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Impact of PSMA PET on Prostate Cancer Management

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Author contributions

ABW and RER made substantial contributions to the conception or design of the work. ABW and RA drafted the work. LFV, IS, AUK, MBR, SSR, JC, PCB, and RER revised the work critically for important intellectual content. All authors approved the version to be published. ABW and RER agree to be 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.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Prostate cancer (PCa) can vary tremendously in its clinical behavior and response to treatment. Due to this and its substantial global incidence [1], there is an ongoing need for improved diagnostic, risk-stratification, and therapeutic approaches to optimize patient outcomes. Prostate-specific membrane antigen positron emission tomography (PSMA PET) has begun to revolutionize the landscape of PCa management from both a diagnostic and therapeutic perspective.

PSMA, a transmembrane glycoprotein, was initially identified on prostate cells in 1987 [2] and cloned and characterized in 1993. [3] It was further noted to be preferentially expressed on malignant versus benign prostate cells [4], prompting researchers to develop it as a target for molecular imaging and theranostic applications [5–7]. While PSMA targeting was initially developed using monoclonal antibodies such as J591, the development of urea-based small molecules capable of binding to PSMA led to the rapid development of radiotracers that have greater sensitivity and specificity than conventional imaging and alternative PET probes for prostate cancer staging. The development of PSMA PET has had a substantial impact on clinical decision-making across the disease continuum of PCa [3–6, 8, 9]. The concept of oligometastatic PCa has evolved in part because of PSMA PET, as has the goal of eradicating oligometastatic disease with metastasis directed therapies [10, 11••]. The usefulness of PSMA as a PCa target goes beyond the clinical settings of staging and diagnosis, as it can be used as a guide for the selection of patients who would benefit from PSMA-targeted radioligand therapy (PSMA-RLT) [12].

PSMA PET has evolved as an imaging tool capable of driving more accurate and targeted approaches to PCa management. This review details the historical development and contemporary impact of PSMA PET in PCa care, highlighting the advancements made and promising future directions which will be guided by clinical trials.

Initial staging and local treatment planning

Initial staging for PCa has grown in importance to not only better define which patients are potentially curable and amenable to definitive local therapy, but also to identify which patients harbor previously occult low burden or oligometastatic disease and thus might be appropriate for emerging treatment approaches (see below) [11••, 13–17].

In terms of localizing the primary tumor for diagnostic biopsy, MRI prior to biopsy is becoming common practice to identify more clinically significant PCa (International Society of Urological Pathology [ISUP] grade group ≥2) and reduce the diagnosis of non-clinically significant disease [18]. In the PRIMARY trial, 291 patients with suspected PCa underwent both MRI and PSMA PET prior to planned biopsy [19]. PSMA PET and MRI combined increased the sensitivity from 83 to 97% and the negative predictive value from 72 to 91% compared to MRI alone. In a pooled analysis of multiple prospective studies, Kawada *et al.* showed PSMA PET increased sensitivity for detecting clinically significant PCa from 84 to 91% compared to MRI alone. We await larger phase III studies on this topic to determine if PSMA PET can be used to help patients avoid unnecessary prostate biopsy.

Phase III trials have evaluated the implications of PSMA PET for the initial staging of PCa after diagnosis. In the proPSMA trial, 302 patients with unfavorable-risk PCa considering curative treatment were randomized from 2017 to 2018 to undergo initial staging with conventional image versus PSMA PET [20•]. Following initial imaging, all patients crossed over to be staged with PSMA PET or conventional imaging. The median serum PSA levels in this study were 16.3 ng/mL in the conventional imaging group and 18.3 ng/mL in the PSMA PET group. PSMA PET had 92% accuracy compared to 65% accuracy for conventional imaging, with concomitant improvements in sensitivity (85% *versus* 38%) and specificity (98% *versus* 91%). PSMA PET detected true metastatic disease in 23% of patients compared to conventional imaging (12%). Accordingly, 28% of patients who underwent PSMA PET as first-line imaging underwent a change in management, while the same was true for only 15% of patients in the conventional imaging group. Other prospective data demonstrate that PSMA PET leads to changes in management in more than half of patients [21].

The pivotal study used for the FDA approval of Ga68-PSMA-11 for the primary staging indication was a single-arm phase III prospective trial of diagnostic efficacy performed at UCSF and UCLA which recruited over 700 patients from 2018 to 2021 with intermediate- and high-risk PCa for initial staging. A subset of 277 men in this study underwent surgery [22••]. The primary outcome for those undergoing surgery was the detection of pelvic nodal disease, which was noted in 40 patients based on PSMA PET (14%). Unlike the proPSMA trial, all patients in this study underwent radical prostatectomy with histopathology as the gold standard. A total of 81% of patients had high-risk disease and 75 patients (27.1%) had pathologically confirmed nodal disease. Of these, 30 (40%) were N1 by PET, while the rest staged N0. Note that 19% (45/237) of men without detectable nodal disease on PET had confirmed N1 disease pathologically. Based on the composite imaging reads from three nuclear medicine physicians, the sensitivity and specificity for pelvic nodal disease was 40% and 95%, respectively.

Subsequent FDA approvals of PSMA PET agents followed in 2021 (F18-DCFPYL), and 2023 (F18-rhPSMA7.3). The pivotal trial used for F18-DCFPYL (OSPREY) lead to similar findings for sensitivity and specificity for nodal metastatic disease were noted for (40% and 98%, respectively, 2016–2018) [23•].

In the LIGHTHOUSE trial which assessed 18F-rhPSMA-7.3 in patients with unfavorable intermediate to very high risk PCa, specificity for nodal metastatic disease was still very high at 96% but sensitivity was somewhat lower at 24% [24•].

In a recent systematic review and meta-analysis, Chow *et al.* assessed 31 studies in which patients underwent both PSMA PET/CT and at least one form of conventional imaging, including multiparametric MRI, for initial staging [25]. Their work showed PSMA PET/CT outperformed all other conventional imaging in terms of nodal and bone staging. While PSMA PET/CT alone was not superior to MRI for T staging, the combination of the two modalities was superior to MRI alone with improvements in both extracapsular extension (sensitivity: 78.7% *versus* 52.9%) and seminal vesicle invasion detection (sensitivity: 66.7% *versus* 51.0%). This is likely related to the added benefit of local extension staging from

MRI which has been shown in multiple studies of patients who have received both imaging tests prior to surgery and might have implications for surgical planning [26, 27].

Based on these studies, PSMA PET is considered a more accurate form of initial staging for patients with unfavorable risk factors, leading to frequent changes in initial management. Although it is unclear if PSMA PET and subsequent management changes result in improved oncologic outcomes, these findings support its use for the initial staging of PCa. The National Comprehensive Cancer Network (NCCN) supports PSMA PET as an initial staging modality for any patient with unfavorable intermediate risk or high-risk disease while the European Association of Urology (EAU) similarly suggests PSMA PET imaging for patients with ISUP grade group 3 or higher or with high-risk PCa [28, 29]. These guidelines do not require prior negative or equivocal conventional imaging.

Localizing recurrence and planning salvage therapy

Prior work has shown that PSMA PET is better able to detect more PCa in patients with BCR compared to choline- or fluciclovine-based PET after primary radiation or surgery [8, 9]. Specifically, when the PSA is ≤0.5 ng/mL in these patients, the detection rate is only 12.5% for Choline-based PET and 50% for PSMA PET. In a similarly designed prospective study of patients with PSA 0.2–2.0 following surgery for PCa, the detection rate for fluciclovine-based PET was 26%, while PSMA-based PET detected PCa in 56% [8].

The pivotal study used for FDA approval of Ga68-PSMA-11 for recurrence indication was a single-arm prospective trial from UCSF and UCLA. PSMA PET was able to detect PCa in 75% of patients with a median PSA of 2.1 including 38% of patients with PSA <0.5 [30•].

The pivotal trial used for F18-DCFPYL (CONDOR) was a phase III, multicenter trial. Patients with BCR (PSA ≥0.2 ng/mL) after surgery or radiation underwent PSMA PET after prior equivocal or negative imaging with conventional imaging or choline or fluciclovine-based PET (2018–2019) [31•]. The study cohort consisted of 208 patients with a median serum PSA of 0.8 ng/mL. To determine the accuracy of PSMA PET, a standard of truth was defined as confirming lesions within 60 days of PET by histology, correlative imaging, or response to treatment. PSMA PET detected PCa in 69% of patients previously found to be negative with conventional imaging and PET imaging led to a change in management in 64% of patients. The largest portion of the 131 patients whose management was changed received systemic therapy in place of salvage local therapy (n= 58; 44%).

Finally, in SPOTLIGHT trial assessed 18F-rhPSMA-7.3, PSMA PET was able to verifiably detect PCa in 57% of patients after BCR after radiotherapy or surgery and a median PSA of 1.27 [32•].

Pozdnyakov *et al.* systematically reviewed retrospective and prospective studies assessing change in management based on PSMA PET for patients with BCR [33]. The 34 studies assessed include 3680 patients with an overall PSMA PET positivity rate of 68%—similar to that of the CONDOR trial. In pooled analysis, results from PSMA PET altered management for 56% of patients. Accordingly, both the NCCN and EAU support the use of PSMA PET for localizing PCa after a BCR [28, 29].

Once PCa is localized following BCR, PSMA PET can also be used to optimize salvage treatment. In a retrospective study in which 99 patients recurred following surgery and received salvage radiotherapy, 36 also had PSMA PET results showing nodal or distant metastatic PCa [34]. Treatment response defined by a serums PSA ≤0.10 ng/mL or 50% reduction was noted in 83% of patients with either a negative PSMA PET or tumor only in the prostate fossa, while the rate was only 53% for patients with nodal or distant metastatic disease. These and other data [35, 36] suggest using PSMA PET as part of a nomogram for determining salvage therapy could help optimize treatment decision making in the recurrence setting. The ongoing PSMA-SRT trial will also evaluate the success rate of salvage radiotherapy for recurrence of PCa after prostatectomy with and without planning based on 68Ga-PSMA-11 PET [37].

Oligometastatic disease and metastasis–directed therapy

Systemic therapies remain the mainstay of treatments for metastatic PCa. However, recent research has sought to define an intermediary state of metastatic disease—oligometastatic—where the introduction of curative local therapies might change the natural history of the disease [38–40]. These approaches have included tumor burden-adapted, metastasis-directed, and local consolidative treatments. While the definitions of oligometastatic disease vary somewhat, most trials anchor definitions of metastatic burden based on conventional imaging [13, 41].

Evidence from retrospective and prospective studies suggest local therapy with surgery or radiation can improve oncologic outcomes for patients with metastatic PCa [13, 42–44]. Two published [13, 15] and one ongoing [45] randomized controlled trials (RCTs) suggest a potential benefit to irradiation of the prostate for patients with low metastatic burden and, in particular, for those with non-regional nodal disease, few bone lesions, and no visceral metastatic disease [45]. Another phase II RCT randomized 200 patients with oligometastatic disease from 2015 to 2019 to either ADT alone or with definitive radiotherapy or surgery of the prostate and showed clinical benefits to local therapy [43]. However, each of these classified metastatic burden based on conventional imaging. Several ongoing trials are investigating definitive treatment directed at the prostate in the setting of metastatic disease, and some of these trials include patients based on the presence of oligometastatic disease [14]. Many include PSMA PET as a potential imaging modality, although others do not, or also include conventional imaging. Thus, the role of PSMA PET for determining candidacy for local definitive therapy in the setting of oligometastatic disease will be determined by few trials and extrapolations from others. It will be important not to exclude men from receiving potentially life-prolonging treatment to the prostate who demonstrate oligometastatic disease on conventional imaging but more extensive disease on PSMA PET.

Metastasis-directed therapies (MDTs) have been evaluated in three RCTs for patients with oligometastatic disease [11••, 16, 17, 46]. Two trials compared observation to MDT, largely with radiotherapy [11••, 17]. The STOMP trial (2012–2015) defined oligometastatic disease using choline-based PET imaging and showed median ADT-free survival was longer in the group that received MDT (21 *vs.* observation: 13 months; unadjusted Hazard ratio [HR]

0.60, 95% confidence interval [CI] 0.40–0.90) [17]. In the ORIOLE trial (2016–2018), oligometastatic status was determined by conventional imaging but post hoc correlations with PSMA PET were performed [11••]. Patients in this trial who received MDT with radiotherapy did benefit in terms of progression at 6 months (19% *vs.* observation: 61%; *P*=0.005). However, patients with any untreated lesions based on PSMA PET were at a much higher risk of progression at 6 months (63% *vs.*16%; *P*=0.006). This suggests that the benefit of MDT might be further enhanced with treatment of all lesions identifiable by PSMA PET. In the phase II EXTEND trial (2018–2020), oligometastatic status in 87 patients was determined by conventional imaging or by fluciclovine-based PET in about one-quarter of patients [16]. In this study, patients were randomized to receive 6 months of hormone therapy with or without MDT. The hormone therapy was ~60% ADT only and ADT in combination with an androgen receptor signaling inhibitor in ~40%. Patients randomized to receive hormonal therapy plus MDT experienced longer median progression-free survival compared to those randomized to hormonal therapy only after a median follow-up of 22 months (not reached *vs.*15.8 months; unadjusted HR 0.25, 95% CI 0.12–0.55). Together, these trials indicate an oncologic benefit for MDT in patients with oligometastatic disease and that PSMA PET might further optimize treatment. Currently accruing trials testing MDT and PSMA-RLT therapy may further optimize outcomes for these patients [47, 48].

In terms of systemic therapy options, patients with metastatic hormone-esensitive PCa are often offered treatment based on burden of metastatic disease defined by the CHAARTED study using conventional imaging [41]. Patients with high burden metastatic disease benefit from triplet therapy in the form of ADT, docetaxel chemotherapy, and an androgen receptor signaling inhibitor [49, 50]. It still remains to be seen how to relate metastatic burden on PSMA PET and treatment efficacies in the context of these landmark systemic therapy trials.

Stage migration with PSMA PET

An emerging group of patients deemed “high-risk” BCR are being evaluated in prospective studies assessing systemic therapies in patients with adverse PSA kinetics but no metastatic disease on conventional imaging [51, 52]. Given the growing role of PSMA PET in this setting and the improved sensitivity of detection of lesions driving increases in PSA, it is likely this group of patients will narrow based on the result of the CONDOR trial and other assessments [53]. Additionally, while the EMPIRE-1 randomized study did show oncologic benefits of 18F-fluciclovine-PET for patients with BCR [54], the EMPIRE-II study (NCT03762759) will randomized patients with recurrence following surgery to 68Ga-PSMA-11 or fluciclovine PET imaging and determine the incremental outcome benefits added by each scan prior to planned radiotherapy. Similarly, three agents are approved for the management of non-metastatic castration-resistant PCa (nmCRPC) [55–57]. More than half of these patients may ultimately have distant metastatic disease on PSMA [58, 59]. How PSMA PET findings should influence the management of these patients will ultimately be subject to clinical trial assessment. Finally, in the initial staging for PCa, bone scan has a poor positive predictive value (0.43) with PSMA PET as the reference. This may affect interpretation of data from the STAMPEDE trial which showed a benefit of prostate

radiotherapy for patients with few bony metastatic lesions as assessed by bone scan since some of these patient might have had non-metastatic disease [60].

Monitoring response to systemic therapy

Current guidelines on phase III clinical trials for advanced PCa rely on conventional imaging with bone scans and CT to determine treatment response [61]. However, as mentioned above, PSMA PET performs better for localizing recurrent disease after definitive treatment than any other imaging technique [31•]. Investigators recently leveraged data from a multicenter retrospective cohort to develop a novel framework for objectively monitoring treatment response for metastatic CRPC (mCRPC) using PSMA PET (RECIP 1.0) [62•]. Using imaging and follow-up data from 124 patients treated with PSMA-RLT, the authors showed RECIP 1.0 defined disease response, stability, and progression were associated with median overall survival (21.7, 13.1, and 8.3 months, respectively). In an adapted comparison to other methods for monitoring radiographic treatment response, RECIP 1.0 demonstrated the best prognostic value and inter-reader reliability [63]. Finally, even in the absence of widespread quantifying software to compute RECIP 1.0, inter-reader agreement based on qualitative (visual) reads was high, suggesting promising potential for the clinical implementation of a PSMA PET-specific monitoring framework [64]. Although continued work is needed to optimize fidelity in the setting of various treatments and potential early "flare" effects [65], we can expect PSMA PET-specific monitoring to integrate into future trial guidelines and clinical practice. We can also ongoing work to continue optimizing PSMA PET in the setting PSMA-RLT to help modify, cease, or intensify treatments based on early changes on imaging [25, 66, 67].

Determining candidacy for radioligand therapy

Lutetium-177 PSMA (Lu-PSMA) is a small molecule that binds with high specificity to PSMA and delivers β particle radiation to tumor cells [68••]. The Food and Drug Administration has approved Lu-PSMA for patients with advanced, PSMA PET-positive mCRPC previously treated with an androgen receptor signaling inhibitor and taxane chemotherapy [69]. This approval relied on results from the VISION trial, a phase III randomized, international open-label study that accrued 831 patients from 2018 to 2019. The VISION trial evaluated Lu-PSMA added to standard of care versus standard of care alone in patients with PSMA PET-positive mCRPC. Overall survival was longer for those patients in the Lu-PSMA arm (15.3 *vs.*11.3 months; unadjusted HR 0.62, 95% CI 0.52–0.74). Similarly, in the phase II TheraP trial, 200 patients were randomized from 2018 to 2019 to cabazitaxel or Lu-PSMA [70]. Treatment response as indicated by a serum PSA reduction of 50% or greater was more frequent in the patients who received Lu-PSMA (66% *vs.*37%). Lu-PSMA also prolonged progression-free survival (unadjusted HR 0.63, 95% CI 0.46–0.86). Several ongoing trials are now using PSMA PET at various stages in PCa progression to select patients for PSMA-RLT: locally advanced (LuTectomy [NCT04430192] and NALuPROST [NCT04297410]; hormone sensitive metastatic (PSMAddition [NCT04720157]; castration resistant prior to taxane chemotherapy (PSMAfore [NCT04689828], ECLIPSE [NCT05204927], and SPLASH

[NCT04647526]). Despite these active trials, there is currently a dearth of evidence on optimal patient selection for Lu-PSMA treatment.

PSMA PET is utilized as a gatekeeper for PSMA-RLT. However, optimal cutoff values for PSMA PET positivity remain an active subject of discussion. PSMA positivity for trial inclusion was defined in the VISION trial as at least one lesion with gallium (68Ga) gozetotide uptake greater than in liver [68••] and in the phase II LuPSMA trial as 1.5 times liver uptake [71]. Notably, the VISION trial only required one positive PSMA PET scan in addition to conventional imaging as opposed to supplementation with 18F-fluorodeoxyglucose (FDG) PET as in the TheraP trial [71].

Better patient selection tools are needed as 58% of patients with mCRPC did not respond to Lu-PSMA despite presenting with PSMA PET–positive lesions in the VISION trial [68••] and, notably, responses to PSMA-RLT in patients who would not qualify for VISION may be as low as 21% [72]. Additionally, intra- and interreader agreement based on the VISION criteria are generally considered to be good [73]. The PSA response was higher in the TheraP trial (66%) in which 18% of patients were excluded from randomization due to FDG PET–positive lesions without any PSMA uptake which may be indicative of neuroendocrine differentiation and poor response to Lu-PSMA [74]. Gafita *et al.* developed a nomogram to predict outcomes after Lu-PSMA treatment in mCRPC [75•]. Their nomogram uses whole-body PSMA tumor burden mean standardized uptake value (SUVmean) in combination with clinical factors such as time-since-diagnosis to achieve a sensitivity of 94% for response to therapy. Results support *in vivo* findings that high PSMA abundance in tumors leads to greater Lu-PSMA deposition at target sites and favorable outcomes [76]. PSMA heterogeneity on PET has also been proposed as explanations for non-response to therapy [77]. Additionally, other PET metric such as PSMA PET tumor to salivary gland ratio or the presence of any lesions with low PSMA expression on PET might further identify patients likely to respond to PSMA-RLT [78, 79]. We expect optimal selection of patients for Lu-PSMA treatment will continue to evolve as trials continue to refine patient inclusion and expand the indications for treatment. Regardless, PSMA PET remains the main feature used to define treatment candidates.

Future directions

Researchers are currently working to enhance our interpretation of PSMA PET imaging. Recent work in advanced, mCRPC has shown PSMA uptake on PET reflects differential tumor biology [80, 81]. This work has begun to show the nature of PSMA regulation and how variations in uptake on PET might indicate a need for further molecular testing or potential personalized treatment avenues. Further work on the topic of how PSMA PET avidity might serve as a biomarker to advance precision care for future patients is needed and, in particular, in the treatment naïve setting.

Targeted prostate biopsy using MRI guidance can optimize PCa detection by increasing the frequency at which clinically significant PCa is sampled while minimizing the over-detection of low-grade, indolent disease [18]. PSMA PET before biopsy might also be used as a form of guidance as well [82], and ongoing clinical trials will help define that role

(NCT05160597; NCT03429244). Finally, many prior clinical trials for metastatic PCa have relied on conventional imaging for the staging and subsequent stratification of treatment intensification [41, 50]. Forthcoming trials relying on PSMA PET will help relate study findings from these earlier works to contemporary patients. Further implementation of PSMA PET in phase III clinical trials are warranted to learn how to use PET imaging to classify patients and determine appropriate care based on tumor burden.

Summary

PCa remains a significant medical challenge, necessitating innovative approaches to enhance diagnostic accuracy and treatment strategies. The advent of PSMA PET has brought a transformative shift in management for patients with PCa. Conventional imaging modalities demonstrate poor accuracy for small lesions and in the setting of low serum PSA values. While PET imaging based on choline and fluciclovine improved upon these modalities, PSMA PET is still superior and aids in more precise initial staging and earlier recurrence localization. These factors result in significant alterations in management decision-making which have been shown to improve patient outcomes.

In the context of recent trials supporting a role for treatments specifically tailored towards the burden of metastatic disease for patients with metastatic hormone sensitive PCa, the increased accuracy of PSMA PET will likely optimize management for those patients who might be candidates for MDT or certain systemic therapy combinations. This will require further use of PSMA PET in phase III clinical trials. PSMA PET can likely homogenize and refine clinical trial recruitment and disease monitoring as this technology is used more commonly in clinical practice and, in particular, in late-stage disease. Targeted RLT based on the cell surface abundance of PSMA will expand in terms of indications based on forthcoming trials. PSMA PET remains the main feature used to define optimal treatment candidates.

In conclusion, PSMA PET imaging has emerged as a practice-changing tool in PCa management. Its capacity to provide accurate staging, monitor treatment response, guide interventions, and even impact clinical trial design underscores its significance in advancing personalized PCa care. As research continues to unveil the full spectrum of its applications, the integration of PSMA PET into routine clinical practice holds the promise of optimizing patient outcomes and shaping the future landscape of precision PCa care.

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Conflict of interest

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PCB sits on the Scientific Advisory Boards of Sage Bionetworks, Intersect Diagnostics Inc. and BioSymetrics Inc.

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Opinion statement

PSMA-PET has been a practice-changing imaging biomarker for the management of men with PCa. Research suggests improved accuracy over conventional imaging and other PET radiotracers in many contexts. With multiple approved PSMA-targeting radiotracers, PSMA PET will become even more available in clinical practice. Its increased use requires an understanding of the prospective data available and caution when extrapolating from prior trial data that utilized other imaging modalities. Future trials leveraging PSMA PET for treatment optimization and management decision-making will ultimately drive its clinical utility.