This has been demonstrated by organized studies that have systematically examined PSMA PET imaging compared with standard imaging.

Two disease phases were of the most interest in the first FDA approval of PSMA PET. The first was staging of the primary disease and the second was recurrence. We focused first on newly-diagnosed high-risk underlying conditions and then on the patient population with biochemical relapse. The approval process for these two purposes was conducted simultaneously for two tracers: $^{18}$F-DCFPyL (2-(3-{1-carboxy-5-[(6-18F-fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid) and $^{68}$Ga PSMA 11.Two clinical trials have been conducted for $^{18}$F-DCFPyL. The first, called OSPREY, focused on patients with clinically localized PC and metastasis, and the second, called CONDOR, focused on patients with biochemical recurrence after radical prostatectomy.

OSPRAY was a prospective, multicenter, open-label, multi-leader Phase 2/3 study[15] led by Pienta and Morris. Two groups were used in this study. Cohort A consisted of 252 high-risk men newly diagnosed with localized prostate cancer and scheduled for radical prostatectomy with pelvic lymphadenectomy. The aim of Cohort A was to compare preoperative imaging with postoperative histopathological findings and evaluate the diagnostic performance of 18F-DCFPyL-PET/CT. In Cohort A, the primary endpoint was extraprostatic disease, such as lymph node metastases. Other important efficacy endpoints included positive predictive value (PPV), negative predictive value (NPV),

detection rate, and sensitivity and specificity between 18F-DCFPyL and conventional imaging[15].

In cohort B, 93 men with radiologic evidence of local recurrence and/or metastatic disease outside previously locally treated sites were scheduled for biopsy of at least one amenable lesion. Again, the aim was to compare imaging results with biopsy results. In Cohort B, the primary efficacy endpoints were sensitivity and PPV for all lesions, prostate-specific antigen (PSA) sensitivity and PPV at baseline, and detection rate comparison between 18F-DCFPyL and conventional imaging[15].

In Cohort A, $^{18}$F-DCFPyL PET/CT demonstrated a median specificity of 97.9%, a sensitivity of 40.3%, a PPV of 86.7%, and a NPV of 86.7% in detecting pelvic lesions in patients with high-risk prostate cancer undergoing radical prostatectomy. Showed 83.2%. With pelvic lymphadenectomy[17]. The results in Group B demonstrated a median sensitivity of 95.8% and a positive predictive value of 81.9% for detecting metastases in patients with suspected recurrent or metastatic lesions visualized by conventional imaging[15]. The primary endpoint of specificity was met, but the primary endpoint of sensitivity was not.A limitation of this study was the comparison with histopathological findings. $^{18}$F-DCFPyL-PET/CT is less sensitive than microscopy, so as the lesion size decreases, the false negative rate will increase. For clinical use, this means that a positive result is likely to be a true positive and a negative result does not rule out disease. False positive results were less common.The population of patients with a rising PSA is the most challenging population to treat. These are patients who have a biochemical recurrence after the initial treatment and have negative conventional imaging. This patient population is where key treatment decisions are made, so it is crucial to detect the disease as early as possible. This was a pertinent issue for decades in biochemically recurrent PC, causing underestimation of disease burden with consequences in either postponement or even omission of salvage therapies.The CONDOR trial, led by Morris et al., was a prospective, multicenter, open-label, single-arm study which enrolled patients with true biochemical recurrence (men with rising PSA ≥0.2 ng/mL after previous prostatectomy or ≥2 ng/mL above the nadir after previous primary radiotherapy)[16]. Patients were required to have negative standard imaging. The primary endpoint was correct localization rate (CLR), with the added criterion of anatomic matching. This included matching of both $^{18}$F-DCFPyL-PET/CT and a composite standard of truth (SOT), which incorporated histopathology findings, additional complimentary imaging results, and/or PSA dynamics after radiotherapy[16]. A secondary objective was examining the portion of patients who had a change in their intended prostate cancer treatment.In the CONDOR study, $^{18}$F-DCFPyL-PET/CT accurately identified prostate cancer metastases in approximately 85% of patients with biochemical recurrence and caused a change in the treatment plan in 63.9% of patients based on comparison with composite truth criteria.

Among patients with PSA <0.5 ng/mL, the disease was detectable in 36.2% of patients. In patients with PSA values between 0.5 ng/mL and 1 ng/mL, the disease detection rate was 51.4%, and the disease detection rate was 66% for PSA values between 1 ng/mL and 2 ng/mL. For patients with PSA between 2 ng/mL and 5 ng/mL, the detection rate was 84.8%, while the detection rate for patients with PSA above 5 ng/mL was 96.7%.

Based on these data, the FDA approved $^{18}$F-DCFPyL as an imaging tool for prostate cancer in May of 2021.

$^{68}$Ga PSMA-11 is the most widely-used PSMA PET imaging agent. Hope, Czernin, Calais and Fendler led two prospective studies investigating the use of 68Ga PSMA-11. The results of the first study were published in 2019. It was a single-arm prospective trial conducted at the University of California, Los Angeles, and San Francisco[16]. It included 635 patients with biochemical recurrence (biochemical recurrence was defined as PSA≥0.2 ng/mL measured more than 6 weeks after prostatectomy, or a PSA rise of 2 or more ng/mL above the nadir after radiotherapy of prostate cancer, either after prostatectomy, radiotherapy or both). No imaging criteria were imposed. The endpoints were positive PPV, detection rate, inter-reader reproducibility, and safety. Based on independent readings, the PET detection rate was 75% in all patients[16]. In patients with biochemical recurrence, the lesion detection rate with $^{68}$Ga-PSMA-11 PET was 97%, 86%, 84%, 57%, and 38% for PSA levels of at least 5.0 ng/mL and 2.0-5.0 ng/mL, 1.0-2.0 ng/mL, 0.5-1.0 ng/mL, and <0.5 ng/mL, respectively[16]. The positive predictive value was 92% in the composite validation and 84% in the histopathological validation[16].The results of the second study were published in 2021. This was a

prospective, multicenter, open-label, single-arm, phase 3 study on diagnostic performance, conducted at the Universities of California, Los Angeles, and San Francisco[17]. 764 patients were included in the study. Inclusion criteria were histopathological proven prostate adenocarcinoma, planned radical prostatectomy and high-risk disease (defined by at least 1 of the following criteria: PSA>10 ng/mL; stage T2b or greater), Gleason score >6, or other risk factors. No prior systemic therapy was allowed, nor were there any prior imaging criteria[17].

Patients underwent $^{68}$Ga-PSMA-11 PET imaging for primary staging[17]. Of the 764 patients, 277 underwent prostatectomy with lymph node dissection[17]. Based on pathology reports, 75 of 277 patients (27%) had pelvic nodal metastases[17]. This study reported a sensitivity of 40% and a specificity of 95% for detecting pelvic lymph node metastases. Of 764 patients, 487 (64%) did not undergo a prostatectomy, of whom 108 patients were lost to follow-up[17].

Based on the results of these studies, $^{68}$Ga-PSMA-11 became the first FDA-approved PSMA PET agent in December 2020.

The widespread use of PSMA PET/CT is changing the way we stage and prognosticate prostate cancer. Patients with high-risk localized prostate cancer will be categorized as metastatic, castration-sensitive disease. Patients with biochemically relapsed disease will be recategorized as castration sensitive disease. Non-metastatic castration-resistant prostate cancer may be classified as metastatic castration-resistant prostate cancer (mCRPC)[18].

PSMA PET/CT will change everything that we think and what we know about prostate cancer.

## PSMA PET/CT for assessment of response or progression

PSA is a poor predictive marker for overall survival. In bone disease, it is very difficult to assess disease dynamics. Currently, radiographic progression-free survival (rPFS) is used as the main measurement tool to assess response to treatment. rPFS and overall survival (OS) are closely correlated in mCRPC[19].

PSMA detects disease recurrence early. Progressive disease has moved from progression on bone scan to progression on PSA or PSMA PET/CT. PSMA imaging usually requires the initiation of treatment (local or systemic) and thus delays the detection of disease (rPFS). This fact will change the way clinical trials are conducted and the endpoints used in clinical trials.

PSMA levels fluctuate due to androgen receptor signaling. All known changes in PSMA expression so far are independent of tumor volume. PSMA fluctuates as a result of treatment and not as a result of tumor shrinkage or enlargement. Much remains to be discovered to clarify what constitutes a favorable or unfavorable change in PSMA.

## Conclusion

PSMA PET/CT imaging has brought previously unseen accuracy in site of disease detection and caused a revolution in PC disease assessment both in definitive and recurrent settings. PSMA PET/CT should be considered a key tool in contemporary staging procedures for PC, and the challenge is how to incorporate these early imaging findings into treatment considerations for PC given the high likelihood of metastasis discovery. PSMA PET/CT findings have an impact on local (surgery/radiotherapy) and systemic treatment (addition of new-generation androgen pathway inhibitors, more prevalent use of androgen deprivation therapy). This has caused a systematic shift in disease management, with newer systemic therapies being employed towards earlier stages of disease, with unknown impact for patients with PC.

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Sažetak

## TRENUTNO STANJE DOKAZA I PRAKSE KORIŠTENJA SLIKOVNOG PRIKAZA SPECIFIČNOG MEMBRANSKOG ANTIGENA PROSTATE (PSMA) U KLINIČKOJ PRAKSI - POGLED ONKOLOGA

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Karcinom prostate najčešći je malignih tumor kod muškaraca diljem svijeta i treća po učestalosti maligna bolest koja uzrokuje smrt. Precizna dijagnostika i stupnjevanje proširenosti bolesti ključni su za uspješnost terapije i personalizaciju liječenja u svim stadijima raka prostate. Pozitronska emisijska tomografija/kompjuterizirana tomografija (PET/CT) specifična za rak prostate, može otkriti mjesta bolesti i kod lokaliziranog i kod rekurentnog karcinoma prostate, kod nižih serumskih vrijednosti prostata specifičnog antigena (PSA) u usporedbi s onima otkrivenim konvencionalnim snimanjem. Trenutna okosnica određivanja stadija karcinoma prostate u nuklearnoj medicini jest PET/CT koji se temelji na specifičnom membranskom antigenu prostate (PSMA), s obzirom na brojne prednosti PSMA u odnosu na druge markere koji se koriste za molekularno oslikavanje raka prostate. U ovom revijalnom pregledu raspravlja se o povijesnoj perspektivi, literaturi, kliničkoj korisnosti i obrascima upotrebe PSMA PET/CT-a u kliničkoj praksi i sažimaju se ključne točke u upotrebi istog u liječenju raka prostate.

Ključne riječi: *PSMA, stupnjevanje proširenosti bolesti, biokemijski povrat, teranostika, PET/CT, dijagnostika nove generacije, rak prostate*