Prostate Cancer Theranostics From Target Description to Imaging

Ian L. Alberts, MD, MA^{a,*}, Robert Seifert, MD^{b,c,d,e}, Kambiz Rahbar, MD^{b,d},
Ali Afshar-Oromieh, MD^a

KEYWORDS

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

KEY POINTS

- Prostate-specific membrane antigen–PET/computed tomography (PSMA-PET/CT) is an established modality in the staging of recurrent prostate cancer, demonstrating superior diagnostic performance compared with conventional imaging modalities, such as CT or MR imaging, and previous-generation nuclear medicine modalities, such as scintigraphy and choline-based radiotracers.
- There is increasing evidence, including clinical trial data, that PSMA-PET/CT has a role in the staging of high-risk prostate cancer.
- PSMA is highly expressed on prostate cancer cells, but is not specific, potentially causing pitfalls. Some prostate cancers express no, or low levels of PSMA, and various factors including the use of hormone deprivation therapy can influence PSMA expression.
- Although a large body of robust evidence shows the superiority of PSMA-PET/CT compared with the present alternatives, further work is needed to elucidate potential differences between PSMA-based radiotracers and to establish the influence of PSMA-PET/CT on clinical outcomes for patients.
- PSMA-PET/CT has an important role for identifying patients suitable for PSMA therapy.

INTRODUCTION

Prostate cancer (PC) is the most common malignancy in men, and the second leading cause of cancer-related death in men.¹ Despite initial therapy at early-stage disease, biochemical recurrence remains a commonly encountered entity and presents a challenge for conventional imaging modalities given their limited abilities to detect disease at early stages of recurrence. Although the exact timing of salvage radiotherapy (SRT) remains a topic of debate, early SRT may be beneficial for some

patients,² and imaging has a demonstrable impact on therapeutic strategy and decision-making.³

Although PC screening with prostate-specific antigen (PSA) is a topic of some controversy, since the advent of PSA testing the proportion of patients presenting with advanced disease has fallen. Nevertheless, a small number of patients continue to suffer from disease at an incurable stage at presentation.⁴ Furthermore, despite significant advances in therapeutics in recent decades, a number of patients develop advanced disease (where the disease has spread beyond the prostate bed). Compared with

^a Department of Nuclear Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland;

^b Department of Nuclear Medicine, University Hospital Münster, Münster, Germany; ^c Department of Nuclear Medicine, University Hospital Essen, Essen, Germany; ^d West German Cancer Centre, Universitätsklinikum Essen, Hufelandstr. 55, 45147 Essen, Germany; ^e German Cancer Consortium (DKTK), German Cancer Research Center, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany

* Corresponding author.

E-mail address: ian.alberts@insel.ch

almost 100% 5-year survival for local or regional disease, the 5-year survival rate for advanced disease is 31%,⁵ where therapeutic options remain of limited efficacy. For example, palliative radium-223 dichloride (Xofigo) therapy is associated with a modest median overall survival of 14.9 versus 11.3 months when compared with placebo.⁶ Nuclear medicine therefore was faced with two concomitant challenges: first, to identify correctly and accurately individuals at early-stage disease, where the likelihood of a definitive cure is greatest, as well as to offer solutions to individuals who have progressed to, or present with, advanced disease. The discovery of ligands for the prostate-specific membrane antigen (PSMA) has allowed nuclear medicine and molecular imaging to rise to both of these challenges in a manner that combines both therapy and diagnostics: theranostics.

PROSTATE-SPECIFIC MEMBRANE ANTIGEN

Before embarking on a description of PSMA in the imaging and therapy of PC, it is worth pausing to consider the broader function of this key molecular target. PSMA, also known as glutamate carboxypeptidase II (GCPII) or N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase I), is a 750 amino-acid type II transmembrane glycoprotein, weighing approximately 100 kDa.⁷ First described in studies of monoclonal antibodies to a novel antigenic marker in PC in the late 1980s,^{8–10} it has rapidly become clear that despite its name, the expression of this transmembrane protein is not restricted to PC. It also can be found in normal prostatic tissue and the vascular endothelium in a wide variety of solid tumors,^{11,12} but not in blood vessels of normal tissues. Physiologic PSMA expression is reported in the lacrimal and salivary glands, the liver, the spleen, the kidneys, and the intestines.¹³ PSMA-ligand uptake has also been observed in benign inflammatory lymph nodes,¹⁴ and numerous publications have demonstrated PSMA-avid peripheral nerve ganglia and in central nervous tissue.^{15–20} The role of PSMA in the prostate and its exact role in PC remains elusive. PSMA appears to have NAALADase activity and folate hydrolase activity, and therefore has many potentially interesting roles in both glutamate and folate metabolism, with implications for the diagnosis and treatment of various cancers as well as neurologic disorders.

PROSTATE-SPECIFIC MEMBRANE ANTIGEN-BASED IMAGING AND THERANOSTICS

The discovery that PSMA is exquisitely overexpressed on PC cells⁹ led to it becoming the focus

of great attention as a potential target for treatment and therapy. Conventional imaging methods such as CT and MR imaging have limited performance in PC,²¹ and traditional nuclear medicine techniques such as bone scintigraphy have a limited role in the exclusion of advanced disease. Instead, various alternatives have been advanced in recent decades: PET imaging with radiolabeled choline tracers have been used,²² capitalizing on the overexpression of choline kinase in PC.²³ In tandem, PSMA-based imaging probes were developed, first with the introduction of In-111 capromab-pendetide (ProstaScint), a radiolabeled anti-PSMA antibody.²⁴ However, it was the introduction of PSMA-PET ligands that revolutionized the molecular imaging of PC.²⁵ ⁶⁸Ga-PSMA-11 (also known as PSMA-HBED, HBED-CC or PSMA-DFKZ), following its first clinical introduction in 2011,¹³ has rapidly established itself as the examination of choice in recurrent PC and increasing data are accumulating about its important role in the staging of high-risk primary PC.²⁶

FACTORS INFLUENCING PROSTATE-SPECIFIC MEMBRANE ANTIGEN EXPRESSION

As described previously, PSMA is not prostate specific. A number of publications also report the phenomenon of PSMA-negative PC. Although an additional PSMA-PET/CT in the context of a negative choline-PET/CT has been described as a potential imaging sequence in jurisdictions in which PSMA-PET might not be universally available, the reverse scenario has received relatively little attention, although there is a role for an additional choline-PET/CT in PSMA-nonexpressing PC.²⁷ Some investigators suggest PET with fludeoxyglucose ¹⁸F-FDG as an adjunct to PSMA imaging before PSMA-based radioligand therapy to identify de-differentiated tumor sites lacking PSMA expression (differentiated PC is normally not FDG avid).²⁸

In addition to variation in tumor biology, PSMA expression can also be modulated by the patient's hormone status. Androgen deprivation therapy (ADT) is an established modality in the treatment of castration-sensitive PC (CSPC), and as such it is estimated that up to a third of all patients referred for PSMA-PET/CT imaging are receiving ADT.²⁹ However, the influence of ADT on PSMA-PET/CT is unclear. Preclinical data indicate upregulated PSMA expression following short-term ADT,^{30–32} making it a potential pre-imaging or therapeutic maneuver to increase lesion uptake. However, there is a paucity of clinical information regarding the effect of long-term ADT on PSMA-PET/CT. A variegated PSMA-imaging response

was observed following short-term ADT in CSPC patients in case reports,^{31,33} in cohorts with small patient numbers^{34–36} and in studies of retrospective design.^{37–39}

The exact relationship between androgen receptor activity and PSMA expression remains elusive. The PSMA receptor is encoded in the folate hydrolase 1 (FOLH1) gene, the expression of which is downregulated by androgens.⁴⁰ As a consequence, ADT leads to an upregulation of FOLH1 expression, potentially explaining a relationship between androgen deprivation and heightened PSMA expression.³⁶ This mechanism may also explain the clinical finding of association between ADT and increased probability of a pathologic PSMA-PET/CT,^{38,41} although this may well be a result of selection bias with patients at more advanced clinical stage being more likely to have ADT prescribed. However, it needs to be emphasized, that only a short duration of treatment for ADT (defined in various publications as 2 days–4 weeks) has been observed to lead to PSMA overexpression^{32,42} or increased uptake of PSMA-ligands.³¹ Following long-duration ADT, the opposite response is seen,³⁸ possibly due to a shrinking of the tumor in CSPC. PSMA expression is likely mediated by a more complex series of cellular signaling pathways. For example, the phosphatidylinositol 3-kinase (PI3K)–AKT pathway is also implicated in PC progression, with downstream implications for cell survival, metabolism, anti-apoptosis, and differentiation.⁴³ Cross-talk between the PI3K–AKT pathway and androgen receptor pathways has been reported.⁴⁴ When coupled with the finding that PSMA initiates upstream signaling of the PI3K–AKT pathway, a more complex picture emerges, which requires further studies to fully explain.⁴⁵

The current iteration of guidelines makes no clear suggestion on the conduct of PSMA-PET/CT with ADT.⁴⁶ Although it is generally recommended to conduct imaging before commencing ADT therapy, the utility of pausing treatment or the length of pause required to return to baseline PSMA expression remains unclear, and requires further investigation.

THE PROSTATE-SPECIFIC MEMBRANE ANTIGEN RADIOLIGANDS

There are now a number of PSMA-based radiotracers described in the literature with various properties, advantages, and disadvantages that may be bewildering to the nonexpert. The first PSMA-based radiotracer introduced into clinical routine was ⁶⁸Ga-PSMA-11. In almost a decade of world-wide use, a large body of experience

and evidence has been gathered for this tracer, largely replacing previous-generation scintigraphy agents and PET agents, such as ¹⁸F-Choline and Fluciclovine. Other PSMA radiotracers for PET imaging have also been introduced with important differences. Use of ⁶⁸Ga-PSMA-11 is currently still hampered by the radiotracer's short half-life (68 minutes).⁴⁷ In contrast, ¹⁸F is readily available through cyclotron production, potentially increasing accessibility of PSMA radiotracers to centers with existing radio-pharmacy facilities, although this advantage must be considered alongside the possibility for cyclotron production of ⁶⁸Ga⁴⁸ and the increasing sensitivity of latest-generation digital PET/CT scanners, which may afford lower applied activities.⁴⁹ The lower positron energy of ¹⁸F may theoretically improve imaging resolution. The longer half-life makes its logistics and handling easier, and may enable acquisition of later images in which lesion uptake and contrast are higher, improving lesion detection and in the discrimination between specific and nonspecific causes of radiotracer uptake.^{20,50,51} Although ¹⁸F-labeled PSMA-11 has been described in the literature, it has not been widely implemented.⁵² ¹⁸F-PSMA-1007, ¹⁸F-rhPSMA-7, or ¹⁸F-DCFPyL are promising alternatives. One advantage of the first two mentioned radiotracers is the very low level of excretion of the radiotracer via the urinary bladder in the first two to three hours. This may aid in the detection of local recurrences. However, whereas a matched-pair retrospective cohort for ⁶⁸Ga-PSMA-11 and ¹⁸F-PSMA-1007 revealed no increased detection rate for the latter, noteworthy was the fivefold increased rate of nonspecific PSMA-avid lesions detected by ¹⁸F-PSMA-1007,⁵³ which can represent a diagnostic conundrum.⁵⁴ Such indeterminate lesions can result in unnecessary investigations, treatments, and interventions,^{55,56} representing a potential important pitfall with this tracer. ¹⁸F-DCFPyL is another important PSMA radioligand, which undergoes renal excretion and is a promising candidate for routine PSMA imaging, with some preliminary data suggesting improved tumor-to-background ratio and potentially greater detection of pathologic lesions, although adequately powered studies with predefined endpoints are required to confirm this.⁵⁷

THERANOSTIC IMAGING

In advanced or end-stage disease, in which existing conventional therapeutic options have been exhausted or declined by the patient, PSMA-endoradioligand therapy is a promising alternative and may offer a life-prolonging treatment for men

with metastatic castration-resistant PC (mCRPC), which the ongoing TheraP trial seeks to confirm.⁵⁸

When selecting candidates for PSMA therapy, an adequate PSMA expression on most PC lesions must be demonstrated to spare the patient any potentially futile therapy with significant side effects. A second consideration is prediction of therapy response, in which pretherapy dosimetry may be of additional utility.⁵⁹ One important consideration here is the pharmacokinetics and behavior of the radiotracer; for the purposes of therapy planning these are assumed to be identical, or that differences, for example, in the radioligand's internalization are negligible. Whereas the limited intraindividual comparative data for PSMA radioligands appear to suggest a difference in lesion radiotracer uptake (SUVmax⁵⁷), Ferdinandus and colleagues⁶⁰ report a univariate analysis of individuals undergoing PSMA therapy, with no relationship between therapy response and PSMA uptake. Although the commonly used therapeutic tracers are ¹⁷⁷Lu-PSMA-617 or ¹⁷⁷Lu-PSMA-I&T, these radioligands are infrequently used (but available) as ⁶⁸Ga-labeled diagnostic tracers. Further studies into the differences between radiotracers for therapy planning and prediction of response is required, as well as in therapy monitoring.

CONTROVERSIES IN PSMA IMAGING

Given the rapid pace of development, a number of controversies and unresolved issues remain to be addressed in the molecular imaging of PC with PSMA probes. Ideally, the best-available evidence would inform the choice of radiotracer for a specific patient at a specific time. In the hierarchy of evidence-based medicine, these would be systematic analyses of multiple, blinded and randomized trials designed to meet specific endpoints with minimization of bias. For a number of valid logistical and regulatory reasons, such data have been difficult to obtain for nuclear medicine studies. A large body of retrospective cohort studies and meta-analyses thereof demonstrate high detection rates for PSMA radioligands, for example, for ⁶⁸Ga-PSMA-11^{41,61} and more recently, for ¹⁸F-based radiotracers.^{62,63} However, there are only limited confirmatory prospective data, which are restricted to a small selection of the available radiotracers. Such data are often of crucial importance for the approval, licensing and remuneration of nuclear medicine studies in various jurisdictions and world-wide implantation of PSMA-imaging services has not been ubiquitous.⁶⁴ Fendler and colleagues⁶⁵ report trial data confirming the diagnostic accuracy of ⁶⁸Ga-PSMA-11, and Morris

and colleagues⁶⁶ report details of an ongoing trial for ¹⁸F-DCDPyl, for example. In the comparison of radiotracers, mostly noncontrolled, nonrandomized cohort studies with small patient numbers are available.⁵⁷ Only Calais and colleagues⁶⁷ have hitherto reported data for a prospective comparative imaging trial in ¹⁸F-Fluciclovine and ⁶⁸Ga-PSMA-11 PET/CT and further trial data are now needed for the comparison of the PSMA radioligands. Few studies report any data for patient outcomes. Although the impact of PSMA-PET on radiation therapy planning has long been known,⁶⁸ no data exist to suggest that individuals undergoing PSMA-guided PET/CT have better outcomes, and trials are under way to resolve this important question.⁶⁹ Indeed, although the detection of advanced metastatic disease may divert the patient from futile local therapy, this commonly occurs in more advanced disease, where the magnitude of the difference between PSMA and previous-generation radiotracers is small.⁷⁰ Whereas the combination of new radiotracers,⁶² optimum imaging protocols,^{71,72} and advanced digital scanners⁷³ act in concert to increase the detection rate at earlier stages of recurrence, the clinical rationale behind this approach remains unclear and there is uncertainty in the oncological literature about the best management approach for these patients. Although the ORIOLE Phase II trial suggests a role for stereotactic ablative radiotherapy in men with oligometastatic PC⁷⁴ this approach lacks a firm solid-evidence base at present and is a topic of debate in the urologic literature.⁷⁵

Finally, there is increasing evidence for the superiority of PSMA-PET/CT in high-risk primary PC compared with conventional imaging modalities. The prospective ProPSMA study recently reported higher accuracy, high clinical impact with 31% of patients undergoing a change in management plan following PET/CT and with good cost efficacy, replacing a battery of studies with a single diagnostic test.²¹

SUMMARY

Since its introduction, PSMA-PET/CT has rapidly established itself as the investigation of choice for imaging PC, largely replacing previous-generation imaging modalities, such as choline-PET/CT, and conventional imaging modalities, such as CT or MR imaging. Demonstrating high diagnostic accuracy, PSMA-PET/CT is able to detect disease at very early stages of recurrence, where the chances of a definitive cure may be at their greatest. It also has an increasingly recognized role in the staging of men with high-risk primary PC. A number of PSMA radioligands are in

established clinical routine, and there is currently only limited data and no single tracer can clearly be advocated over the others at present. Further clinical trial data, comparing and contrasting radiotracers and reporting outcome-based data are necessary to further increase the implementation of this very promising imaging modality.

CLINICS CARE POINTS

- PSMA PET/CT is well-established imaging tool for recurrent prostate cancer.
- There is increasing recognition of the utility of PSMA PET/CT in high risk primary prostate cancer.
- Despite the increasing emphasis on early detection of disease in recurrence, studies are required to show improvement in patient-level outcomes when using PSMA PET/CT.
- A number of PSMA-radioligands are available for use, with limited evidence to guide their choice.
- PSMA PET/CT has a clear role in theragnostics, where PSMA radioligands can identify patients suitable for PSMA-therapy.

DISCLOSURE

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