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TOPIC PAPER

PSMA PET applications in the prostate cancer journey: from diagnosis to theranostics

R. S. Eapen[1,2,3,8] · T. C. Nzenza[1,2,3,4] · D. G. Murphy[1,5] · M. S. Hofman[5,6] · M. Cooperberg[7] · N. Lawrentschuk[1,2,3]

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Abstract

The heterogeneity of prostate cancer has made imaging modalities of crucial importance in this disease. Accurate diagnosis and staging of the volume and extent of disease, especially in advanced and metastatic prostate cancer, can help to tailor the timing and modalities of treatment. While MRI has been effective in the detection of significant prostate cancer, its use in the identification and quantification of extraprostatic disease is limited. This gap is now being filled by PSMA PET. PSMA PET scans have now been shown to have a role in all stages in the prostate cancer journey. Emerging evidence has shown its promise in primary staging, restaging and theranostics. In this paper, we review the evidence for the use of PSMA PET in the various stages of prostate cancer, from initial diagnosis to advanced metastatic disease where other systemic treatments have failed.

Keywords PSMA · PET · Prostate cancer · Staging · Theranostics · Lutetium

Introduction

Prostate cancer continues to be one of the most commonly diagnosed cancers around the world and a leading cause of cancer death in developed countries [1]. The advent of prostate-specific antigen (PSA) screening has resulted in a significant proportion of patients being diagnosed at an early, organ confined stage. However, a subset of patients will present with or progress to high risk, advanced or metastatic disease, reflecting the heterogeneity of this disease [2]. Accurate diagnosis and staging combined with effective therapeutic options are critical in the treatment of these patients. Moreover, in patients who develop a PSA recurrence following curative treatment, initiating salvage treatment early is beneficial. Additionally, identifying and locating disease sites in patients with low volume or oligometastatic disease may shift the paradigm of treatment for these patients [3]. Traditional imaging modalities such as computed tomography (CT) and bone scan have significant limitations, especially at low PSA levels. This prompted interest in positron emission tomography (PET) using choline or fluorodeoxyglucose-based tracers in the staging of advanced disease. However, these tracers also have limitations in the settings of early metastatic disease or biochemical recurrence. Multi-parametric magnetic resonance imaging (mpMRI) has value in the detection of significant prostate cancer (PI-RADS > 4); however, its sensitivity in the identification of extraprostatic disease is low at 29% [4].

Gallium-68 (^{68}Ga) and fluorine-18 (^{18}F) prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PSMA PET/CT) has emerged as

RS Eapen and TC Nzenza are joint first authors.

✉ R. S. Eapen
renu.eapen@outlook.com

1 Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia

2 Department of Surgery, University of Melbourne, Austin Hospital, Melbourne, Australia

3 Olivia Newton-John Cancer Research Institute, Austin Hospital, Melbourne, Australia

4 Young Urology Researchers Organisation (YURO), Melbourne, Australia

5 Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia

6 Department of Molecular Imaging, Peter MacCallum Cancer Centre, Melbourne, Australia

7 Department of Urology, Helen Diller Comprehensive Cancer Centre, University of California, San Francisco, USA

8 Department of Urology, Austin Hospital, Melbourne, Australia

a promising diagnostic and staging tool in advanced primary and recurrent prostate cancer. Despite the advent of docetaxel chemotherapy and other systemic treatments for metastatic prostate cancer such as enzalutamide and abiraterone, many patients progress and are troubled by treatment-related toxicity. In this group of patients, Lutetium-177 (^{177}Lu)-labelled PSMA ligand may have promising results in treating metastatic castration-resistant prostate cancer (mCRPC) [5, 6].

In this paper, we review the role of PSMA in the diagnosis and treatment of advanced prostate cancer. In light of new evidence [6], we also evaluate the role of ^{177}Lu PSMA radionuclide treatment in theranostics for mCRPC (Fig. 1).

PSMA, the molecule

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein with folate hydrolase activity [7]. It has a 707-amino acid extracellular segment and is normally expressed on the apical surface of prostatic cells surrounding the prostatic ducts, whereas in dysplastic cells, it is expressed on the luminal surface [8, 9]. PSMA is highly specific for benign and malignant prostate epithelial cells. However, it is overexpressed by a factor of 100–1000 times in prostate cancer cells [10]. This expression is further increased during the development of metastases and castration-resistant disease [11]. This potential for a target in prostate cancer imaging led to the development of several PSMA small molecule inhibitors labelled with ^{68}Ga and ^{18}F that bind rapidly and with high affinity to the PSMA receptor but also have rapid plasma clearance. This results in images with high tumour-to-background contrast resulting in high sensitivity and specificity compared to choline PET [12].

Applications of PSMA PET

Triage

Finding the balance between missing clinically significant cancer and over diagnosis is crucial in the management of prostate cancer. Guidelines on screening for prostate cancer have been constantly changing over the years. Recently, the US Preventative Services Task Force (USPSTF) has updated their 2012 recommendation on screening for prostate cancer (C recommendation for men aged 55–69 years and D recommendation for men 70 years and older) [13]. Multiparametric Magnetic Resonance Imaging (mpMRI) has emerged as a front runner in the early diagnosis of prostate cancer. Results from PROMIS and PRECISION have shown that MRI can spare a significant proportion of men from having a prostate biopsy, while still improving the detection of clinically significant cancer on targeted prostate biopsy [14, 15]. However, the significance of MRI invisible disease that may be missed, especially if MRI negative patients are not routinely biopsied, is concerning. A quarter of clinically significant cancers were missed (defined as ISUP grade 2

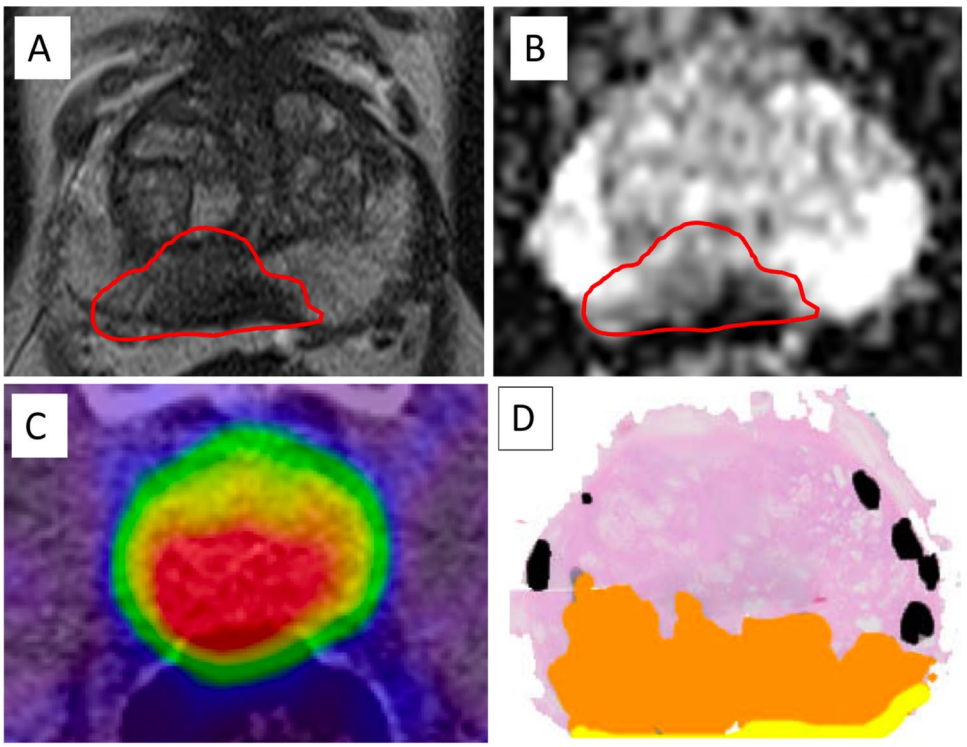

Fig 1 A 63-year-old male, PSA 6.1; cT2b, ISUP grade group 3 prostate cancer. **a**, **b** mpMRI demonstrates PIRADS 5 lesion right posterior zone; **c** PSMA PET/CT demonstrates corresponding avidity; **d** final pathology—pT3a grade group 3 negative margins

or higher) in PROMIS [14]. Thus, there has been interest in the potential for the use of PSMA PET/CT in the initial diagnosis of prostate cancer. PSMA PET demonstrates high tumour contrast compared to mpMRI with a study of 53 patients in a population subset with known intermediate-to-high-risk disease, demonstrating superiority of PSMA PET compared to mpMRI [16]. As PSMA expression increases with higher ISUP grade, there may be a role for using PSMA PET to characterize tumour biology akin to histopathology. Further research, however, is required to establish the value of PSMA PET for patient triage. Lopci et al. described a potential role for PSMA PET/CT when MRI is contraindicated or when MRI was negative [17]. Although they hypothesized a potential role for PSMA PET/CT in detecting prostate cancer in this subset of patients, it would be hard to draw any solid conclusions from this study as the sample size was very small, comprising only 45 patients (Table 1; Fig. 2).

Table 1 Summary of meta-analyses in the use of PSMA PET/CT in the setting of BCR

Meta-analysis	Year published	No. of studies	No. of patients	Outcome
Han et al. [29]	2018	15 (5 prospective, 10 retrospective)	1163	Pooled impact on patient management 54%
Perera et al. [27]	2016	16	1309	Sensitivity 80% Specificity 97%
von Eyben et al. [28]	2016	15 (9 restaging)	1256 (983 restaging)	Pooled proportion of change in management of 54%

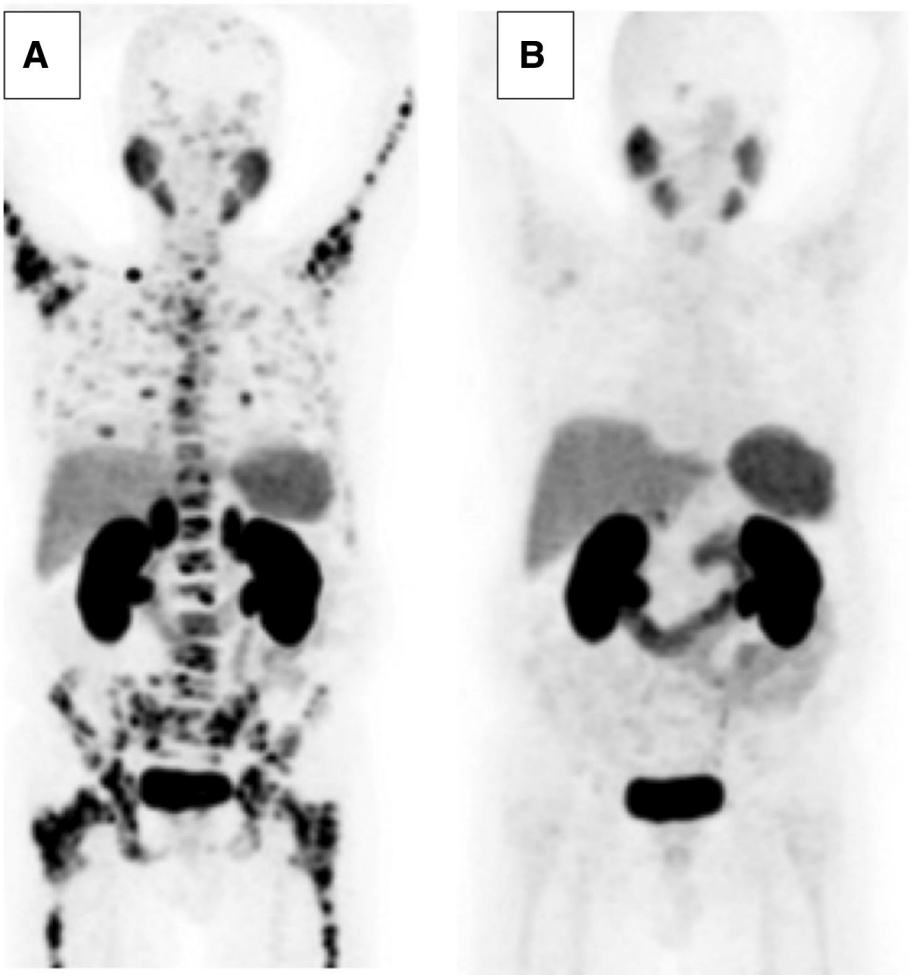

Fig 2 A 76-year-old male, progressive mCRPC post-docetaxel, abiraterone and enzalutamide. **a** baseline PSMA PET/CT with high volume bone and adrenal metastases; **b** excellent response following two cycles of Lu-PSMA

Verdict

Evidence still heavily in favour of mpMRI. Limited evidence at present to support use of PSMA PET/CT in this role but further research is needed.

Primary staging

The use of image for staging is advised in high-risk patients based on the D'Amico risk classification. Most international guidelines recommend the use of CT, bone scintigraphy or MRI in primary staging of newly diagnosed high-risk prostate cancer. However, these modalities have shown limited accuracy in correctly staging the extent of prostate cancer. In a meta-analysis by Hovels et al., CT had a pooled sensitivity of 42% and a specificity of 82%. MRI did not fare much better with a sensitivity of 39% and specificity of 82% [18]. Other imaging modalities such as choline PET have also not shown convincing results in this regard. However, over the last few years, PSMA PET imaging has promised to be a potential game changer, although much of the published literature is of a retrospective nature. A recent systematic review by Corfield et al. studied the results from the use of PSMA PET/CT in 12 studies with a total of 322 patients [19]. Although the results were promising in favour of PSMA PET/CT (sensitivity ranging from 33 to 99% and specificity greater than 90%), only 38% of studies included a reference standard to support their findings. This highlights the need for larger volume prospective studies to validate the use of PSMA PET in primary staging. Nevertheless, evolving experience suggests superiority of PSMA PET/CT compared to conventional imaging with sub-centimetre nodal disease and bone metastases, that are occult on bone scintigraphy/CT, frequently identified [20]. This has led to widespread adoption of PSMA PET/CT in some countries such as Australia. Furthermore, the superior performance of PSMA PET/CT to identify lymph node metastases is improving risk stratification [21], and novel radio-guided surgery technologies are harnessing this to improve lymph node yields [22, 23]. Whether this leads to improved outcomes is not yet clear [24].

Encouragingly, a multicentre, randomised clinical trial (proPSMA) is currently recruiting in Australia and this looks to provide more robust evidence into the utility of PSMA PET in primary staging for high-risk prostate cancer [25]. proPSMA looks at newly diagnosed prostate cancer patients with at least ISUP grade group 3, clinical stage T3 or a PSA of/higher than 20 ng/ml. These patients are then randomised to PSMA PET/CT or conventional imaging (CT and bone scintigraphy) with cross-over to the other imaging arm provided there is, at most, only oligometastatic disease on first-line imaging. The results of proPSMA, if positive, will validate the role of PSMA PET/CT in primary staging of prostate cancer and potentially serve as the gold standard imaging modality replacing the current conventional imaging (CT and Bone scan).

Verdict

Very promising results to validate the role of PSMA PET/CT in primary staging

Biochemical recurrence (BCR)

Most of the studies investigating the role of PSMA PET in prostate cancer have been done in the setting of biochemical recurrence, even though this work still largely involves retrospective studies. Other imaging modalities such as CT, bone scintigraphy and choline PET have not shown the desired sensitivity and specificity in their attempts to accurately identify sites of disease recurrence in the setting of PSA rise following initial treatment. In patients with negative choline PET/CT, a study showed that PSMA PET/CT detected the site of disease recurrence in 44%, indicating the superiority of PSMA PET/CT [26].

Three meta-analysis studies looking at the use of PSMA PET/CT in the setting of biochemical recurrence have been published. In a 2016 meta-analysis, Perera et al. analysed 16 studies comprising 1309 patients and found that PSMA PET/CT positivity increased with PSA level from 42% when PSA was less than 0.2 ng/ml to 95% when PSA was greater than 2 ng/ml. In this study, sensitivity and specificity were 80% and 97%, respectively, on a per lesion analysis [27]. von Eyben et al. reported results of their meta-analysis which included 15 studies comprising 1256 (9 studies were in restaging). This study reported a detection rate of 50% for PSA levels 0.2–0.49 ng/ml and a detection rate of 56% for PSA levels 0.5–0.99 ng/ml [28]. More recently, Han et al. published results of their meta-analysis on the management impact of 68 Ga-PSMA PET. This included 15 studies with a total of 1163 patents and found a pooled proportion of change in management of 54% based on the scan [29].

PSMA PET has proved a valuable tool in guiding both salvage radiotherapy and surgery in the biochemical recurrence setting [30, 31]. The European Association of Urology now recommends PSMA PET/CT use in biochemical recurrence, particularly in the setting of PSA recurrence after radiotherapy (Level of evidence 2b) [32]. Recently, PSMA PET hookwire localization of lymph node metastases has also been described as a novel technique to accurately guide salvage lymph node dissection [33]. However, whether metastasis-directed therapy has a role in improving outcomes for patients with PET-identified disease remains uncertain [34, 35].

Verdict

Role for PSMA PET CT recognized in biochemical recurrence to guide salvage treatment options.

^{177}Lu PSMA in theranostics

Theranostics is a portmanteau of "therapy" and "diagnostics", with the first application being in thyroid disease [36]. Since then, the applications have extended to other diseases including neuroendocrine tumours, melanoma and recently, metastatic prostate cancer. The extracellular expression of PSMA and its specificity to prostatic tissue has given rise to the use of PSMA-targeted radionuclide therapy in the treatment of mCRPC [5] In particular, Lutetium-177(^{177}Lu)-PSMA-617 (LuPSMA) has demonstrated encouraging results. LuPSMA is a small molecule that binds with higher affinity to PSMA and also has rapid plasma clearance, resulting in favourable tumour and normal tissue dosimetry compared to the antibody J591 [6]. Several retrospective trials have reported encouraging therapeutic benefit with both PSA and imaging responses [37–44]. Calopedos et al's systematic review and meta-analysis of ten retrospective studies including over 369 000 patients assess the therapeutic response of 177Lu PSMA in the treatment of mCRPC [5]. They demonstrated that 68% (95% CI 61–74) of patients experienced some PSA decline and the pooled proportion of patients with more than 50% PSA decline was 37% (CI 22–52). This is comparable to the 39.2% of patients with docetaxel-resistant mCRPC, who experienced a > 50% PSA decline after treatment with cabazitaxel [45].

Until recently, there was no prospective data supporting the use of Lutetium-177(^{177}Lu)-PSMA-617 (LuPSMA) radionuclide treatment. Hofman et al.'s prospective phase 2 study is the first to show not only the anti-tumour effects of LuPSMA, but also improved quality of life and reduced toxicity [6]. In this single arm, single-centre, phase 2 trial, 30 patients with advanced prostate cancer, who had progressed after chemotherapy (docetaxel or cabazitaxel) and a second generation anti-androgen (abiraterone or enzalutamide), were administered up to four cycles of intravenous LuPSMA. A PSA decline of > 50% was seen in 17 (57%) of patients. PSA progression was noted in 27 (90%) of patients. A median time to PSA progression of 7.6 months was recorded, as was a median overall survival of 13.5 months. Also encouraging was the high tolerance of the treatment. No immediate adverse events occurred. The most common adverse events were mild grade 1 events that did not require intervention, including dry mouth in 26 (87%) patients and dry eyes in 5 (17%). Grade 3–4 thrombocytopenia did occur in 8 (27%) patients; however, only 4 (13%) instances were attributed to LuPSMA. An additional promising finding was the effect of LuPSMA on pain palliation with 37% of patients who had pain at baseline experiencing rapid relief after 1 cycle of IV LuPSMA. In contrast, only 9% of patients experienced pain relief in the TROPIC trial [45]. The dose of LuPSMA in this trial was individualized to each patient based on their tumour burden and clinical characteristics, raising the possibility of "personalized treatment" [6].

Verdict

PSMA radionuclide therapy has high anti-tumour activity and low toxicity in metastatic prostate cancer. Further research is needed to compare this to existing standards-of-care. The TheraP Trial (Trial number: NCT03392428) comparing 177Lu-PSMA617 Theranostic Versus Cabazitaxel in Progressive Metastatic Castration-Resistant Prostate Cancer is an example of ongoing research in this topic.

Conclusion

The use of PSMA-based imaging in prostate cancer shows great promise and has a wide range of applications through the prostate cancer journey. Although most of the evidence has been based on retrospective studies, it is important to recognize the clinical equipoise that studies examining the majority of conventional imaging widely used today were also retrospective. Nonetheless, it is encouraging that large prospective studies are underway worldwide that will provide high-level evidence on the role of PSMA PET imaging in various aspects of prostate cancer from diagnosis/primary staging to its role in theranostics.

Author contribution RSE Joint 1st author. Project development, evidence analysis, manuscript writing; TCN Joint 1st author. Project development, evidence analysis, manuscript writing; DGM Evidence analysis, manuscript editing, figures; MSH Evidence analysis, manuscript editing; MC manuscript editing and approval; NL manuscript editing and approval

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest regarding the publication of this paper. As this is a review of the current literature, there were no human participants or animals involved.

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