

Prostate specific membrane antigen (PSMA) as a biomarker in early and localized advanced prostate cancer: a narrative review

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Prostate-specific membrane antigen (PSMA) is a surface membrane antigen that is highly overexpressed in prostate cancer, with heterogenous expression throughout the natural history of the disease. This has generated significant interest as a potential biomarker for use in early diagnosis and treatment of prostate cancer. We reviewed the literature surrounding PSMA and its current clinical applications in diagnosing and managing early prostate cancer that is confined to the prostate and local lymph nodes. A search on PubMed, Medline, and Web of Science was performed using the following keywords: "PSMA", "Prostate Specific Membrane Antigen", "Prostate cancer", "Biomarker", "Diagnosis". We considered all available articles relevant to the topic of PSMA as a biomarker in early prostate cancer when

developing this narrative review. Key articles assessing the biology of PSMA, as well as its use as a potential diagnostic and therapeutic target in early prostate cancer, were assessed. The role of PSMA PET as a potential diagnostic and risk stratification tool was assessed. The current use of antibody-drug conjugates and radioligand therapy targeting PSMA was assessed, along with any current evidence to support their use in early prostate cancer. PSMA is heavily expressed throughout the early stages of prostate cancer, and this has significant therapeutic implications. There is a growing body of evidence that shows PSMA PET can play a role in the diagnosis, risk stratification, and prognostication of localised prostate cancer. PSMA-targeted therapies such as Lu-177 currently do not have any proven benefit in treating early prostate cancer; however, this remains an area of ongoing research.

Key Words: prostate specific membrane antigen (PSMA), positron emission tomography (PET), radioligand therapy, prostate cancer

Introduction

Prostate cancer is one of the most common cancers worldwide, with an increasing incidence with age amongst men.¹ Given the large disease burden worldwide, there has been significant interest in identifying early biomarkers that can allow for screening and early diagnosis of prostate cancer. This led to the development of the serum prostate specific antigen

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(PSA) test, which has proven useful in decreasing the number of men diagnosed with metastatic and advanced prostate cancer.² However, population-wide PSA screening for prostate cancer remains a controversial concept,^{3,4} due to the poor specificity of the test, and uncertain impact on overall mortality.⁵ Given the imperfection of PSA as a standalone marker of early prostate cancer, there has been significant interest in the development of additional biomarkers and imaging modalities to aid in the detection and diagnosis of early prostate cancer.

One of the more useful markers identified for prostate cancer is prostate specific membrane antigen (PSMA)—a transmembrane protein that is highly expressed in normal prostate epithelium, as well as proximal renal tubules, and to a lesser extent in the small bowel, salivary glands, and brain.⁶ More importantly, PSMA is highly over-expressed in most prostate cancers—it was first discovered by assessing monoclonal antibodies developed by inoculating mice with a human prostate cancer cell line, LNCaP.⁷ From when it was first described, this has attracted significant interest for its potential use as a target for immune-based therapies, and molecular imaging of prostate cancer.^{8,9} However further research has demonstrated that PSMA can also be over-expressed in a wide variety of solid-organ tumours, including renal cell carcinoma, breast, bladder, and colorectal cancer.¹⁰ This is largely related to its role in mediating angiogenesis and neovascularization within the tumour.¹¹ Whilst the role PSMA plays in angiogenesis is not fully understood,¹¹ mouse models have suggested that it achieves this by modulating integrin signal transduction, and PSMA inhibition suppresses angiogenesis.¹² As such, increases in PSMA expression may transform vascular endothelium into an angiogenic state, providing a survival advantage to solid organ tumours.¹³

PSMA is a type II transmembrane glycoprotein encoded by the FOLH1 gene. It is also known as glutamate carboxypeptidase II (GCPII) or N-acetyl-l-aspartyl-l-glutamate peptidase I (NAALADase),¹⁴ which refers to its biological functions. Outside the prostate, PSMA cleaves terminal glutamate from the neurodipeptide, N-acetyl-aspartyl-glutamate (NAAG) in neuronal synapses. It also catalyzes the cleavage of terminal glutamates from poly- and gamma-glutamate folates present within the small intestine, allowing for uptake of folates via other carriers. Within the prostate, PSMA is most heavily expressed within the secretory cells of the luminal epithelium, particularly in cells that are androgen receptor positive.¹⁴ Although its physiological role within the prostate is not well understood, there

is a clear association with prostate cancer. This is likely due to its effect on folate metabolism, which could confer a survival benefit in folate-depleted conditions.¹⁵ Given the necessity of folate in a variety of cellular processes essential for rapid cell division, this likely applies selection pressure leading to over-expression within cancerous cells.

However, the expression of PSMA throughout the natural history of prostate cancer can be heterogeneous and can change with treatment such as androgen deprivation.¹⁴ Whilst in the earlier stages of cancer it is usually highly expressed, as the cancer advances, it can lose PSMA expression.¹⁴ This is particularly noted in castrate-resistant disease, as well as prostate cancers showing neuroendocrine differentiation.¹⁶ Lab-based and pre-clinical studies have demonstrated increased PSMA expression after the treatment with androgen receptor (AR) inhibitors,^{17,18} suggesting that AR signalling may play a role in suppressing PSMA expression in advanced prostate cancer. However, the role of AR signalling and PSMA expression is a nuanced one and not fully understood.¹⁹ Prostate cancers can demonstrate heterogeneous expression at similar stages of disease, suggesting factors such as tumour micro-environment play an important role in regulating PSMA expression.²⁰ Ultimately, the regulation of PSMA expression throughout the natural history of prostate cancer is an area of ongoing research, and has clinical implications given the role PSMA has as a target for diagnostic imaging and clinical therapy.

The characterisation and study of PSMA has led to many advances in diagnostics and therapeutics of prostate cancer. Although these advances have been most significant in advanced prostate cancer, there is a growing body of evidence to support their use in characterising and diagnosing early prostate cancers. At the forefront of the clinical utility of PSMA is its use in staging advanced prostate cancers to identify metastatic disease.

Radioligands that bind to PSMA have been used to develop PSMA positron emission tomography (PET) scans, which far exceed conventional imaging in specificity and sensitivity of identifying metastatic disease.²¹ However, further evidence has started to demonstrate that PSMA-targeted imaging may be useful in earlier prostate cancer. As the use of PSMA PET scans has moved into routine clinical practice, there has been growing interest in assessing their role in the diagnosis and detection of early prostate cancer. There has also been a growing body of evidence to demonstrate that PSMA PET can provide valuable information in risk-stratifying patients with earlier prostate cancer. A five-point PRIMARY score

can be applied to intraprostatic lesions that are avid on PSMA PET, which is predictive of the likelihood of clinically significant prostate cancer being present.²² PSMA is also actively under investigation as a potential molecular target to deliver drugs and therapeutics for men with early prostate cancer. This approach has been promising in men with advanced disease, and therapeutics such as radioligand therapy are currently under investigation for use in earlier stages of prostate cancer. Overall, PSMA is an important molecular target that is under investigation for a variety of diagnostic, prognostic, and therapeutic uses in early prostate cancer.

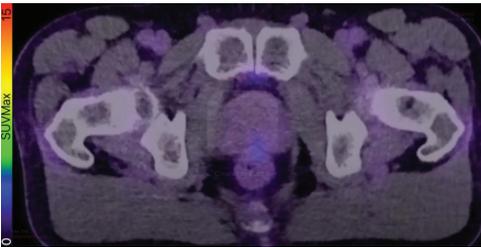
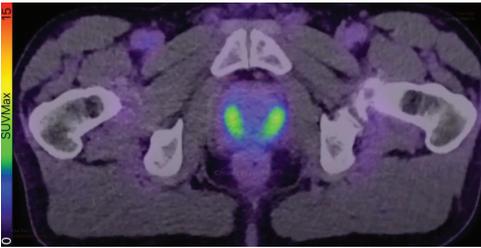
Given the growing body of literature demonstrating the utility of PSMA as a biomarker in prostate cancer, it is important to explore and assess how this may impact clinical practice. The goal of this review is to assess, analyse and critically appraise the evidence regarding the use of PSMA as a molecular target for diagnosis, prognosis and treatment of prostate cancer, with a focus on early and localized advanced prostate cancer.

PSMA in Diagnosing Early Prostate Cancer

Regardless of the complex regulation expression of PSMA in advanced prostate cancer, it is most often highly expressed in early stages of the disease. This has led to the development of the PSMA PET scan, which uses a radiolabelled tracer that binds

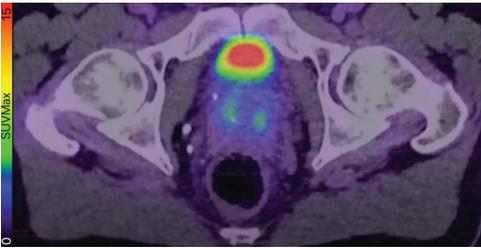
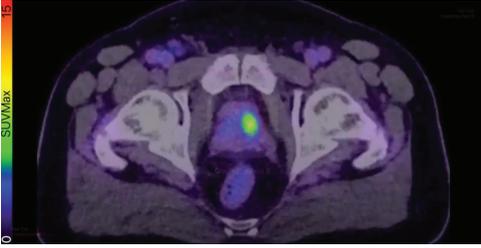
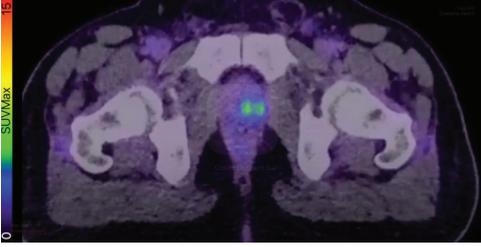
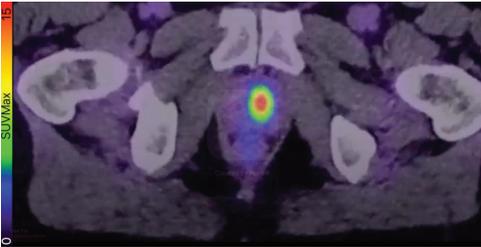
to the PSMA on the surface of cells, allowing for a PSMA-specific PET scan. This has revolutionised imaging within prostate cancer, as it is far more sensitive and specific for detecting metastatic disease than conventional computed tomography (CT) and bone scan's.^{23,24} Recently, emerging evidence has also shown that PSMA PET can have a role in the diagnosis and risk stratification of prostate cancer. The maximum standardised uptake value (SUV_{max}) of an intraprostatic lesion on PSMA PET is closely correlated with both the presence of prostate cancer and its grade group.²⁵ The PRIMARY trial developed a 5-point scoring system for intra-prostatic lesions that are avid on PSMA PET.²² The PRIMARY scoring system assigns a score from 1–5 for the primary intraprostatic lesion, based on the pattern of uptake, its SUV_{max} (Table 1). This score correlates strongly with the likelihood of clinically significant prostate cancer being present.^{22,26,27} The PRIMARY trial demonstrated that combining a PSMA PET with a multiparametric magnetic resonance imaging (mpMRI) prior to prostate biopsy can increase sensitivity and negative predictive value in diagnosing clinically significant prostate cancer.²⁶ The PRIMARY score itself has also proven to be a good tool at detecting clinically significant prostate cancer, with a PSMA PET scan showing equivalent diagnostic accuracy at detecting clinically significant prostate cancer when compared to mpMRI.²² This demonstrates that the utility of PSMA as a target for molecular-based imaging is relevant not only in metastatic disease but

TABLE 1. The 5-point PRIMARY score. Adapted from Emmett et al. with original scans²²

PRIMARY score	PET/CT
Score 1. No Pattern Low Grade Activity Only	
Score 2 Diffuse TZ (Pattern A) It spares the prostate peripheral margin on fused PET/CT. This pattern can have moderate variation in TZ intensity.	

(Continued)

TABLE 1. (Continued)

PRIMARY score	PET/CT
Score 2 CZ activity (Pattern B) Frequently symmetrical. This pattern is classified as a PRIMARY score of 4 if it extends to the prostate peripheral margins on fused PET/CT	
Score 3 Focal TZ (Pattern C) Focal activity well above the background TZ activity (visually at least twice background TZ)	
Score 4 Focal PZ (Pattern D) Any focal activity involving the peripheral prostate margin on fused PET/CT or apically (no minimum intensity)	
Score 5 Intense uptake $SUV_{max} > 12$	

Note. PET, positron emission tomography; CT, computed tomography; TZ, transition zone; CZ, central zone; PZ, peripheral zone; SUV_{max} , the maximum standardised uptake value.

also earlier in the disease course in detecting early prostate cancer.

The diagnostic utility of PSMA PET in detecting early prostate cancer is also confirmed in studies assessing the utility of PSMA PET to guide transperineal prostate biopsies. A systematic review assessed 10 different studies, and in a meta-analysis of 6 studies, found that for clinically statistically significant prostate cancer, a PSMA PET-guided prostate biopsy had a sensitivity of 0.89 and a specificity of 0.65.²⁸ This high level of diagnostic accuracy demonstrates the strong correlation between molecular imaging and pathological diagnosis of prostate

cancer. Although the authors were unable to identify any studies directly comparing MRI-guided to PSMA-guided prostate biopsies, this is a promising approach. With the high accuracy of the PRIMARY score,²² and promising results of PSMA PET guided biopsies, PSMA PET may become a viable alternative in first-line imaging for men with suspected prostate cancer, or be incorporated in pre-biopsy diagnostic algorithms. Although the evidence base remains immature, this demonstrates the promising role PSMA PET has as a tool to guide prostate biopsies and accurately detect clinically significant prostate cancer.

Another recent comprehensive systematic review and meta-analysis was able to identify 12 studies involving 1533 patients that assessed the utility of PSMA PET in detecting prostate cancer²³ The review that PSMA PET had a sensitivity of 82%, specificity of 67%, positive predictive value (PPV) of 77% and negative predictive value (NPV) of 73% for detecting clinically significant (International Society of Urological Pathology [ISUP] 2 or above) prostate cancer. They also found that when combined with mpMRI, the sensitivity increased to 91%, with a comparable specificity of 68%. This reflects the utility that PSMA has as a biomarker for early prostate cancer and suggests that it may have a complementary effect in identifying primary prostate cancers when combined with mpMRI. This suggests that there may be a role in using PSMA to help select patients for prostate biopsy, allowing for the reduction of the number of biopsies and reducing the number of insignificant prostate cancers detected at biopsy.

These results are highly promising and suggest PSMA PET has the potential to become a useful adjunct, or even an alternative to mpMRI in selecting patients to undergo transperineal prostate biopsy. MRI is a time-consuming scan that has a number of contraindications and safety concerns. Gadolinium-based MRI contrast agents are not suitable for men who have significantly impaired renal function²⁹ whilst a hepatically excreted PSMA PET tracer ¹⁸F PSMA-1007 is available,³⁰ and can provide similar diagnostic performance in both local lesions and distant disease—although it has higher rates of benign bone uptakes.³¹ Patients with implantable devices such as cardiac pacemakers or cochlear implants require additional screening and safety assessment of the device prior to undergoing MRI, and some older devices may be MRI-incompatible.²⁹ Image acquisition may be impaired by prosthetic hip joints, leading to decreased cancer detection rate.³² Many men find MRI scanners to be claustrophobic, making them intolerable to a certain percentage of the population. The emergence of PSMA PET may provide an alternative for selecting men for prostate biopsy in these groups of men who would otherwise face significant barriers to or be unable to undergo an mpMRI for the detection of prostate cancer, although further evidence is required to establish it in this role.

Given that many men may have contraindications to mpMRI, PSMA PET may also have a role in the management of low-risk prostate cancer for men placed on active surveillance. There is a growing use of interval mpMRI throughout the course of active surveillance,³³ meaning that men may potentially be subjected to multiple scans throughout the course of

their lifetime. PSMA PET may therefore be of even more importance in this cohort of men, however, a recent review found that data to support its routine use in active surveillance is lacking.³⁴ There are currently two prospective trials currently enrolling patients that will provide further data regarding the potential use of PSMA PET in active surveillance,^{35–37} and early studies have suggested that PSMA PET may be useful in active surveillance by detecting occult clinically significant prostate cancer,³⁸ and as a tool to decrease the need for repeat confirmatory biopsy.³⁹

PSMA as a Prognostic Indicator in Prostate Cancer

Lymph node involvement is perhaps one of the most important prognostic factors in prostate cancer, as it demonstrates advanced disease. It is associated with worse rates of biochemical recurrence-free survival and overall survival.⁴⁰ Traditionally, detection of lymph nodes was done via extended pelvic lymph node dissection (ePLND), as conventional imaging modalities such as CT have a low sensitivity for the detection of lymph node metastasis. However, ePLND is a comorbid procedure and is associated with high rates of lymphocele, infection, and venous thromboembolism.⁴¹ Given that systematic reviews have failed to demonstrate an oncological benefit from ePLND, it remains a highly morbid way of providing prognostic information for men with prostate cancer.⁴² To select patients for lymph node dissection, clinicians have traditionally relied on various nomograms that risk-stratify patients based on clinicopathological features.⁴³ This allows for the selection of only high-risk patients for ePLND, reducing its use in men with low risk of lymph node metastasis, where it is likely to be of little diagnostic or prognostic value. However, in the era of highly specific PSMA-PET scans, there has been a significant debate regarding the ongoing utility of ePLND and whether it can be supplanted by medical imaging with or without the use of a nomogram.

PSMA-PET has shown significant potential in improving these nomograms. Traditional nomograms such as Briganti 2019⁴⁴ and Memorial Sloan Kettering Cancer Center (MSKCC)⁴⁵ combine various clinico-pathological features to predict the rate of lymph node involvement. These features include age, PSA, type of biopsy (MRI-Targeted *vs.* systemic), Gleason score, and clinical T stage.^{44,45} However, given the high specificity for detecting lymph node invasion, there has been considerable research into potentially incorporating PSMA-PET findings

into pre-operative nomograms. Meijer et al.⁴⁶ first reported that incorporation of PSMA-PET findings into a nomogram significantly improved the predictive ability of the MSKCC, Briganti 2017 and Briganti 2019 nomograms. Muehlemitter et al.⁴⁷ subsequently developed their own nomogram, which incorporated volumetric factors of PSMA-avid lesions and the presence of miN1 disease into their model.⁴⁷ Their PSMA-based model showed similar calibration, with a superior AUC, suggesting that with a risk cut-off of 17%, 50% of lymph node dissections could be spared, whilst only missing 4.8% of patients with lymph node invasion.⁴⁷ Both of these models were recently externally validated and compared to the MSKCC and Briganti 2012 models by van Bergen et al.⁴⁸ This study confirmed the finding that the models developed using PSMA-PET parameters outperformed traditional nomograms based on clinicopathological features alone.⁴⁸ Although a key shortcoming of these models is that they systematically underperform in assessing patients without evidence of lymph node invasion on PSMA PET (miN0 disease). Subsequently, the Briganti 2023 model has been developed,⁴⁸ and externally validated in this patient group without using parameters from PSMA PET. This demonstrates the importance of patient selection when using nomograms in risk assessment, as they will only be applicable to similar populations in which they were developed. These nomograms, developed by Meijer et al.⁴⁶ and Muehlemitter et al., likely overestimated the prevalence of positive lymph nodes, as they included miN1 (patients with detectable nodes on PSMA-PET) in the population they developed their nomogram. Multiple attempts at external validation of shown that this leads to a decreased accuracy and reduced AUC when examining populations that are miN0.^{48,49} This limits the applicability of these models in this sub-group of patients, who are the most important to risk-stratify, as PSMA-PET's high specificity all but confirms the presence of nodal disease in miN1 patients. Ultimately, whether PSMA-PET is a useful parameter to be incorporated into pre-operative nomograms to help identify patients for ePLND is an area of ongoing research, but remains uncertain given recent results suggesting the Briganti 2023 nomogram outperforms nomograms incorporating PSMA parameters when assessing miN0 patients.⁴⁹

PSMA PET has ushered in a new era of staging lymph nodes for prostate cancer. A meta-analysis pooled specificity for detecting lymph node invasion of 95%, with a sensitivity of 54%.⁵⁰ This allows for accurate, non-invasive assessment of lymph nodes prior to definitive treatment, giving the clinician and patient valuable prognostic information which can

be used to guide treatment choices. However, the relatively low sensitivity of PSMA PET at detecting lymph nodes limits its ability to entirely replace traditional methods of staging lymph nodes, as it will miss a significant proportion of patients with positive lymph nodes. PSMA PET may also fail to involve lymph nodes in ductal prostate cancers, which can express variable PSMA uptake.^{51,52} Although data suggest that a high percentage of men can safely be excluded from ePLND based on PSMA PET findings,⁵³ whether it is possible to fully omit patients from lymph node dissection based on PET alone remains a controversial topic. A systematic review and meta-analysis of the data suggested that high-risk patients could not be safely excluded from ePLND due to the lower negative predictive value within this cohort of 83%.⁵⁰ This suggests that within high-risk cohorts, 17% of men with lymph node metastasis may be missed based on PSMA PET alone, although there may be some value within the intermediate-risk group, which had a higher negative predictive value.⁵⁰ Whether it is safe to exclude patients from ePLND based on PSMA-PET alone remains an ongoing area of research, with an ongoing randomised control trial in the Netherlands investigating this topic. The PSMA-SELECT trial will randomise patients to either receive routine ePLND or ePLND guided by PSMA findings, with a primary endpoint of biochemical recurrence at 2 years. The results of this trial are eagerly awaited and should help clarify the oncological safety of omitting nodal dissection based on PSMA findings. Ultimately, PSMA-PET represents a fundamentally new way to stage for lymph-node invasion. Given the significant morbidity of staging via ePLND, and that a systematic review failed to demonstrate a strong oncological benefit from the nodal dissection,⁴² PSMA PET represents a new paradigm in lymph node assessment due to its non-invasive nature.

The prognostic value of PSMA PET is not limited to its assessment of lymph node invasion. In early prostate cancer, PSMA PET is also proving to be useful in risk-stratifying men with newly diagnosed prostate cancer based on radiomic features of the primary tumour.⁵⁴ This is particularly evident when examining the relationship of PSMA PET SUV_{max} with the Gleason score of the cancer. Studies have consistently demonstrated that a higher SUV_{max} is correlated with a higher percentage of pattern 4 disease at the time of final prostatectomy.^{55,56} This pattern was found across multiple studies, in a systematic review of 14 studies involving 1975 patients, which demonstrated that the pooled mean SUV_{max} increased with ISUP grade group.²⁵ A higher SUV_{max} was also

associated with a higher pathological T stage group, and may be associated increased risk of biochemical recurrence post-surgery. This is an unsurprising finding, as it is well-established that patients with a higher percentage of pattern 4 and increasing grade group demonstrate an increased risk of biochemical recurrence post-surgery.⁵⁷⁻⁵⁹ This demonstrates that PSMA PET may be able to play an important role in risk-stratification and prognostication prior to definitive management, as it can non-invasively provide characterise the risk of the primary cancer.

More interestingly, patients with T3/T4 disease were found to have a higher SUV_{max} than those with organ-confined disease, although this finding was limited by heterogeneity between studies and evidence of small study effects. This finding is in keeping with a different review by Mazzone et al., which found a pooled sensitivity 71% and specificity of 84% for extracapsular detection (pT3a disease), and a pooled sensitivity 71% and specificity of 93% for detecting seminal vesicle invasion (T3b disease).²³ Chen et al. also found that a higher SUV_{max} was predictive of a shorter time to biochemical recurrence across all cohorts.²⁵ This provides compelling evidence that PSMA can be used as a marker of worse grades and advanced stage of localised disease. Given that higher grade groups, extra-prostatic disease, and short time to biochemical recurrence are all predictors of worse outcomes,⁶⁰ this implies that PSMA PET assessment of the primary tumour can provide some prognostic information regarding the risk of the underlying disease. Although the data is promising, it remains to be seen whether PSMA PET will become routinely incorporated into risk assessment and prognostication of localised prostate cancers.

PSMA is also a potentially useful tool for risk-stratifying prostate cancer on immunohistochemistry. Multiple studies have demonstrated that PSMA is a useful stain in detecting and diagnosing prostate cancer on both biopsy and radical prostatectomy specimens. PSMA expression is higher in cancerous glands than in benign glands, and increases with cancer's Gleason score, and is correlated with a higher PSA.⁶¹ This suggests that PSMA immunostaining may have potential utility in providing prognostic information regarding cancer aggressiveness. This is also implied by numerous studies, which have demonstrated a significant correlation between PSMA immunostaining and SUV_{max} on PSMA PET.⁶²⁻⁶⁵ This finding has also been confirmed in a recent prospective study, which identified that PSMA staining as measured by the immunoreactive score of both prostate biopsies and radical prostatectomy specimens was predictive of SUV_{max} on a

linear regression model.⁶³ Whilst logically unsurprising, research has demonstrated that low levels of PSMA staining on the primary tumour at the time of radical prostatectomy are a significant predictor of having a negative PSMA scan—when assessing for biochemical recurrent disease.⁶⁴ Given the association between SUV_{max} and PSMA immunostaining, biopsy results may be useful in selecting patients for which patients may have positive findings on PSMA-PET.⁶⁶ Droghetti et al. found that not only is the amount of PSMA expression correlated with SUV_{max} and PSMA-PET findings, but that the pattern of PSMA expression is relevant as well.⁶⁶ They found that a membranous pattern of PSMA expression was associated with a higher SUV_{max} and total lesion activity than a cytosolic expression pattern. This is likely due to membranous PSMA being more available to bind to the radiotracer.

It is a logical progression to assume that if PSMA immunostaining is associated with SUV_{max} , and SUV_{max} is associated with aggressiveness of a tumour, and markers for adverse pathological outcomes, then PSMA staining may directly correlate with disease aggressiveness. This was actually the finding of one study by Hupe et al.,⁶⁷ which examined the use of PSMA staining in risk-stratification. The authors found that PSMA expression on biopsy was correlated with established prognostic biomarkers, including lymph node metastasis, locally recurrent tumours, and distant disease.⁶⁷ Most importantly, they found that higher levels of PSMA expression on both prostate biopsy and final radical prostatectomy specimen predicted biochemical recurrence post-surgery. This is an important finding, which needs to be investigated further, as it suggests that immunohistostaining performed at the time of initial biopsy can provide important prognostic information regarding the tumour. If confirmed in more studies, then PSMA staining could potentially become a routine part of tumour risk assessment, and could be incorporated into clinical decision-making tools, such as pre-operative nomograms to help select patients for ePLND. However, further evidence is needed prior to PSMA IHC becoming routinely implemented into clinical practice.

Overall, PSMA is a highly promising biomarker for risk-stratifying prostate cancer. PSMA staining may be associated with higher-risk disease, and is associated with SUV_{max} on PSMA PET scan. SUV_{max} is an important radiomic marker on PSMA PET, which has been associated with worsened disease grade group. Whether measurements from a PSMA PET, such as the SUV_{max} , can be incorporated into pre-operative nomograms to improve performance is an

ongoing area of research, as it may help select patients for ePLND.

PSMA as a Therapeutic Target for Early Prostate Cancer

PSMA has also garnered significant interest as a potential molecular target for drugs to treat prostate cancer. There are two main approaches to PSMA-targeted drug therapy been developed: Antibody-drug conjugates (ADCs), and radioligand therapy. Antibody drug conjugates bind a cytotoxic agent to a monoclonal antibody specific for a cellular antibody, such as PSMA. The cytotoxic agent is then internalised by endocytosis at the target cell, allowing for targeted delivery of the cytotoxic agent to specific cells expressing that receptor.⁶⁸ This approach has proven successful in other cancers, with multiple FDA-approved Antibody-drug conjugates for leukaemia, lymphoma, breast, cervical, and urothelial cancer.⁶⁹ To date, clinical trials of antibody-drug conjugates targeting PSMA in prostate cancer have undergone early clinical trials.⁶⁸ however, these have been limited to phase I/II trials in advanced metastatic prostate cancer. Results from these trials have also been far from promising and have been limited by significant treatment-related side effects. We were able to identify three separate ADCs that have been trialled in humans. Monomethylauristatin E (MMAE) has undergone both phase I and II trials with results published.^{70,71} In the phase II trial, 119 patients with metastatic castrate resistant prostate cancer (mCRPC) were recruited, with a plan to complete 8 cycles of treatment. Unfortunately, 62% withdrew before the 5th cycle due to adverse effects, with 51% suffering severe adverse events. There was a rather limited response as well, with a >50% decline in PSA only observed in 14% of patients, which is a relatively modest response. Similarly, the ADC MLN2704 was highly limited by its treatment-related toxicity in a phase I/II trial for men with mCRPC.⁷² 71% of patients experienced peripheral neuropathy whilst on treatment, and only a limited effect was identified, with only 8% of patients having a PSA decrease greater than 50%.⁷² One other ADC has been studied in a phase I trial for men with mCRPC. MEDI 3726 was studied in 33 men with mCRPC, however, the trial was limited by poor tolerability.⁷³ 90% of the patients had treatment-related adverse events, with 45% of these being grade 3 or 4. As such, no maximum tolerated dose (MTD) was able to be identified.⁷³ Overall, so far, human trials involving ADCs have been limited to men with mCRPC and

have all demonstrated significant toxicities, with very limited response demonstrated. No phase III trial has been published. This suggests that ADCs may have a limited effect in prostate cancer and significant side effects. Whilst it is certainly possible for safer and more efficacious ADCs to be developed for prostate cancer, more research is needed. All studies so far have been conducted in men with mCRPC, so any potential use for ADCs treating early prostate cancer is purely speculative.

In contrast, the clinical utility of radioligand therapy for prostate cancer has progressed beyond the clinical trial stage and is now approved for select men with metastatic prostate cancer. Radioligand therapy conjugates a radioactive isotope to a monoclonal antibody for a certain antigen. This then delivers the isotope to the targeted cells, where it undergoes decay and delivers a dose of radiation to the cells and the surrounding microenvironment, inducing a cytotoxic effect.⁷⁴ The most promising agent is Lutetium-177-PSMA-617 (Lu-177), which demonstrated a survival benefit in metastatic castrate-resistant prostate cancer in patients previously treated with androgen deprivation, ARPI, and chemotherapy.⁷⁵ As a result of the ground-breaking vision trial, Lu-177 got approval for use in humans and has increasingly been used and investigated in earlier stages of the disease process in treatment algorithms. A phase II trial suggested that Lu-177 was superior to the second-line chemotherapy agent Cabazitaxel.⁷⁶ More recently, trials have assessed Lu-177 for efficacy at earlier stages of the disease process and have shown improved progression-free survival in patients naïve to taxane-based chemotherapy.^{77,78} A phase II trial also demonstrated a benefit when commenced at the same time as ARPI therapy.⁷⁹ All these trials contribute to a growing body of evidence that Lu-177 is effective in earlier stages of mCRPC, and that earlier initiation of Lu-177 treatment may offer some survival benefit over the standard-of-care approach to introduction of ARPI, then taxane-based chemotherapy.

Alternative conjugates for delivering Lu-177 for radioligand therapy have also been investigated. Lu-PNT2002, also known as Lu-PSMA-I&T, is the second most widely used lutetium-based radiopharmaceutical in prostate cancer.⁸⁰ It is currently being evaluated in the setting of castrate resistant prostate cancer that has progressed after a single ARPI.⁸¹ The phase I results demonstrated a favourable dosimetry and safety profile, with early promising results, although the final outcomes of the trial are still pending.⁸¹ Other Lutetium-based radiopharmaceuticals which have been investigated for use in prostate cancer include [¹⁷⁷Lu]-LNC1011,⁸² ¹⁷⁷Lu-rhPSMA-10.1,⁸³

TABLE 2. Lu-177-based radiopharmaceuticals that have been investigated for prostate cancer

Radiopharmaceutical	Phase	Disease stage	Drug status
Lu-PNT2002 (Lu-PSMA-I&T) ⁸¹	III	mCRPC	Phase I arm showed a favourable safety profile; phase II/III trial ongoing.
¹⁷⁷ Lu-LNC1011 ⁸²	I	mCRPC	Stage I trial demonstrated good initial safety and efficacy
¹⁷⁷ Lu-rhPSMA-10.1 ⁸³	I	mCRPC	Stage I trial demonstrated good initial safety and efficacy
¹⁷⁷ Lu Ludotadipep ⁸⁴	I	mCRPC	Stage I trial demonstrated good initial safety and efficacy
¹⁷⁷ Lu-labeled J591 ⁸⁵	I	Metastatic or recurrent prostate cancer	Stage I trial demonstrated good initial safety and efficacy
PSMA-Targetted CT1403 ⁸⁵	Pre-clinical	Mouse model	Demonstrated preclinical efficacy and dosimetry

Note. mCRPC, metastatic castration-resistant prostate cancer.

TABLE 3. Key clinical trials demonstrating efficacy of Lu-177 at different stages of prostate cancer treatment, organised from the latest in disease treatment algorithm (VISION), to the earliest use in the treatment algorithm (LuTectomy)

Trial	Year	Phase	Disease stage	Key results
VISION ⁷⁵	2021	III	mCRPC, treated with both an ARPI and taxane-based chemotherapy.	Compared to standard of care, Lu-177 improved progression-free survival (median 8.7 vs. 3.4 months) and overall survival (15.3 vs. 11.3 months)
TheraP ⁷⁶	2021	II	mCRPC treated with docetaxel, for whom cabazitaxel was considered the next appropriate treatment	Lu-177 was superior to Cabitaxel, with increased rates of PSA response (66% vs. 37%) and decreased rates of grade 3/4 adverse events (33% vs. 53%)
UpFrontPSMA ⁷⁷	2024	II	De-novo high-volume mHSPC patients who hadn't received docetaxel	Treatment with Lu-177 prior to initiation of docetaxel in patients with mHSPC increased anti-tumour activity, without increasing toxicity.
PSMAFore ⁷⁸	2024	III	mCRPC patients treated who had progressed on a single ARPI, but had not commenced taxane-based chemotherapy yet	Compared to the change of ARPI, treatment with Lu-177 increased radiographic progression-free survival (11.6 vs. 5.59 months), with a lower incidence of grade 3–5 adverse events.
ENZA-p ⁷⁹	2024	II	mCRPC not previously treated with docetaxel or ARPI	Patients treated with Enzalutamide plus Lu-177 had an increased PSA progression-free survival (13 vs. 7.8 months) and enhanced anti-cancer activity.
LuTectomy ⁸⁸	2024	I/II	Adjuvant treatment, prior to radical surgery	Adjuvant Lu-177 treatment is safe and feasible and is able to deliver targeted radiation to the prostate cancer.

Note. mCRPC, metastatic castration-resistant prostate cancer.

¹⁷⁷Lu-Ludotadipep,⁸⁴ ¹⁷⁷Lu-labeled J591 monoclonal antibodies,⁸⁵ and PSMA-Targetted CT1403⁸⁶ (Table 2). However, so far, all of these have only been studied in the pre-clinical, or stage I/II setting, and are not yet approved for human use. All these therapies were investigated for metastatic disease and are not applicable to early prostate cancer.

Yet at this stage, radioligand therapy for prostate cancer remains limited to patients with advanced disease. PSMA is heavily expressed in earlier stages of prostate cancer, as such, there is significant interest in its potential clinical utility earlier in the disease course. There is currently an ongoing phase III clinical trial trying to assess for a benefit in the metastatic hormone-sensitive setting.⁸⁷ If successful, this would represent a major breakthrough as the use of Lu-177 would be pushed back prior to the development of castrate-resistant disease. However, the use of Lu-177 has also been investigated even earlier in the disease process. Recently, the LuTect omy trial demonstrated the safety and feasibility of using Lu-177 as neoadjuvant therapy prior to radical prostatectomy in men with high-risk prostate cancer.⁸⁸ Although the phase I/II trial was not designed or powered to detect any benefit to survival or recurrence rate, it has proven the feasibility of radioligand therapy in earlier disease stages, prior to radical surgery. Whether Lu-177 may have a role in the treatment of early prostate cancer is a promising topic for further research, however, more evidence is needed before it can be considered to have a role in the treatment of localised prostate cancer. Key clinical trials are progressively investigating the use of Lu-177 at the earlier stages of prostate cancer treatment, demonstrating that there is intense research interest in this topic (Table 3).

Conclusion

In summary, our review highlights the role PSMA plays as a biomarker in the diagnosis, risk-stratification, and prognostication of early and localized advanced prostate cancer. PSMA PET scans allow for far more accurate staging of high-risk disease, and can aid in selecting patients for lymph node dissection. PSMA PET also offers comparable accuracy to mpMRI in detecting clinically significant prostate cancer and targeting transperineal biopsies. PSMA is also an important stain for pathologists and may offer insights into underlying disease aggressiveness. PSMA also represents an emerging therapeutic target, with PSMA-targeted radioligand therapy demonstrating benefit in metastatic disease. Subsequently, clinical trials have progressively

assessed the use of Lu-177 in earlier disease stages, including in the adjuvant setting. Overall, PSMA is a useful biomarker in early and localized advanced prostate cancer with a role in disease detection and risk stratification, and potentially as a target for therapeutics.

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Conception and design: Marlon Perera and Jonathon Carll. Data collection: Jonathon Carll and Jacinta Bonaddio. Analysis and interpretation of results: Jonathon Carll, Nathan Lawrentschuk, Marlon Perera. Draft manuscript preparation: Jonathon Carll, Thilakavathi Chengodu, Dixon Woon. Final manuscript review and revision: Jonathon Carll, Jacinta Bonaddio, Marlon Perera, Nathan Lawrentschuk, Thilakavathi Chengodu, Dixon Woon. All authors reviewed the results and approved the final version of this manuscript.

Availability of Data and Materials

This is a review article with no original data collected or stored. All data analyzed in this review article are derived from publicly available sources, primarily peer-reviewed journal articles. All sources cited in this review are accessible through standard academic databases and repositories.

Ethics Approval

Not applicable.

Conflicts of Interest

Jonathon Carll—No conflicts exist. Jacinta Bonaddio—No conflicts exist. Marlon Perera—No conflicts exist. Nathan Lawrentschuk declares the following conflicts: Proctor for both Robotic

Surgery (Device Technologies Australia) and Focal Therapy with Nanoknife (Getz Healthcare Australia). Thilakavathi Chengodu—No conflicts exist. Dixon Woon—No conflicts exist.

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