

Recurrent Prostate Cancer Diagnostics with 18F-PSMA-1007 PET/CT

Subjects: **Radiology, Nuclear Medicine & Medical Imaging**

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Early diagnosis of recurrent prostate cancer is a cornerstone for further adequate therapy planning. Therefore, clinical practice and research still focuses on diagnostic tools that can detect prostate cancer in early recurrence when it is undetectable in conventional diagnostic imaging. ¹⁸F-PSMA-1007 PET/CT is a novel method to evaluate patients with biochemical recurrent PCa.

F-PSMA

PET/CT

prostate cancer

local recurrence

lymph nodes

bone metastases

biochemical relapse

1. Introduction

Prostate cancer (PCa) is one of the most common malignancies that affect men worldwide. Prostate cancer is the second most commonly occurring cancer in men and the fourth most common cancer overall ^[1]. A total of 1,414,259 new cases of prostate cancer and 375,304 related deaths were reported in 2020 globally ^[2]. A systematic review of autopsy studies reported a prevalence of PCa at age <30 years of 5% (95% confidence interval [CI]: 3–8%), increasing by an odds ratio (OR) of 1.7 (1.6–1.8) per decade, to a prevalence of 59% (48–71%) by age >79 years ^[3]. The main radical treatment methods for primary prostate cancer are prostatectomy and radiation therapy. Despite that, recurrence of the PCa is frequent and patients with clinically intermediate or high-risk prostate cancer after initial radical treatment need clinical follow-up. Biochemical recurrence is when PSA levels rise in the blood to a certain threshold after prostate cancer treatment—radical prostatectomy or radiation therapy ^[4]. The biochemical persistence is defined as a PSA level persistence/recurrence after radical prostatectomy such that the PSA fails to fall to undetectable levels ^[5].

Serum prostate-specific antigen (PSA) is a biomarker for prostate cancer screening and a reliable marker of PCa recurrence after initial treatment.

Prostate specific membrane antigen (PSMA) is a glycoprotein that is hyper expressed in prostate cancer tissues while its degree of expression correlates with tumor aggressiveness, metastatic disease and disease recurrence. In recent years, PSMA positron emission tomography/computed tomography (PET/CT) has become the gold standard for the staging of primary prostate cancer and restaging biochemical recurrent prostate cancer patients. PSMA

labeled radioligands have outperformed conventional imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy, and previous generation radiopharmaceuticals [6][7][8].

PET/CT is a functional and anatomical non-invasive radiological hybrid imaging modality. Several radiopharmaceuticals with different diagnostic sensitivity and specificity are used in the detection and staging of prostate cancer, in the evaluation of treatment efficacy and localization of recurrence [9].

¹⁸F-PSMA-1007 is a novel PSMA-based radiopharmaceutical. Fluorine-18 (¹⁸F) labelled PSMA radiotracers have several advantages over Gallium-68 (⁶⁸Ga) labelled radioligands: ¹⁸F is a cyclotron produced isotope with a longer half life and a lower positron energy compared to ⁶⁸Ga, which leads to improved spatial resolution [10]. Additionally, due to non-urinary excretion, studies with ¹⁸F-PSMA-1007 have improved detection rates especially in local relapses and pelvic lymph node metastases in proximity to the urinary tract [8][11].

According to several publications, ¹⁸F-PSMA-1007 PET/CT tests are highly valuable for detecting prostate cancer biochemical recurrences. Giesel et al. analyzed 251 patients, and 204 (81.3%) of them had evidence of recurrence on ¹⁸F-PSMA-1007 PET/CT examination. The detection rates (DR) were 94.0% (for PSA levels greater than or equal to 2), 90.9% (for PSA levels 1 to less than 2), 74.5% (for PSA levels 0.5 to less than 1), and 61.5% (for PSA levels 0.2 to less than 0.5 ng/mL) [12]. Sprute et al. conducted a study using ¹⁸F-PSMA-1007 PET/CT on 96 patients with prostate cancer. In this study ¹⁸F-PSMA-1007 PET/CT had a lesion-based sensitivity of 81.7%, a specificity of 99.6%, a positive predictive value (PPV) of 92.4%, and a negative predictive value (NPV) of 98.9% for detecting positive lymph nodes larger than 3 mm [13]. When compared to bone scintigraphy (BS), ¹⁸F-PSMA-1007 PET/CT was more effective in detecting small lesions with minimal osteosclerosis or excluded degenerative change although bone scintigraphy is sufficiently sensitive to detect small bone metastasis in most of the recurrent cases [14].

Despite the specificity of ¹⁸F-PSMA-1007, physiological uptake of this radiotracer can be seen in the salivary glands, gallbladder, prostate, kidneys, liver, lacrimal glands, spleen and small intestine [15]. However, concentrated foci with localized abnormal radioactivity uptake are considered positive, such as avid uptake in lymph nodes and bones, which can be diagnosed as metastases [16].

2. ¹⁸F-PSMA-1007 Radiotracer Characteristics

PSMA is a type II transmembrane glycoprotein with enzymatic carboxypeptidase activity that is expressed in the cytosol of normal prostatic cells. PSMA is highly overexpressed on the membrane of prostate cancer cells. The intensity of membranous PSMA expression correlates positively with tumor grade, rises under androgen deprivation and in metastatic and castration-resistant cancer, thus rendering it an appropriate target for imaging and treatment [17].

PSMA is an excellent target for several reasons: preferential, marked overexpression by most PCa cells, positive correlation of its expression with tumor grade and disease stage, low presence in the bloodstream by virtue of its

transmembrane localization, and internalization and retention within tumor cells after binding to its ligand. Moreover, in personalized medicine there is increased interest in the use of PSMA for therapeutic approaches—in the theranostics setting, that means combining imaging diagnosis with targeted radionuclide therapy [17][18].

Several PSMA ligands, differing slightly in chemical structure, are commercially available and they may be radiolabeled with different positron-emitting isotopes as Gallium-68 (^{68}Ga), Fluorine-18 (^{18}F) or Copper-64 (^{64}Cu) to obtain PET radiopharmaceuticals used in clinical practice. Labeling of PSMA agents with ^{18}F may offer numerous advantages, including longer half-life and improved image resolution. Due to the lower positron energy, the theoretical achievable resolution of ^{18}F is slightly better in comparison to ^{68}Ga [19][20][21][22][23][24]. Studies with ^{18}F -PSMA-1007 also suggest improved detection rates especially in local relapses and pelvic lymph node metastases in proximity to the urinary tract when compared to ^{68}Ga -PSMA-11 PET/CT [11].

The ^{18}F -PSMA-1007 seems to be more favorable among other ^{18}F -PSMA ligands candidate compounds because it demonstrates high labeling yields, better tumor uptake and non-urinary background clearance [25]. In ^{18}F -PSMA-1007 PET/CT, physiological uptake can be seen in the liver, gallbladder, prostate, kidneys, salivary glands, lacrimal glands, spleen and small intestine [15].

In several studies no drug-related pharmacological effects or physiologic responses were not reported in the patients. All observed parameters (e.g., blood pressure, heart rate and body temperature) remained normal and unchanged during and after the ^{18}F -PSMA-1007 PET/CT examination. Overall, no adverse events due to ^{18}F -PSMA-1007 administration were reported in the included studies. No patient reported subjective symptoms [15][26].

3. ^{18}F -PSMA-1007 PET/CT Scanning Protocol

All patients described in the studies underwent ^{18}F -PSMA-1007 PET/CT. The time interval between injection and image acquisition varies from 57.7 ± 4.9 min to 120 ± 10 min after injection of ^{18}F -PSMA-1007. The ^{18}F -PSMA-1007 solution was given by intravenous bolus injection [8][14].

All patients received regular whole-body ^{18}F -PSMA-1007 PET/CT scans (in the most cases from head to the thighs). The popular scanner model was Biograph-mCT PET/CT (Siemens, Erlangen, Germany) [8][12][15][25][27]. The administered ^{18}F -PSMA-1007 individual dose ranged from 159 ± 31 MBq to 363.93 ± 69.40 MBq [27][28]. It was confirmed that ^{18}F -PSMA-1007 can be safely administered and results in a mean effective dose of 12.8 ± 0.6 $\mu\text{Sv}/\text{MBq}$. Therefore, the total radiation dose is lower than for other PSMA PET agents and in the same range as ^{18}F -DCFPyL [29].

In most of the studies all images were interpreted by two physicians—radiologists and/or nuclear medicine physicians in consensus. Image analysis was performed using an appropriate workstation and software. Focal uptake of ^{18}F -PSMA-1007 higher than the surrounding background and not associated with physiologic uptake was considered suggestive of malignancy. Moreover, typical pitfalls in PSMA ligand PET imaging (e.g., uptake in celiac

and other ganglia, fractures and degenerative changes) were considered. If at least one PSMA positive lesion suspicious for PCa was described, the PET/CT was counted as positive [8][12][30].

4. Local Recurrence

Local recurrence of prostate cancer is defined as focal uptake of ^{18}F -PSMA-1007 radiotracer higher than the surrounding background and not associated with physiologic uptake in PET/CT. It has been reported that the detection rate (DR) of ^{18}F -PSMA-1007 PET/CT in local recurrence is related to PSA serum values. Results of the meta-analysis by Ferrari et al. confirmed that ^{18}F -PSMA-1007 PET/CT demonstrated a good detection rate in biochemical recurrent prostate cancer (81.3%) and higher PSA values were associated with higher DR [31]. In addition, in a study by Lengana et al., the detection rate depending on the PSA level was determined. The detection rates for PSA levels 0–<0.5 ng/mL were 31.3% for 0.5–<1 ng/mL—33.3%, for 1–2 ng/mL detection rate were 55.6% and for PSA level > 2 ng/mL detection rate were 72.2%. In this study 7 (29.2%) of the positive patients had been described as negative or equivocal on conventional imaging. In addition, an optimal PSA cut-off level was determined—1.3 ng/mL [32]. See **Figure 1** for an example of local recurrence in the prostate bed in PET/CT.

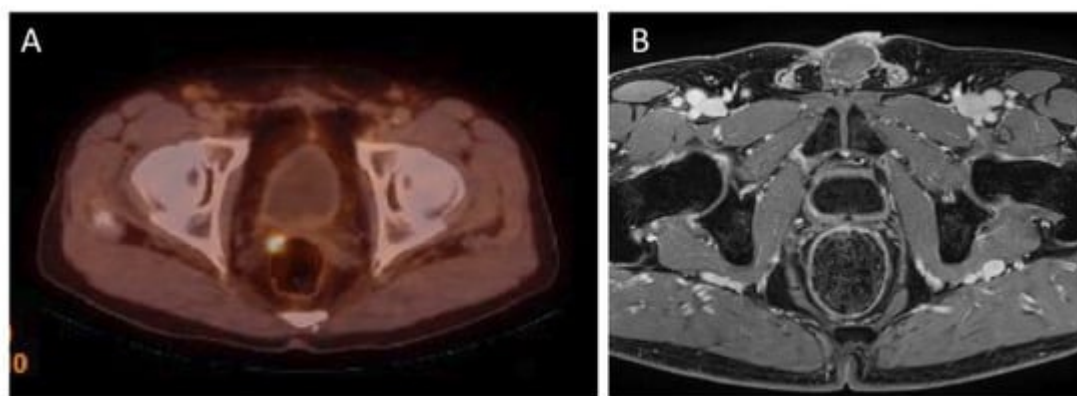


Figure 1. (A)— ^{18}F -PSMA-1007 PET/CT examination of a patient (74 years old) after radical prostatectomy eight years before, Gleason Score 7(3 + 4), current PSA level 0.29 ng/mL. ^{18}F -PSMA-1007 focal uptake in right side tissues adjacent to the prostate bed, in the level under seminal vesicle, pararectally with SUVmax = 6.9 was detected, confirming local recurrence. (B) this lesion cannot be seen on the corresponding MRI examination (Images from Riga Stradins University Radiology research laboratory archive).

Giesel et al. conducted a retrospective multicenter study with 251 patients, with a median age of 70 years. Of these 251 patients, 204 (81.3%) had evidence of recurrence on ^{18}F -PSMA-1007 PET/CT. The detection rates were 94.0% (PSA levels of greater than or equal to 2 ng/mL), 90.9% (PSA level 1 ng/mL to less than 2 ng/mL), 74.5% (PSA level 0.5 ng/mL to less than 1 ng/mL) and 61.5% (PSA level 0.2 ng/mL to less than 0.5 ng/mL). The overall detection rate was 80.2% [12]. Similar results were obtained in a meta-analysis by Treglia et al.—the pooled DR of ^{18}F -PSMA-1007 PET/CT in biochemical prostate cancer recurrence patients was 81% (95% CI: 71–88%). The pooled DR was 86% for PSA level \geq 0.5 ng/mL (95% CI: 78–93%) and 49% for PSA level < 0.5 ng/mL (95% CI: 23–

74%). It was concluded that detection rate of ^{18}F -PSMA-1007 PET/CT is related to PSA values with significant lower DR in patients with PSA < 0.5 ng/mL [23].

In a study by Watabe et al., 28 patients with biochemical recurrent prostate cancer underwent ^{18}F -PSMA-1007 PET/CT. Biochemical recurrence was defined as a continuous increase in PSA after radical prostatectomy or radiation therapy without any apparent recurrent lesions on conventional diagnostic imaging. The detection rates were 66.7% (PSA level 0.1–0.5 ng/mL), 85.7% (PSA level 0.5–1.0 ng/mL) and 100% (PSA level above 1.0 ng/mL). In 53% of biochemical recurrent prostate cancer patients who were suspected of local recurrence, focal uptake was detected adjacent to the bladder on ^{18}F -PSMA-1007 PET/CT. This suggested a significant advantage of ^{18}F -PSMA-1007 as compared to other PSMA ligands due to minimal physiological urine excretion [14].

The maximum standardized uptake value (SUVmax) is widely used for measuring the uptake of tracer by malignant tissue [33]. Increased ^{18}F -PSMA-1007 uptake values reflect the viability of cancer cells, and can be imaged and quantified using PET/CT. It was proved that mean prostate maximum standardized uptake value (SUVmax) was significantly higher in prostate cancer than in benign lesions (19.56 ± 18.11 vs. 4.21 ± 1.5 , $p = 0.00001$), in patients with PSA > 20 ng/mL versus PSA < 20 ng/mL (19.1 ± 20.6 vs. 6.01 ± 5.4 , $p = 0.0052$) and in patients with Gleason's score (GS) score > 7 vs. GS ≤ 7 (28.1 ± 20.3 vs. 10.2 ± 8.9 , $p = 0.010$). In that study, Chandra et al. concluded that PSMA PET/CT can differentiate benign and malignant lesions of the prostate with very high accuracy [34].

In several studies, the detection rate of ^{18}F -PSMA-1007 PET/CT was compared with ^{68}Ga -PSMA-11 PET/CT. Lengana et al. conducted a prospective study where ^{18}F -PSMA-1007 PET/CT was performed in the same patients after ^{68}Ga -PSMA-11 PET/CT examination. Local recurrence diagnosed on each of these studies was compared against the final diagnosis based on a clinical follow-up and histological correlation. ^{18}F -PSMA-1007 PET/CT was able to detect more sites of recurrence as compared to ^{68}Ga -PSMA-11 PET/CT; the sites were mainly localized within the prostate and surrounding pelvic structures [35]. In a study conducted by Hoffmann et al., ^{18}F -PSMA-1007 PET/CT showed prostate cancer lesions in 87.5%, while ^{68}Ga -PSMA-11 PET/CT identified them in 88.9%. In this study for ^{18}F -PSMA-1007 PET/CT biochemical recurrent patients who were treated with radical prostatectomy, a PSA level of 1.08 ng/mL was found to be the optimal cut-off level for predicting positive and negative scans [36].

5. Lymph Node Metastases

Lymph nodes adjacent to the primary tumor are often the first site of metastases. Additionally, lymph node metastases are commonly detected in prostate cancer recurrence. Detection of lymph node metastasis is one of major prognostic significance for prostate cancer, although lymph node metastases are themselves rarely life threatening [37][38]. See **Figure 2** for example of lymph node metastasis.

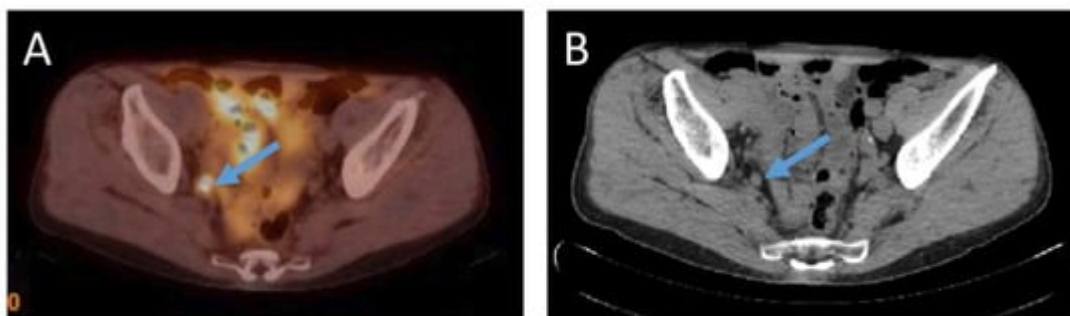


Figure 2. (A)— ^{18}F -PSMA-1007 PET/CT examination of a patient (74 years old) after radical prostatectomy ten years before, Gleason Score 6 (3 + 3), current PSA level 4.77 ng/mL. ^{18}F -PSMA-1007 uptake in an 8 mm in size obturator right side lymph node with SUVmax = 13.7 was detected. (B) an 8 mm in size round shaped obturator right side lymph node in corresponding computed tomography image in axial plane (Images from Riga Stradins University Radiology research laboratory archive).

6. Bone Metastases

Bone metastases are typical in advanced stages of prostate cancer. Imaging of bone metastases is important for localization and characterization, and for evaluation of their size and number and for follow-up after therapy. Bone metastases formation is triggered by cancer initiating cells in the bone marrow and is facilitated by the release of several growth factors [19]. **Figure 3** shows an example of bone metastasis.

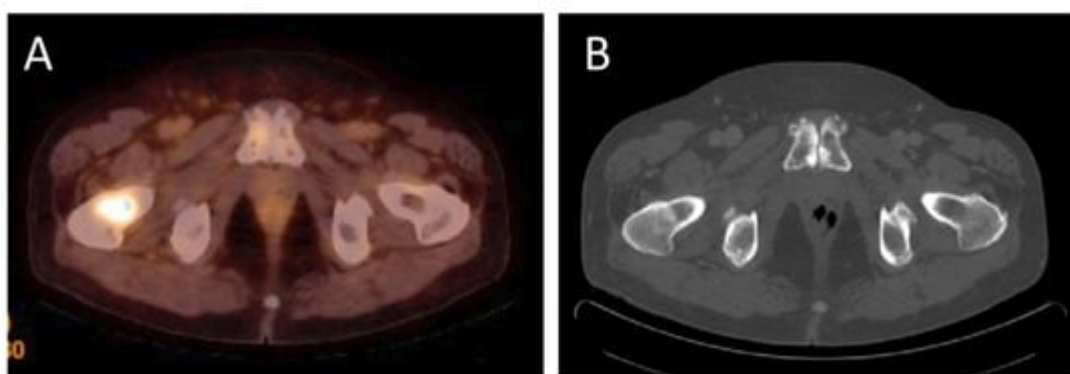


Figure 3. (A)— ^{18}F -PSMA-1007 PET/CT examination of a patient (69 years old) after radical prostatectomy seven years before, current PSA level 3.9 ng/mL. ^{18}F -PSMA-1007 uptake in the right femur with SUVmax = 5.7 was detected to approve metastatic activity. (B) in computed tomography mild, local sclerotic lesion in the right femoral neck was inconclusive (Images from Riga Stradins University Radiology research laboratory archive).

Watabe et al. conducted a study in which biochemical prostate cancer recurrence was defined as a continuous increase in PSA level after radical prostatectomy or radiation therapy without any apparent recurrent lesions on conventional diagnostic imaging (CT and bone scintigraphy). In this study, results show that the SUVmax was 4.1 ± 1.6 in bone metastasis. Among the PET positive biochemical prostate cancer recurrence patients ($n = 26$), bone metastases were detected in 15.4% (4/26). When compared to bone scintigraphy, ^{18}F -PSMA-1007 PET/CT was

more effective in detecting small lesions with minimal osteosclerosis or excluding degenerative changes, although bone scintigraphy (BS) is sufficiently sensitive to detect small bone metastasis in most of the recurrent cases. It is reported that caution is advised when interpreting bone uptake of ^{18}F -PSMA-1007, especially in the ribs, due to potential false-positive findings [14][39].

In a study conducted by Ahmadi Bidakhvidi et al., several parameters predicting ^{18}F -PSMA-1007 PET/CT scan positivity in biochemical recurrent prostate cancer patients were analyzed. As a result, PSA velocity and PSA value were significantly correlated with the number of involved bone, lymph node and soft tissue lesions in univariable analysis, but multivariable analysis confirmed PSA value as an independent predictor of the number of bone lesions (IRR 1.003, $p = 0.0002$). It was concluded that a higher pathological primary tumor staging was significantly correlated with a lower number of bone lesions in multivariable analysis [40].

In another study conducted by Wondergem et al., 120 consecutive patients scanned with ^{18}F -PSMA-1007 PET/CT were match-paired with 120 patients scanned with ^{18}F -DCFPyL PET/CT. In this study all 240 PET/CT scans were reviewed by two readers and scored according to the criteria of the PSMA Reporting and Data System. Inter-reader agreement and the detection rate for suspected lesions were scored for different anatomic locations, such as the prostate, prostatic fossa, lymph nodes and bone. Regarding suspected bone lesions, almost perfect inter-reader agreement was found at all localizations for ^{18}F -DCFPyL. For ^{18}F -PSMA-1007, lower inter-reader agreement was found for lesions in the thoracic region and whole skeleton and to a lesser extent for suspected bone lesions in the pelvis. Both readers scored a significantly greater number of equivocal bone lesions in the thoracic region with ^{18}F -PSMA-1007 at the expense of the number of scans without bone lesions [41].

In a study conducted by Dietlein et al., intraindividual comparison of ^{18}F -PSMA-1007 PET/CT with other PSMA ligands (renally excreted) in patients with recurrent prostate cancer was performed. In this study participated 27 patients whose PET/CT results were obtained with ^{68}Ga -PSMA-11, ^{18}F -DCFPyL or ^{18}F -JK-PSMA-7 and were interpreted as equivocal or negative or as oligometastatic disease. Within 3 weeks, a second PET scan with ^{18}F -PSMA-1007 was performed. The confidence in the interpretation of PSMA positive regional findings was scored on a 5 point scale, first in routine diagnostics and then by an independent second evaluation. Discordant PSMA positive skeletal findings were examined by contrast-enhanced MRI. It was explored that ^{18}F -PSMA-1007 PET/CT detected a significantly higher number of PSMA-positive bone marrow findings than did PET/CT with 3 other tracers. However, ^{18}F -PSMA-1007 exhibits unspecific PSMA tracer accumulation in the bone marrow in a relevant number of patients. Therefore, skeletal lesions, which were detected with ^{18}F -PSMA-1007 PET/CT, require verification through MRI or simultaneous PET/MRI. Imaging with ^{18}F -PSMA-1007 PET/CT may therefore be applicable primarily to patients with a high probability of locally restricted disease or as a follow-up test in cases with equivocal findings adjacent to the urinary tract. When there is suspicion on distant metastases, particularly in the bone marrow, ^{68}Ga -PSMA-11, ^{18}F -DCFPyL or ^{18}F -JK-PSMA-7 may be more suitable because of their higher specificity in the bone marrow [39].

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