Advances in Urologic Imaging

Prostate-Specific Membrane Antigen Ligand PET Imaging

Michael S. Hofman, MBBS, FRACP, FAANMS[a,b],
Amir Iravani, MD, FRACP[a,*],
Tatenda Nzenza, BMedSci, MBBS, PGDipAnat[c],
Declan G. Murphy, MBBS, FRACS[d]

KEYWORDS

• Prostate cancer • Prostate-specific membrane antigen • PET • PSMA PET/CT • PSMA PET

KEY POINTS

- Prostate-specific membrane antigen PET (PSMA PET) imaging is a valuable diagnostic tool with promising performance for detection of prostate cancer and its metastases.
- PSMA PET imaging has the advantage of high specificity, independence of PSA-level, and low nonspecific tracer uptake in surrounding tissue.
- Although PSMA imaging has been most commonly investigated in the biochemical recurrence of prostate cancer, an increasing number of studies are exploring its utility in the different aspects of prostate cancer management.
- Multiple studies have consistently shown high clinical impact of PSMA imaging in guiding the management of prostate cancer.
- PSMA may prove an important imaging biomarker in prostate cancer, paving the way for precision medicine.

INTRODUCTION

Prostate cancer (PCa) is one of the most common malignancies in men worldwide and leads to substantial morbidity and mortality. Imaging is indicated in multiple aspects of PCa management, including primary diagnosis, staging, localization of recurrent disease, and response assessment in metastatic disease. Currently, conventional imaging modalities, including, bone scintigraphy, computed tomography (CT), and MRI, are used to detect primary and metastatic PCa for staging and risk stratification.

The main limitation of conventional imaging modalities is their low sensitivity in detecting metastases in primary diagnosis or in recurrent PCa,

Portions of this article were previously published in *PET Clinics* 12:2, April 2017.
Disclosure Statement: The authors have nothing to disclose.
[a] Department of Cancer Imaging, Centre for Molecular Imaging, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria 3000, Australia; [b] Sir Peter MacCallum Department of Oncology, University of Melbourne, 305 Grattan Street, Melbourne, Victoria 3000, Australia; [c] Sir Peter MacCallum Department of Surgical Oncology, University of Melbourne and Austin Hospital, 305 Grattan Street, Melbourne, Victoria 3000, Australia; [d] Sir Peter MacCallum Department of Surgical Oncology, University of Melbourne, 305 Grattan Street, Melbourne, Victoria 3000, Australia
* Corresponding author.
E-mail address: Amir.iravani@petermac.org

Urol Clin N Am 45 (2018) 503–524
https://doi.org/10.1016/j.ucl.2018.03.016

especially with low prostatic-specific antigen (PSA) levels when disease is often small in volume. In a meta-analysis of 24 studies the pooled sensitivity and specificity of CT for lymph node (LN) diagnosis was 42% and 82% respectively. For MRI, this review reported the pooled sensitivity and specificity of 39% and 82%, respectively.[1]

Molecular imaging with PET using an increasing list of biologically relevant radiotracers is facilitating precision and personalized medicine in PCa.[2] Prostate-specific membrane antigen (PSMA) has received a resurgence of attention over the last few years as a useful biomarker in the imaging of PCa. Among the available tracers and ligands available to image PSMA-expressing tumors, ^{68}Ga-PSMA HBED-CC or ^{68}Ga-PSMA-11, developed by the Heidelberg group in Germany, has become a successful radiotracer for PET/CT imaging with rapid adoption across many countries.[3–5] Subsequently, second-generation fluorinated PSMA agents (fluorine 18 [^{18}F]-DCFPyL and ^{18}F-PSMA-1007) offered several advantages, especially the possibility of large-scale batch production; but published experience with these agents remains limited. In this article, the current position of the literature in the role of advanced molecular imaging in different aspects of PCa management is presented.

RADIOLABELED PROSTATE-SPECIFIC MEMBRANE ANTIGEN LIGANDS

PSMA is a type II integral membrane glycoprotein that was first detected on the human prostatic carcinoma cell line LN cancer of prostate (LNCaP).[6] It consists of 750 amino acid integral membrane glycoprotein (100–120 kDa), with a 19 amino acid intracellular component, a 24 amino acid intramembrane segment, and a large 707 amino acid extracellular domain.[7] It has several enzymatic functions and is known to be upregulated in castrate-resistant and metastatic PCa.[8] PSMA is not specific to the prostate gland and is expressed in other normal tissues, including salivary glands, duodenal mucosa, proximal renal tubular cells, and subpopulation of neuroendocrine cells in the colonic crypts. In PCa, PSMA is overexpressed in the order of 100 to 1000 times compared with normal prostate tissue.[9] Overexpression occurs in greater than 90% of local PCa lesions as well as in metastatic LNs and bone metastases.[10–12] There is no known natural ligand for PSMA, and the reasons for its upregulation in PCa remain unclear. PSMA undergoes constitutive internalization and, therefore, can serve not only as an imaging biomarker but is also suitable for theranostic agents by attaching to radioactive molecules enabling targeted delivery of radiation to the sites of tumors.[13–17]

PSMA expression seems to increase with higher tumor grade and pathologic stage. Of clinical importance is that PSMA expression is upregulated when tumors become androgen independent and also following antiandrogen therapy (ADT).[18] This characteristic makes PSMA particularly valuable because it has potential as an early indicator of tumor progression after ADT and could play a role as a prognostic factor for disease recurrence.[19]

One of the first imaging probes specifically targeting PSMA was indium 111 (^{111}In)–capromab pendetide, an ^{111}In-labeled anti-PSMA antibody.[20] A significant limitation of capromab pendetide is binding to the intracellular epitope of the transmembrane PSMA glycoprotein. Therefore, capromab pendetide either binds to viable tumor cells following internalization or to dying cells with disrupted cellular membranes. Furthermore, slow plasma clearance of the antibody results in relatively poor tumor-to-background contrast; the application of ^{111}In-capromab pendetide for imaging prostatic malignancies remained limited.[21,22]

Subsequently, high affinity antibodies directed against extracellular epitopes of PSMA have been developed, such as J415, J533, and J591.[23] It was shown that ^{111}In-J591 accurately targets bone and soft tissue metastatic PCa lesions[24] and that lutetium 177 (^{177}Lu)–labeled J591 can be used safely in radioimmunotherapy directed against micrometastatic PCa.[25] Major disadvantages limiting the use of radiolabeled monoclonal antibodies as theranostic radiopharmaceuticals are their relatively long circulatory half-life (3–4 days), poor tumor penetration, and low tumor-to-normal tissue ratios, especially at early time points. Small molecules, in contrast, exhibit rapid extravasation, rapid diffusion in the extravascular space, and faster blood clearance which results in high tumor-normal tissue contrast early after injection of the tracer.

In search for PSMA tracers with such favorable characteristics, modified forms of N-acetyl-L-aspartyl-L-glutamate peptidase (NAALAdase) inhibitors, which were originally developed for possible neuroprotective effects in neurologic disorders, such as amyotrophic lateral sclerosis,[26] have been evaluated for their potential to diagnose and treat PCa. A series of preclinical studies evaluated the role of radiolabeled small-molecule PSMA-inhibiting ligands for imaging of human PCa using various radionuclides, such as carbon 11 (^{11}C),[27] ^{18}F,[28] iodine 123 (^{123}I),[29] technetium-99m (^{99m}Tc),[30,31] and ^{68}Ga.[32,33] Overall, the