



# PSMA as a Target for Advanced Prostate Cancer: A Systematic Review

Safiya-Hana Belbina<sup>1</sup>, Mia Rose Schmolze<sup>2</sup>, Sofia Gereta<sup>1</sup> and Aaron A. Laviana<sup>1,3\*</sup>

<sup>1</sup> Dell Medical School at the University of Texas, Austin, TX, United States, <sup>2</sup> The University of Texas Rio Grande Valley School of Medicine, Edinburg, TX, United States, <sup>3</sup> Department of Surgery and Perioperative Care, University of Texas At Austin Dell Seton Medical Center, Austin, TX, United States

**Objective:** Prostate-specific membrane antigen (PSMA) is a cell-surface protein widely expressed on most prostate cancer cells that has rapidly emerging clinical utility in the realm of prostate cancer. This systematic review aims to evaluate the efficacy as well as cost-effectiveness of PSMA in the roles of diagnosis and treatment in prostate cancer management.

**Background:** The use of PSMA in the initial staging of patients, early detection of recurrence, and response monitoring are critical to improving prostate cancer treatment. We performed a systematic review of the role of Gallium-68 (<sup>68</sup>Ga)-PSMA in the initial detection of prostate cancer and detection of biochemical recurrence (BCR) as well as the role of Lutium-177 (<sup>177</sup>Lu)-PSMA in theranostics. We also investigated the cost-effectiveness of both ligands in comparison to the current standard of care.

**Methods:** In February 2022 we performed a systematic and comprehensive review of the existing literature. We identified and screened articles published from 1983 up to January 2022 through PubMed. Only 1 study was included prior to 2011. We included articles that investigated the efficacy or cost-effectiveness of PSMA in prostate cancer detection and therapy. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines eligible articles were selected, and relevant information was extracted from the original articles.

**Results:** A total of 26 articles were included in the analysis of this systematic review. These studies were heterogeneous and were comprised of five prospective studies including 336 patients, three retrospective analyses including 540 patients, one phase III trial, one survival analysis, one randomized control trial, three systematic reviews, three meta-analyses, two *in-vivo* studies, three reviews, and four cost analyses.

**Conclusion:** The diagnostic and therapeutic role of PSMA appears more efficacious and potentially less expensive than the standard treatment for patients with BCR of prostate cancer. Current evidence suggests PSMA will also fill an unmet need in initial diagnostics of prostate cancer and ligand therapy. However, a consensus has not yet been reached on cost-effectiveness of PSMA and further prospective studies are needed.

**Keywords:** radioligand, prostate cancer, 177Lu-PSMA, 68Ga-PSMA, mCRPC, PSMA cost analysis, PSMA - prostate specific membrane antigen, PSMA

## OPEN ACCESS

### Edited by:

Trushar Patel,  
University of South Florida,  
United States

### Reviewed by:

Reza Sari Motlagh,  
Medical University of Vienna, Austria  
Enrico Checcucci,  
Candiolo Cancer Institute (IRCCS),  
Italy

### \*Correspondence:

Aaron A. Laviana  
Aaron.laviana@austin.utexas.edu

### Specialty section:

This article was submitted to  
Urologic Oncology,  
a section of the journal  
Frontiers in Urology

**Received:** 05 April 2022

**Accepted:** 23 June 2022

**Published:** 18 July 2022

### Citation:

Belbina S-H, Schmolze MR, Gereta S  
and Laviana AA (2022) PSMA as  
a Target for Advanced Prostate  
Cancer: A Systematic Review.  
Front. Urol. 2:912558.  
doi: 10.3389/fruro.2022.912558

## INTRODUCTION

Prostate cancer is the second most common cause of cancer-related deaths in men in the United States. In 2021, prostate cancer accounted for 13.1% of all new cancer cases and 5.6% of all cancer-related deaths. Current treatments have proven to be highly effective resulting in a five-year relative survival rate of nearly 100% in localized disease. However, the five-year survival rate significantly decreases to 30.6% in those with metastatic disease (1). As such, accurate initial staging of patients, early detection of recurrence, and response monitoring are critical to improving prostate cancer treatment.

Current guidelines for assessing metastasis recommend a) skeletal scintigraphy (bone scan) and b) abdominal and pelvic computed tomography (CT), both of which have their limitations. Bone scintigraphy has a sensitivity of 79% and a specificity of 82% for metastatic lesions (2). Although CT has a high sensitivity for metastases to cortical bone, it is limited in its sensitivity to tumors restricted to the marrow space. CT also has a low sensitivity when screening for lymphatic disease (42%) and is fairly poor in detecting smaller volume and size metastases (3). As such, there is a substantial need to improve detection of metastatic prostate cancer with prostate-specific membrane antigen (PSMA) and its concomitant ligands, becoming a noteworthy research focus of late.

Prostate specific membrane antigen (PSMA) is a type II transmembrane antigen expressed in all forms of prostate tissue as well as other benign tissues such as salivary glands, duodenal mucosa, and neuroendocrine cells (4, 5). PSMA expression in these benign tissues is significantly lower than in prostate cancer lesions where PSMA expression is notably increased. In healthy prostate cells, PSMA is localized to the cytoplasm and apical side of the epithelium. During malignant transformation, PSMA is transferred to the luminal surface of the prostate ducts and presents a large extracellular domain to ligands.

It is important to note that PSMA differs from prostate-specific antigen (PSA) both biologically and in its clinical role. Unlike PSA, a glycoprotein enzyme detected in serum, PSMA is a transmembrane protein that is often used in conjunction with positron emission tomography (PET) to aid in its detection. Increased PSMA expression correlates with cancer aggressiveness and is an independent indicator of a poor prognosis (6). These properties of PSMA have made the protein a promising candidate for prostate cancer therapy research.

From a research perspective, PSMA studies have focused on three main avenues a) initial prostate cancer detection and staging, b) radioligand therapy, and c) prostate cancer recurrence monitoring. The potential role of PSMA in the detection and treatment of prostate cancer as well as its economic value are discussed below.

## METHODS

This systematic review aims to investigate the following question: In men initially diagnosed with prostate cancer and in men with

recurrent disease (P), is the use of PSMA (I) in comparison with the current standard of care (C) potentially more precise and accurate in detecting diseases, more beneficial in reducing morbidity and mortality outcomes, and more cost-effective (O). We chose to follow the PRISMA guidelines. Bias in the literature selected was assessed using predefined criteria outlined below and the Cochrane Tool. Ethical approval and patient consent were not required because all analyses were based on previously published studies.

## Literature Search And Eligibility Criteria

We systematically searched PubMed using relevant keywords in February 2022 for papers and reviews published from January 1983 to January of 2022. Retrieved studies and reviews were hand-searched and hand-selected. Inclusion criteria included (1) *in-vitro* studies published after 1982, (2) all other studies published after 2010, (3) full text only, (4) relevant data for extraction, (5) sufficient data for extraction.

Of 521 articles identified in the literature search, 419 were excluded due to ineligible year of publication, irrelevant title or abstract, or not a full paper. 102 reports were then assessed for eligibility, 74 of these were excluded due to duplicate results, irrelevant outcomes, or irrelevant interventions. 26 studies were then included in the review. This process is demonstrated in **Figure 1**.

## Included Studies

This systematic review includes a total of 26 articles: five prospective studies including 336 patients, three retrospective analyses including 540 patients, one phase III trial, one survival analysis, one randomized control trial, three systematic reviews, three meta-analyses, two *in-vivo* studies, three reviews, and four cost analyses. Baseline information extracted from these studies include: first author, published year, title, purpose, study design, number of samples, and results. These studies and characteristics (excluding results) are summarized in **Table 1**.

## METHODOLOGICAL QUALITY ASSESSMENT

Articles were selected by title and abstract by 1 methodologist, and full articles were reviewed by the other authors. All studies were evaluated for bias and generalizability by a predefined set of criteria. The included studies were required to provide (1) appropriate study methodology, (2) appropriate sample size and follow-up, (3) relevant study objectives, (4) comprehensive and objective reporting of findings (5) discussion on the limitation and generalizability of findings, (6) detail on source of funding. The validity of the one randomized control trial included in this review were assessed using the Cochrane tool for assessing risk of bias in randomized trials (**Table 2**). Hofman et al. had 4 participants lost to follow up or withdrawal, however this was a small loss and balanced. As such, we evaluated this study as low risk for bias.

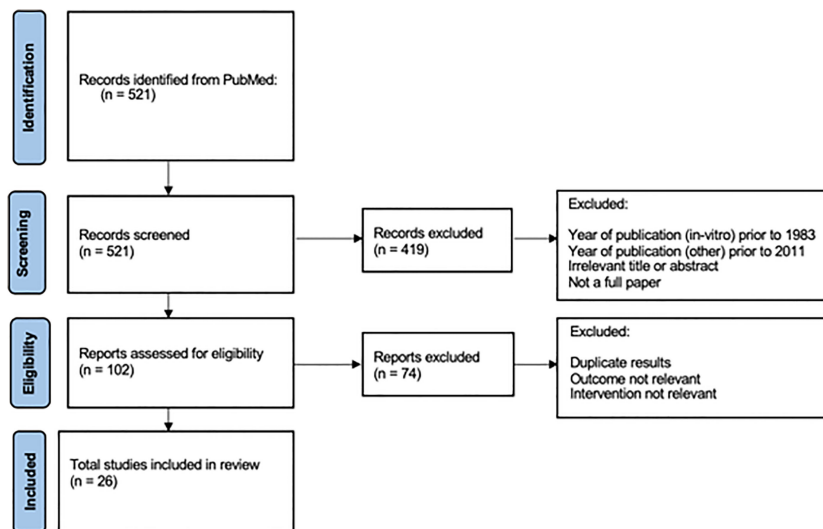


FIGURE 1 | Literature search PRISMA flow diagram (1983-2022).

## RESULTS

### PSMA in Prostate Cancer Detection

The current standards for the initial diagnosis and staging of prostate cancer include a transrectal or transperineal ultra-sound (TRUS) guided biopsy often with magnetic resonance imaging (MRI) fusion when appropriate. Although biopsy is an effective screening tool, it is an invasive procedure with the potential morbidity of hematuria, hematochezia, hemospermia, and urosepsis (the latter when done *via* a transrectal approach) and may contribute to over-treatment (7). MRI, meanwhile, is non-invasive and considered an effective screening tool for clinically significant cancer due to its high sensitivity. Nevertheless, it is limited by its relatively low specificity and high range of negative predictive values (NPVs), thus necessitating a biopsy to confirm diagnosis (8). These limitations result in an unmet need for alternative, non-invasive diagnostic and staging modalities.

The first synthesized PSMA ligands, such as J591, aimed to fill this need but were restricted by their limited ability to penetrate tumors. These antibodies also had long half-lives, which resulted in an extended delay between time of injection and imaging. Furthermore, this resulted in high antibody accumulation before decay, which prolonged patient radiation exposure.

More recently, small-molecule PSMA inhibitors have been developed, further advancing PSMA therapy. These small molecule inhibitors are highly accurate in localizing prostate cancer lesions, have fast tumor uptake, and are rapidly excreted to minimize radiation exposure (9). Gallium-68 ( $^{68}\text{Ga}$ )-PSMA has become one of the primary small-molecule tracers used in both the staging of *de novo* and recurrent disease.

### Detection for Prostate Cancer Recurrence

Biochemical recurrence (BCR) following radical prostatectomy is conventionally defined as a PSA value greater than 0.2ng/mL on

two separate occasions. However, the sensitivity of conventional imaging is poor, especially for PSA values this low (10). One of the first clinical roles of PSMA was for better detection of metastatic disease within this space. **Figure 2** shows a PSMA PET/CT for detection of metastatic disease from a patient with BCR following radical prostatectomy treated by the Department of Surgery and Perioperative Care University of Texas at Austin Dell Seton Medical Center. The scan was performed with Piflufolostat F-18, a newly approved F-18-labeled PSMA-targeted PET imaging agent. The scan revealed metastatic disease in multiple lymph nodes, identified in the right pelvic sidewall that are metabolically active.

A prospective study by Van Leeuwen et al. analyzed 300 patients with BCR following radical prostatectomy who underwent  $^{68}\text{Ga}$ -PSMA PET/CT. They found pathologic uptake in 54% of the cohort that resulted in significant management change in 28.6%. The management changes included enlarging the volume of the radiation template, shrinking the radiation field, adding adjuvant androgen deprivation therapy, or converting to a salvage lymph node dissection (11).

A systematic review by Tan et al. compared the detection rates of conventional imaging versus PSMA PET/CT based on 43 studies and 5113 patients with BCR prostate cancer and no known metastatic disease. For PSMA tracers, the detection rates were 45% for patients with PSA levels < 0.5 ng/mL, 61% for patients with PSA level 0.5-0.9 ng/mL, 78% for patients with PSA level 1.0-1.9 ng/mL, and 94% for patients with PSA level >2 ng/mL. Importantly, the rate of detection at PSA values of less than 0.5ng/mL were reported to be significantly higher than that of conventional imaging (12). Along these lines, a 2015 study by Morigi et al. prospectively compared detection capabilities of  $^{68}\text{Ga}$ -PSMA-11 versus conventional imaging using  $^{18}\text{F}$ -fluoromethylcholine in 38 patients with recurrent prostate

**TABLE 1 |** Summary of included studies and study characteristics.

Author	Title	Purpose	Design	Number of Samples
<b>Shen et al. (2014)</b> (2)	Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis	Compare the diagnostic performance of choline-PET/CT, MRI, bone SPECT, and bone scintigraphy (BS) in detecting bone metastases in patients with prostate cancer.	Comprehensive meta-analysis	16 articles consisting of 27 studies
<b>Yang et al. (2011)</b> (3)	Diagnosis of bone metastases: a meta-analysis comparing <sup>18</sup> F-FDG PET, CT, MRI and bone scintigraphy	To perform a meta-analysis to compare (18)FDG PET, CT, MRI and bone scintigraphy (BS) for the diagnosis of bone metastases.	Comprehensive meta-analysis	67 articles consisting of 145 studies
<b>Horoszewicz et al. (1982)</b> (4)	LNCaP model of human prostatic carcinoma	The characterization of the LNCaP prostate cancer cell line	<i>In-vitro</i> report	n/a
<b>O'Keefe et al. (2018)</b> (5)	A Perspective on the Evolving Story of PSMA Biology, PSMA-Based Imaging, and Endoradiotherapeutic Strategies	Cover the evolution of knowledge on the biology of prostate-specific membrane antigen (PSMA) and its translation to therapy	Review	60 articles
<b>Chang (2004)</b> (6)	Overview of prostate-specific membrane antigen	Evaluate the possible diagnostic and therapeutic role of PSMA	Review	51 articles
<b>Wenzel et al. (2020)</b> (7)	Complication Rates After TRUS Guided Transrectal Systematic and MRI-Targeted Prostate Biopsies in a High-Risk Region for Antibiotic Resistances	Evaluate complication rate of TRUS compared to transperineally	Retrospective review	230 patients
<b>Satapathy et al. (2021)</b> (8)	Diagnostic Accuracy of <sup>68</sup> Ga-PSMA PET/CT for Initial Detection in Patients With Suspected Prostate Cancer: A Systematic Review and Meta-Analysis	Evaluate the diagnostic performance of <sup>68</sup> Ga-PSMA PET/CT in the initial detection of PCa in patients with clinical or biochemical findings suspicious for PCa	Systematic review	7 studies comprising 389 patients
<b>Jones et al. (2020)</b> (9)	PSMA Theranostics: Review of the Current Status of PSMA-Targeted Imaging and Radioligand Therapy	Broad overview of the current status of PSMA theranostics, including current evidence, potential clinical impact, and active areas of research.	Review	82 articles
<b>Tu et al. (2020)</b> (10)	The Role of <sup>68</sup> Ga-PSMA Positron Emission Tomography/Computerized Tomography for Preoperative Lymph Node Staging in Intermediate/High Risk Patients With Prostate Cancer: A Diagnostic Meta-Analysis	To evaluate the accuracy of <sup>68</sup> Ga-PSMA positron emission tomography/computerized tomography (PET/CT) for preoperative lymph node staging	Diagnostic Meta-Analysis	11 studies comprising 904 patients
<b>Leeuwen et al. (2016)</b> (11)	<sup>68</sup> Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment	To examine the detection rates of ( <sup>68</sup> Ga-PSMA-positron emission tomography (PET)/computed tomography (CT) in patients with biochemical recurrence (BCR) after radical prostatectomy (RP), and also for the impact on their management.	Prospective cohort study	70 patients
<b>Tan et al. (2019)</b> (12)	Imaging of Prostate Specific Membrane Antigen Targeted Radiotracers for the Detection of Prostate Cancer Biochemical Recurrence after Definitive Therapy: A Systematic Review and Meta-Analysis	The detection of biochemical recurrence after definitive therapy for prostate cancer stratified by prostate specific antigen levels and using prostate specific membrane antigen targeted radiotracers.	Systematic review and Meta Analysis	5,113 patients in 43 studies
<b>Morigi et al. (2015)</b> (13)	Prospective Comparison of <sup>18</sup> F-Fluoromethylcholine Versus <sup>68</sup> Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy	Prospectively compare the detection rates of ( <sup>68</sup> Ga-PSMA versus ( <sup>18</sup> F-fluoromethylcholine PET/CT in men who were initially managed with radical prostatectomy, radiation treatment, or both and were being considered for targeted therapy.	Prospective comparison	38 patients
<b>Bluemel et al. (2016)</b> (14)	<sup>68</sup> Ga-PSMA-PET/CT in Patients With Biochemical Prostate Cancer Recurrence and Negative <sup>18</sup> F-Choline-PET/CT	Investigating the value of Ga-PSMA-PET/CT in biochemically recurring prostate cancer patients with negative F-choline-PET/CT	Prospective sequential clinical imaging approach	125 patients
<b>Pfister et al. (2016)</b> (15)	Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with ( <sup>68</sup> Ga-PSMA-HBED-CC than with ( <sup>18</sup> F-Fluoroethylcholine PET/C	To assess the sensitivity, specificity, positive and negative predictive value and accuracy per lesion of ( <sup>68</sup> Ga-PSMA PET/CT	Prospective study	38 patients
<b>Abufaraj et al. (2019)</b> (16)	Prospective evaluation of the performance of [ <sup>68</sup> Ga]Ga-PSMA-11 PET/CT(MRI) for lymph node staging in patients undergoing superextended salvage lymph node dissection after radical prostatectomy	To assess the accuracy of [ <sup>68</sup> Ga]-PSMA-11 PET/CT for lymph node (LN) staging in patients with biochemical recurrence (BCR) after radical prostatectomy (RP).	Prospective study	65 patients

(Continued)

**TABLE 1 |** Continued

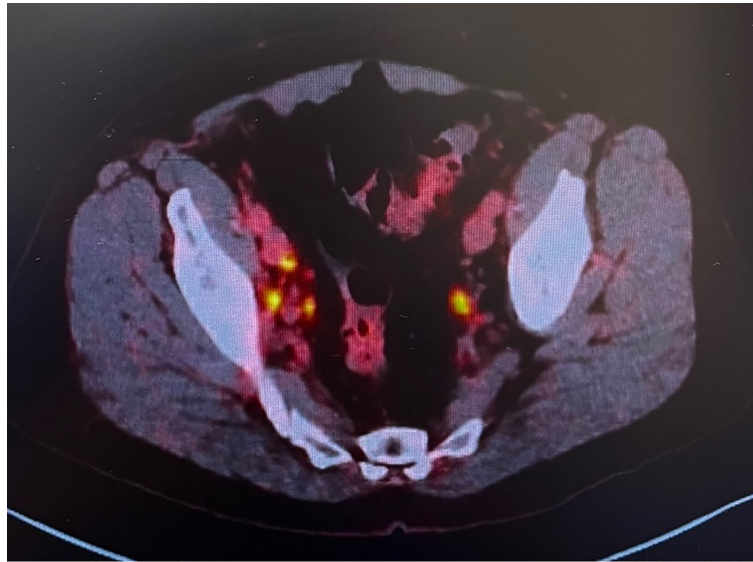
Author	Title	Purpose	Design	Number of Samples
<b>Hofman et al. (2020)</b> (17)	Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomized, multicentre study	Investigate whether novel imaging using prostate-specific membrane antigen (PSMA) PET-CT might improve accuracy and affect management.	Randomized control trial	302 men
<b>Armstrong et al. (2020)</b> (18)	Five-year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer from the PREVAIL Trial	Evaluate long-term benefits and risks of enzalutamide in the final prespecified PREVAIL analysis.	Survival analysis	1717 patients
<b>Benesova et al. (2015)</b> (19)	Preclinical Evaluation of a Tailor-Made DOTA-Conjugated PSMA Inhibitor with Optimized Linker Moiety for Imaging and Endoradiotherapy of Prostate Cancer	Investigate both detection and optimal treatment of prostate cancer by a tailor-made novel naphthyl-containing DOTA-conjugated PSMA inhibitor	<i>In-vivo</i> study	n/a
<b>Eyben et al. (2018)</b> (20)	Third-line treatment and <sup>177</sup> Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review	Elucidate whether <sup>177</sup> Lu-PSMA RLT and third-line treatment have similar effects and adverse effects	Systematic review	Twelve studies including 669 patients
<b>Meyrick et al. (2021)</b> (21)	Real-World Data Analysis of Efficacy and Survival After Lutetium-177 Labelled PSMA Ligand Therapy in Metastatic Castration-Resistant Prostate Cancer	Aimed to identify features that are associated with response to radioligand therapy and greater survival	Retrospective cohort analysis	191 patients
<b>Sartor et al. (2021)</b> (22)	Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer	Evaluating <sup>177</sup> Lu-PSMA-617 in patients who had metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor–pathway inhibitor and one or two taxane regimens and who had PSMA-positive gallium-68 ( <sup>68</sup> Ga)-labeled PSMA-11 positron-emission tomographic–computed tomographic scans	Phase 3 trial	831 patients
<b>Cardet et al. (2021)</b> (23)	Is Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Imaging Cost-effective in Prostate Cancer: An Analysis Informed by the proPSMA Trial	To determine the cost-effectiveness of PSMA-PET/CT when compared with conventional imaging.	cost-effectiveness analysis	n/a
<b>Gordon et al. (2020)</b> (24)	Exploratory cost-effectiveness analysis of <sup>68</sup> Gallium-PSMA PET/MRI-based imaging in patients with biochemical recurrence of prostate cancer	Evaluated the cost-effectiveness of <sup>68</sup> Ga-PSMA PET/MRI for staging men with prostate cancer biochemical recurrence	cost-effectiveness analysis	n/a
<b>Parikh et al. (2020)</b> (28)	Cost-effectiveness of <sup>68</sup> Ga-PSMA-11 PET/CT in Prostate Cancer Patients with Biochemical Recurrence	Evaluated the cost-effectiveness of obtaining PSMA PET/CT vs. proceeding directly to salvage radiotherapy in patients with biochemical recurrence and prostate specific antigen < 1.0 ng/ml.	Markov-based cost-effectiveness analysis	270 patients
<b>Grochtdreis et al. (2018)</b> (26)	Cost-effectiveness analyses and cost analyses in castration-resistant prostate cancer: A systematic review	Systematically review studies on the cost-effectiveness of treatments and costs of castration-resistant prostate cancer (CRPC) and metastasizing castration-resistant prostate cancer (mCRPC) on their methodological quality and the risk of bias	Cost-analyses and systematic review	38 articles

cancer. They found that in patients with biochemical failure and low PSA levels, PSMA had a significantly higher detection rate and a higher overall impact on management. When PSA was 0.5-2.0ng/mL the detection rate was 69% for <sup>68</sup>Ga-PSMA versus 31%

using <sup>18</sup>F-fluoromethylcholine. When PSA was above 2.0 the detection rate was 86% for <sup>68</sup>Ga-PSMA versus 57% using <sup>18</sup>F-fluoromethylcholine. In addition, there was a 54% management impact due to <sup>68</sup>Ga-PSMA imagine alone (13). Another study

**TABLE 2 |** Cochrane Tool for Assessing Risk of Bias in Included Randomized Control Trials.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Lack of selective reporting (reporting bias)	Lack of other source of bias	Risk of bias
<b>Hofman et al., 2020</b> (17)	Yes	No	No	Yes 4 lost to follow up or withdrew.	Yes	Yes	Low



**FIGURE 2** |  $^{68}\text{Ga}$ -PSMA PET/CT with intense tracer bilateral nodal uptake from Department of Surgery and Perioperative Care University of Texas at Dell Seton Medical Center.

which only performed  $^{68}\text{Ga}$ -PSMA PET/CT in patients with negative  $^{18}\text{F}$ -fluoromethylcholine PET/CT scans found that  $^{68}\text{Ga}$ -PSMA identified areas of recurrent disease in 43.8% of patients with negative  $^{18}\text{F}$ -fluoromethylcholine scans (14).

PSMA has also shown utility when specific to identifying lymph node metastases. A study of 38 patients planning to undergo salvage lymphadenectomy found that  $^{68}\text{Ga}$ -PSMA PET/CT had better performance than  $^{18}\text{F}$ -fluoromethylcholine PET/CT as the PSMA tracer had a significantly higher NPV (88.8%  $^{18}\text{F}$ -fluoromethylcholine versus 96.6%  $^{68}\text{Ga}$ -PSMA) and higher accuracy to detect metastatic lesions (82.5%  $^{18}\text{F}$ -fluoromethylcholine versus 91.9%  $^{68}\text{Ga}$ -PSMA) (15). Another prospective study of 65 patients with biochemical recurrence who underwent  $^{68}\text{Ga}$ -PSMA PET/CT prior to salvage lymph node dissection reported sensitivity ranging from 72%-100% and specificity ranging from 96%-100% (16).

### Initial Prostate Cancer Detection

Until recently, few studies have considered the role of  $^{68}\text{Ga}$ -PSMA PET/CT in the initial diagnosis of prostate cancer. A recent meta-analysis of seven studies comprising 389 patients evaluated  $^{68}\text{Ga}$ -PSMA PET/CT in initial prostate cancer diagnosis and found that the therapy had an excellent sensitivity of 97% and negative likelihood ratio of 5%. The researchers concluded that  $^{68}\text{Ga}$ -PSMA PET/CT has a high diagnostic accuracy for the initial detection of prostate cancer and has great potential as a rule-out test (8).

ProPSMA is a recent prospective randomized, multicentered study of 339 patients with high-risk, localized prostate cancer that investigated the accuracy of  $^{68}\text{Ga}$ -PSMA PET/CT versus conventional imaging. The primary outcomes were accuracy of first-line imaging for identifying pelvic nodal or distant-metastatic

disease. The authors found that PSMA PET/CT had 27% greater accuracy than conventional imaging and outperformed conventional imaging in the detection of both pelvic nodal disease and distant metastases. The study also demonstrated that PSMA PET/CT resulted in less equivocal imaging and less radiation exposure, as well as greater sensitivity (85% vs 38%) and specificity (98% vs. 91%) (17). Altogether,  $^{68}\text{Ga}$ -PSMA PET/CT has superior diagnostic accuracy versus conventional imaging and may be a viable replacement. The 2021 National Comprehensive Cancer Network (NCCN) guidelines have been updated to reflect these changes as stated: “The NCCN panel has recognized the increased sensitivity and specificity of PSMA-PET tracers, compared to conventional imaging (CT, MRI) for detecting micrometastatic disease, at both initial staging and biochemical recurrence. The updated guidelines state that the NCCN Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as equally effective, if not more effective front-line imaging tools for these patients” (27).

### PSMA Theranostics

PSMA also appears to have a profound role in theranostics. Although there are an increasing number of medications and therapies approved for metastatic castration-resistant prostate cancer (mCRPC), median survival for chemotherapy-naïve patients remains only approximately 31-35 months (18). As such, there is a clinical need for therapies with an increased response. Recent developments of PSMA radioligands, specifically the small-molecule PSMA inhibitor  $^{177}\text{Lu}$ -PSMA, have demonstrated the potential to fill this need. Although multiple radioligands exist,  $^{177}\text{Lu}$ -PSMA has the preferred pharmacokinetic profile due to its reduced kidney uptake and

low toxicity (19).  $^{177}\text{Lu}$ -PSMA is a macromolecular radiolabeled humanized monoclonal antibody that targets the extracellular region of PSA. Patients with a positive  $^{68}\text{Ga}$ -PSMA PET/CT are candidates for treatment with  $^{177}\text{Lu}$ -PSMA radioligand therapy (RLT), which targets the lesions revealed by  $^{68}\text{Ga}$ -PSMA PET/CT. Current data suggests that RLT decreases PSA in mCRPC, although its improvement with regard to overall survival is less certain. More data into its theranostics benefit are below.

A recent systematic review and meta-analysis found that  $^{177}\text{Lu}$ -PSMA RLT is particularly effective against advanced stage mCRPC refractory to standard therapeutic options such as enzalutamide and carbazitaxel. This study found patients with mCRPC treated with  $^{177}\text{Lu}$ -PSMA RLT had better treatment effects and fewer adverse effects versus third-line treatment agents.  $^{177}\text{Lu}$ -PSMA RLT resulted in a PSA decline  $\geq 50\%$  more often than the third line treatment (44% versus 22%,  $p=0.0002$ ). They also report that adverse effects of third-line treatment caused discontinuation of treatment more often than for  $^{177}\text{Lu}$ -PSMA (22 of 66 patients versus 0 of 469 patients,  $p<0.001$ ) (20). With regard to overall survival, initial studies reported rates comparable to the currently available third-line therapies (9).

A recent retrospective study of 191 patients with mCRPC treated with  $^{177}\text{Lu}$ -PSMA RLT found a low toxicity profile and a durable overall survival with median values (interquartile ranges) of 12 (5-18) months, PSA progression-free survival of 4 (3-8) months, and PET/CT progression-free survival of 6 (3-10) months. Most of the included patients (89.5%) had previously received first and second line systemic therapies. However, important factors associated with increased survival included having predominantly lymph node metastatic disease, chemotherapy-naïve status, and lower baseline PSA levels (21). These findings suggest  $^{177}\text{Lu}$ -PSMA RLT may provide some efficacy in mCRPC treatment and that  $^{177}\text{Lu}$ -PSMA is a promising candidate for therapy. Nevertheless, these findings are somewhat limited due to the lack of a comparative group.

Another recent international open-label, phase 3 randomized trial evaluating  $^{177}\text{Lu}$ -PSMA-617 RLT reported prolonged imaging-based progression-free survival and overall survival when RLT was added to standard care in patients with advanced, PSMA positive mCRPC (22). This study randomized 831 patients to either receive  $^{177}\text{Lu}$ -PSMA-617 RLT plus standard care or standard care alone. The standard care excluded chemotherapy, immunotherapy,  $^{223}\text{Ra}$ , and investigational drugs. The investigation found that  $^{177}\text{Lu}$ -PSMA-617 RLT significantly prolonged imaging-based progression-free survival (median 8.7 versus 3.4 months) and overall survival (median 15.3 months versus 11.3 months). It is important to note that the incidence of 30-day adverse events (Clavien-Dindo grade 3 or above) was higher with  $^{177}\text{Lu}$ -PSMA-617 RLT than without (52.7% versus 38%). However, quality of life was not affected, and the authors reported the adverse events may have been overestimated relative to control since the treatment duration varied among patients treated with  $^{177}\text{Lu}$ -PSMA-617. This trial was also limited as it was not double blinded and lacked a placebo group. While the theranostic

potential of  $^{177}\text{Lu}$ -PSMA-617 is promising, these conclusions remain limited with randomized control trials still pending.

### PSMA: Cost-Effective or Cost-Prohibitive?

Although the diagnostic and therapeutic potential of PSMA is promising, especially as its clinical applications continue to grow, the cost of treatment must also be factored in when considering applicability. Cardet et al. performed a cost-effectiveness analysis for PSMA as a diagnostic tool utilizing data from the proPSMA study and prospectively defined key inputs to compare the costs of patients with high-risk prostate cancer who underwent conventional imaging versus  $^{68}\text{Ga}$ -PSMA PET/CT. The analysis reports that the frank cost of PSMA PET/CT is essentially cost equivocal for metastatic disease detection versus conventional imaging (\$1,140 AUD versus \$1,181 AUD). For the cost-analysis, the authors adopted a societal perspective by assigning a monetary value to the cost associated with image delivery time to recognize the time-costs associated with the new imaging modality. From this perspective, overall scan costs increased but PSMA PET/CT cost remained lower with a cost of \$1,203 AUD versus \$1,412 AUD for conventional imaging. When the cost per scan was combined with the overall accuracy of detection, PSMA PET/CT remained most cost-effective as it was less costly and more accurate. The authors also analyzed PSMA PET/CT cost in relation to the accuracy of detection for each metastasis type (nodal and distant metastasis) separately. They found that PSMA PET/CT detection of nodal disease compared to conventional imaging resulted in a cost saving of \$959 AUD per additional accurate detection, and PSMA PET/CT detection of distant metastasis resulted in a cost saving of \$1,412 AUD per additional accurate detection (23). When this cost-saving was weighted against the probability of accurate metastasis detection observed from the proPSMA trial, PSMA PET/CT remained superior with a cost saving of \$428 AUD per additional accurate diagnosis. This societal perspective cost-analysis importantly demonstrates that PSMA PET/CT is more cost-effective than conventional imaging for both metastasis types.

Another cost-effectiveness analysis of  $^{68}\text{Ga}$ -PSMA PET/CT as a modality to detect prostate cancer recurrence was performed by Gordon et al. using a decision-analytic model with Markov modelling chains. The primary measured outcomes were health system costs and years of survival over 10 years. The cost model was sensitive to the percentage of patients whose  $^{68}\text{Ga}$ -PSMA prostate cancer lesions were successfully detected, the cost of usual care, and  $^{68}\text{Ga}$ -PSMA follow-up investigations. In this study, utilizing  $^{68}\text{Ga}$ -PSMA cost \$39,426 USD versus \$44,667 USD with standard therapy.  $^{68}\text{Ga}$ -PSMA was found to be slightly more effective at 0.07 life years gained. The likelihood that  $^{68}\text{Ga}$ -PSMA was cost-effective at acceptable thresholds was 87% at the threshold of \$34,626 USD. In all values tested,  $^{68}\text{Ga}$ -PSMA remained superior in cost-savings and higher life years. As such, the authors concluded that  $^{68}\text{Ga}$ -PSMA PET/CT, as a modality to detect prostate cancer recurrence, was cost-effective relative to usual care (24).

Parikh et al. also performed a Markov-based cost-effectiveness analysis focused on patients with metastatic M1 disease using  $^{68}\text{Ga}$ -PSMA PET/CT. They explored the cost-effectiveness of obtaining  $^{68}\text{Ga}$ -PSMA PET/CT versus proceeding directly to salvage radiotherapy for patients with BCR and a PSA < 1.0ng/mL. This differs from the previously discussed analysis which compared  $^{68}\text{Ga}$ -PSMA against the standard imaging modalities. Their analysis derived costs from Medicare fee schedules and the Veteran Affairs oral drug pricing list. Utilizing a life-long time horizon and willingness to pay threshold of \$100,000/quality adjusted life years (QALY),  $^{68}\text{Ga}$ -PSMA PET/CT (\$2,647 USD) was found to have a higher cost of \$17,300 USD and a higher effectiveness of 0.29 QALYs versus no  $^{68}\text{Ga}$ -PSMA PET/CT. This translated to an incremental cost-effectiveness ratio of \$60.4K/QALY below the pre-determined threshold. For their threshold analysis, PSMA PET/CT needed to be equal to or greater than \$14,004 USD to no longer remain cost effective. With costs currently well below that, the authors concluded that  $^{68}\text{Ga}$ -PSMA is cost-effective (28).

With the above studies suggesting that  $^{68}\text{Ga}$ -PSMA is cost-effective or, at least, cost-neutral, adopting  $^{68}\text{Ga}$ -PSMA as the standard of care for the detection of recurrent prostate cancer deserves merit. With regard to initial prostate cancer detection, cost analysis studies still need to be performed. Nevertheless, given its diagnostic accuracy, it will also likely be cost-effective as well.

The cost-effectiveness of  $^{177}\text{Lu}$ -PSMA-617 in theranostics needs to be determined, as the price of lutetium is still being finalized. Given the need for multiple treatments, it is reasonable to assume that the therapy will be costly. Nevertheless, treatment of metastatic prostate cancer is already associated with high personal and economic burden. Mean annual costs per patient with prostate cancer in the USA is estimated at \$10,612 in initial phase after diagnosis, \$2,134 for continuing care, and \$33,691 in the last year of life. The total economic expenditure cost was estimated at \$9.8 billion in 2006 (25). Grochtdreis et al. recently performed a systematic review of the cost-effectiveness of mCRPC treatments. They identified 38 articles on various mCRPC treatments and found that the cost-effectiveness of mCRPC is heavily dependent on the willingness to pay per quality adjusted life year gained (26). As such,

high QALYs based on randomized control trials are needed to make informed decisions on the management of mCRPC and the financial impact it has on patients and the healthcare system. How lutetium falls into this, especially with a potentially very steep price tag, remains to be determined.

## CONCLUSION

The diagnostic and therapeutic role of PSMA is an active and evolving area of research. This new advanced molecular imaging appears more efficacious and potentially cheaper than the standard treatment for patients with BCR of prostate cancer. High quality data and well performed cost-analysis have strengthened the enthusiasm for this new medical technology. Although a consensus has not yet been reached on its role as an initial diagnostic tool or ligand therapy, current evidence demonstrates that it will likely fill these unmet needs in prostate cancer management with the NCCN already incorporating it into its prostate cancer guidelines.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception: AL; study design: AL and S-HB; data collection: AL and S-HB; analysis and interpretation of results: AL, S-HB, MS, and SG; draft manuscript preparation AL, S-HB, MS, and SG. All authors reviewed the results and approved the final version of the manuscript.

## REFERENCES

1. *Cancer of the Prostate - Cancer Stat Facts*. NIH: SEER (2021). Available at: <https://seer.cancer.gov/statfacts/html/prost.html>.
2. Shen G, Deng H, Hu S, Jia Z. Comparison of Choline-PET/ct, MRI, SPECT, and Bone Scintigraphy in the Diagnosis of Bone Metastases in Patients With Prostate Cancer: A Meta-Analysis. *Skeletal Radiol* (2014) 43(11):1503–13. doi: 10.1007/s00256-014-1903-9
3. Yang H-L, Liu T, Wang X-M, Xu Y, Deng S-M. Diagnosis of Bone Metastases: A Meta-Analysis Comparing 18fdg Pet, CT, MRI and Bone Scintigraphy. *Eur Radiol* (2011) 21(12):2604–17. doi: 10.1007/s00330-011-2221-4
4. Horoszewicz JS, Leong SS, Kawinski E. LNCaP Model of Human Prostatic Carcinoma. *Cancer Res* (1983) 43(4):1809–18.
5. O'Keefe DS, Bacich DJ, Huang SS, Heston WD. A Perspective on the Evolving Story of PSMA Biology, PSMA-Based Imaging, and Endoradiotherapeutic Strategies. *J Nucl Med* (2018) 59(7):1007–13. doi: 10.2967/jnumed.117.203877
6. Chang SS. Overview of Prostate-Specific Membrane Antigen. *Rev Urol* (2004) 6(10):S13–8.
7. Wenzel M, Theissen L, Preisser F, Lauer B, Wittler C, Humke C, et al. Complication Rates After Trus Guided Transrectal Systematic and MRI-Targeted Prostate Biopsies in a High-Risk Region for Antibiotic Resistances. *Front Surg* (2020) 7.
8. Surasi DS. Editorial Comment on “Diagnostic Accuracy of 68GA-PSMA PET/CT for Initial Detection in Patients With Suspected Prostate Cancer: A Systematic Review and Meta-Analysis.”. *Am J Roentgenol* (2021) 216(3):607.
9. Jones W, Griffiths K, Barata PC, Paller CJ. PSMA Theranostics: Review of the Current Status of PSMA-Targeted Imaging and Radioligand Therapy. *Cancers* (2020) 12(6):1367. doi: 10.3390/cancers12061367
10. Tu X, Zhang C, Liu Z, Shen G, Wu X, Nie L, et al. The Role of 68ga-PSMA Positron Emission Tomography/Computerized Tomography for Preoperative Lymph Node Staging in Intermediate/High Risk Patients With Prostate Cancer: A Diagnostic Meta-Analysis. *Front Oncol* (2020) 10.
11. van Leeuwen PJ, Stricker P, Hrubby G, Kneebone A, Ting F, Thompson B, et al. 68ga-PSMA has a High Detection Rate of Prostate Cancer Recurrence Outside the Prostatic Fossa in Patients Being Considered for Salvage Radiation Treatment. *BJU Int* (2016) 117(5):732–9. doi: 10.1111/bju.13397
12. Tan N, Bavadian N, Calais J, Oyoyo U, Kim J, Turkbey IB. Imaging of Prostate Specific Membrane Antigen Targeted Radiotracers for the Detection of Prostate Cancer Biochemical Recurrence After Definitive Therapy: A



- Systematic Review and Meta-Analysis. *J Urol* (2019) 2(2):231–40. doi: 10.1097/JU.0000000000000198
13. Morigi JJ, Stricker PD, van Leeuwen PJ, Tang R, Ho B, Nguyen Q, et al. Prospective Comparison of 18F-Fluoromethylcholine Versus 68ga-PSMA Pet/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and are Being Considered for Targeted Therapy. *J Nucl Med* (2015) 56(8):1185–90. doi: 10.2967/jnumed.115.160382
  14. Bluemel C, Krebs M, Polat B, Linke F, Eiber M, Sarnick S, et al. 68ga-PSMA-PET/CT in Patients With Biochemical Prostate Cancer Recurrence and Negative 18F-Choline-PET/CT. *Clin Nucl Med* (2016) 41(7):515–21. doi: 10.1097/RLU.0000000000001197
  15. Pfister D, Porres D, Heidenreich A, Heidegger I, Kneuchel R, Steib F, et al. Detection of Recurrent Prostate Cancer Lesions Before Salvage Lymphadenectomy is More Accurate With 68ga-PSMA-HBED-Cc Than With 18F-Fluoroethylcholine PET/CT. *Eur J Nucl Med Mol Imaging* (2016) 43(8):1410–7. doi: 10.1007/s00259-016-3366-9
  16. Abufaraj M, Grubmüller B, Zeitlinger M, Kramer G, Seitz C, Haitel A, et al. Prospective Evaluation of the Performance of [68ga]Ga-PSMA-11 Pet/CT (MRI) for Lymph Node Staging in Patients Undergoing Superextended Salvage Lymph Node Dissection After Radical Prostatectomy. *Eur J Nucl Med Mol Imaging* (2019) 46(10):2169–77. doi: 10.1007/s00259-019-04361-0
  17. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-Specific Membrane Antigen Pet-CT in Patients With High-Risk Prostate Cancer Before Curative-Intent Surgery or Radiotherapy (PropSMA): A Prospective, Randomized, Multicentre Study. *Lancet* (2020) 395(10231):1208–16. doi: 10.1016/S0140-6736(20)30314-7
  18. Armstrong AJ, Lin P, Tombal B, Saad F, Higano CS, Joshua A, et al. Five-Year Survival Prediction and Safety Outcomes With Enzalutamide in Men With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer From the Prevaïl Trial. *Eur Urol* (2020) 78(3):347–57.
  19. Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical Evaluation of a Tailor-Made DOTA-Conjugated PSMA Inhibitor With Optimized Linker Moiety for Imaging and Endoradiotherapy of Prostate Cancer. *J Nucl Med* (2015) 56(6):914–20. doi: 10.2967/jnumed.114.147413
  20. von Eyben FE, Roviello G, Kiljunen T, Uprimny C, Virgolini I, Kairemo K, et al. Third-Line Treatment and 177Lu-PSMA Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: A Systematic Review. *Eur J Nucl Med Mol Imaging* (2018) 45(3):496–508. doi: 10.1007/s00259-017-3895-x
  21. Meyrick D, Gallyamov M, Sabarimurugan S, Falzone N, Lenzo N. Real-World Data Analysis of Efficacy and Survival After Lutetium-177 Labelled PSMA Ligand Therapy in Metastatic Castration-Resistant Prostate Cancer. *Target Oncol* (2021) 16(3):369–80. doi: 10.1007/s11523-021-00801-w
  22. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *New Engl J Med* (2021) 385(12):1091–103. doi: 10.1007/s10585-020-10027-1
  23. de Feria Cardet RE, Hofman MS, Segard T, Yim J, Williams S, Francis RJ, et al. Is Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography Imaging Cost-Effective in Prostate Cancer: An Analysis Informed by the PROPSMA Trial. *Eur Urol* (2021) 79(3):413–8. doi: 10.1016/j.eururo.2020.11.043
  24. Gordon LG, Elliott TM, Joshi A, Williams ED, Vella I. Exploratory Cost-Effectiveness Analysis of 68gallium-PSMA PET/MRI-Based Imaging in Patients With Biochemical Recurrence of Prostate Cancer. *Clin Exp Metastasis* (2020) 37(2):305–12.
  25. Roehrborn CG, Black LK. The Economic Burden of Prostate Cancer. *BJU Int* (2011) 108(6):806–13. doi: 10.1111/j.1464-410X.2011.10365.x
  26. Grochtdreis T, König H-H, Dobruschkin A, von Amsberg G, Dams J. Cost-Effectiveness Analyses and Cost Analyses in Castration-Resistant Prostate Cancer: A Systematic Review. *PLoS One* (2018) 13(12). doi: 10.1371/journal.pone.0208063
  27. GlobeNewswire News Room. *NCCN Guidelines Updated to Include PSMA-Pet Imaging* (2021). Available at: <https://www.globenewswire.com/news-release/2021/09/14/2296247/0/en/NCCN-Guidelines-Updated-to-Include-PSMA-PET-Imaging.html>.
  28. Parikh NR, Johnson D, Raldow A, Steinberg ML, Czernin J, Nickols NG, et al. Cost-Effectiveness of 68ga-PSMA-11 PET/CT in Prostate Cancer Patients With Biochemical Recurrence. *Int J Radiat Oncol Biol Phys* (2020) 108(3).

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Belbina, Schmolze, Gereta and Laviana. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.