PSMA for PET Imaging of Prostate Cancer

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Received: May 22, 2018
Revision received: May 24, 2018
Accepted after revision: July 6, 2018
BKK Med J 2018;14(2): 95-100.
DOI: 10.31524/bkkmedj.2018.09.016
www.bangkokmedjournal.com

Abstract

^{18}F-fluorodeoxyglucose (FDG or ^{18}F-FDG) is the most widely used radiotracer for Positron Emission Tomography/Computed Tomography (PET/CT) imaging. However, using FDG for PET/CT imaging in prostate cancer is limited because a large fraction of prostate cancer shows limited FDG uptake. Previously, radiolabeled choline derivative such as ^{18}F-fluorocholine and ^{11}C-choline were considered as a more suitable alternative to FDG for prostate cancer imaging. They are used as PET tracers for staging and restaging of prostate cancer. Although the specificity of radiolabeled choline is quite high, the sensitivity is rather poor. Currently, targeting the prostate specific membrane antigen (PSMA) with molecular imaging agents has been increasingly investigated. PSMA is expressed in most prostate cancer and it is an ideal target for diagnosis and treatment. There are many PSMA agents available nowadays. This article will give brief overview about PSMA ligands for PET imaging and therapy of prostate cancer.

Keywords : PSMA, PSMA imaging, Ga-68 PSMA

Prostate cancer is the most commonly diagnosed cancer in men worldwide. Among men in the United State, prostate cancer is the third leading cause of death from malignancy.[1] According to American Cancer Society, about 1 man in 7 will be diagnosed with prostate cancer during his lifetime.[2] Prostate cancer develops mainly in older men. About 6 cases in 10 are diagnosed in men aged 65 or older, and it is rare before age 40. The average age at the time of diagnosis is about 66. Prostate cancer has high cure rate when detected early. Molecular Imaging technologies dramatically improve prostate cancer diagnosis and treatment. Although FDG is the most widely use PET tracer, using FDG for PET/CT imaging in prostate cancer is limited because a large fraction of prostate cancer shows limited FDG uptake.[3] In the past decade, alternative tracers for prostate cancer imaging are radiolabeled choline derivative such as ^{18}F-fluorocholine and ^{11}C-choline. They are used as PET tracers for staging and restaging of prostate cancer.[4] According to a meta-analyses report, in primary nodal imaging the specificity is as high as 95% but the sensitivity is very poor (49%).[5] Due to the lack of sensitive imaging for prostate cancer, more research has been focused on the development of new tracers that have better sensitivity and specificity. In recent years, targeting the prostate specific membrane antigen (PSMA) with ^{68}Ga-labeled and ^{18}F-labeled PET tracers has gained highest clinical impact.

PSMA ligands

PSMA is a type II transmembrane glycoprotein that is significantly (100-fold to 1000-fold) overexpressed in nearly all prostatic cancer cells compared with normal prostatic cells.[6-9] The level of PSMA expression rises with an increase in tumor grade, pathological stage and biochemical recurrence. PSMA PET/CT had a significant impact on the management of prostate cancer. A cohort study reported that radiotherapy management was changed for 50.8% when using ^{68}Ga-PSMA-11 PET/CT for radiotherapy planning.[10]

Several imaging probes specifically targeting PSMA were developed. Since the 1980s, several studies have been made to target specific regions of the intracellular or extracellular domain of PSMA with monoclonal antibodies labeled with different isotopes for nuclear medicine imaging.[11] One of the first PSMA imaging agents was ^{111}In-labeled anti-PSMA antibody (^{111}In-capromab pendetide, ProstaScint®).[12] The effectiveness of antibodies as diagnostic radiopharmaceuticals is limited by a long circulating half-life resulting in a high unspecific background activity and poor tumor penetrability. Thus, the application of ^{111}In-capromab pendetide for imaging of prostate cancer is limited because it has high non-specific uptake and relatively poor tumor-to-background ratios.

Besides the development of PSMA monoclonal antibodies, small molecule PSMA inhibitors with high affinity gained a lot of interest. Because of their small size, they have better tumor penetration than antibodies. A series of studies have been made to evaluate the role of small molecule inhibitors of PSMA labeled with ^{123}I, ^{99m}Tc, ^{18}F, ^{111}In, and ^{68}Ga.[13-24] PSMA inhibitors fall into 3 families: urea-based, phosphorous-based, and thiol-based [25] as shown in Figure 1. A study by Chen et al., compared PSMA ligands with different linker lengths and has shown that an increased linker length enhanced the affinity for PSMA and increased tumor uptake.[26]

Urea-based inhibitors have a high affinity and specificity for PSMA and fast and efficient internalization into the cells. Several clinical studies evaluating PSMA ligands have been performed. Examples of small molecule PSMA ligands are shown in Figure 2. Among these agents, the ^{68}Ga- and ^{18}F-labeled compounds have attracted the most attention because they can be used for PET/CT imaging. Currently, the most widely used PET tracer for prostate cancer imaging is ^{68}Ga-PSMA-11.[24] ^{68}Ga-PSMA-11 has many synonyms. Here is the list of ^{68}Ga-PSMA-11 in difference writing.

- ^{68}Ga labeled Glu-NH-CO-NH-Lys(Ahx)-HBED-CC
- ^{68}Ga-labeled Glu-urea-Lys(Ahx)-HBED-CC
- ^{68}gallium-PSMA ligand Glu-urea-Lys(Ahx)-HBED-CC
- ^{68}Ga-PSMA ligand Glu-urea-Lys(Ahx)-HBED-CC
- [^{68}Ga] prostate-specific membrane antigen 11
- [^{68}Ga] prostate-specific membrane antigen 11
- [^{68}Ga]GaPSMA-11
- ^{68}Ga-HBED-CC-PSMA
- ^{68}Ga-labeled Glu-NH-CO-NH-Lys(Ahx)-HBED-CC
- ^{68}Ga-PSMA-11
- Ga-68-labeled PSMA-11
- gallium Ga-68 PSMA-11
- gallium-68 PSMA ligand Glu-urea-Lys(Ahx)-HBED-CC

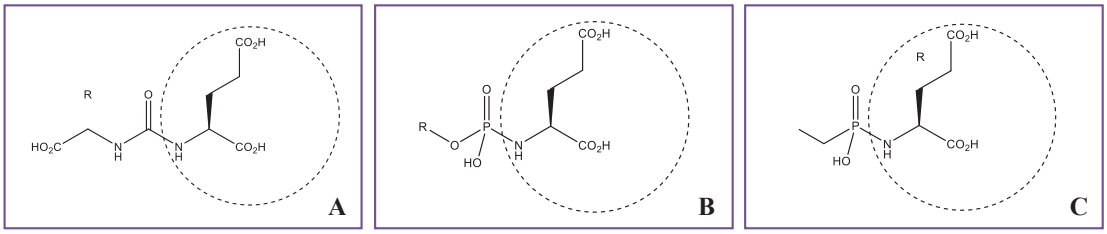

Figure 1: Small molecule PSMA inhibitors for prostate cancer studies (A) the urea-based compounds, (B) the glutamate phosphoramidates and (C) the 2-(phosphinylmethyl) pentanedioic acids. The binding domains are shown in the circle.

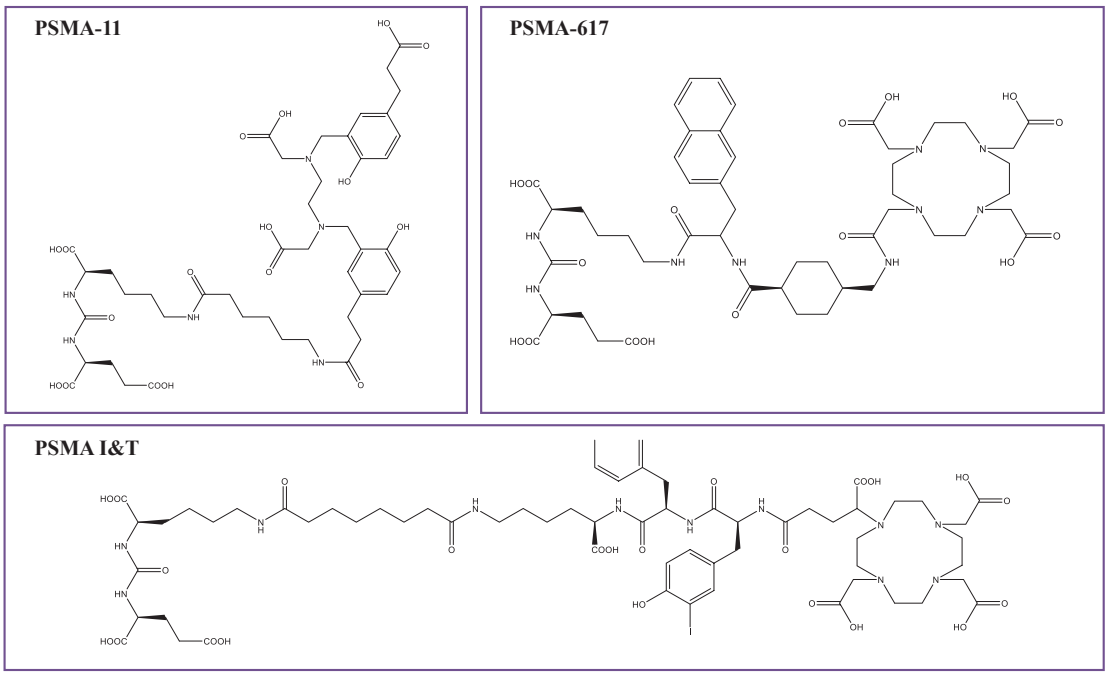

Figure 2: Example of small molecule PSMA ligands.

ISSN 2287-0237 (online)/ 2287-9674 (print)

^{68}Ga-PSMA-11

^{68}Ga-PSMA-11 has a disadvantage with respect to production capacity and nuclear properties. The half-life of ^{68}Ga is only 68 minutes. Therefore, delivery of sufficient amount of tracer activities to a remote center is quite challenging. ^{68}Ga (Gallium-68) is produced with ^{68}Ge (Germanium-68) generator. Preparation of ^{68}Ga-PSMA-11 is relatively easy. One batch of production of ^{68}Ga-PSMA-11 can be used with 2-4 patients per generator elution. The main advantage of ^{68}Ga-PSMA-11 is the commercially availability of ^{68}Ge/^{68}Ga generators. The long half-life of ^{68}Ge (271 days) permits the generator to be used for several months or up to a year. The short half-life of ^{68}Ga (68 minutes) allows multiple elution of the generator on the same day. For a center that does not have access to a cyclotron and has a moderate number of patients, the price of these generators is a reasonable investment.

^{68}Ge/^{68}Ga generator was first developed in 1950. The first commercial ^{68}Ge/^{68}Ga generator was introduced in late 1990s which resulted in the blossoming of the ^{68}Ga-PET. Pharmaceutical grade generators appeared on the market in 2014. Examples of commercial ^{68}Ge/^{68}Ga generator are shown in Figure 3. A generator is a self-shield system housing a parent/daughter radionuclide mixture in equilibrium. Figure 4 shows a schematic presentation of the cross section of a column-based generator. Commercial generators consist of a short chromatographic column packed with a solid support in a shielding container. ^{68}Ge which is produced from a high energy cyclotron from stable ^{69}Ge isotope is absorbed onto a column filled with inorganic, organic or mixed matrix. ^{68}Ge decays to ^{68}Ga and ^{68}Ga decays to stable ^{68}Zn as shown in Figure 5. ^{68}Ga is washed off the column with an appropriate solution. Then ^{68}Ga can be used for tracers labeling.

Figure 3: Example of commercial ^{68}Ge/^{68}Ga Generators.

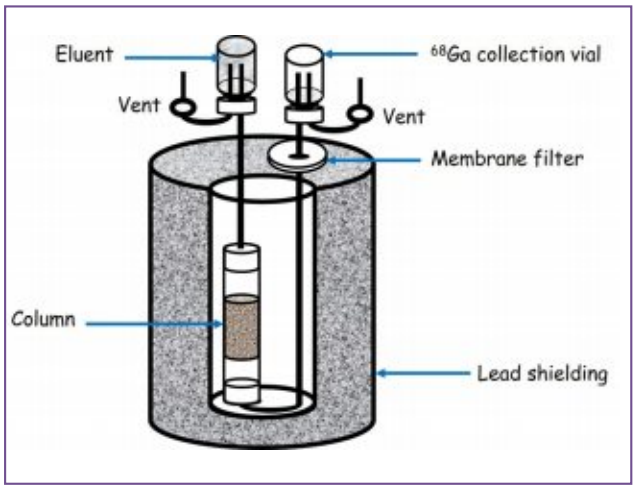

Figure 4: Schematic presentation of the cross section of a column-based generator.

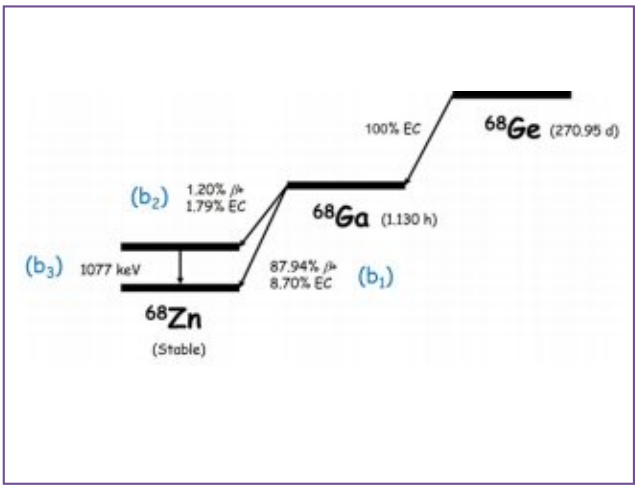

Figure 5: Schematic decay of ^{68}Ge.

PSMA-11 contains the chelator HBED-CC (N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine –N, N'-diacetic acid). The chelator HBED-CC allows labeling with kit formulations at room temperature without critical radiochemistry demands.[27] ^{68}Ga-PSMA-11 can be prepared by several methods. It can be prepared with an automate synthesis system which can provide the reliability, reproducibility and safety of radiopharmaceutical productions. In recent times, the widespread, routine clinical use of ^{68}Ga-PSMA-11 demands availability of a ready-to-use kit formulation to enable convenient radiopharmaceutical preparation. A freeze-dried kit vial for formulation of ^{68}Ga-PSMA-11 was developed by a number of centers.[28,29] This method will provide convenient preparation of ^{68}Ga-PSMA-11. Satpati D., et al reported that ^{68}Ga-PSMA-11 could be prepared in >98 % radiochemical yield and purity using the freeze-dried kit vials. The development of a simple and ready-to-use freeze-dried kit for preparation of ^{68}Ga-PSMA-11will contribute to a major step towards the widespread use of ^{68}Ga-PSMA-11 for prostate cancer imaging with PET/CT.

^{68}Ga has physical half-life of only 68 minutes. Therefore, delivery of sufficient radiopharmaceutical activities to a remote center is challenging. One batch of ^{68}Ga-PSMA-11 production can be used with 2-4 patients. In large centers with many patients, several productions per day are required, or multiple generators are needed to produce sufficient amount of activities. The centers which have quantitative demand, the use of ^{18}F-labeled PSMA tracers may be more efficient. High activities of ^{18}F can be produced with a cyclotron. The physical half-life of ^{18}F is 109.77 minutes. The ^{18}F-labeled PSMA tracers are developed. Two promising ^{18}F-labeled PSMA tracers which are under clinical investigation are ^{18}F-DCFPyL and ^{18}F-PSMA-1007. PSMA-1007 is ((3S,10S,14S)-1-(4-(((S)-4-carboxy-2-((S)-4-carboxy-2-(6-^{18}F-fluoronicotinamido)butanamido)butanamido) methyl) phenyl)-3-(naphthalen-2-ylmethyl)-1,4,12-trioxo-2,5,11,13-tetraazahexadecane-10,14,16-tricarboxylic acid) and DCFPyL is (2-(3-{1-carboxy-5-[(6-18F-fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid). The chemical structures of ^{18}F-PSMA-1007 and ^{18}F-DCFPyL are shown in Figure 6. Due to longer half-life of ^{18}F and the possibility to produce in high activity, the ^{18}F-labeled PSMA enable centralized production and delivery to distant centers. ^{18}F has a lower positron energy than ^{68}Ga (0.68 MeV for ^{18}F vs. 1.90 MeV for ^{68}Ga). Thus PET imaging with ^{18}F-labeled tracers have better spatial resolution than ^{68}Ga-labeled tracers.

Besides diagnostic imaging, radiolabeled PSMA ligands also have potential for radionuclide therapy of prostate cancer. Several PSMA ligands are currently investigated clinically for diagnostic and therapeutic purposes. Some PSMA ligands can be labeled with either ^{68}Ga for PET imaging or ^{177}Lu (Lutetium-177) for radionuclide therapy. ^{177}Lu physical properties are good to use as therapeutic radionuclide. ^{177}Lu is a medium-energy beta emitter (490 keV) with a maximum tissue penetration of < 2 mm. The emission characteristics match the lesion size/volume to be treated to ideally focus energy within the tumor rather than in the tissue surrounding the lesion. ^{177}Lu has a relatively long physical half-life of 6.73 days. These physical properties of ^{177}Lu allow for the delivery of a high radiation dose to prostate cancer cells. These PSMA ligands which can be labeled either with ^{68}Ga or ^{177}Lu have potential to be used for both diagnostic and therapeutic purposes. Example of such agents are PSMA I&T and DKFZ-617. PSMA I&T (for Imaging and Therapy) is DOTAGA-(I-y)fk(Sub-KuE). It is DOTAGA-couple PSMA ligands by increasing the hydrophilicity of the ligand by substitute DOTA by 1,4,7,10-tetraazacyclododecane-, 1-(glutaric acid)-4,7,10-triacetic, resulting in DOTAGA-FFK(Sub-KuE) which can be labeled with both ^{68}Ga and ^{177}Lu.30 DOTA-conjugated DKFZ-^{617} PSMA ligand is another tracer which has mainly been used for therapy may be used for diagnostic application too. The results show that ^{177}Lu-PSMA is a safe treatment option for metastatic prostate cancer patients and has a low toxicity profile.

Positive responses to therapy in terms of decline in PSA are reported and more than 40% of patients showed more than 50 % PSA decline.[31,32] Comparison of the properties of ^{68}Ga, ^{18}F, and ^{177}Lu is shown in Table 1.

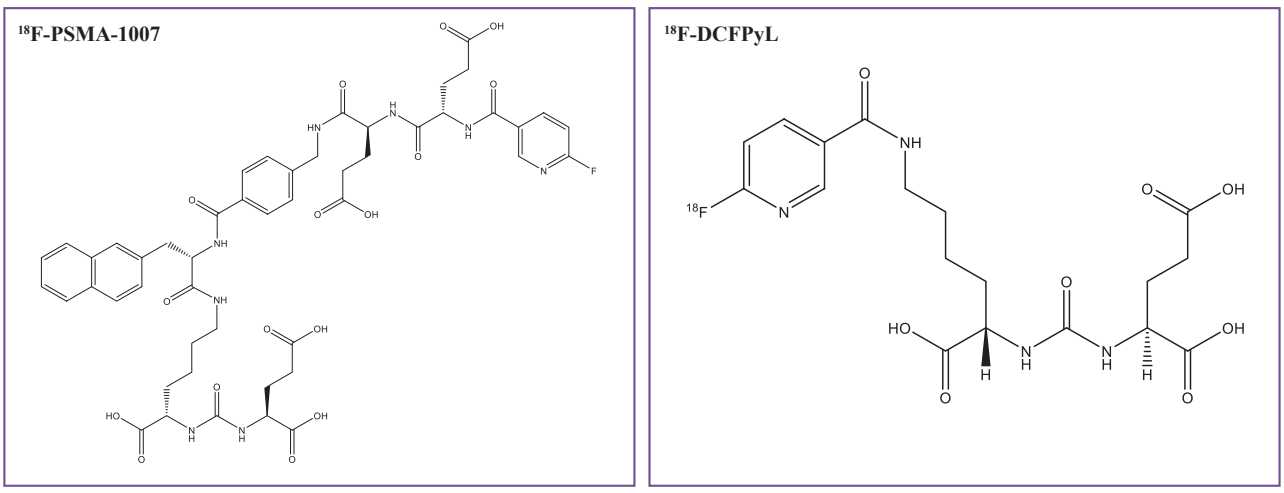

Figure 6: ^{18}F-PSMA-1007 and ^{18}F-DCFPyL.

ISSN 2287-0237 (online)/ 2287-9674 (print)

Table 1: Comparison of ^{68}Ga, ^{18}F and ^{177}Lu

Parameter	^{68}Ga	^{18}F	^{177}Lu
Half-life	• 68 minutes • Complete decay within a few hours after examination, thus less radiation exposure to relatives. • Only shippable to close satellite center.	• 110 minutes Satellite shipping is possible. • positron emission : 0.65 MeV • Better image quality than ^{68}Ga	• 6.73 days • Relatively long physical half-life is good for therapy purpose.
Decay mode	• Positron emission: 1.90 MeV • Image quality is poorer than ^{18}F due to longer positron range		• Beta- decay: 490 keV • X-ray: 113 keV (3%), 210 keV (11%) • Medium-energy (beta)-emitter and maximal tissue penetration of <2 mm provide better irradiation of small tumors than longer (beta)-range.
Production	• Generators	• Cyclotron	• Reactor produced
Imaging/Therapy	• PET Imaging	• PET Imaging	• Therapy

Conclusion

It appears that PSMA shows great promise not just in detecting prostate cancer, but also as a target for radionuclide therapy. At present, there are many radiolabeled PSMA ligands available for imaging and therapy. ^{68}Ga-PSMA-11 is currently the most widely used for prostate cancer imaging with PET/CT. Development of ^{18}F-PSMA shows promising results. In the future, PSMA imaging will be used more widely due to the availability of tracers. The use of PSMA PET/CT resulted in a change of the therapeutic management in up to 50% of cases. The currently available data clearly shows that PSMA imaging has a clinical impact on the diagnosis of prostate cancer. Radiolabeled PSMA tracers also have high potential for therapeutic approaches.

Acknowledgements

The author thanks the PET center and Cyclotron facility team at Wattanosoth Cancer Center including doctors, nurses, physicists, technologists, chemists, engineers and pharmacists. During the past 12 years, they have put a lot of effort into continued improvements in quality and range of services. Also, the author is very grateful for the support from the executive of the Bangkok Hospital and Wattanosoth Cancer Hospital.

References

1. Siegel R, Miller K, Jemal A. Cancer Statistic, 2017. *CA Cancer J Clin* 2017;67:7-30.
2. American Cancer Society. Cancer Facts & Figures 2018. Atlanta, *Ga: American Cancer Society*; 2018.
3. Gambhir SS, Czermin J, Schwimmer J, et al. A tabulated summary of the FDG PET literature. *J Nucl Med* 2001;42: 1S-93S.
4. Bouchelouche K, Tagawa ST, Goldsmith SJ, et al. PET/CT Imaging and Radioimmunotherapy of Prostate Cancer. *Semin Nucl Med*. 2011;41:29-44.
5. Evangelista L, Guttilla A, Zatttoni F, et al. Utility of choline positron emission tomography/computed tomography for lymph node involvement identification in intermediate- to high-risk prostate cancer: a systematic literature review and meta-analysis. *Eur Urol*. 2013;63:1040-8.
6. Silver DA, Pellicer I, Fair WR, et al. Prostate-specific membrane antigen expression in normal and malignant human tissues. *Clin Cancer Res*. 1997;3:81-5.
7. Mannweiler S, Amersdorfer P, Trajanoski S, et al. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. *Path Oncol Res*. 2009;15:167-72.
8. Bostwick DG, Pacelli A, Blute M, et al. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer*. 1998;82:2256-61.
9. Troyer JK, Beckett ML, Wright GL. Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids. *Int J Cancer*. 1995;62:552-8.

10. Sterzing F, et al. 68Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. *Eur J Nucl Med Mol Imaging*. 2016;43:34-41.
11. Ghosh A, Heston W.D. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. *J Cell Biochem*. 2004;91:528-39.
12. Horoszewicz JS, Kawinski E, Murphy GP. Monoclonal antibodies to a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients.*Anticancer Res.* 1987;7:927-35.
13. Foss CA, et al. Radiolabeled small-molecule ligands for prostate-specific membrane antigen; in vivo imaging in experimental models of prostate cancer. *Clin Cancer Res*. 2005;11:4022-8.
14. 14. Hillier S. M. et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. *Cancer Res.* 2009;69:6932-40.
15. Kularatne SA, Zhou Z, Yang J, et al. Design, synthesis and preclinical evaluation of prostate-specific membrane antigen targeted 99mTc-radioimaging agents. *Mol Pharm*. 2009;6: 790-800.
16. Rowe S. P, et al. PSMA-Based [18F]DCFPyL PET/CT Is Superior to Conventional Imaging for Lesion Detection in Patients with Metastatic Prostate Cancer. *Mol Imaging Biol*. 2016;18:411-9.
17. Chen Y. et al. 2-(3-{1-carboxy-5-[(6-[19F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, [18F] DCFPyl, a PSMA-based PET imaging agent for prostate cancer. *Clin Cancer Res*. 2011;17:7645-53.
18. Giesel FL, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. *Eur J Nucl Mol Imaging*. 2017;44:678-88.
19. Benerjee SR. et al. A modular strategy to prepare multivalent inhibitors of prostate-specific membrane antigen (PSMA). *Oncotarget*. 2011;2:1244-53.
20. Afshar-Oromieh A. 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;42:197-209.
21. Kallur KG., et al. Clinical Utility of Gallium-68 PSMA PET/CT Scan for Prostate Cancer. *Indian J Nucl Med*. 2017;32:110-7.
22. Uprimny C, et al. Early PET imaging with [68]Ga-PSMA-11 increases the detection rate of local recurrence in prostate cancer patients with biochemical recurrence. *Eur J Nucl Med Mol Imaging*. 2017; 44:1647-55.
23. Kesch C, et al. 68Ga or 18F for Prostate Cancer Imaging? *J Nucl Med*. 2017;58:687-8.
24. Rowe SP., et al. PET imaging of prostate-specific membrane antigen in prostate cancer: current state of the art and future challenges. *Prostate Cancer Prostatic Dis*. 2016;19:223-30.
25. Lutje S, et al. PSMA Ligands for Radionuclide Imaging and Therapy of Prostate Cancer: Clinical Status. *Theranostics*. 2015;5:1388-401.
26. Chen Y, et al. Synthesis and biological evaluation of low molecular weight fluorescent imaging agents for the prostate-specific membrane antigen. *Bioconjug Chem* 2012; 23:2377-85.
27. Eder M, et al. Tetrafluorophenolate of HBED-CC: A versatile conjugation agent for 68Ga-labeled small recombinant antibodies. *Eur J Nucl Med Mol Imaging* 2008;35:1878-86.
28. Eberhan T, et al. Development of a Single Vial Kit Solution for Radiolabeling of 68Ga-DKFZ-PSMA-11 and Its Performance in Prostate Cancer Patients. *Molecules*. 2015; 20:14860-78.
29. Satpati D, et al. Convenient Preparation of [(68)Ga]DKFZ-PSMA-11 Using a Robust Single-Vial Kit and Demonstration of Its Clinical Efficacy. *Mol Imaging Biol*. 2016; 18:420-7.
30. Weineisen M, Simecek J, Schottelius M, et al. Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer. *EJNMMI Res*. 2014;4:63.
31. Ahmadzadehfar H, Eppard E, Kürpig S et al. Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate resistant metastatic prostate cancer. *Oncotarget* 2016;7:12477-88.
32. Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J Nucl Med* 2017;58:85-90.

ISSN 2287-0237 (online)/ 2287-9674 (print)