REVIEW ARTICLE

clinical

Radiotheranostics in advanced prostate cancer: Current and future directions

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The discovery of small molecules that target the extracellular domain of prostate-specific membrane antigen (PSMA) has led to advancements in diagnostic imaging and the development of precision radiopharmaceutical therapies. In this review, we present the available existing data and highlight the key ongoing clinical evaluations of PSMA-based imaging in the management of primary, biochemically recurrent, and metastatic prostate cancer. We also discuss clinical studies that explore the use of PSMA-based radiopharmaceutical therapy (RPT) in metastatic prostate cancer and forthcoming trials that investigate PSMA RPT in earlier disease states. Multidisciplinary collaboration in clinical trial design and therapeutic administration is critical to the continued progress of this evolving radiotheranostics field.

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PSMA AND PROSTATE CANCER

Prostate cancer (PCa) is the second most common cancer in men worldwide, and the fifth leading cause of death from cancer [1]. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glutamate carboxypeptidase located on the prostate secretory-acinar epithelium, and is the most prostate-specific cell surface antigen yet identified [2–6]. PSMA was cloned as the target of the 7E11-C5 antibody [3], which was previously shown to bind the surface of prostate epithelial cells and the serum of prostate cancer patients [2]. PSMA has a relatively restricted normal expression, including salivary and lacrimal glands, proximal renal tubules, liver, etc. [7]. The majority of adenocarcinomas of the prostate demonstrate PSMA expression in the primary and metastatic lesions, and the level of PSMA expression is approximately 1000-fold higher than that of normal prostate tissue [8]. PSMA expression by immunohistochemistry has been correlated with de-differentiated, metastatic, or castrate-resistant disease [9, 10]. Since internalization occurs after binding of small-molecule ligands to PSMA, these molecules are ideal candidates for radioligand therapy [11].

PSMA PET IMAGING

Due to the low specificity and sensitivity of FDG positron emission tomography (PET) in prostate cancer [12], functional imaging of prostate malignancies has been explored using a variety of radiotracers targeting PSMA [13]. 7E11-C5 labeled with ^{111}In (ProstaScint®) became the first Food and Drug Administration (FDA) approved SPECT imaging tracer in prostate cancer [14]. However, because 7E11-C5 only recognizes the intracellular portion of PSMA, it mainly identifies dead cells. Liu et al. [15] isolated the first monoclonal antibody to the extracellular domain of PSMA, the binding of which led to receptor dimerization and endocytosis. This led to the development of a humanized version of the antibody, J591, which demonstrated potential for molecular imaging in castrate-resistant prostate cancer [16]. Multiple small molecule ligands that bind to the extracellular domain of PSMA have also been developed, with shorter biological half-lives and improved tumor-to-background ratio. These include ^{68}Ga-PSMA-11, ^{18}F-DCFPyL, and ^{68}Ga-PSMA-617. ^{68}Ga-PSMA-11 (Locametz®) PET and ^{18}F-DCFPyL (Pylarify®) PET gained FDA approval in 2020 and 2021, respectively. Other FDA approved PCa-specific PET tracers include carbon 11 (C-11) choline, which relies on aberrant choline metabolism in PCa, and ^{18}F-fluorocyclobutane-1-carboxylic acid fluciclovine (Axumin®), which is an analog of L-leucine that is preferentially taken up by PCa and gliomas. In a network analysis comparing the diagnostic performance of radiotracers in recurrence PCa, small molecule inhibitors (PSMA-11, PSMA-1007, DCFPyL) were superior to choline-based tracers, however, there was no evidence that any one PSMA radiotracer had improved diagnostic characteristics compared with another [17]. As such, the appropriate use criteria for PSMA PET imaging refers to all PSMA PET tracers as interchangeable [12].

In a prospective trial comparing ^{68}Ga-PSMA-11 PET to ^{18}F-fluciclovine in patients with biochemical recurrence (BCR) and prostate specific antigen (PSA) ≤ 2 ng/mL, PSMA PET had a better detection rate at all regions with the exception of the prostate bed, where the two imaging modalities were similar in performance [18]. In head-to-head comparison of ^{68}Ga-PSMA-11 PET with multiparametric magnetic resonance imaging MRI (mpMRI) in patients

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with intermediate- and high-risk disease, the overall cancer detection rate was 85% with PSMA PET vs. 83% with mpMRI [19].

Despite high detection rates, there are non-trivial rates of false negative and false positive. Up to 10% of prostate cancers do not express PSMA, including many neuroendocrine or dedifferentiated castrate-resistant prostate cancers (CRPC) [20]. False negatives also include the aforementioned PET detection limit of nodes ≤ 5 mm in size that may have microscopic burden of disease. Commonly seen false positives may be related to normal biodistribution of PSMA in the sympathetic ganglia. Brain tumors that have demonstrated PSMA uptake include meningioma, neurofibroma, and glioma [21, 22]. Pulmonary sarcoidosis and granulomatosis have also demonstrated mild uptake [23]. Ganglia are a common pitfall as they can mimic lymph nodes, however, the intensity of uptake, the shape, and the exact location along the sympathetic trunk may help distinguish them from nodal metastases [24]. PSMA uptake in benign bone lesions can be challenging due to propensity of prostate cancer to metastasize to the bone. PSMA uptake has been described in healing bone fractures [25], degenerative changes in Paget's disease [26], and fibro-osseous lesions including hemangiomas and fibrous dysplasia [27].

Several reporting criteria exist in an effort to standardize PSMA PET interpretation: PSMA-RADS criteria [28], EANM criteria [29], and PROMISE criteria [30]. These are based on the amount of radiotracer uptake, on how typically radiotracer is distributed within the site, and on the presence of an anatomic correlate. External validation of the three proposed criteria have demonstrated good inter-reader, intra-reader, and inter-criteria reproducibility, with the lung nodules being the most frequent cause of disagreement [31]. This was incorporated into molecular imaging (MI)-RADS [32], which reports a PSMA expression score based on PSMA uptake relative to blood, liver, and parotid gland, which then informs a 5-point confidence score. Standardized imaging interpretation and reporting guidelines will facilitate data comparison between studies and improve reproducibility within clinical trials.

PSMA PET IN INITIAL DIAGNOSIS AND STAGING

PRIMARY was the first prospective phase II trial that evaluated PSMA PET in the diagnosis of PCa in men with elevated PSA and/or abnormal physical exam. The addition of PSMA PET to MRI improved sensitivity (97% vs. 83%, $p < 0.001$) and negative predictive value (91% vs. 72%, $p < 0.001$) compared to MRI-guided biopsy alone [33]. The advantage of PSMA PET is most compelling in the setting of negative or equivocal MRI findings, where a positive or negative PSMA correlated with presence of absence of PCa in 90% of patients [33]. In a meta-analysis comparing imaging to histopathology at prostatectomy, the sensitivity and specificity of ^{68}Ga-PSMA-11 at initial staging were 74% and 96%, respectively [34]. Zhang et al. demonstrated feasibility of using PSMA PET to guide targeted biopsies to detect clinically significant disease, with detection rates similar to that of systematic transrectal ultrasound-guided biopsies [35].

Maximum standardized uptake value (SUV_{max}) of PSMA PET has been shown to correlate with aggressive disease. In a review of over one thousand patients staged with PSMA PET prior to prostatectomy, with a median PSA of 6 ng/mL, the SUV_{max} correlated with grade group, where a $SUV_{max} \geq 11$ improved the detection of ≥ Gleason grade group 3 (GG3) disease [36]. Higher PSMA avidity was associated with worse progression free survival (PFS) and worse BCR-free survival (BRFS) in patients with intermediate-risk disease (≤GG3) [37, 38]. On Cox regression analysis, PSMA intensity was associated with BRFS (HR per 5-unit increase = 1.10, 95% CI 1.01–1.19) by a magnitude that was similar to PSA (HR per 5-unit increase = 1.10, 95% CI 1.03–1.18), and independent of biopsy Gleason score [38].

Prospective trials have established the utility of PSMA PET in the staging of nodal and distant metastases in high-risk patients. In proPSMA, patients with at least one high-risk feature (PSA ≥ 20 ng/mL, ≥ GG3, or ≥ cT3) were randomized to upfront ^{68}Ga-PSMA-11 vs. conventional imaging, and PET performed better at detecting any metastasis (nodal or distance) with a sensitivity of 85% (compared to 38% by conventional) and specificity of 98% (compared to 91% by conventional) [39]. In OSPREY, using histopathology as gold standard, the sensitivity of ^{18}F-DCFPyL in detection of pelvic nodal metastasis in high-risk patients was comparable to conventional imaging, approximately 40%, but with 3-fold higher positive predictive values (PPV: 86.7% vs. 28.3%). Furthermore, sensitivity increased to 60% when lymph nodes were larger than 5 mm in the short-axis, reflecting the inherent spatial limitations of PET resolution [40].

Nodal staging of intermediate-risk patients was examined in the SALT and PEPPER, prospective studies that examined the diagnostic accuracy of ^{18}F-DCFPyL and ^{68}Ga-PSMA-11, respectively. Both trials enrolled patients with negative bone scans who were able to undergo extended pelvic lymph node dissection. Both agents demonstrated a similar sensitivity of 40% and a specificity of over 91% [41, 42]. As expected, the PPV of PSMA PET increased with increased pre-test probability. In the SALT study of patients with Memorial Sloan Kettering Cancer Center (MSKCC) nomogram probability of ≥ 8% risk of lymph-node metastases, the overall prevalence of lymph node metastasis was 14.5% and PSMA PET PPV was 54.8% [41]. In PEPPER, which required MSKCC nomogram probability of ≥ 10% risk of lymph-node metastases [42], the overall prevalence of nodal metastasis was 37.9% and PSMA PET PPV was 77%.

PSMA PET IN BIOCHEMICAL RECURRENCE

In the setting of biochemical recurrence (BCR), PSMA PET has a very high PPV of 99% [34], and remains high at 84% when assessed strictly by histopathologic validation with substantial inter-reader reproducibility [43]. The sensitivity of detection was highly dependent on PSA levels, with a detection rate of 63% at PSA < 2 ng/mL versus 94% when the PSA was > 2 ng/mL [34]. In a retrospective review of 200 patients with castrate-resistant disease judged non-metastatic by conventional imaging (M_0 CRPC), with a median PSA of 5.3 ng/mL, 55% of those patients had PSMA-positive metastatic disease [44]. Whether earlier detection of metastatic disease will truly affect the natural history of the patient is unknown, and there is significant concern regarding the potential effects of stage migration and lead-time bias on clinical trials [45].

Table 1 lists trials of PSMA imaging agents in the biochemical recurrent and/or metastatic space include PROPER-ABX (NCT04239742), SPOTLIGHT (NCT04186845), PROfind (NCT03490032), and SECuRE (NCT04868604), and in newly diagnosed disease include LIGHTHOUSE (NCT04186819) and GuideView (NCT04838626). PRIMARY2 (NCT05154162) and PICture (NCT04487847) both investigate the potential added value of PSMA PET to mpMRI in patients with suspected cancer. These agents vary by the PET tracer and the PSMA-binding ligand. For instance, ^{68}Ga can be made by an on-site ^{68}Ge/^{68}Ga generator, while ^{18}F production requires a cyclotron. ^{18}F-PSMA-1007 and ^{18}F-rhPSMA-7.3 have the advantage of lower urinary excretion, which can improve the ability to detect lesions in close proximity to the urinary tract [46, 47]. Radiohybrid (rh) is a class of molecules where the PSMA ligand is connected to two separate binding sites for radiometals, where the radioactivity of each binding site is modulated by radioisotope exchange. The advantage is that a diagnostic and therapeutic pair of compounds will have similar biodistribution and pharmacokinetics [48].

MANAGEMENT IMPLICATIONS USING PSMA PET

Given its superior detection rate compared to conventional imaging, it is not surprising that PSMA PET results in a change

Table 1. Select ongoing prospective PSMA PET trials in the diagnosis / staging of PCa.

Trial	Study design	Population	Primary outcome
PRIMARY2 NCT05154162	Phase III Randomized PSMA PET/CT (pelvic-only view) ± TPTPbx VS No PET + TPTPbx	suspected PCa (based on elevated PSA and/or abnormal DRE), and negative/equivocal mpMRI (≤ PI-RADS 3)	Presence of significant PCa (≥ GG2) Cost/benefit of the addition of PSMA PET
PICture NCT04487847	Phase I/II Single arm ^{18}F-PSMA-1007 plus mpMRI	suspected PCa (based on elevated PSA and/or abnormal DRE)	Compare mpMRI, ^{18}F-PSMA-1007 PET and histopathology
LIGHTHOUSE NCT04186819	Phase III Single arm ^{18}F-rhPSMA-7.3	newly diagnosed UIR, HR, or VHR PCa, and planned to undergo RP and PLND	Patient-level sensitivity and specificity of ^{18}F-rhPSMA-7.3 for detecting LN metastases compared to histopathology
GuideView NCT04838626	Phase II/III Single arm ^{18}F-CTT1057	newly diagnosed HR PCa, and planned to undergo RP and PLND	Patient-level sensitivity in the primary and LN disease, and region-level specificity of the LN disease, compared to histopatholgoy
PROPER-ABX NCT04239742	Phase II Single arm ^{18}F-fluciclovine and ^{18}-F-PSMA-1007	BCR, at PSA of 0.2 ng/mL – 5 ng/mL	Comparison of detection efficacy between the two radiotracers
SPOTLIGHT NCT04186845	Phase III Single arm ^{18}F-rhPSMA-7.3	BCR, at PSA > 0.2 ng/mL (after RP) or PSA nadir + 2.0 ng/mL (after RT)	PPV of ^{18}F-rhPSMA-7.3, using histopathology or confirmatory imaging as standard of truth
SECuRE NCT04868604	Phase I/II Single arm ^{64}Cu-SAR-bisPSMA	mCRPC, with ≥ 1 metastatic lesion based on conventional imaging (CT, MR, bone scan)	Safety and tolerability, dosimetry
PROfind NCT03490032	Phase I/II Single arm ^{68}Ga-PSMA-R2	Phase I – BCR, at PSA > 0.2 ng/mL (after RP) or PSA nadir + 2.0 ng/mL (after RT) Phase II – metastatic disease (both castration sensitive or castration resistant), with ≥ 1 metastatic lesion based on conventional imaging (CT, MR, bone scan)	Safety and tolerability, dosimetry

BCR Biochemical recurrence, *DRE* Digital rectal exam, *HR* High risk, *mpMRI* Multiparametric magnetic resonance imaging, *LN* Lymph node, *mCRPC* Metastatic castrate-resistant prostate cancer, *RP* Radical prostatectomy, *RT* Radiotherapy, *PCa* Prostate cancer, *PLND* Pelvic lymph node dissection, *PPV* Positive predictive value, *PSA* Prostate-specific antigen, *PSMA* Prostate-specific membrane antigen, *TPTPbx* Transperineal template prostate biopsy.

in definitive radiation therapy (RT) volume. In a retrospective review from UCLA in intermediate- and high-risk patients without evidence of nodal or distant metastases by conventional imaging, with a median PSA of 13.9, ^{68}Ga-PSMA-11 PET identified disease outside of standard RT fields in 37% of patients [49]. Similarly, in high- and very high-risk patients, with a median PSA of 16 ng/mL, RT was altered in 53% of patients [50]. Boost to an avid lymph node accounted for 24% of changes, followed by metastasis directed RT to bone metastases and extension of nodal clinical target volume (CTV) to include PSMA-avid nodes.

The CONDOR trial investigated ^{18}F-DCFPyL in men with biochemical recurrence after prostatectomy or prior radiation with negative or equivocal conventional imaging and showed that almost 64% of patients had a change in intended management based on ^{18}F-DCFPyL findings [51]. In the salvage setting, about 20–30% of patients will have at least one PSMA PET lesion that is not covered by traditional salvage RT fields. In a retrospective review of patients with BCR after prostatectomy and PSA < 2.0 ng/mL (median PSA of 0.4 ng/mL), 30% of patients were found to have at least one PSMA PET-avid lesion outside salvage RT fields [52]. In a single arm prospective trial analyzing diagnostic sensitivity of ^{68}Ga-PSMA-11 in patients with BCR after prostatectomy, over half of which did not have conventional imaging, PET imaging findings resulted in a change in the intended management in 68% of patients [53]. In a post-hoc analysis of this trial in patients with a PSA < 1.0 ng/mL, almost half (49%) had a ^{68}Ga-PSMA-11 positive lesion, and 52% of those PSMA PET-avid lesions were outside the consensus RT volumes [54]. The majority of these (64%) were extra-pelvic lesions, and the remaining (36%) were within the pelvis but still outside the consensus volumes [54].

It remains to be determined whether changes in management resulting from PSMA PET information will translate to oncologic benefit. Furthermore it is uncertain whether M1 disease defined by conventional imaging reflects the same disease state and trajectory as M1 disease on molecular imaging. Table 2 summarizes select ongoing clinical trials that are investigating whether changes in management by molecular imaging translate into oncologic benefit: EMPIRE II (NCT03762759), PSMA SRT (NCT03582774), PSMA-PETgRT (NCT03525288) [55], NCT04794777, INDICATE (NCT04423211), and PATRON (NCT04557501).

PSMA PET IN OLIGOMETASTATIC DISEASE

The use of PSMA PET in oligometastatic disease, based on a pragmatic cut-off of 3–5 lesions, was explored in PSMA MRgRT, where patients with BCR and M0 disease by conventional imaging underwent metastasis directed therapy (MDT) to all sites of PSMA-avid disease without receiving concurrent hormonal therapy. The median time to PSA progression was 17.7 months and the median time to starting ADT was not reached [56]. Furthermore, complete metabolic response on PSMA PET at 4 months post MDT was prognostic for biochemical control. Similar results were observed in STOMP, where choline (^{11}C or ^{18}F) PET directed MDT improved median ADT-free survival to 21 months compared to 13 months with observation ($p = 0.11$) [57]. The 5-year ADT free survival was 34% vs. 8% ($p = 0.06$) and there were no reported CTCAE Gr ≥ 2

Table 2. Select ongoing prospective trials evaluating outcomes of PET/CT guided management.

Trial	Phase, status, patient population	Study design	Primary endpoint
EMPIRE II NCT03762759	II Recruiting Post-RP BCR M0 by CI (^{99m}Tc-MDP, ^{18}F-NaF PET, CT, MRI)	^{18}F-fluciclovine guided treatment VS ^{68}Ga-PSMA-11 guided treatment	DFS
PSMA SRT NCT03582774	III Accrual complete Post-RP BCR	^{68}Ga-PSMA-11 guided treatment VS CI guided treatment	5 y bRFS
PSMA-PETgRT NCT03525288	II Accrual complete HR, BCR, or Oligometastatic	^{18}F-DCFPyL PSMA guided treatment VS CI guided treatment	5 y FFS *Secondary endpoint: new lesions detected in 46% (HR) and 45% (BCR), leading to treatment intensification* (Menard 2020)
PATRON NCT04557501	III Recruiting HR, N1, or post-RP BCR	018F-DCFPyL PSMA guided treatment VS CI guided treatment	5 y FFS
NCT04794777	III Recruiting Post-RP and pN0 → first time BCR	PSMA PET (^{68}Ga or ^{18}F-1007) VS CI guided treatment	10 y PFS
INDICATE NCT04423211	III Recruiting Post-RP BCR M0 by CI (^{99m}Tc-MDP, pelvic CT, pelvic MRI)	• Based on ^{18}F-fluciclovine: No extrapelvic uptake • ADT + SRT VS • ADT + SRT • + apalutamide Extrapelvic uptake • ADT + SRT + apalutamide VS • ADT + SRT + apalutamide + MDT	10 y PFS

ADT Androgen deprivation therapy, *BCR* Biochemical recurrence, *bRFS* Biochemical recurrence free survival, *CI* Conventional imaging, *DFS* Disease free survival, *FFS* Failure free survival, *HR* High risk, *mpMRI* Multiparametric magnetic resonance imaging, *MDT* Metastasis directed therapy, *PCa* Prostate cancer, *PFS* Progression free survival, *PSA* Prostate-specific antigen, *PSMA* Prostate-specific membrane antigen, *RP* Radical prostatectomy, *SOC* Standard of care, *SRT* Salvage radiation therapy, 99 mTch-MDP Technetium 99m-methyl diphosphonate.

toxicities [58]. In contrast, ORIOLE enrolled participants with metastatic disease based on conventional imaging, and still demonstrated decreased from progression at 6 month of 61% vs. 19%, favoring MDT ($p = 0.005$) [59]. Sixteen of the 36 patients had baseline PSMA-PET imaging prior to treatment, which were blinded to the investigative team. Post hoc analysis noted that total consolidation of PSMA-avid lesions improved PFS (HR 0.26, $p = 0.0055$) and decreased the incidence of new metastases at 6 months from 63% with subtotal consolidation to 16% with total consolidation ($p = 0.006$) [59]. In the updated pooled analysis of STOMP and ORIOLE, MDT improved median PFS to 11.9 months compared with 5.9 months for observation (HR 0.44, $p < 0.001$) [60]. Notably, patients with a high-risk mutational signature (pathogenic somatic mutations in *ATM*, *BRCA1/2*, *RB1*, or *TP53*) derived a greater PFS benefit from MDT relative to no MDT (HR 0.05, $p < 0.01$) compared to those without the high-risk mutations (HR 0.42, $p = 0.01$) [60].

PSMA LIGANDS AND RADIOPHARMACEUTICAL OPPORTUNITIES

Multiple small molecule PSMA-targeted radiopharmaceuticals with beta or alpha-emitting radionuclides have been developed for prostate cancer therapy, including the recently FDA-approved ^{177}Lu-PSMA-617 (^{177}Lu vipivotide tetraxetan: Pluvicto®). Lutetium-177 has a convenient physical half-life of 6.7 days and emits β particles (maximum energy 497 keV) in the therapeutic range with a relatively low proportion of γ emission (113 keV at 6% and 208 keV at 11%). Its maximal tissue penetration of < 2 mm significantly reduces bystander dose to adjacent normal tissues. As a result of these favorable characteristics, ^{177}Lu has emerged as a promising therapeutic radionuclide for multiple targets. Binding of the PSMA receptor induces dimerization and internalization of the complex, effectively trapping the radionuclide within the prostate cancer cell, where it subsequently induces double-strand DNA (dsDNA) damage leading to apoptosis (Fig. 1). Notably, other therapies that target PSMA are also in development, including radionuclide-conjugated antibodies, antibody-drug conjugates, T-cell recruiting bispecific agents, and cellular approaches with PSMA-directed chimeric antigen receptor (CAR)-T cells [61].

CLINICAL DATA SUPPORTING THE USE OF ^{177}LU-PSMA-617 RPT

Metastatic castrate-resistant prostate cancer (mCRPC) remains an incurable disease. Figure 2 outlines the current landscape of treatment options, which includes conventional chemotherapy, such as docetaxel and cabazitaxel, additional androgen receptor signaling inhibitor (ARSI), such as abiraterone and enzalutamide, bone-seeking radiopharmaceuticals such as radium-223 dichloride, and most recently, ^{177}Lu-PSMA-617 radioligand therapy.

The LuPSMA trial was the first prospective phase 2 study to evaluate ^{177}Lu-PSMA-617 in 30 patients with mCRPC that had progression on standard treatment, demonstrated PSMA avid disease on PSMA PET imaging and, notably, and did not harbor discordant ^{18}F-FDG-avid disease that was not PSMA-positive. Patients received up to 4 cycles of ^{177}Lu-PSMA-617 at a mean of 7.5 GBq each. The primary endpoint of a ≥ 50% decline in PSA was

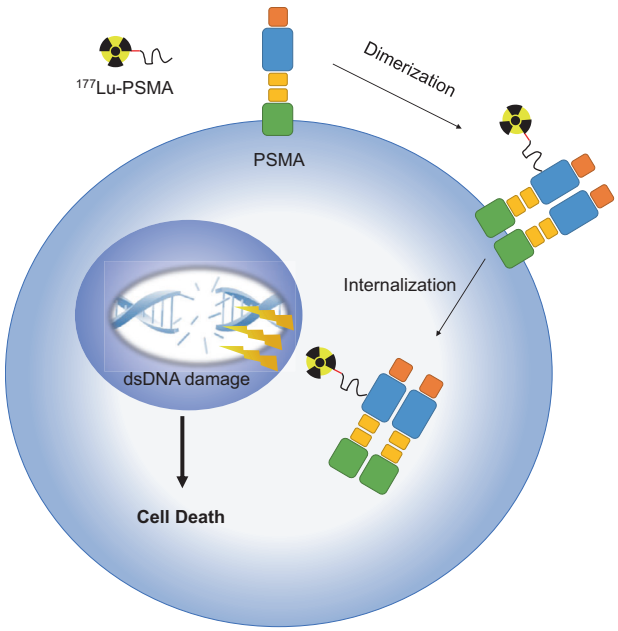

Fig. 1 Mechanism of action of ^{177}Lu-PSMA radioligand therapy. PSMA-617 and PSMA-I&T are low-molecular weight ligands (in black) with high binding affinity to PSMA, connected to the radionuclide by a linker (in red). Once bound, receptor dimerization can lead to internalization of the receptor-ligand complex. This allows concentration of the radionuclide, ^{177}Lu, within the cell. Ionizing radiotherapy may produce DNA double-strand breaks in the cell and neighboring cells (up to ~2 mm), ultimately leading to cell death.

achieved in 57% of patients [62]. Importantly, all patients who reported pain at baseline noted decrease in pain at all timepoints. Based on these clinically meaningful improvements, TheraP was developed to test ^{177}Lu-PSMA-617 against cabazitaxel in a randomized fashion in patients with mCRPC who had progression on docetaxel. In this 200-patient trial, PSA response of ≥ 50% was achieved in 66% vs. 37% ($p < 0.001$) of patients who received ^{177}Lu-PSMA-617 vs. cabazitaxel, respectively [63]. While the median PFS was similar between both arms at 5.1 months, the 12-month PFS was 19% vs. 3% (HR 0.63, 95% CI 0.46–0.86), favoring ^{177}Lu-PSMA-617 [63]. At a median follow-up of 36 months, the restricted mean survival time was similar between both arms (19.1 months vs. 19.6 months) [64].

In 2021, the VISION phase III trial testing ^{177}Lu-PSMA-617 was completed. VISION randomized 831 patients to ^{177}Lu-PSMA-617 (7.4 GBq) plus standard of care (SOC) vs. SOC alone [65]. Of the 1003 patients who underwent ^{68}Ga-PSMA-11 imaging, 87% had at least one PSMA positive lesion and were eligible for randomization. While patients with PSMA non-avid lesions were not eligible (required $SUV_{max} \geq$ liver), FDG PET was not required, which may explain why response rates were lower in VISION than compared to LuPSMA and TheraP. This was a pre-treated population, with virtually all having previously received docetaxel and ~40% receiving two prior regimens of ARSI. Nevertheless, the addition of ^{177}Lu-PSMA-617 to SOC demonstrated superior radiographic progression-free survival (rPFS) of 8.7 months vs. 3.4 months with SOC alone (HR 0.4, 95% CI 0.29–0.57). Median overall survival (OS) also favored the ^{177}Lu-PSMA-617 arm at 15.3 months vs. 11.3 months with SOC alone (HR 0.62, 95% CI 0.52–0.74) [65]. Of note, while rPFS was evaluated in the set of 581 patients enrolled after corrective measures to reduce drop-out in the SOC arm, the OS benefit persisted in the entire cohort. Brief pain inventory (BPI-SF) and patient reported outcomes (EQ-5D, FACT-P) also favored the ^{177}Lu-PSMA-617 arm. Results from VISION led to the Food and Drug Administration (FDA) approval of ^{177}Lu-PSMA-617 in March 2022 for the treatment of PSMA-positive mCRPC (by ^{68}Ga-PSMA-11) having previously been treated with ARSI and taxane-based chemotherapy [66].

Ongoing phase 2 and 3 trials are evaluating ^{177}Lu-PSMA therapy in earlier line and earlier stage prostate cancer. This includes studies in men with chemo-naïve metastatic castrate resistant prostate cancer (SPLASH NCT04647526; PSMAFore NCT04689828; ENZA-P NCT04419402, ECLIPSE NCT05204927), metastatic castration-sensitive prostate cancer (UpFrontPSMA NCT04343885, PSMAddition NCT04720157), oligometastatic castration-sensitive prostate cancer (Bullseye NCT04443062; LUNAR NCT05496959), and locoregionally advanced or high-risk prostate cancer (LuTectomy NCT04430192; PROQURE-1 NCT05162573) (Fig. 2). Of note, ^{177}Lu-PSMA-I&T (in ECLIPSE) and ^{177}Lu-PNT2002 (in SPLASH) differ in formulations, but both contain the same urea-binding motif, linker and DOTAGA chelator [67].

In high-risk prostate cancer, Globan et al. [68] demonstrated safety and feasibility of administering up to 3 doses of neoadjuvant ^{177}Lu-PSMA-I&T at 7.4 GBq per dose, given every two weeks, followed by surgery 4 weeks after the last dose. There were no Common Terminology Criteria for Adverse Events (CTCAE) Gr > 3 events during ^{177}Lu-PSMA treatment and no intraoperative complications. Positive margins were identified in 53% of patients. In the phase 1 portion of LuTectomy, 10 patients were received 1 dose of 5 GBq of ^{177}Lu-PSMA-617, proceeded by surgery 6 weeks later [69]. Preliminary results presented at the 2022 European Association of Urology showed a median absorbed dose of 48 Gy in the prostate and 50 Gy in the lymph nodes, with no CTCAE Gr ≥ 1 adverse events or Clavien-Dindo Gr ≥ 3 events. There were no cases of pathologic complete response or minimal residual disease in that study.

BIOMARKERS TO PREDICT BENEFIT FROM ^{177}LU-PSMA

Heterogeneity of PSMA receptor activity (i.e. lack of dimerization and internalization), and varying levels of PSMA expression on tumor cells may account for the lack of response in some patients. Furthermore, differences in intrinsic cellular DNA-repair capabilities may also contribute to primary resistance. Therefore, biomarkers are needed to predict response to ^{177}Lu-PSMA RPT. From the LuPSMA trial, tumor SUV_{mean} was found to be positively correlated to whole-body tumor dose determined by single photon emission computed tomography (SPECT) dosimetry of ^{177}Lu. Patients who achieved at least a 50% decline in PSA at 12 weeks had a median whole-body absorbed tumor dose of 14.1 Gy, compared to a whole-body tumor dose of 9.6 Gy in those who experienced less than a 50% PSA decline [70]. PSMA PET surrogate calculations from TheraP showed that a $SUV_{mean} \geq 10$ predicted a much greater odds of PSA response in patients who received ^{177}Lu-PSMA-617 compared to cabazitaxel, with an odds ratio of 12.19 for $SUV_{mean} \geq 10$ vs. 2.22 for $SUV_{mean} < 10$ ($p = 0.039$). The PSMA PET SUV_{mean} did not predict for response to cabzitaxel [71]. Similarly, results from VISION found whole-body tumor SUV_{mean} was associated with improved PFS (HR 0.86, 95% CI 0.82–0.91) and OS (HR 0.88, 95% CI 0.84–0.91) on multivariate analysis [72].

Data from the outcomes of RESIST-PC (study closed early due to sponsorship transfer) [73] and LuPSMA [62] were combined to develop a nomogram to predict outcomes after treatment with ^{177}Lu-PSMA-617, which was both internally and externally validated [74]. Clinical characteristics that were predictive for both OS and PSA-progression-free survival included time since diagnosis (years), chemotherapy status (yes or no), tumor SUV_{mean} (continuous variable), bone metastasis (present or absent), and liver metastasis (present or absent). The total number of lesions (< 20 or ≥ 20) was a predictor for OS, while pelvic nodal metastasis (present or absent) was a predictor for PSA-PFS. With a modest C-index of 0.71, an optimal cutoff score was used to stratify

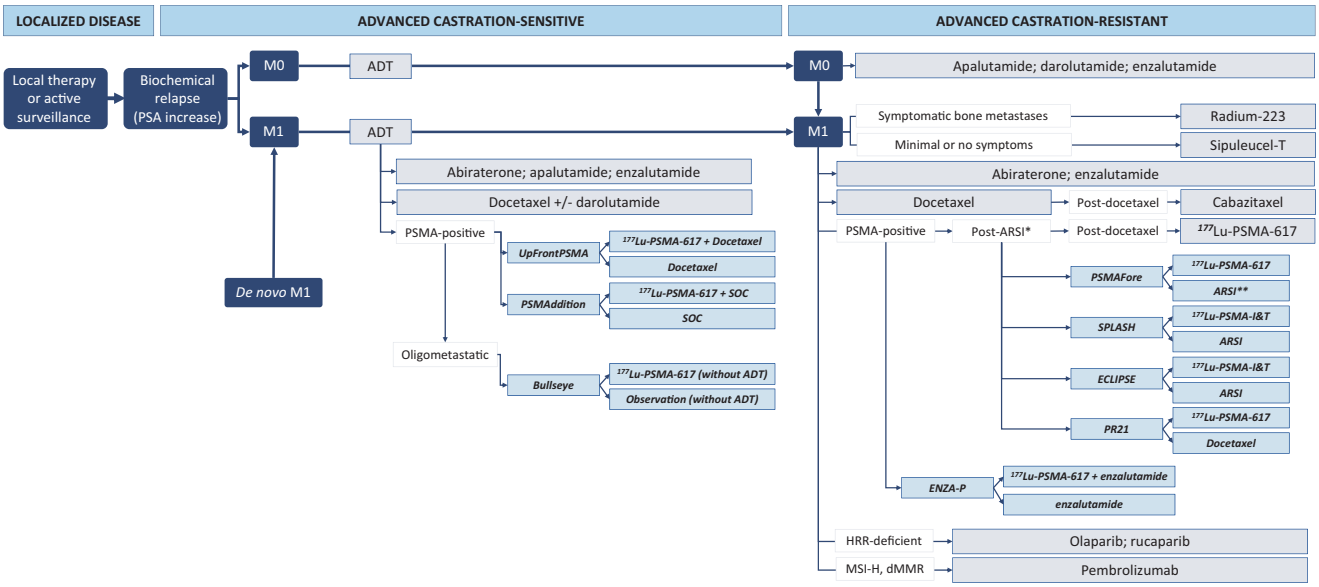

Fig. 2 Current treatment landscape for non-metastatic (M0) and metastatic (M1) prostate cancer. SOC regimens are outlined in gray boxes, ongoing Phase 2 and 3 trials are highlighted in light-blue boxes and italicized. ECLIPSE uses 7.4GBq of ^{177}Lu-PSMA-I&T, while SPLASH uses 6.8GBq of ^{177}Lu -PNT2002. ARSI Androgen receptor signaling inhibitors, dMMR Deficient mismatch repair, HRR Homologous recombination repair, MSI Microsatellite instability, SOC Standard of care. **Progression on previous treatment with one ARSI (abiraterone or enzalutamide or darolutamide or apalutamide) **an ARSI that has not been previously tried.*

patients into low-risk vs. high-risk, where median OS was 24.9 months vs. 7.9 months ($p < 0.0001$) and PSA-PFS was 6.6 months vs. 2.5 months ($p = 0.022$), respectively [74]. While prospective validation is needed, these nomograms that are predictive of outcomes after ^{177}Lu-PSMA in patients with mCRPC serve to guide individual clinical decision making.

The cytotoxic effects of radiation stems from either direct action (direct breakage of DNA atomic bonds) or indirect action (through ionization of water and creation of free radicals to induce DNA damage). The proportion of direct versus indirect effects is related to the linear energy transfer (LET), where alpha particles (e.g., ^{223}Ra) have a much higher LET than beta particles (e.g. ^{177}Lu). Higher LET will create more double-stranded breaks (DSBs), which are the main lethal event in inducing cell death, and is less dependent on the cell cycle phase and presence of hypoxia. Therefore, the type of radiation utilized and the integrity of genes that mediate the DNA damage response (DDR) pathway will influence the cytotoxic responsiveness to radiation. Aberrations in DSB repair mechanisms are increasingly recognized in mCRPC patients, where the prevalence of DDR germline and somatic mutations range from 8% to 12% [75, 76] and 20% to 25% [77], respectively. In a retrospective single-institution review of 28 mCRPC patients who received ^{223}Ra, 80% of patients with HR mutations experienced a ≥ 30% decline in alkaline phosphatase (ALP) compared to 39% patients without HR mutations ($p = 0.04$) [78]. While there were no differences in PSA response, there was a trend towards improved median OS in patients who were HR-deficient (36.9 months vs. 19 months, $p = 0.11$) [78]. This is consistent with data suggesting that ALP decline was prognostic for OS independently of PSA changes in mCRPC patients with bone metastases who received chemotherapy [79]. Likewise, a multicenter cohort review noted that the presence of DDR aberrations in patients receiving ^{223}Ra was associated with a longer median OS compared to those without mutations (36.3 months vs. 17 months, $p = 0.01$) [80]. Preliminary results from the prospective observational biomarkers study, PROPRADIUM (NCT02925702), also demonstrated improved ALP responses (> 30% decline in ALP at 12 weeks) in patients with germline HR-mutations (75% vs. 43%, $p = 0.036$), with a similar trend towards improvement in median OS (14.4 months vs. 10.6 months, $p = 0.066$) [81]. While there was one case report of extraordinary PSA response in a mCRPC patient with germline DDR mutations following ^{177}Lu-PSMA-617 [82], a predefined retrospective review of 40 patients (42.5% of whom were DDR-deficient) did not identify any associations between pathogenic DDR aberrations and responsiveness to PSMA-RPT, regardless of the radionuclide used (^{177}Lu or ^{225}Ac) [83]. However, since only 7/40 patients received ^{225}Ac by itself, there was unlikely to be sufficient power to determine whether patients with damage repair deficiencies benefited more from an alpha emitter. This "synthetic lethality" hypothesis that defects in mechanisms of DNA repair would render a tumor more susceptible to high-LET radiation is prospectively explored in NCT04489719. An excellent review of genomic biomarkers utilized in radiotherapy can be found here [84].

RADIATION DOSIMETRY OF ^{177}LU-PSMA-617

Patient-specific dosimetry is not standardized for ^{177}Lu-PSMA-617. Patients in VISION received a fixed dose of 7.4 GBq (200 mCi) per cycle. In TheraP, administered dose per cycle was between 6.0–8.5 GBq, adjusted based on tumor burden, patient's weight, and renal function. The dose of ^{177}Lu-PSMA used was informed by safety data from ^{177}Lu-DOTATATE [85] and applying external beam radiation therapy (EBRT) absorbed dose constraints on bone marrow and kidney. While the convenience of a fixed dose has allowed ease of RPT integration into clinical workflow, patient-specific dosimetry using SPECT to directly image ^{177}Lu could inform modification of the injected activity in order to increase the therapeutic index [86].

Current dosimetric normal organ constraints are primarily based on toxicity data from EBRT [87, 88]. However, there are critical differences between EBRT and RPT. First, while EBRT is generally prescribed as a dose to a point or volume, RPT is usually prescribed as an activity per injection, body weight, or surface area. Second, treatment with ^{177}Lu-PSMA is greatly protracted, with 6 weeks between each dose. This is opposed to daily treatment with EBRT where there is normally a 24-hour interval in

between each treatment. Kidneys have a low α/β ratio (~2.6) [89], and as such, are very sensitive to the dose per fraction [90]. Third, ^{177}Lu-PSMA is continuous therapy at a low and exponentially decreasing dose-rate due to source decay over time. This is in contrast to the relatively high dose-rate of EBRT. Fourth, ^{177}Lu-PSMA uptake in areas of disease may be heterogeneous and vary by metastatic site or patient, and normal tissue uptake and corresponding dose are also variable. Violet et al. [70] found an inverse correlation between parotid dose and total volume of disease, suggesting a "sink effect", in which the higher the burden of disease the more ^{177}Lu-PSMA-617 is removed from circulation, thus resulting in less of the dose reaching normal organs.

There has been very limited acute renal toxicity observed in TheraP and VISION, as well as in most retrospective studies of ^{177}Lu-PSMA. In VISION, the CTCAE Gr 3–4 renal effects – defined as any increase in blood creatinine or blood urea, acute kidney injury, proteinuria, or decreased urine output – were not statistically different between the two arms, at 3.4% in the ^{177}Lu-PSMA-617 plus SOC vs. 2.9% in the SOC arm [65]. However, late radiation nephrotoxicity was not yet investigated in these trials, and recent studies have indeed demonstrated late radiation nephropathy in patients receiving excess cycles of ^{177}Lu-PSMA [91].

Dosimetry studies using SPECT will be particularly critical in studies investigating dose escalation, re-treatment with RPTs, predictive variables for RPT biodistribution such as tumor burden, and combinations of external beam and RPT. In VISION, 15% of patients receiving ^{177}Lu-PSMA also received concurrent palliative EBRT, without noticeable added toxicity [65].

ALPHA EMITTERS

As a calcium analogue, ^{223}Ra directly targets the bone mineral hydroxyapatite, which is present and incorporated at the highest rate in areas of increased bone turnover, such as osteoblastic bone metastases. In contrast, the target of ^{177}Lu-PSMA is the transmembrane receptor PSMA, which is overexpressed on prostate cancer cells. Therefore, while ^{223}Ra localizes only to the bone, ^{177}Lu-PSMA will target any cell with PSMA expression, including nodal or visceral metastases. ^{223}Ra is an alpha emitter, and thus has an exquisitely short radiation path length of up to 0.05 mm. In contrast, ^{177}Lu is a beta emitter with a path length >10 times longer. These properties each have advantages and disadvantages. A shorter path length can reduce bystander normal tissue damage but may leave some tumor cells under-dosed with alpha emitting RPT. Other bone-targeting agents include β-emitters such as ^{32}P, ^{153}Sm, and ^{90}Sr, which have historically been used for palliation of pain, but their deeper tissue penetrance and consequent hematologic toxicities have limited their utility [92].

^{223}Ra dichloride (Xofigo®) gained FDA approval in 2013 for the treatment of men with symptomatic mCRPC bone metastases without known visceral metastases [93] (Table 3). This was based on the pivotal ALSYMPCA randomized phase III trial demonstrating an overall survival (OS) benefit (median OS of 11.3 m to 14.9 m, $p < 0.001$) [94]. Small institutional studies have shown that with more than 5 FDA approved lines of therapy in the mCRPC setting, success from ^{223}Ra after multiple lines of therapy is likely suboptimal due to the probability of a greater extent of non-osseous disease and inability to complete all therapy [95]. Furthermore, the phase III ERA 223 trial testing the combination of ^{223}Ra with abiraterone acetate plus prednisolone noted an absolute increase of 18% in the incidence of fractures in the combination therapy arm compared to abiraterone alone (29% versus 11%, respectively), where 79% of these fractures occurred at sites without bone metastases (i.e. non-pathologic fractures) [96]. Post-hoc analysis revealed that fractures were less common in patients taking bone health agents (BHA). As a result, the ongoing PEACE III trial (NCT02194842), which randomizes patients

Table 3. Comparison of patient selection and key outcomes from the ALSYMPCA and VISION trials.

Trial	Design, and n	Patient selection (clinical parameters)	Patient selection (imaging parameters)	RPT dose	Key endpoints and QoL
ALSYMPCA [76]	Phase III, international, double-blind ^{223}Ra + SOC versus SOC $n = 921$	• Symptomatic mCRPC • Post-docetaxel, unfit or declined (57% received docetaxel) • must remain on LHRH agonist or history of bilateral orchiectomy	• ≥ 2 bone metastases via skeletal scintigraphy • no known visceral metastases • no malignant lymphadenopathy > 3 cm in short-axis diameter	^{223}Ra, 50 kBq/kg 4-week cycles, up to 6 cycles	1° endpoint: median OS favored ^{223}Ra (14.9 m vs 11.3 m, $p < 0.001$) Median time to symptomatic skeletal event was longer in ^{223}Ra (15.6 m vs 9.8 m, $p < 0.001$) Increase in ≥ 10 points in FACT-P favored ^{223}Ra (25% vs 16%, $p = 0.02$)
VISION [60]	Phase III, international, open label ^{177}Lu-PSMA-617 + SOC versus SOC $n = 831$	• mCRPC with disease progression •≥1 ARSi •1–2 previous taxane regimens • must remain on LHRH agonist or history of bilateral orchiectomy	• PSMA PET SUV_{max} of tumor ≥ SUV of liver • FDG-PET not required	^{177}Lu-PSMA-617, 7.4 GBq 6-week cycles, up to 6 cycles	1° endpoint: OS favored ^{177}Lu-PSMA-617 (15.3 m vs 11.3 m, $p < 0.001$) Median time to symptomatic skeletal event was longer in ^{177}Lu-PSMA-617 (11.5 m vs 6.8 m, $p < 0.001$) Median time to decrease in FACT-P was longer in ^{177}Lu-PSMA-617 (5.7 m vs 2.2 m, HR 0.54, 95% CI 0.45–0.66)

APP Abiraterone plus prednisone or prednisolone, *ARSI* Androgen receptor signaling inhibitors), *FACT-P* Functional Assessment of Cancer Therapy – Prostate, *FDG* [18 F] F-FDG PET, *GBq* Gigabecquerel, *kBq* Kilobecquerel, *LHRH* Luteinizing-hormone releasing hormone, *m* Months, *mCRPC* Metastatic castrate-resistant prostate cancer, *OS* Overall survival, *PSMA* Prostate-specific membrane antigen, *^{223}Ra dichloride*, *RPT* Radiopharmaceutical therapy, *SOC* Standard of care, *SUV_{max}* Maximum standard uptake value.

Table 4. Comparison of ^{223}Ra dichloride and ^{177}Lu-PSMA-617 in daily practice.

RPT agent	Maker	Target	Therapeutic emission	Approximate range in tissue	Therapeutic dosing	Excretion	Mean effective half-life	Common side effects
^{223}Ra dichloride	Bayer	Bone hydroxyapatite	α particle	0.05 mm	50 kBq per kg body weight, once every 4 weeks, total of 6 cycles	fecal	6.5 ± 3.1 days	nausea, diarrhea, vomiting, cytopenias
^{177}Lu-PSMA-617	Novartis	PSMA	β particle	0.67 mm	7.4 GBq fixed dose, once every 6 weeks, total of 6 cycles	renal	1.7 ± 0.4 days	fatigue, nausea, vomiting, anemia, cytopenias, xerostomia, xerophthalmia

kBq Kilobecquerel, *GBq* Gigabecquerel, *PSMA* Prostate-specific membrane antigen, *RPT* Radiopharmaceutical therapy.

to enzalutamide with or without ^{223}Ra, mandated the use of preventative BHA and noted a reduction of fractures to < 4% on both arms since implementation of BHA [97].

There are key differences in the patient populations between VISION and ALSYMPCA: 1) virtually all patients had previous exposure to docetaxel as was mandated by the VISION trial, in contrast to 57% in ALSYMPCA; 2) visceral metastases (lung and/or liver) were identified in 24% of patients on VISION using PSMA PET, while ALSYMPCA required no evidence of visceral metastases by conventional imaging.

Therefore, based on current evidence, situations that may be more appropriate for using ^{223}Ra over ^{177}Lu-PSMA-617 include patients with low or absent PSMA PET SUV expression, discordant FDG-positive disease on FDG-PET, and/or bone-predominant/only disease. Conversely, the presence of visceral disease or significant burden of nodal disease may favor ^{177}Lu-PSMA-617 provided that these lesions express PSMA avidly. Table 4 provides a comparison between the two RPTs. A detailed review of ^{223}Ra including mechanism of action [98] and its use in the treatment of bone metastases in mCRPC can be found here [99].

Alpha labeled PSMA agents include ^{213}Bi, ^{225}Ac, ^{211}At, and ^{227}Th. In a meta-analysis of 256 mCRPC patients treated with ^{225}Ac-PSMA agents, a ≥ 50% decline in serum PSA was achieved in 62.8% patients, with estimated median PFS and OS of 9.1 months and 12.8 months, respectively [100]. While CTCAE Gr ≥ 3 xerostomia was limited to 1.2%, Gr 1–2 xerostomia ranged from 36% to 100% and was a major reason for treatment discontinuation [100]. On-going phase I/II studies evaluating small molecule PSMA-targeted alpha therapy include ^{227}Th-PSMA (NCT03724747 [101]), ^{225}Ac-PSMA-617 (NCT04597411), and TATCIST (^{225}Ac-PSMA-I&T, NCT05219500).

CONCLUSIONS

PSMA PET has superior diagnostic accuracy compared to conventional imaging in both the initial staging of prostate cancer and in the setting of disease recurrence, with improved sensitivity at higher PSA values relative to lower PSA. Integration of PSMA PET imaging into radiation therapy decision-making and planning may improve biochemical EFS, and consolidation of all PSMA PET-avid lesions in oligometastatic disease may increase PFS and reduce the incidence of new metastases. Ongoing clinical trials will explore whether changes in clinical decision-making will translate into oncologic benefit. PSMA-targeted therapy with ^{177}Lu-PSMA-617 is effective and well-tolerated in heavily pre-treated patients with PSMA-expressing mCRPC. PSMA PET SUV is prognostic for treatment response (SUV_{mean} ≥ 10). Additional biomarkers are needed to predict therapy response and to enable better patient selection. The field of RPT in oncology is expanding, and embracing a multi-disciplinary approach involving radiation oncology, medical oncology, and nuclear medicine is important in the comprehensive strategic care of patients with advanced prostate cancer.

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AUTHOR CONTRIBUTIONS

AYJ – study design, draft, manuscript preparation and revision; APK – study design, manuscript revision; QL – manuscript revision; ESA – conceptualization, supervision, study design, manuscript revision. All authors reviewed and approved the final version of the manuscript.

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ADDITIONAL INFORMATION

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