Comparative study of the most commonly-used radiopharmaceuticals for PSMA prostate PET/CT imaging

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Abstract
Prostate cancer (PCa) is one of the most common malignancies and cause of cancer death in men. Prostate-specific antigen (PSA) is the most used biomarker in the detection of early PCa. Lately, scientists have been using prostate-specific membrane antigen (PSMA), a glycol-protein that is over-expressed in PCa cells in positron emission tomography/computed tomography (PET/CT) scans to detect PCa. Gallium-68-PSMA radiotracers, such as ^{68}Ga-PSMA-11, ^{68}Ga-PSMA-617 and ^{68}Ga-PSMA I&T, were firstly introduced in 2011 and fluorine-18-PSMA based radiotracers followed with ^{18}F-PSMA-1007,N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-^{18}F-fluorobenzyl-L-cysteine (^{18}F-DCFBC) and 2-(3-(1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid (^{18}F-DCFPyL), also known as PYLARIFY, being the most used and showed superior results compared to conventional imaging techniques. Differences depending on half-life, clearance and normal organ uptake are being detected through research to determine which of the radiotracers, is the most suitable for each patient. Two of them, ^{68}Ga-PSMA-11 and PLYRIFY, have already been approved by the Food and Drug Administration (FDA). The future of hybrid imaging for PCa is very promising if we consider the advantages of PSMA radiotracers compared to non-PSMA radioligands.

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Introduction

Prostate cancer (PCa) is the second most common malignancy and the fifth leading cause of cancer death in men with 1.414.259 new PCa cases and 375.304 deaths estimated globally in 2020 by the GCO (Global Cancer Observatory) [1]. Although the disease is complex, systematic staging and precise localization of the abnormalities using the right imaging techniques will improve treatment selection and give us better results for each different patient [2]. Even though accurate determination of recurrence is important for effective management, typical imaging techniques are not sensitive enough, especially when patients have low prostate-specific antigen (PSA) values [2]. Prostate-specific membrane antigen (PSMA) is a transmembrane glycol-protein that is found mainly in the epithelium of surrounding prostatic ducts. Patients who express it usually have clinically similar PCa and when it's over-expressing, is shown to be a sensitive biomarker of aggressive disease [3]. Affirming results were reported for positron emission tomography/computed tomography (PET/CT) using PSMA-radioligands, especially in early biochemical recurrence (BCR). By investigating the utilization of these modalities in identical cases, we have got the chance to compare results and choose on the most suitable modality in patients with different characteristics [3]. The stage and tumor grade are designated by PSMA levels and also by aneuploidy and BCR. Usually when PSMA expression levels are higher we have poorer prognostic outcomes [4]. The first and most used radiopharmaceutical is gallium-68 (^{68}Ga)-PSMA-11 which was introduced in 2011 by the German Cancer Research Centre (GCRC). Its isotope production is relatively simple by using a ^{68}Ge/^{68}Ga (germanium-gallium) generator [4]. Gallium-68-PSMA-617 is another ^{68}Ga-labeled ligand and it is synthesized using an IT manual synthesis module [5]. Last but not least, the group of ^{68}Ga-PSMA radiopharmaceuticals also includes, ^{68}Ga-PSMA-I&T (Imaging and Therapy) which can also be used for imaging when combined with other radiotracers [6]. 2-(3-(1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid (^{18}F-DCFPyL) (PLYRIFY) is also a widely used radio tracer that was introduced as a successor to N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-^{18}F-fluorobenzyl-L-cysteine (^{18}F-DCFBC). Compared to ^{68}Ga-labeled tracers, ^{18}F-labeled compounds have longer half-life, allowing late imaging, a higher production capacity and a more centralized production. Fluorine-18-PSMA-1007 is another ^{18}F-tracer characterized by mainly hepatobiliary excretion, therefore it

has a reduced urinary excretion [4].

PSMA-binding variants

^{68}Ga-PSMA-11

In 2011 the first PSMA ligand, ^{68}Ga-PSMA-11 (also known as ^{68}Ga-PSMA-HBED-CC[7]), was introduced by the GCRC [4]. The ^{68}Ga-PSMA was prepared using a lyophilized PSMA-11 Sterile Cold Kit (ANMI SA, Liege, Belgium) and a ^{68}Ge/^{68}Ga generator [2]. Physical and biological (in blood) half-life of ^{68}Ga-PSMA-11 are approximately 68min and 6.5min, respectively [8]. When it comes to normal organ biodistribution, research showed that the highest activities were observed in the kidneys and bladder, followed by the salivary glands. Liver, spleen and proximal small bowel also demonstrated uptake and low background activity was noted in the blood-pool (thoracic aorta) [7]. In primary staging PCa, Herlemann et al. (2020) showed that ^{68}Ga-PSMA-11 PET/CT scan is highly accurate for preoperative lymph node staging in patients with intermediate to high risk PCa [9]. Also, it shows to have greater precision in identifying nodal and distant metastases vs. conventional imaging such as CT and bone scan, before surgery or radiotherapy in high-risk PCa [4]. For metastatic cancer, a research calculated the positive predictive value (PPV) of ^{68}Ga-PSMA11 PET/CT as 92% [4]. Gallium-68-PSMA-11 is injected intravenously, it has a fast clearance from the blood and is gathered mostly in the kidneys, liver, spleen, and salivary glands by 7%,15%,2% and 0.5%, respectively [10]. In after treatment of PCa setting, researchers find that BCR occurs in at least 20%-30% of patients [11]. Prostate-specific membrane antigen PET /CT demonstrates the greatest advantage over other imaging methods, with multiple studies show-ing that ^{68}Ga-PSMA-11 PET/CT can de-tect the likely site of recurrence (local, nodal or distant) in most cases [3]. Also, it can be effective when PSA values are low (0.2-1.0ng/mL), even when doubling time is rapid and tumor grade is high and this can be explained by the PSMA-11 dependence of PSA doubling times and initial Gleason Scores (GS) [3]. Although, Afshar et al. (20-15) studies data from 319 men with BCR, showed that ^{68}Ga-PSMA-11 PET/CT was highly specific for PCa [12], it was also shown that it performs with a significantly higher diagnostic accuracy than bone scintigraphy, PET/CT and scintigraphy sensitivity were 99%-100% for PET/CT and 87%-89% for scintigraphy and as for specificity 88.2%-100% for PET/CT and 61%-96% scintigraphy [3]. On the 1st of December 2020, 9 years after its discovery, ^{68}Ga-PSMA-11 became the first Food and Drug Administration (FDA) approved PSMA-PET/CT imaging radiopharmaceutical [13].

^{68}Ga-PSMA-617

One of the greatest achievements on PSMA-targeted radiopharmaceuticals study has been the modification of PSMA-11 to PSMA-617, with the first published clinical theranostic approach to be reported in 2014 [14]. Prostate-specific membrane antigen-617 exhibits pharmacokinetic features that are similar to PSMA-11 and can be labeled with actinium-255, ^{68}Ga, lutetium-177 (^{177}Lu), indium-111(^{111}In), or yttrium-993. Scientists obtained DKFZ-PSMA-617 from ABX advanced biochemical compounds (Radeberg, Germany) and ^{68}Ga from a ^{68}Ge/^{68}Ga generator and used to label PSMA ligand. Gallium-68-PSMA-617 was synthesized by incubating $^{68}GaCl_3$ with the ligand in a pH=4.0 buffer at 85°C for 5min [15]. In detecting lymph node or bone metastases in PCa, ^{68}Ga-PSMA-617 PET/CT has shown higher sensitivity, specificity, and accuracy than traditional imaging methods [16]. In preclinical studies, this radiotracer has demonstrated one of the highest binding affinities to PSMA and a highly efficient internalization into PCa [17]. In normal organ uptake, significant PSMA-617 is noted in the salivary glands and kidneys and to a lesser extent in lacrimal glands, liver, spleen, and bowel as well. In addition, there was a small increase in radiotracer uptake in the salivary and lacrimal glands between early and late imaging [17]. Bone metastases exhibited the greatest standardized uptake values (SUV) of all the lesions, followed by LN metastases, local relapses, and primary tumors. Gallium-68-PSMA-617 shows lesions of PCa with high contrast, especially in late images with maximum contrast of tumor lesions seen between 3 and 4 hours after injection. The radiation exposure of a PET scan with ^{68}Ga-PSMA-617 is approximately 0.021mSv/MBq [17]. Gallium-68-PSMA-11 and ^{68}Ga-PSMA-617 accumulate similarly in most organs, however ^{68}Ga-PSMA-617 renal clearance was substantially faster than ^{68}Ga-PSMA-11 [18]. Gallium-68-PSMA-617 PET/CT showed a patient-based sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of 87.88%, 88.24%, 87.88%, and 88.24%, respectively [19].

^{68}Ga-PSMA-I&T

Recently, ^{68}Ga-DOTAGA-(3-iodo-y)fk(Sub-KuE), also known as ^{68}Ga-PSMA I&T, was introduced as an alternative to ^{68}Ga-PSMA-11 [20]. Compared to other ligands, PSMA-I&T can be labelled alternatively with lutetium (^{177}Lu-PSMA I&T) without significant changes in affinity, which may be useful for treatment of PCa [20]. In research in November 2016, in 58 of 83 patients (69.9 %) ^{68}Ga-PSMA I&T PET/CT revealed at least one lesion suggestive for recurrent prostate cancer and there were no adverse effects in any of the patients [20]. For detection of recurrent PCa, the same research ^{68}Ga-PSMA-I&T PET/CT showed high potential and it enabled detection of morphologic correlates to biochemical relapse in about half of the patients even at low PSA levels (below 0.5ng/mL) [20]. The detection rate of ^{68}Ga-PSMA I&T increased with increasing PSA-levels up to 100% and it is comparable to ^{68}Ga-PSMA HBED-CC [20]. Research showed high normal organ uptake in the salivary glands [21]. In one study the calculated per-region sensitivity, specificity, PPV, NPV, and accuracy for detection of LNM were 35.0%, 98.4%, 63.6%, 95.0%, and 93.0%, respectively [22]. According to a 2017 study, adding ^{68}Ga-PSMA-I&T PET/CT to the diagnostic algorithm has no value in patients with a low GS (7 or less) and a low PSA level (5ng/mL), with metastatic disease detected in only one patient (out of 11) with serum PSA less than 5ng/mL (irrespective of GS) and metastases found in four patients (out of a total of 26) with GS 7 or less (all with PSA >5ng/mL). Likelihood of finding metastatic disease increases with increased GS and PSA value [23]. Gallium-68-PSMA-I&T has the ability to co-register biochemical information and structural information, this can help us establish a staging protocol for primary PCa with complete guide on disease status, thus allowing more informed treatment decisions [23]. High

detection rate of ^{68}Ga-PSMA I&T PET/CT was confirmed in the context of biochemical relapse of PCa, enabling lesion detection even in the setting of low PSA levels ≤0.2ng/mL in 38.9% of cases [24].

^{18}F-PSMA-1007

In August 2016, scientists decided to use for the first time, the yet experimental radiopharmaceutical, ^{18}F-PSMA-1007 using PET/CT imaging [25]. Several ^{18}F-labeled PSMA agents have become available, such as ^{18}F-DCFPyL and ^{18}F-DCFBC [26]. Compared to ^{68}Ga-PSMA labeled ligands, ^{18}F-PSMA-1007 does have some superior characteristics. Firstly, ^{18}F is produced by a cyclotron giving us a higher available amount of radioisotope compared with the capacity of the ^{68}Ga generator [25]. It has a higher image resolution because of its low positron emission energy and its partially hepatobiliary excretion might facilitate the evaluation of the prostate bed and pelvis [25]. Longer half-life of ^{18}F is another advantage, 109 minutes compared to 68 minutes of ^{68}Ga radioisotope [26]. Fluorine-18-PSMA-1007 shows a unique biodistribution compared to the other PSMA-ligands as excretion follows the hepatobiliary route, instead of the more common urinary pathway providing advantaged to primary staging and local recurrence as there is less uptake in the PCa surrounding tissues, and there is a slightly different organ dose distribution with a higher dose to the liver parenchyma and lower radiation dose to the urinary bladder [3]. Also, it has similar theranostic potential to ^{68}Ga-PSMA-11 or ^{68}Ga-PSMA-I&T with comparable radiation dose [3]. Fluorine-18-PSMA-1007 had a high sensitivity of 74% and 62% in BCR patients with low (0.5-1ng/mL) and very low (0.2-0.5ng/mL) PSA, according to a recent study. Over 150 BCR patients with a PSA level of 0.2-0.5ng/mL had a detection rate of over 60% in this study, which was most likely owing to the difference energy profile employing fluorine vs. gallium. Nodes as small as 1mm were detected with a very high sensitivity reaching 95% [3]. An independent study of 10 patients using ^{18}F-PSMA-1007 found that the sensitivity was 71%, the specificity was 81%, the PPV was 83%, and the NPV was 68%, with a total agreement accuracy of 75% [27]. Since PSMA-1007 has a similar structure to PSMA-617, it can also be used as a theranostic [3]. Research in 2018 demonstrated that ^{18}F-PSMA-1007 showed advantage in detecting PCa lesions (both primary and metastases) than ^{18}F-flurodeoxyglucose (^{18}F-FDG) and the uptake in malignant tissues was more likely to be found in ^{18}F-PSMA-100728.

^{18}F-DCFBC & ^{18}F-DCFPyL

PYLARIFY® (piflufolastat ^{18}F) injection (also known as ^{18}F-DCFPyL or PyL) with chemical type {2-(3-(1-carboxy-5-[^{18}F] fluoropyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid}, is another widely used, second-generation, PSMA based radiotracer that was introduced as a successor to ^{18}F-DCFBC [4]. Fluorine-18-DCFBC or N-[N-[(S)-1,3-dicarboxypropyl] carbamoyl]-4-[^{18}F] fluorobenzyl-l-cysteine, was the first-generation agent and was also a small-molecule urea-derivative PSMA-targeted inhibitor of PSMA. Fluorine-18-DCFPyL was developed to overcome the limitation of ^{18}F-DCFBC which bound serum proteins, it has a long clearance time from the blood pool which interfered with lymph-node detection in the retroperitoneum and pelvis adjacent to large blood vessels, and it has greater binding affinity for PSMA [3]. Gorin et al. evaluated the diagnostic performance of ^{18}F-DCFPyL PET/CT in staging high-risk PCa in 25 men. In this study, ^{18}F-DCFPyL correctly identified 5 of the 7 cases with clinically occult positive lymph nodes when compared with surgical pathology, while over staging the remaining two cases [3]. In the metastatic setting, ^{18}F-DCFPyL-identified sites of distant disease in 12% of the patients. Fluorine-18-DCFPyL had statistically significant higher uptake in kidneys, urinary bladder, and lacrimal gland and has a renal clearance [28]. Turkbey et al. found that ^{18}F-DCFBC may detect recurrences (local or lymph node) in 60.3% of patients with no indication of disease on conventional imaging in the BCR setting [3]. Fluorine-18-DCFBC outperformed conventional imaging and detected a larger number of lesions in lymph nodes, bone, and soft tissue with a sensitivity of 92% compared to 71% for traditional imaging methods. Rowe et al. also showed that ^{18}F-DCFPyL PET/CT outperformed conventional imaging in the metastatic setting, detecting a higher number of positive lesions of local recurrence, lymph nodes, and bones. When it came to detecting disease in pelvic lymph nodes, ^{18}F-DCFPyL-PET/CT had a specificity of 96%-99%, a sensitivity of 31%-42%, and a PPV of 78%-91%. In cohort B, the sensitivity and PPV for detecting metastatic lesions were 93% to 99% and 81% to 88%, respectively [29]. In 2021, the FDA approved ^{18}F-DCFPyL for use in PCa imaging and it is now the first commercially available PSMA PET imaging agent for PCa [30].

Non-PSMA ligands

Many (non-PSMA) tracers have been investigated for their use in PCa PET-imaging, and thus far, four of them have been approved by the FDA [31]. Fluorine-18-fluciclovine, (anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid; also known as ^{18}F-FACBC) is a synthetic non-metabolized leucine amino acid analog PET radiotracer that has recently been approved by the FDA for the diagnosis of recurrent Pca [31]. Carbon-11-choline and ^{18}F-choline, choline is an important component of cell membrane phospholipids and is metabolized and internalized into cells by choline kinase, an enzyme that is overexpressed in certain tumors, such as PCa [31]. For the past 10 years, ^{11}C-choline and ^{18}F-choline PET tracers have influenced PCa imaging, especially in BCR, and are FDA approved for use in patients with recurrent disease. Both of these tracers are sensitive and specific for disease detection in high-risk staging and BCR after radical therapy in patients with high PSA levels and high PSA velocities [31]. Fluorine-18-FDG is the most widely used PET radiotracer, and is mostly used at many stages of disease in a wide range of cancers (such as PCa) and it is FDA approved for oncologic imaging. Fluorine-18-FDG though, is not so useful in PCa imaging since it is a glucose analog that is taken up by cells by way of glucose transporter (GLUT) proteins, and it is trapped in the cell as FDG-6-phosphatase [31]. Fluorine-18-FDG PET/CT has low overall sensitivity and specificity in the detection of primary disease, a higher sensitivity of ^{18}F-FDG PET/CT in the detection of primary disease has been reported in patients with higher PSA levels and advanced cancer [31]. Investigators have reported that ^{18}F-FDG PET/CT has a sensitivity of 80% and a PPV of 87% for the detection of prostate cancer with a GS of 7 or more in men with an intermediate or greater risk of PCa on the basis of their PSA levels [31]. ^{18}F-sodium fluoride, also known as ^{18}F-NaF is an analog of the hydroxyl group in hydroxyapatite bone crystals and is an avid bone seeker.

Direct comparison of PSMA-based radioligands

PSMA Radioligands	Clearance	Normal organ uptake									Half-life (min)	FDA approved (year)
		Kidneys	Bladder	Salivary glands	Liver	Spleen	Small Bowel	Lacrimal glands	Blood pool	Intestine		
^{68}Ga-PSMA-11	Blood (accumulated kidneys & liver)[10]	High	High	High	Medium	Medium	Medium	-	Low	-	68	2020
^{68}Ga-PSMA-617	Renal[18]	High	-	High	Medium	Medium	Medium	Medium	-	-	68	-
^{68}Ga-PSMA-I&T	Blood pool/circulation[36]	-	-	High	-	-	-	-	-	-	68	-
^{18}F-PSMA-1007	Hepatobiliary[37]	-	Low	-	High	-	-	-	-	-	109.7	-
^{18}F-DCFBC	Blood pool (primarily urinary)[38]	High	High	-	-	-	Medium	-	Medium	Low	109.7	-
^{18}F-DCFPyL PYLARIFY	Renal[40]	High	High	-	-	-	-	High	-	-	109.7	2021

Fluorine-18-NaF was first approved by the FDA in the 1970s for bone scintigraphy [31]. Fluorine-18-NaF PET/CT is a sensitive imaging technique for the detection of bone metastases in patients with PCa and can be used for diagnosis at staging. Still, ^{18}F-NaF PET/CT is not recommended by the EAU guidelines, because it does not assess soft tissue and has limited specificity and also because of its cost, and its availability [31]. Gallium-68-DOTA-peptides (^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC (32)) are a group of PET/CT tracers that bind to somatostatin receptors (SST) that are over-expressed on NET (neuroendocrine tumors) cells [33] and have shown promising results for imaging of NET lesions in comparison to conventional octreotide scans [32]. On the 1st of June in 2016, the U.S. FDA approved Netspot™, the first kit for the preparation of ^{68}Ga-DOTATATE injection for PET imaging, as a diagnostic tool to help clinicians determine the location and extent of NET [32].

PPV/NPV

- ^{68}Ga-PSMA-11 In BCR, with pathology as a gold standard, the PPV was 0.99 (95% CI, 0.96-1.00) and the NPV was 0.85 (95% CI, 0.75-0.93) [34]
- ^{68}Ga-PSMA-617 PPV of 88.24%, NPV of 88.24% [19]
- ^{68}Ga-PSMA I&T PPV 95.0% and NPV 93.0% [22]
- ^{18}F-PSMA-1007 PPV of 83% and NPV of 68% [27]
- ^{18}F-DCFPyL PPV 68.1% and NPV 84.8% [35]

In conclusion, the future of hybrid imaging for PCa is very promising. In contrast to conventional imaging techniques, PSMA PET/CT radiotracers show superior specificity and sensitivity for detecting PCa. By comparing the different PSMA radiopharmaceuticals and understanding their properties we can identify the most suitable imaging method for each patient. The PSMA radiotracers made a paradigm shift, opening new horizons in PET/CT imaging and they significantly changed patient management. Two of the PSMA-radiotracers have already been approved by the FDA which indicates that this imaging method will most probably replace conventional imaging.

Bibliography

1. Cancer Today. https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=1&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmsc=1&include_nmsc_other=1.
2. Paymani Z, Rohringer T, Vali R et al. Diagnostic Performance of [^{18}F] Fluorocholine and [^{68}Ga]Ga-PSMA PET/CT in Prostate Cancer: A Comparative Study. *J Clin Med* 2020; 9(7): 2308.
3. Czarniecki M, Mena E, Lindenberg L et al. Keeping up with the prostate-specific membrane antigens (PSMAs): an introduction to a new class of positron emission tomography (PET) imaging agents. *Transl Androl Urol* 2018; 7(5): 831-43.
4. Ceci F, Oprea-Lager D E, Emmett L et al. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. *Eur J Nucl Med Mol Imaging* 2021; 48: 1626-38.
5. Qin C, Gai Y, Liu Q et al. Optimized Application of ^{68}Ga-Prostate-Specific Membrane Antigen-617 Whole-Body PET/CT and Pelvic PET/MR in Prostate Cancer Initial Diagnosis and Staging. *Front Med (Lausanne)* 2021; 8: 657619.
6. McCarthy M, Langton T, Kumar D, Campbell A. Comparison of PSMA-HBED and PSMA-I&T as diagnostic agents in prostate carcinoma. *Eur J Nucl Med Mol Imaging* 2017; 44(9): 1455-62.
7. Ferreira G, Iravani A, Hofman MS, Hicks RJ. Intra-individual comparison of ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL normal-organ biodistribution. *Cancer Imaging* 2019; 19(1): 23.
8. Kesch C, Kratochwil C, Mier W et al. ^{68}Ga or ^{18}F for Prostate Cancer Imaging? *J Nucl Med* 2017; 58(5): 687-8.
9. Tu X, Zhang C, Liu Z et al. The Role of ^{68}Ga-PSMA Positron Emission Tomography/Computerized Tomography for Preoperative Lymph Node Staging in Intermediate/High Risk Patients With Prostate Cancer: A Diagnostic Meta-Analysis. *Front Oncol* 2020; 10: 1365.
10. Sandgren K, Johansson L, Axelsson J et al. Radiation dosimetry of [^{68}Ga]PSMA-11 in low-risk prostate cancer patients. *EJNMMI Phys* 2019; 6(1): 2.
11. Paller CJ, Antonarakis ES. Management of biochemically recurrent prostate cancer after local therapy: evolving standards of care and new directions. *Clin Adv Hematol Oncol* 2013; 11(1): 14-23.

new directions. *Clin Adv Hematol Oncol* 2013; 11(1): 14-23.
12. Afshar-Oromieh A, Avtzi E, Giesel FL et al. The diagnostic value of PET/CT imaging with the ^{68}Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2015; 42(2): 197-209.
13. Hennrich U, Eder M. [^{68}Ga]Ga-PSMA-11: The First FDA-Approved ^{68}Ga-Radiopharmaceutical for PET Imaging of Prostate Cancer. *Pharmaceuticals (Basel)* 2021; 14(8): 713.
14. Kopka K. A short history of transforming the diagnostic tracer PSMA-11 into the theranostic variant PSMA-617. *Endocr Abstr* 2016; 47.
15. Liu C, Liu T, Zhang N et al. ^{68}Ga-PSMA-617 PET/CT: a promising new technique for predicting risk stratification and metastatic risk of prostate cancer patients. *Eur J Nucl Med Mol Imaging* 2018; 45(11): 1852-61.
16. Wang J, Zang J, Wang H et al. Pretherapeutic ^{68}Ga-PSMA-617 PET May Indicate the Dosimetry of ^{177}Lu-PSMA-617 and ^{177}Lu-EB-PSMA-617 in Main Organs and Tumor Lesions. *Clin Nucl Med* 2019; 44(6): 431-8.
17. Afshar-Oromieh A, Hetzheim H, Kratochwil C et al. The Theranostic PSMA Ligand PSMA-617 in the Diagnosis of Prostate Cancer by PET/CT: Biodistribution in Humans, Radiation Dosimetry, and First Evaluation of Tumor Lesions. *J Nucl Med* 2015; 56(11): 1697-705.
18. Umbricht CA, Benešová M, Schmid RM et al. ^{44}Sc-PSMA-617 for radiotheragnostics in tandem with ^{177}Lu-PSMA-617-preclinical investigations in comparison with ^{68}Ga-PSMA-11 and ^{68}Ga-PSMA-617. *EJNMMI Res* 2017; 7(1): 9.
19. Li Y, Han D, Wu P et al. Comparison of ^{68}Ga-PSMA-617 PET/CT with mp-MRI for the detection of PCa in patients with a PSA level of 4-20ng/ml before the initial biopsy. *Sci Rep* 2020; 10: 10963.
20. Berliner C, Tienken M, Frenzel T et al. Detection rate of PET/CT in patients with biochemical relapse of prostate cancer using [^{68}Ga]PSMA I&T and comparison with published data of [^{68}Ga]PSMA HBED-CC. *Eur J Nucl Med Mol Imaging* 2017; 44(4): 670-7.
21. Herrmann K, Bluemel C, Weineisen M et al. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. *J Nucl Med* 2015; 56(6): 855-61.
22. Cytawa W, Seitz AK, Kircher S et al. ^{68}Ga-PSMA I&T PET/CT for primary staging of prostate cancer. *Eur J Nucl Med Mol Imaging* 2020; 47(1): 168-77.
23. Meyrick DP, Asokendaran M, Skelly LA et al. The role of ^{68}Ga-PSMA-I&T PET/CT in the pretreatment staging of primary prostate cancer. *Nucl Med Commun* 2017; 38(11): 956-63.
24. Schmuck S, Nordlohne S, von Klot A. C et al. Comparison of standard and delayed imaging to improve the detection rate of [^{68}Ga]PSMA I&T PET/CT in patients with biochemical recurrence or prostate-specific antigen persistence after primary therapy for prostate cancer. *Eur J Nucl Med Mol Imaging* 2017; 44: 960-8.
25. Giesel FL, Kesch C, Yun M et al. ^{18}F-PSMA-1007 PET/CT Detects Micrometastases in a Patient With Biochemically Recurrent Prostate Cancer. *Clin Genitourin Cancer* 2017; 15(3): e497-e499.
26. Treglia G, Annunziata S, Pizzuto DA et al. Detection Rate of ^{18}F-Labeled PSMA PET/CT in Biochemical Recurrent Prostate Cancer: A Systematic Review and a Meta-Analysis. *Cancers (Basel)* 2019; 11(5): 710.
27. Sprute K, Kramer V, Koerber SA et al. Diagnostic Accuracy of ^{18}F-PSMA-1007 PET/CT Imaging for Lymph Node Staging of Prostate Carcinoma in Primary and Biochemical Recurrence. *J Nucl Med* 2021; 62(2): 208-13.
28. Zhou X, Li Y, Jiang X et al. Intra-Individual Comparison of ^{18}F-PSMA-1007 and ^{18}F-FDG PET/CT in the Evaluation of Patients With Prostate Cancer. *Front Oncol* 2021; 10: 585213
29. ^{18}F-DCFPyL, PSMA-Targeted PET Imaging Agent, Provokes High CLR and PPV. Targeted Oncology https://www.targetedonc.com/view/18f-dcfpyl-psma-targeted-pet-imaging-agent-provokes-high-clr-and-ppv.
30. FDA Approves ^{18}F-DCFPyL as First PSMA PET Imaging Agent Available for Prostate Cancer. Cancer Network https://www.cancernetwork.com/view/fda-approves-18f-dcfpyl-as-first-psma-pet-imaging-agent-available-for-prostate-cancer.
31. Wallitt KL, Khan SR, Dubash S et al. Clinical PET Imaging in Prostate Cancer. *Radiographics* 2017; 37(5): 1512-36.
32. Raj N, Reidy-Lagunes D. The Role of ^{68}Ga-DOTATATE Positron Emission Tomography/Computed Tomography in Well-Differentiated Neuroendocrine Tumors: A Case-Based Approach Illustrates Potential Benefits and Challenges. *Pancreas* 2018; 47(1): 1-5.
33. Ambrosini V, Campana D, Tomassetti P et al. PET/CT with ^{68}Gallium-DOTA-peptides in NET: an overview. *Eur J Radiol* 2011; 80(2): e116-e119.
34. Hope TA, Goodman JZ, Allen IE et al. Metaanalysis of ^{68}Ga-PSMA-11 PET Accuracy for the Detection of Prostate Cancer Validated by Histopathology. *J Nucl Med* 2019; 60(6): 786-93.
35. Bodar YJL, Jansen BHE, van der Voorn JP et al. Detection of prostate cancer with ^{18}F-DCFPyL PET/CT compared to final histopathology of radical prostatectomy specimens: is PSMA-targeted biopsy feasible? The DeTeCT trial. *World J Urol* 2021; 39(7): 2439-46.
36. Weineisen M, Schottelius M, Simecek J et al. ^{68}Ga- and ^{177}Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies. *J Nucl Med* 2015; 56(8): 1169-76.
37. dos Santos G, Monica R, Javier G et al. Intraindividual Comparison of novel ^{18}F-PSMA-1007 and Al^{18}F-PSMA-HBED-CC PET/CT in the Prospective Evaluation of Prostate Cancer Patients with Biochemical Relapse: First experience in Uruguay. *J Nucl Med* 2021; 62: 1326.
38. Cho SY, Gage KL, Mease RC et al. Biodistribution, tumor detection, and radiation dosimetry of ^{18}F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. *J Nucl Med* 2012; 53(12): 1883-91.
39. Mena E, Lindenberg ML, Turkbey IB et al. ^{18}F-DCFPyL PET/CT Imaging in Patients with Biochemically Recurrent Prostate Cancer After Primary Local Therapy. *J Nucl Med* 2020; 61(6): 881-9.
40. Robu S, Schmidt A, Eiber M et al. Synthesis and preclinical evaluation of novel ^{18}F-labeled Glu-urea-Glu-based PSMA inhibitors for prostate cancer imaging: a comparison with ^{18}F-DCFPyl and ^{18}F-PSMA-1007. *EJNMMI Res* 2018; 8(1): 30.