Editorial Commentary

Prostate specific membrane antigen (PSMA) imaging: the past is prologue

Peter L. Choyke[1], Kirsten Bouchelouche[2]

[1]Molecular Imaging Program, National Cancer Institute, Bethesda, MD, USA; [2]Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, Aarhus, Denmark

Correspondence to: Peter L. Choyke, MD. Molecular Imaging Program, National Cancer Institute, Building 10, Room B3B69F, Bethesda, MD 20892, USA. Email: pchoyke@nih.gov.

Provenance: This is an invited article commissioned by the Section Editor Dr. Xiao Li (Department of Urology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Comment on: Rowe SP, Gorin MA, Pomper MG. Imaging of prostate-specific membrane antigen with small-molecule PET radiotracers: from the bench to advanced clinical applications. Annu Rev Med 2019;70:461-77.

Submitted Apr 30, 2019. Accepted for publication Jul 28, 2019.
doi: 10.21037/tau.2019.07.20
View this article at: http://dx.doi.org/10.21037/tau.2019.07.20

In just a few short years prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has transformed the management of prostate cancer patients. Where did this revolutionary idea come from? In this review by Rowe, Gorin and Pomper, several of the pioneers of the "PSMA revolution" provide an overview of the evolution of PSMA PET imaging and its potential future. Here, we cast additional light on the story of PSMA PET.

PSMA PET for prostate cancer is one of the most important ideas to emerge in the last two decades. However, its discovery was not a foregone conclusion. In 1996, Jackson *et al.* described high-affinity agents targeting N-Acetylated alpha-linked acidic dipeptidase (NAALADase), an enzyme that cleaves N-Acetylaspartylglutamic acid into glutamate and N-Acetyleacetic acid. These agents had over 1,000 times the potency of previous inhibitors and it was thought this might be used as therapy for some neurologic conditions (1). Martin Pomper, a neuroradiologist at Johns Hopkins, came across this article and thought it might be functionalized for PET imaging in the brain to study glutamatergic transmission. However, the compounds involved were too hydrophilic for brain imaging, but noting the sequence homology between NAALADase and PSMA described by Carter *et al.* that same year, he pivoted to the study of prostate cancer (2). In 2001 Kozikowski *et al.*, then at Georgetown University, had been working on inhibitors of NAALADase as neuroprotective agents and, after a chance meeting with Pomper, began a collaboration focused on prostate cancer imaging based on Kozikowski's NAALADase binding urea scaffold (3). A highly desirable feature of the enzyme-substrate binding of the urea scaffold is that once bound, hydrophilic compounds are trapped and accumulate within the cell leading to high tumor to background levels. The first such agent was initially described as 11C-MeCys-C(O)-Glu or 11C-(S)-2-[3-((R)-1-carboxy-2-methylsulfanyl-ethyl)-ureido]-pentanedioic acid (MCG), an ^{11}C-labeled PET agent developed for proof-of-principle for imaging PSMA in the periphery, and published by Pomper *et al.* in 2002 (4). Subsequently, the Pomper lab went on to create numerous preclinical agents, culminating in the first practical human PSMA PET agent, ^{18}F-DCFBC, reported in 2008 (5). Meanwhile, Banerjee *et al.*, working in Pomper's lab, described the first radiometalated PSMA-targeted imaging agent in 2008 (6). They found that an approximately 20Å linker between the chelator, in that case for ^{99m}Tc, and the urea targeting scaffold was required for effective binding. They hypothesized that the long linker moved the chelator outside of the active site of PSMA. They then synthesized the first ^{68}Ga-labeled PSMA inhibitor in 2010 using 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate (DOTA) as the chelator (7). Thus, the stage was set for the clinical introduction of PSMA PET imaging.

In 2012 Eder and the group at Heidelberg synthesized a ^{68}Ga-labeled PSMA PET compound using the HBED-CC chelator, which eventually became known as PSMA-11 (8).

PSMA 617, another agent developed later, was a minimal modification of this which allowed binding of ^{177}Lu-177 and ^{225}Ac for targeted radionuclide treatment (9). These agents rapidly entered clinical use in Germany owing to unique laws permitting experimental low dose radioactive agents to be investigated in patients and the impressive results immediately emerged. This led researchers in many other countries to image prostate cancer patients, especially those with biochemical recurrence using one of the ^{68}Ga-labeled compounds. Early clinical experience in many countries outside the US led to several regulatory approvals. At about the same time as the development of PSMA-11, the 2nd generation of ^{18}F-labeled PSMA agents emerged in the form of ^{18}F-DCFPyl reported in 2011 by the Pomper group, which has subsequently progressed to Phase III trials in the United States (10). Thus, it is likely that both ^{18}F-DCFPyl and ^{68}Ga PSMA-11 or other ^{68}Ga-labeled compounds will be widely available in the coming years. One "final" note to this interesting and continuing story is the development of another ^{18}F based compound, ^{18}F-PSMA-1007 by the Heidelberg group in 2016 which shows less urinary excretion than ^{18}F-DCFPyl (11). Thus, a series of serendipitous events led to the discovery of a new PET imaging agent that has led to explosive development of other agents.

Thus, in less than 10 years great strides have been made in the development of PSMA PET imaging with very promising clinical results for the diagnosis, staging, recurrence detection and metastatic disease detection. A criticism of the existing literature is its anecdotal nature and the failure of investigators to join forces in multi-institutional and trans-national trials. Nevertheless, we owe a debt of gratitude to the pioneers of human PSMA imaging who showed how useful this agent could be and how reproducible it was around the world. This provided a strong impetus to develop it commercially.

While most of us believe that this new diagnostic method will result in life saving management changes for patients, there is actually little evidence at this point. It is true that clinicians have instituted a number of management changes in response to PSMA findings—including deferring androgen deprivation therapy, changing radiotherapy plans, and selecting alternative salvage therapies—but it will take years before we can be sure that these interventions benefit the patient in a meaningful way. This will require a well organized, disciplined and international approach to understanding how to use this agent. Indiscriminate use of PSMA PET and treatment modification based on its findings outside of clinical research studies may make it impossible to conduct randomized trials in the future. Therefore, it is important that such studies begin soon.

There are many other questions raised by PSMA PET imaging including its role in forecasting prognosis, in targeting biopsies of disease and particularly, in the treatment of oligometastatic disease. It is highly tempting to think that just a few lesions on a PSMA scan might be amenable to cure using targeted stereotactic body radiation therapy or similar targeted therapy but it must be understood that there is often sub-detectable disease already widely metastatic at the time of "oligometastasis" and that focal therapies may not provide meaningful gains for the patient, although they may be quite costly for the patient and the medical system.

The possibility of using PSMA as a target for therapy is very exciting. Early studies suggest that treatment with targeted radionuclide therapy using PSMA-targeted beta-emitters such as ^{177}Lu-177 can result in responses especially in prostate-specific antigen (PSA) in patients with recurrent and metastatic disease (12). In theory, this treatment would occur at any PSMA positive site and therefore could be considered systemic therapy. However, not all prostate cancers express PSMA. In this case, patients might be exposed to needless high levels of radiation which could cause irreversible damage. Even more effective than beta emitters are alpha emitters such as ^{225}Ac which can be chelated to a PSMA targeting agent. Although such agents appear to be highly effective against the tumor they also cause irreversible damage to organs that have high uptake of PSMA inhibitors such as the salivary glands and kidneys. In the case of salivary glands, severe xerostomia has been observed in some patients with prostate cancer following ^{225}Ac PSMA therapy. Therefore, there is much interest in finding agents that are not taken up in the salivary glands or can be blocked from doing so.

We congratulate the authors on producing a highly worthwhile read on a rapidly emerging topic. Given the impact of this discovery it is worthwhile reviewing its interesting history. While the impact of PSMA-targeted ligands are yet to be fully understood there is little doubt the changes will be profound, in no small part due to the efforts of the authors.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Jackson PF, Cole DC, Slusher BS, et al. Design, synthesis, and biological activity of a potent inhibitor of the neuropeptidase N-acetylated alpha-linked acidic dipeptidase. J Med Chem 1996;39:619-22.
2. Carter RE, Feldman AR, Coyle JT. Prostate-specific membrane antigen is a hydrolase with substrate and pharmacologic characteristics of a neuropeptidase. Proc Natl Acad Sci U S A 1996;93:749-53.
3. Kozikowski AP, Nan F, Conti P, et al. Design of remarkably simple, yet potent urea-based inhibitors of glutamate carboxypeptidase II (NAALADase). J Med Chem 2001;44:298-301.
4. Pomper MG, Musachio JL, Zhang J, et al. 11C-MCG: synthesis, uptake selectivity, and primate PET of a probe for glutamate carboxypeptidase II (NAALADase). Mol Imaging 2002;1:96-101.
5. Mease RC, Dusich CL, Foss CA, et al. N-[N-[(S)-1,3-Dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC: a new imaging probe for prostate cancer. Clin Cancer Res 2008;14:3036-43.
6. Banerjee SR, Foss CA, Castanares M, et al. Synthesis and evaluation of technetium-99m- and rhenium-labeled inhibitors of the prostate-specific membrane antigen (PSMA). J Med Chem 2008;51:4504-17.
7. Banerjee SR, Pullambhatla M, Byun Y, et al. 68Ga-labeled inhibitors of prostate-specific membrane antigen (PSMA) for imaging prostate cancer. J Med Chem 2010;53:5333-41.
8. Eder M, Schäfer M, Bauder-Wüst U, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem 2012;23:688-97.
9. 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;56:1697-705.
10. Chen Y, Pullambhatla M, Foss CA, et al. 2-(3-{1-Carboxy-5-[(6-[18F]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.
11. Giesel FL, Hadaschik B, Cardinale J, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging 2017;44:678-88.
12. Hofman MS, Violet J, Hicks RJ, et al. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol 2018;19:825-33.

Cite this article as: Choyke PL, Bouchelouche K. Prostate specific membrane antigen (PSMA) imaging: the past is prologue. Transl Androl Urol 2019;8(4):283-285. doi: 10.21037/tau.2019.07.20

