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# PROSTATE-SPECIFIC MEMBRANE ANTIGEN (PSMA)-TARGETED THERAPIES IN THE TREATMENT OF PROSTATE CANCER: ADVANCES, EFFICACY, AND FUTURE DIRECTIONS

**Mr. Akash Waghe[1], Mr. Aditya Rautmare[1], Ms. Siddhi Ramgude[1], Ms. Saloni Jaiaswal[1], Dr. Dipak Pawar [2], Dr. Devesh Chavan[2], Mr. Prasad Chavan[2], Dr. Swaraj Tawale[3*]**

[1.] Department of Pharmacy Practice, K. T. Patil College of pharmacy, Dharashiv
[2.] Department of Pharmacology, Aditya College of Pharmacy, Beed
[3.] Department of Pharmacology, K. T. Patil College of pharmacy, Dharashiv
*Corresponding Author: Dr. Swaraj tawale, Email: swarajtawale15@gmail.com

## ABSTRACT

One of the most common cancers to be identified in men globally, prostate cancer continues to be a significant source of cancer-related morbidity and mortality, especially in advanced stages [1,2]. Due to its significant increase in prostate cancer cells, particularly in high-grade, metastatic, and castration-resistant illness, while exhibiting little expression in normal tissues, prostate-specific membrane antigen (PSMA) has become a very intriguing molecular target [5,6]. Positron emission tomography (PET) imaging based on PSMA has greatly enhanced disease detection, staging precision, and patient selection for targeted therapy [8–11].

PSMA-targeted radioligand therapies, especially lutetium-177-labeled PSMA-617, have shown significant improvements in progression-free and overall survival in patients with metastatic castration-resistant prostate cancer, building on these diagnostic advancements. This has led to regulatory approvals and integration into clinical practice [12–15]. The therapeutic landscape is further expanded by alpha-emitting radioligands like actinium-225–PSMA and newly developed PSMA-directed immunotherapeutic strategies such antibody–drug conjugates, bispecific T-cell engagers, and chimeric antigen receptor T-cell treatments [16–21]. Despite promising results, toxicity-related issues, tumor heterogeneity, resistance mechanisms, and appropriate patient selection persist [18,22]. This review offers a thorough summary of the biological justification for PSMA targeting, the available clinical data in favor of PSMA-based imaging and therapeutic approaches, related drawbacks, and potential future directions for improving customized and multimodal prostate cancer treatment approaches.

## INTRODUCTION

One of the most prevalent malignancies in males, prostate cancer poses a serious threat to world health [1,2]. Advanced and metastatic prostate cancer continues to be a major cause of cancer-related death, despite the fact that localized illness is frequently linked to good long-term results [2, 3]. The increased prevalence in elderly populations and improved detection technologies further contribute to the growing clinical burden [1].

Prostate cancer has a wide range of clinical behaviors, from aggressive disease with early metastases and treatment resistance to indolent tumors appropriate for active surveillance [3,4]. Serum prostate-specific antigen testing, digital rectal examination, and systematic biopsy are examples of traditional diagnostic techniques that have improved early detection but are constrained by overdiagnosis and overtreatment, which have a detrimental effect on quality of life [4]. Furthermore, especially in recurrent and advanced settings, prostate-specific antigen kinetics alone are inadequate to appropriately reflect tumor load or disease progression [3,4].

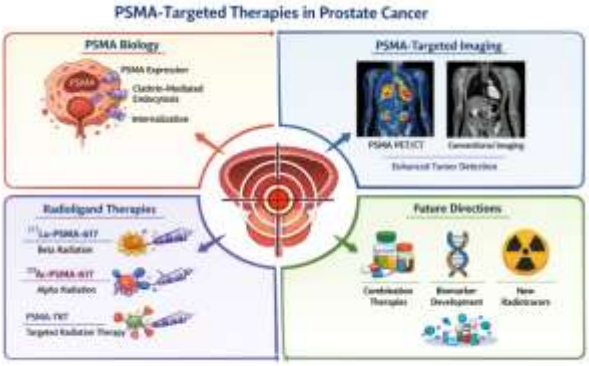
Androgen restriction therapy remains the cornerstone of treatment for advanced prostate cancer; nonetheless, most patients eventually progress to castration-resistant prostate cancer (CRPC) [3,4]. Durable responses in metastatic CRPC are still rare, despite the availability of next-generation androgen receptor-targeted drugs, chemotherapy, and bone-directed therapies [12,31–33]. This highlights the need for innovative diagnostic and treatment methods.

Prostate-specific membrane antigen is a type II transmembrane glycoprotein expressed by the FOLH1 gene and demonstrates glutamate carboxypeptidase activity [5,7]. Prostate cancer cells have a significant overexpression of PSMA, with elevated expression seen in high-grade tumors, metastatic lesions, and castration-resistant illness [6,7]. Crucially, PSMA experiences ligand-mediated internalization, which promotes intracellular transport and retention of therapeutic and diagnostic substances, improving therapeutic efficacy and imaging contrast [7]. Because of these characteristics, PSMA is a perfect target for targeted treatment and molecular imaging. Because PSMA-targeted PET

imaging allows for extremely sensitive detection of primary tumors, lymph node involvement, and distant metastases, even at low levels of prostate-specific antigen, it has revolutionized the staging and restaging of prostate cancer [8–11]. Furthermore, by directing treatment selection and identifying biochemical recurrence earlier than traditional imaging modalities, PSMA PET imaging has shown a substantial influence on clinical decision-making [8,9,34). PSMA-targeted radioligand treatments, which selectively administer lethal radiation to tumor cells while sparing surrounding healthy tissues, have become a viable therapy option based on advancements in imaging [12–15]. PSMA-directed immunotherapeutic approaches are being explored concurrently to improve antitumor effectiveness and overcome resistance mechanisms [19–23].

The purpose of this review is to provide an overview of the biological underpinnings of PSMA targeting, current clinical evidence that supports PSMA-based imaging and therapeutic approaches, related safety concerns and limitations, and future directions in prostate cancer management that center on combination strategies and customized treatment paradigms.

**Fig No 1** PSMA – Targeted Therepies in Prostate Cancer (24)




**Methodology of Review**

The databases PubMed, Scopus, and Google Scholar were thoroughly searched for this narrative review. Peer-reviewed literature published in English up to 2024 were identified using keywords including “prostate cancer,” “prostate-specific membrane antigen,” “PSMA PET,” “radioligand therapy,” “lutetium-177 PSMA,” and “PSMA immunotherapy.” Clinical trials, systematic reviews, meta-analyses, and original research articles were all included; conference abstracts, case reports, and non-peer-reviewed sources were not. A manual screening of the reference lists of the chosen publications was done to find more pertinent research.

**Biology of Prostate-Specific Membrane Antigen**

PSMA is extensively expressed on the surface of prostate cancer cells and displays low expression in most normal tissues, contributing to a favorabletumor-to-background ratio for imaging and therapy [5,6]. Its capacity to internalize upon ligand binding greatly increases PSMA-targeted drugs' intracellular accumulation, enhancing therapeutic efficacy and diagnostic sensitivity [7]. Tumor aggressiveness, metastatic potential, and resistance to androgen deprivation therapy are all correlated with elevated PSMA expression [6, 7].

**Table 1. Expression and Biological Characteristics of PSMA (25)**

| Feature | Description |
|---|---|
| Gene name | FOLH1 |
| Protein type | Type II transmembrane glycoprotein |
| Normal tissue expression | Low (salivary glands, kidneys, small intestine) |
| Expression in prostate cancer | High, especially in high-grade and metastatic disease |
| Expression in mCRPC | Very high |
| Internalization | Rapid ligand-mediated internalization |
| Clinical relevance | Ideal target for imaging and targeted therapy |

**PSMA-Based Imaging in Prostate Cancer**

to traditional imaging modalities, PSMA PET imaging utilising radiotracers like gallium-68–PSMA-11 and fluorine-18–labeled PSMA compounds has shown greater sensitivity and specificity [8,11]. PSMA PET imaging has been demonstrated in clinical studies to increase staging accuracy, modify therapeutic choices, and facilitate early diagnosis

of recurrent illness at low levels of prostate-specific antigen [8,9,25,35]. According to worldwide standards, PSMA PET imaging should be included into clinical practice [3,10].

**PSMA-Targeted Radioligand Therapy**

**Lutetium-177 PSMA-617**

A beta-emitting radioligand treatment called lutetium-177–PSMA-617 targets tumour cells that express PSMA with radiation. The VISION and TheraP studies indicated significant increases in progression-free survival, overall survival, and prostate-specific antigen response rates in patients with metastatic castration-resistant prostate cancer [12–14]. Its favourable effectiveness and controllable toxicity profile have been validated by subsequent real-world and long-term follow-up investigations [15].

**Table 2. Major Clinical Trials of $^{177}$Lu-PSMA-617 (26)**

| Trial name | Year | Patient population | Key outcome |
|---|---|---|---|
| VISION | 2021 | mCRPC post-ADT & chemo | Improved OS & PFS |
| TheraP | 2021 | mCRPC | Higher PSA response vs cabazitaxel |
| REAL-WORLD studies | 2022–2024 | mCRPC | Confirmed safety & efficacy |

**Actinium-225 PSMA**

Actinium-225 PSMA Actinium-225-labeled PSMA molecules are a new type of alpha-particle radioligand treatment that has strong cytotoxic effects and high linear energy transfer. Patients with severe illness, particularly those who are resistant to beta-emitting treatments, have shown encouraging results in early clinical trials [16,17]. Salivary gland toxicity and other negative effects, however, continue to be significant constraints that call for more optimisation [18].


**Fig No. 2 Actinium-225 PSMA (27)**

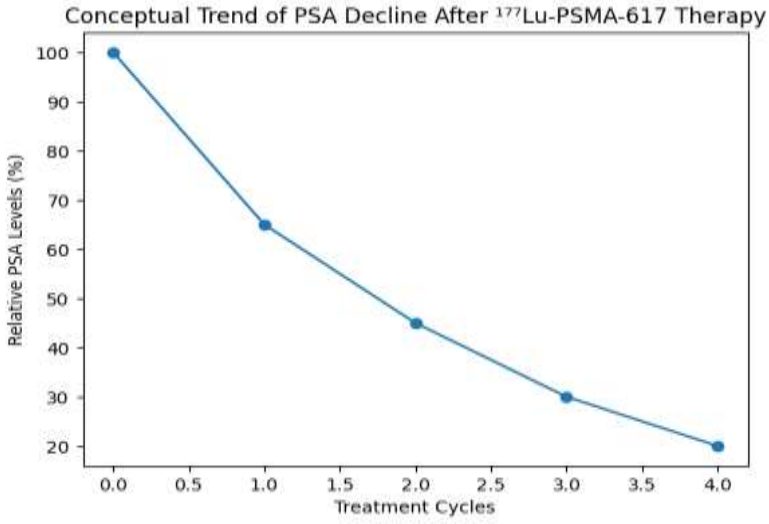



**Figure No 3 Conceptual trend of prostate-specific antigen (PSA) decline following $^{177}$Lu-PSMA-617 radioligand therapy**.

**Explanation of the Graph**

The normal trend in prostate-specific antigen (PSA) levels following treatment with $^{1}$Lu-PSMA-617 radioligand therapy is depicted graphically. Relative PSA readings gradually decrease with each treatment cycle, as the picture illustrates. This decrease is a result of targeting PSMA-expressing prostate cancer cells effectively and delivering beta radiation locally, which damages tumour cells and lessens the burden of the illness.(35)

Early therapeutic response is indicated by the PSA's initial fall during the first treatment cycle, but persistent anticancer activity is shown by a decline that persists over consecutive cycles. Major clinical trials assessing PSMA-based radioligand treatment in

Patients with metastatic castration-resistant prostate cancer have consistently documented such PSA patterns. The general trend shows that $^{1}$Lu-PSMA-617 has the ability to produce significant biochemical reactions with repeated treatment, even if individual patient responses may differ.

It is crucial to remember that the graph does not depict specific patient data, but rather a conceptual overview based on published clinical results. However, in PSMA-targeted radioligand therapy, it successfully illustrates the therapeutic use of PSA as a surrogate measure for treatment response. (36,37)

**PSMA-Directed Immunotherapeutic Approaches**

Additionally, PSMA has been investigated as a target for immunotherapeutic approaches such as chimeric antigen receptor T-cell treatments, antibody–drug conjugates, and bispecific T-cell engagers [19–21]. Although immune-related toxicities, inconsistent responses, and limited durability continue to be obstacles, early-phase clinical studies have shown anticancer efficacy [21–23].

**Limitations and Safety Considerations**

PSMA-targeted treatments are linked to a number of drawbacks, including haematologic toxicity, xerostomia, renal radiation exposure, and heterogeneous PSMA expression across tumours, despite notable therapeutic advancements [18,22]. Furthermore, research on resistance mechanisms and ideal patient selection standards is still continuing [24]. Long-term safety data are still being developed, especially for immunotherapeutic techniques and more recent alpha-emitting radioligands. (38,39)

**Table 3. Common Adverse Effects of PSMA-Targeted Therapies(32)**

| Organ system | Adverse effects |
|---|---|
| Hematologic | Anemia, thrombocytopenia |
| Salivary glands | Xerostomia |
| Gastrointestinal | Nausea, vomiting |
| General | Fatigue |
| Renal | Mild nephrotoxicity (rare) |

**Future Directions**

Future studies concentrate on improving PSMA-targeted treatments by combining them with immunotherapy, chemotherapy, androgen receptor-targeted drugs, as well as DNA damage repair inhibitors [31,34]. It is anticipated that developments in radiotracer development, dosimetry, and biomarker-driven patient selection would enhance treatment results and customise the treatment of prostate cancer [10,11,37].

**Table 4. Comparison of PSMA-Targeted Therapies( 33)**

| Therapy type | Example | Radiation type | Key advantage | Main limitation |
|---|---|---|---|---|
| β-emitter RLT | $^{177}$Lu-PSMA-617 | Beta | Proven survival benefit | Myelosuppression |
| α-emitter RLT | $^{225}$Ac-PSMA | Alpha | High tumorkill | Xerostomia |
| CAR-T therapy | PSMA CAR-T | None | Immune-mediated kill | Cytokine release |
| BiTEs | PSMA-CD3 BiTE | None | T-cell activation | Immune toxicity |

**CONCLUSION**

Prostate cancer treatment has greatly improved thanks to PSMA-targeted imaging and treatment approaches, especially in advanced and castration-resistant stages. Emerging immunotherapeutic strategies and radioligand treatments like lutetium-177–PSMA-617 provide intriguing paths to better patient outcomes. Continued research focused at improving these tactics, resolving safety issues, and incorporating personalised therapy approaches is required to fully realise the therapeutic potential of PSMA-targeted medicines in prostate cancer care.

**REFERENCES**

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249.

2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):17–48.
3. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU–EANM–ESTRO–ESUR–ISUP–SIOG guidelines on prostate cancer—2023 update. Eur Urol. 2023;84(2):111–123.
4. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer. J Clin Oncol. 2016;34(12):1402–1418.
5. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3(1):81–85.
6. Perner S, Hofer MD, Kim R, Shah RB, Li H, Möller P, et al. Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. Hum Pathol. 2007;38(5):696–701.
7. Ghosh A, Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91(3):528–539.
8. 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). Lancet. 2020;395(10231):1208–1216.
9. Fendler WP, Calais J, Eiber M, Flavell RR, Mishoe A, Feng FY, et al. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer. JAMA Oncol. 2019;5(6):856–863.
10. Barwick TD, Eccles A, Cowan R, Rockall A. Imaging of prostate-specific membrane antigen (PSMA) in prostate cancer. Br J Radiol. 2024;97(1160):20230491.
11. Calais J, Czernin J. PSMA theranostics: current status and future directions. J Nucl Med. 2022;63(1):1–10.
12. 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. N Engl J Med. 2021;385(12):1091–1103.
13. Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (TheraP). Lancet Oncol. 2018;19(6):825–833.
14. Violet J, Sandhu S, Iravani A, Ferdinandus J, Thang SP, Kong G, et al. Long-term follow-up of patients treated with 177Lu-PSMA-617. J Nucl Med. 2020;61(6):857–865.
15. Rahbar K, Ahmadzadehfar H, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy. J Nucl Med. 2017;58(1):85–90.
16. Kratochwil C, Bruchertseifer F, Rathke H, Bronzel M, Giesel FL, Apostolidis C, et al. Targeted alpha therapy of metastatic prostate cancer with 225Ac-PSMA-617. Eur J Nucl Med Mol Imaging. 2016;43(7):1239–1247.
17. Sathekge M, Bruchertseifer F, Knoesen O, Reyneke F, Lawal I, Lengana T, et al. 225Ac-PSMA-617 in chemotherapy-naïve patients with advanced prostate cancer. Eur J Nucl Med Mol Imaging. 2019;46(1):129–138.
18. Feuerecker B, Knorr K, Welzel G, Reimold M, Rauscher I, Herrmann K, et al. Toxicity and efficacy of 225Ac-PSMA therapy. J Nucl Med. 2021;62(2):171–177.
19. Tagawa ST, Milowsky MI, Morris M, Vallabhajosula S, Christos P, Akhtar NH, et al. Phase I study of antibody–drug conjugate targeting PSMA. J Clin Oncol. 2013;31(4):411–418.
20. Petrylak DP, Smith DC, Appleman LJ, Fleming MT, Hussain A, Dreicer R, et al. A phase II study of PSMA-ADC in metastatic CRPC. Clin Cancer Res. 2016;22(5):106–113.
21. Hummel HD, Kufer P, Grüllich C, Seggewiss-Bernhardt R, Deschler-Buggisch A, Weisel K, et al. Pasotuxizumab, a PSMA-targeted BiTE immunotherapy. J Clin Oncol. 2021;39(4):385–395.
22. Sharma P, Pachynski RK, Narayan V, Fléchon A, Gravis G, Galsky MD, et al. Nivolumab plus ipilimumab in metastatic CRPC (CheckMate 650). J Clin Oncol. 2020;38(5):1–10.
23. Antonarakis ES, Piulats JM, Gross-Goupil M, Goh J, Ojamaa K, Hoimes CJ, et al. Pembrolizumab for treatment-refractory metastatic CRPC (KEYNOTE-199). J Clin Oncol. 2020;38(5):395–405.
24. Virgolini I, Decristoforo C, Haug A, Fanti S, Uprimny C. Current status of theranostics in prostate cancer. Eur J Nucl Med Mol Imaging. 2021;48(11):340–356. doi:10.1007/s00259-020-05125-6.
25. Ghosh A, Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91(3):528–539.
26. Emmett L, Crumbaker M, Tran B, Pham HT, Adamson J, Narayan V, et al. *Real-world outcomes of Lutetium-177 PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer: Prospective registry (REALITY study).* Eur J Nucl Med Mol Imaging. 2021;48:2812–2822.
27. Kratochwil C, Bruchertseifer F, Giesel FL, Weis M, Verburg FA, Mottaghy F, et al. 225Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer. *J Nucl Med.* 2016;57(12):1941–1944. doi:10.2967/jnumed.116.178873.
28. 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.*N Engl J Med.* 2021;385(12):1091–1103
29. Hofman MS, Emmett L, Violet J, et al. [$^{177}$Lu]Lu-PSMA-617 versus cabazitaxel in patients with mCRPC (TheraP trial): a randomised, open-label, phase 2 trial.*Lancet.* 2021;397(10276):797–804.

30. Violet J, Sandhu S, Iravani A, Ferdinandus J, Thang SP, Kong G, et al. Long-term follow-up of patients treated with $^{177}$Lu-PSMA-617 radioligand therapy. *J Nucl Med.* 2020;61(6):857–865.
31. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer. N Engl J Med. 2014;371(5):424–433.
32. Emmett L, Willowson K, Violet J, et al. Lutetium-177 PSMA radionuclide therapy for men with prostate cancer: A review of safety and efficacy. Cancer Imaging. 2019;19(1):23.
33. Hummel HD, Kufer P, Grüllich C, et al. Pasotuxizumab, a BiTE® immune therapy targeting PSMA, in metastatic castration-resistant prostate cancer. J Clin Oncol. 2021;39(5):484–493.
34. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus prednisone in metastatic CRPC. Lancet Oncol. 2012;13(10):983–992.
35. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213–223.
36. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020;382(22):2091–2102.
37. Emmett L, Tang R, Nandurkar R, Hruby G, Roach P, Watts J, et al. 3-year freedom from progression after PSMA PET-guided therapy. Lancet Oncol. 2020;21(1):129–138.
38. Rowe SP, Gorin MA, Pomper MG. Imaging of prostate-specific membrane antigen using PET. Urol Clin North Am. 2018;45(3):503–514.
39. Barwick TD, Sheikhbahaei S, Jones KM, Lindenberg L, Shih JH, Agarwal PK, et al. PSMA-based theranostics in prostate cancer: recent advances. EurUrol Focus. 2023;9(2):260–269.