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Advances in PSMA Alpha Theragnostics

Mariza Vorster, MD, PhD,* and Mike Sathekge, MD, PhD†,‡

Alpha theranostics offer an attractive alternative form of therapy, which has best been investigated and documented with ^{225}Ac-PSMA in patients with prostate cancer. Advantages offered by targeted alpha therapy include overcoming radiation resistance, oxygen independence, effecting double-stranded DNA breakages within the tumors with anticipated improved clinical outcomes and an acceptable side effect profile. The previous Seminars article on this topic, published in 2020, had to rely mostly on published case reports and small observational studies. In the last few years, however, several meta-analyses have emerged that evaluate the safety and efficacy of ^{225}Ac-PSMA in prostate cancer patients, followed most recently by a multi-center retrospective study initiated by WARMTH. The findings of these publications, together with the exploration of TAT offered in clinical conditions other than as a last resort, is the focus of this updated overview. Unresolved clinical issues that remain, include the appropriate selection of patients that would benefit most from treatment with ^{225}Ac-PSMA, treatment timing within the disease landscape, optimal dosing schedule, dosimetry, when and how to best use combination therapies and minimization and treatment of side effects, particularly that of xerostomia.

Introduction

Searching Google Scholar for the terms "Ac225" + "PSMA" over "anytime" rewards the reader with an impressive 796 results. Restricting publications to those "since 2020" results in 532 results, which means that around two thirds of the published scholarly literature on ^{225}Ac-PSMA had appeared since the previous Seminars article on this topic in 2020 by esteemed colleagues Kratochwil, Hawerkom and Giesel.[1] At that time, the available evidence consisted of mainly preclinical experiments, preliminary dosimetry attempts and a few retrospective observational studies. In less than five years, we now have convincing evidence from several meta-analyses,[2-5] that targeted alpha therapy with ^{225}Ac-PSMA is a safe and effective alternative treatment strategy for patients with metastatic prostate cancer. Reports on 5-year survival are also starting to emerge.[6] In addition, there is a multitude of registered ongoing prospective clinical trials that aim to evaluate various forms of ^{225}Ac-PSMA in different clinical settings against a range of conventional treatment strategies.[7] Production and access to actinium-225 remains amongst the unresolved issues, together with appropriate clinical indications, dosing- and combination strategies.

The Best Evidence to Date

In the first published meta-analysis and systematic review by Satapathy et al. in 2021,[2] the authors summarized available data on the evolving role of actinium PRLT, reported according to the PRISMA statement.[8] Their analysis included 10 full length articles that reported on treatment response and/or survival outcomes. Quality assessments for inclusion of publications were based on the Newcastle-Ottawa scale[9] with 4 stars or more considered a good quality publication. For a study to be included in the analysis, a minimum of ten patients were required with no exclusions regarding prior treatment, which resulted in a total patient number of 256. Treatment response assessments included the biochemical response (best s-PSA response) and imaging response with

*Department of Nuclear Medicine at Inkosi Albert Luthuli Hospital, University of KwaZulu-Natal, KwaZulu-Natal, South Africa.
†Department of Nuclear Medicine, University of Pretoria & Steve Biko Academic Hospital, Private Bag X169, Pretoria 0001, South Africa.
‡Nuclear Medicine Research Infrastructure (NuMeRI), Steve Biko Academic Hospital, Pretoria 0001, South Africa.
Address reprint requests to Mariza Vorster, MD, PhD, Department of Nuclear Medicine at Inkosi Albert Luthuli Hospital, University of KwaZulu-Natal E-mail: marizavorster@gmail.com

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PSMA-based PET/CT reported according to the PERCIST criteria. Outcome measurements included progression free survival (PFS) and overall survival (OS). The authors combined partial and complete responders as a single group of molecular responders. Frequencies of hematological- and non-hematological side effects were reported according to standardized grading systems.

A biochemical response (consisting of a greater than 50% drop in s-PSA) was reported in just over 60% of patients and an imaging response on ^{68}Ga-PSMA PET/CT in 74%. They reported a progression-free survival (PFS) of just over 9 months and overall survival (OS) of over a year. The major side effect experienced, was that of xerostomia (as expected) and occurred in just under 73% of patients.[2]

Grade 3 side effects occurred rarely (with only anemia occurring in greater than 10% of patients). Less than 10% of patients discontinued treatment because of unacceptable side effects. The authors concluded that ^{225}Ac-PSMA should be considered a safe and effective alternative treatment strategy in patients with metastatic castrate-resistant prostate cancer (mCRPC). Compared to the 46% response rate reported by Yadav et al. in a 2019 meta-analysis on ^{177}Lu-PSMA, the response with ^{225}Ac-PSMA was clearly superior.[10]

Limitations of the meta-analysis by Satapathy et al., include the significant heterogeneity that existed within the clinical settings (regarding study design, the type of PSMA used, dosing schedules, activity administered and side effect reporting). See Table 1 for further details. Significant statistical heterogeneity also existed within all aspects of the analysis apart from nephrotoxicity analysis.

A 2022 systematic review and meta-analysis by Ma et al.,[3] evaluated the efficacy and safety of ^{225}Ac-PSMA- 617-targeted alpha therapy (TAT) in metastatic castration-resistant prostate cancer (mCRPC). These authors included six retrospective studies (also assessed for quality according to the Newcastle-Ottawa scale and reported according to the PRISMA statement) for a total of 201 patients analysed. Included studies required at least 10 participants, patients had to be diagnosed with mCRPC based on ^{68}Ga-PSMA PET/CT and had to have completed at least one treatment cycle of ^{225}Ac-PSMA-617. Only retrospective studies were included and hormone-sensitive patients that received ^{225}Ac-PSMA were excluded, together with those that suffered from severe leukopenia, low platelets and renal failure. The particular in- and exclusion criteria that were applied by these authors probably explains the lower number of studies included in a later meta-analysis. (Application of such strict exclusion criteria, may however not be a true reflection of typical daily clinical practice).

Dosing schedules of included studies varied (as in the meta-analysis by Satapathy et al.[2]) between a fixed dose of 100 kBq/kg and other dosing strategies that resulted in a range of 4-9 MBq administered per cycle (and a range of 1-6 cycles administered). A study by Sen et al.[11] was included in this meta-analysis, but not in the one by Satapathy. This study included 38 heavily pre-treated patients (all of whom had received Docetaxel). All patients had an ECOG of <2, and almost 90% had a Gleason score of above 8. Unfortunately, the baseline s-PSA values were not reported. Interestingly, these authors reported hearing loss (in 2 patients) as a side effect of treatment.[11]

The primary endpoint for included studies was biochemical treatment response evaluation according to the criteria defined by the Prostate Cancer Clinical Trials Working Group 3[12] (PCWG3), which included any prostate specific antigen (PSA) decrease and PSA decrease greater than 50% from baseline. Secondary endpoints included reports on overall survival (OS), progression-free survival (PFS), molecular response, and any toxicity. Molecular response was based on ^{68}Ga-PSMA PET/CT interpreted according to the RECIST 1.0 criteria[13] and as in the case of the previous authors, the proportion of patients with complete response (CR) and partial response (PR) was grouped together as the combined molecular response rate. The pooled biochemical response demonstrated any decrease in s-PSA in 87% of patients, with a decrease of more than 50% detected in just over 66%. They also found a pooled overall survival of just over a year (12.5 months) and progression-free survival of just over 9 months (9.1). Their report of a higher s-PSA response rate reflects the strict selection of only four studies (with a specific focus on biochemical response) and the absence of any significant heterogeneity.[3]

Consistent with the previously discussed meta-analysis, xerostomia was the most frequently reported side effect, with any degree of occurring in 77.1%, and grade 3 occurring in only 3.0%. Anemia was the next most common side effect, with any degree reported in 30.3% and grade 3 accounting for 7.5%. Grade 3 leukopenia was reported in 4.5% and thrombocytopenia in 5.5%. Grade 3 nephrotoxicity occurred in 3% of patients. Other less frequently reported side effects included nausea, anorexia, weight loss, fatigue, constipation, hypo-albuminemia, dysuria, and xeropthalmia. (Attributing these clinical complaints to side effects as a result of treatment rather than expected symptoms resulting from the underlying disease process, is of course tricky in retrospective studies without control arms).

Three of the included studies (those by van der Doelen,[14] Feuerecker[15] and Sen[11]), reported on aspects of patient's quality of life. These were based on patient responses to questionnaires, such as the European Organization for Cancer Research and Treatment (EORTC-QLQ30) quality of life questionnaire.[16] Results included reports of improved pain, reduced need for analgesics and augmented response to analgesics. Patients' pain assessments were assessed and reported with use of the Standard Pain Numerical Scale (NPS) and Brief pain Inventory Questionnaire (BPI) for multidimensional pain assessment. The NPS score declined from 5 at baseline to 1 only eight weeks after the second dose of ^{225}Ac-PSMA-617 treatment.[17]

The authors concluded (consistent with the authors of previously discussed meta-analyses) that treatment with ^{225}Ac-PSMA-617 represents an effective alternative treatment option with a good safety profile for patients with metastatic castrate-resistant prostate cancer.[3]

Table 1 Summary of Meta-Analyses Findings

Primary Author & Year	No of Included Studies & Patients	Patient Population Characteristics	No (%) of Pro-Spective Studies	Study Type & Rx Arms	PSMA Type, Dosing	s-PSA Response and CI	Imaging Response	PFS and OS (Months), 95% CI	Xero-Stomia 95% CI	Hemat S/E, Any Grade(>Gr 3)	Renal, Toxicity, Any Grade (>Gr 3)
Satapathy,[2] 2021	10; *n* = 256	Med age = 69.9 yr advanced, progressive mCRPC, exhausted/ ineligible for conventional Rx	1/10; (10%)	Observational, No comparator	617 (9), I&T (1), 100 kBq/kg, 3x de-escalation, 1x tandem	Any response:**66.5%;** >50% decline; **62.8%** (53.4-71.7)	74% on ^{8}Ga-PSMA, PET/CT	**PFS:9.1** (3.6-14.5); **OS: 12.8** (4.5-21.0)	**72.7%**(5%-90%); Grade 3 in 1.2%	Anemia **68.4%** (12.3%); Leukopenia: **35%** (8.3%); Thrombocytopenia: **29.5%** (6.3%)	**19%** (3.8%)
Ma,[3] 2022	6, *n* = 201	All patients previously received and failed 2nd/3rd line therapies (e.g. abilaterol, enzalutamide, apalutamide and ^{177}Lu-PSMA-617)	Zero (0)	Observational; No comparator	617 N/R	Any decline in **87%** (82%-92%), >50% drop in **66.1%** (60%-73%)	54% (25%-84%); PERCIST 1.0	**PFS:9.1** (2.6-15.7), **OS: 12.5,** (6.2-18.8)	Any degree: **77.1%,** Grade 3, 3%	Anemia (any) **30.3%;** Grade 3: 7.5%; Grade 3 Leukopenia: 4.5% Grade 3; Thrombocytopenia: 5.5%	N/R Grade 3 in 3%
Lee & Kim,[4] 2022	9, *n* = 263	Not stated	2/9 (22%)	Observational; No comparator	617 (8), I&T (1), Therapeutic dose range per cycle (reported in 3 studies): 1.5-13 MBq, cycles ranged from 1 to 8.	Any decline in **83.57%;** (78.62%-87.77%), >50%; **60.99%** (54.92%-66.83%)	N/R	**PFS: 9.15** (6.69-11.03); **OS: 11.77** (9.51-13.49)	**Gr 1/ 2; 62.81%** (39.34%-83.46%); Gr 3: N/R	Anemia: Gr 1/2 N/R **(14.39%)** (7.76%−22.63%) Leukopenia: Gr 1/2 N/R; (4.12%) (0.97%-9.31%) Thrombocytopenia; Gr 1/2 N/R (7.18%) (2.70%-13.57%)	N/R
Parida,[5] 2023	8, *n* = 226	Median age: 69.85 yrs, Patients with metastatic castration-resistant prostate cancer (mCRPC), that have received ^{225}Ac-PSMA alpha radioligand therapy, following failure on multiple conventional forms of treatment	1/8, (12.5%)	Observational, Single arm studies with small populations	617 (7), I&T (1), Varied dosing schedules; Median number of treatments: 3 cycles (range 1-8 cycles)	Any decline: **81%** (73-89), >50%, Decline, **60%**	Molecular response (RECIST/PERCIST) assessed in four studies; Overall, **28.6%** (21%-37%); Disease Progression	Pooled median for 5 studies **PFS:** 6 months (IQR 5.5-7); Pooled median OS of four studies was **12.75** months (IQR 8.1-17.5 months)	**73.9%** (67.6%-79.5%)	Anemia grade 3 or higher; **10.75%,** (6.7%-16.1%) in seven studies; Leukopenia: **5.9%** (2.9%-10.6%) in six studies, **Thrombocytopenia:** 4.73%, (2.1%-9.1%) in six studies	**3.76%,** (1.5%7.6%)

A meta-analysis by Lee and Kim[4] that was published in the JNM later in 2022, also evaluates the effects of ^{225}Ac-labeled Prostate Specific Membrane Antigen (PSMA) radioligand therapy (RLT) in metastatic castration-resistant prostate cancer. The authors included nine studies with a total of 263 patients in their analysis, and similarly assessed the quality of the publications according to the Newcastle−Ottawa Scale[9] (scores of included studies ranged from 6 to 8). A study that was not included in the previously mentioned meta-analyses, is the one by Rosar[18] consisting of fifteen ^{177}Lu-naive mCRPC patients with a poor prognosis (defined as the presence of visceral metastases, high total tumor burden with diffuse bone metastases or a short PSA doubling time of <2 months) who received ^{225}Ac-PSMA-617 augmented ^{177}Lu-PSMA-617 RLT.[18]

Therapeutic responses were based on any s-PSA decline as well as those greater than 50%. The pooled proportion of patients with more than a 50% PSA decline was 61% using a random-effects model (in light of the I^2 statistic of 25.25%). For any PSA decline, the pooled proportion was 84% and due to the absence of any heterogeneity in this analysis, a fixed-effects model could be used. Survival outcomes were reported as an estimated mean PFS of just over 9 months (9.15) and an OS of just short of a year, at 11.77 months. These results are again consistent with those of the previously discussed two meta-analysis.[4]

Xerostomia and bone marrow side effects were reported without mention of nephrotoxicity. The pooled proportion of grade 1/2 xerostomia following ^{225}Ac-PSMA therapy was reported as 62.81% and for grade 3/4 anemia this was 14.39%. The pooled proportion of patients with leukocytopenia grade 3 or 4 was 4.12% and for thrombocytopenia grade 3 or 4 it was 7.18%.

The authors concluded (consistent with other meta-analyses) that ^{225}Ac-PSMA RLT may be an effective treatment option for patients with mCRPC and that the most common adverse effects were those of xerostomia and hematotoxicity. Limitations (as with the previous analyses), relate to heterogeneity in clinical practice and protocols and the absence of control arms. This meta-analysis excluded any imaging response assessments and also omitted any data on aspects related to quality of life evaluations.[4]

A 2023 systematic review and meta-analysis by Parida et al.,[5] also focuses on the efficacy and safety of actinium-225 PSMA radioligand therapy in metastatic prostate cancer, and includes eight studies for a total of 226 patients analyzed. The researchers included original clinical studies on ^{225}Ac-PSMA RLT with at least nine patients, and require studies that reported on biochemical response, imaging, survival and toxicity. Reporting was according to the PRISMA statement[8] following quality assessment according to the Newcastle-Ottawa score[9] as with the previous meta-analyses. All of the studies that were included in this analyses, had been included in the previously discussed meta-analyses.

Any decline of s-PSA was found in 81% of patients with 60% of the patients demonstrating a greater than 50% s-PSA decline. In addition, a pooled HR for radioligand naive patients of 0.22 was reported. The most common toxicity reported was xerostomia that was seen in 73.9 % of patients, with most of these being confined to grades one and two. Other reported side effects included hematologic toxicity and nephrotoxicity.[5]

Seven out of the eight selected studies included patients who had received prior treatment with ^{177}Lu-PSMA, which supports the idea that therapy with ^{225}Ac-PSMA may overcome radiation resistance encountered with ^{177}Lu-PSMA treatment. In line with the other meta-analyses discussed, the authors concluded that ^{225}Ac-PSMA RLT is a safe and potentially effective treatment option for patients with metastatic castrate-resistant prostate cancer. Limitations highlighted within this meta-analyses include non-standardized reporting practices amongst studies in addition to the well-known heterogeneity.[5]

The four recent meta-analyses on the use of ^{225}Ac-PSMA RLT[2-5] were all performed according to the PRISMA statement and all made use of the Newcastle-Ottawa score to select the studies with the highest quality. The biggest studies that were consistently included, are those by Sathekge,[19] Kratochwil[20] and Yadav,[21] and as expected, the overall results of these meta-analyses closely reflect the findings of these studies. In order to obtain the most reliable results from the pooled populations, heterogeneity has to be as low as possible to allow the use of a fixed effects model (rather than the random effects model). Unfortunately, this is only very rarely the case and most analyses report a high percentage of heterogeneity that necessitates analysis according to the random effects model. Heterogeneity exists mostly with regards to the following aspects: inconsistent dosing schedules, variable imaging modalities used, non-standardized use of treatment response criteria, lack of inclusion of ECOG, Gleason and baseline s-PSA, lack of the use of quality of life questionnaires, omission of data on PFS and OS, baseline s-PSA and its response after the first cycle, side effects and toxicity.

In what is to date the largest retrospective study, the data from 488 patients collected from seven centers considered to represent Australia, India, Germany, and South Africa were combined and analyzed with the aim of evaluating the safety and tumor control achieved by ^{225}Ac-PSMA targeted radionuclide therapy.[22] Patients of any age and any ECOG with metastatic castrate-resistant prostate cancer who had received at least one cycle of 8 MBq of ^{225}Ac-PSMA were included. Overall, patients had a median age of 68.1 years, they were heavily pre-treated (treatments included taxanes, chemotherapy, treatment with ^{177}Lu-PSMA and radium-223) and had received a median of two cycles of TAT each (1174 cycles administered in total). The authors reported an overall survival of 15.5 months and a progression-free survival of 7.9 months. Xerostomia was the most frequent side effect reported in 68% of patients, followed by hematological side effects (as expected) and detailed in Table 2. Consistent with previously published data, a decline of greater than 50% in s-PSA was associated with a longer median progression-free survival. Poorer outcomes were associated with those patients with an ECOG of greater than two, those who had

Table 2 Combined Meta-Analyses Results Comparison With WARMTH Results

	Satapathy[2] 2021	Ma[3] 2022	Lee[4] 2022	Parida[5] 2023	Median Combined	WARMTH Act[22] 2024
Any biochemical Response %	66.5	87	83.57	81	**82.3%**	**73%**
>50%	62.8	66.1	60.99	60	**61.9%**	**57%**
Molecular response %	74	54	N/R	28.6	**54%**	**N/R**
PFS (months)	9.1	9.1	9.15	6	**9.1** months	**7.9** months
OS (months)	12.8	12.5	11.77	12.75	**12.6** months	**15.5** months
Xerostomia % (Gr 3)%	72.7 N/R	77.1 (3)	62.81 N/R	73.9 N/R	**73.3%**	**68%** (after the 1st cycle)
Anemia % (Gr 3)%	12.3	30.3 (7.5)	N/R (14.39)	N/R (10.75)	**10.75%**	**81% (13%)**
Leukopenia % (Gr 3)%	8.3	N/R (4.4)	N/R (4.12)	5.9 N/R		**44% (4%)**
Thrombocytopenia % (Gr 3)%	6.3	N/R (5.5)	N/R (7.18)	4.73 N/R		**54% (7%)**
Nephrotoxicity % (Gr 3)%	3.8	N/R (3)	N/R N/R	3.76 N/R	**3.78%**	**5%**

anemia prior to therapy, patients with visceral- or peritoneal metastases and those who received prior treatment with taxane-based chemotherapy, ADT and ^{177}Lu-PSMA.[22]

Combining the results from the four meta-analyses as a median value for each outcome parameter and every side effect reported, it is expected that these results should be similar to those obtained by the WARMTH study. The biggest differences are noted with regards to the poorer biochemical response (73% vs 82.3%) and progression-free survival (7.9 vs 9.1 months) reported from the WARMTH data (See Table 2). The overall response reported by WARMTH is slightly better (15.5 vs 12.6 months), whilst the molecular response was not reported. Side effects appear similar to those of the combined meta-analyses with regards to xerostomia (68% vs 73.3%) grade 3 anemia (13% vs 10.75%) and nephrotoxicity (5% vs 3.78%), with the rest of the data difficult to compare in the absence of more detailed reporting. Observed differences could possibly be attributed to less stringent inclusion criteria (compared to the PRISMA statement requirements), possible omission of important contributors and a greater risk of bias.

Side Effects Management

Although several attempts have now been made to try to minimize the frequency and severity of xerostomia, there is insufficient evidence to date to advocate one approach over another. Strategies that have been implemented to various levels of success, include cooling of salivary glands,[23,24] botulinum injections,[25] monosodium glutamate,[26-28] and anticholinergic agents,[29] amongst others. De-escalation strategies and tandem treatment approaches present practical approaches that seem promising. Future solutions may very well be found in newer formulations of PSMA,[30] novel chelators[31] and innovative delivery systems.[32] Very little is reported regarding the management of hematotoxicity of any grade, and inclusion of this aspect in a treatment guideline may be valuable.

Interesting Clinical Scenarios

The earliest reports by the Heidelberg group, highlighted elegantly by means of a swimmer's plot,[20] the positive effect of targeted alpha therapy with actinium-225 on the duration of tumor control. Even in patients with metastatic castrate-resistant prostate cancer that have already exhausted many (if not all) conventional treatment modalities. Reports on the use of ^{225}Ac-PSMA in clinically hopeless situations is accumulating, with several case study reports emerging on the successful treatment of widespread lung metastases[33] and brain metastases.[34] The combined information provided by the discussed meta-analyses echo the positive effect on outcomes and the relatively low frequency of side effects. It therefor seems pertinent to evaluate ^{225}Ac-PSMA's performance earlier on in the treatment landscape for a fair comparison and level playground with other treatment modalities.

The first pilot study to evaluate this possibility, included 17 chemo-naïve patients[35] with advanced metastatic prostate cancer that were either ineligible for chemotherapy or who declined such therapy. These patients were treated according to a de-escalation dosing strategy, and the majority had received three cycles of treatment that was administered two months apart. Treatment response was assessed based on s-PSA levels and image findings on ^{68}Ga-PSMA PET/CT. Fourteen patients demonstrated a s-PSA decline of greater or equal to 90% (of whom seven patients had an undetectable s-PSA after two or three cycles). Fifteen patients had a greater than 50% decline in lesion avidity on ^{68}Ga- PSMA-PET/CT, which included 11 patients with complete resolution of all metastatic lesions. Patients remained in remission for 12 months post-therapy. Side effects consisted mostly of grade 1 and 2 xerostomia. Grade 3 anemia occurred in a single patient with widespread bone marrow metastases and nephrotoxicity was reported in one patient with a single kidney and pre-existing renal impairment. This remarkable result in a group of chemo-naïve patients make a compelling case for further evaluation of targeted radionuclide therapy early on in the disease process. This sentiment has also recently been expressed by Agrawal in a paper entitled: "...Is it the new beginning?".[36]

Next, let us consider the post-androgen deprivation (ADT) setting. ADT successfully deprives the tumor of androgens, normalizes serum levels of prostate-specific antigen and produces an objective tumor response in over 90% of patients for an average duration of 18-36 months. The subsequent treatment strategy often includes newer anti-androgen drugs such as abiraterone acetate and enzalutamide or sipuleucel-T, depending on patient suitability, physician preference, and availability. Low- and middle income countries often do not have access to the afore-mentioned drugs, which prompted the Pretoria group in South Africa to evaluate the use of ^{225}Ac-PSMA in this clinical setting.[37] Fifty-three patients with mCRPC were treated with a total of 167 cycles of ^{225}Ac-PSMA directly after their androgen deprivation treatment (ADT) and evaluated for outcomes and side effects.

Forty-eight patients (91%) demonstrated a s-PSA decline of at least 50%, and 51 patients (96%) had any decline in PSA. PET findings with ^{68}Ga-PSMA became negative in an impressive 57% of patients. A s-PSA decline of at least 50% was predictive of both progression-free (PFS) and overall survival (OS). The estimated median PFS was just under two years (22 months) for patients with a PSA decline of at least 50% compared to just four months for patients with a PSA decline of less than 50%. Similarly, the median estimated OS was 9 months for patients with a PSA decline of less than 50% but was not yet reached at the last follow-up (at 55 months post-treatment) for patients with a PSA decline of at least 50%. As demonstrated in previous studies, the most frequently reported toxicity was grade 1 and 2 xerostomia, which was observed in 81% of patients. No severe hematotoxicity occurred, and three patients suffered from grade 3-4 nephrotoxicity. Once again, these impressive results, make a compelling case for further comparative studies earlier on in the treatment of prostate cancer.[37]

In a 2023 study, the Pretoria group reported the preliminary findings on a group of 21 hormone-sensitive prostate cancer patients treated with 68 cycles of ^{225}Ac-PSMA. Eighty-six percent of patients demonstrated a greater than 50% decline in s-PSA (which became undetectable in four patients). The median PFS was 9 months and 50% of the patients were still alive at 34 months post-treatment.[38]

Widespread skeletal metastases represents another interesting clinical scenario, whereby PET/CT imaging resembles the well-known "superscan" appearance first coined on whole body scintigraphy. Diffuse bone marrow involvement is one of the long accepted theoretical indications for targeted alpha therapy thought to minimize the off-target radiation. In order to evaluate whether hematological toxicity would be a clinically relevant concern in this treatment setting, 106 patients with widespread skeletal metastases were reviewed retrospectively.[39] Those with more than 20 skeletal metastases or a superscan appearance on baseline imaging were included and the vast majority of included patients (92.5%) entered treatment with abnormal bone marrow parameters. A good s-PSA response was achieved in just over 80% of patients with a median PFS of 14 months (95% CI: 8.15-19.86) and OS of 15 months (95% CI: 12.8-17.2) achieved. Age, the number of treatment cycles received, and the presence of renal dysfunction were significant predictors of hematologic toxicity.[39]

Patients with oligometastatic disease provides another interesting consideration.[40] The majority of such patients may be best served by surgical- or external beam radiation therapy approaches. However, in cases where the lesions are difficult to access surgically, or where radiation to surrounding vital tissues are inevitable, treatment with ^{225}Ac-PSMA should be considered and it would be interesting to evaluate the outcomes and toxicity in such patient populations.

Imaging

An integral part of ^{225}Ac-PSMA TAT eligibility determination of prostate cancer patients, is the demonstration of sufficient target expression (See Fig. 1 for a suggested eligibility scheme). PSMA-based imaging has convincingly been demonstrated to be superior to conventional imaging modalities such as CT and bone scintigraphy. This was probably most elegantly demonstrated in the ProPSMA trial[41] and supported by the recent inclusion of ^{68}Ga-PSMA PET/CT in the NCCN guidelines for prostate cancer management.[42] Several SPECT and PET imaging options for evaluation of sufficient PSMA expression exist. For SPECT imaging, the largest body of evidence exists for ^{99m}Tc-PSMA,[43] whilst various options are available for PET imaging, with PSMA-11 and PSMA I&T amongst the most commonly formulations used.

A study by Albalooshi et al.[44] compared ^{99}Tc-PSMA to ^{68}Ga-PSMA in 28 men with prostate cancer. Participants underwent both studies around two weeks apart without any interim interventions. The authors found that ^{68}Ga-PSMA PET/CT detected more lesions compared to ^{99m}Tc-PSMA SPECT/CT, but that ^{99m}Tc-PSMA SPECT/CT was as accurate as ^{68}Ga-PSMA PET/CT in M-staging. Detection rate was comparable between the two techniques particularly in patients with PSA levels greater than 2.1 ng/ml.[44] A larger, more recent study retrospectively analyzed the PSMA-SPECT/CT scans of 20 healthy volunteers compared to a 100 prostate cancer patients and found high accuracy with ^{99m}Tc-PSMA-I&S in primary staging, local recurrence and metastatic detection during restaging. Their findings led them to conclude that ^{99m}Tc-PSMA-I&S-SPECT/CT could be easily integrated into routine clinical practice. Direct comparisons in larger prospective studies are needed.[45]

PSMA for PET imaging is most frequently labelled to gallium-68 or fluorine-18, depending on access to and availability of gallium-68 generators or nearby cyclotrons. These options include the FDA-approved (for staging and biochemical recurrence in prostate cancer) ^{68}Ga-PSMA-11, ^{18}F-DCFPyL, ^{18}F-PSMA-1007 as well as ^{68}Ga- PSMA-I&T, and ^{18}F-rhPSMA.

A systematic review and meta-analysis that included 24 studies,[46] recently investigated whether ^{18}F-PSMA PET/CT is significantly different from ^{68}Ga-PSMA in the primary diagnosis and/or secondary staging of prostate cancer following biochemical recurrence. The two most commonly used ^{18}F based PSMA tracers were ^{18}F-DCFPyL and ^{18}F-PSMA-1007.

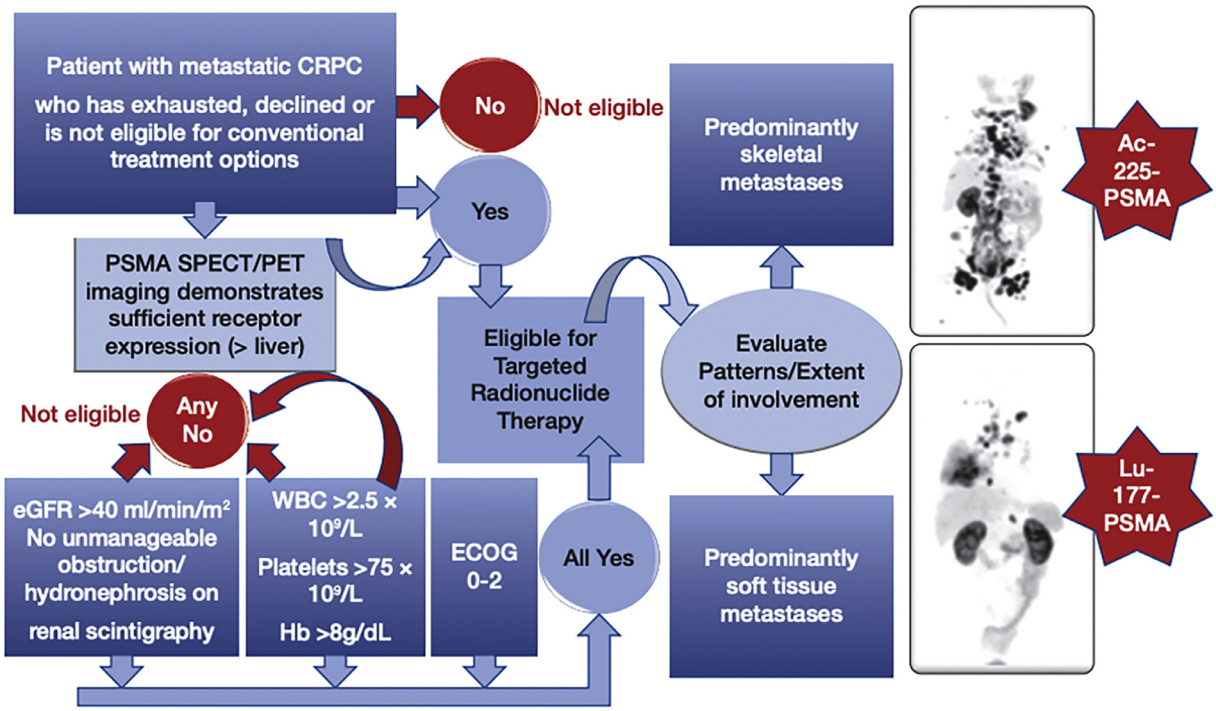

Figure 1 A suggested eligibility assessment (used with permission Vorster M & Sathekge MM. Theranostics in Metastatic Castrate Resistant Prostate Cancer 2021 May).[56]

Newer tracers like ^{18}F-JK-PSMA-7, ^{18}F-rhPSMA-7 and ^{18}F-AlF-PSMA-11 were evaluated in a limited number of studies. ^{18}F-DCFPyL demonstrated a similar lesion detection rate to ^{68}Ga-PSMA-11 with a greater local lesion detection rate due to its predominant hepatobiliary excretory route. However, ^{68}Ga-PSMA-11had a similar local lesion detection rate in studies where furosemide was administered prior to the scan. ^{18}F-PSMA-1007 also demonstrated significant uptake in benign bone lesions.

The authors concluded that imaging with ^{18}F-DCFPyL was comparable to ^{68}Ga-PSMA-11 PET/CT and preferred ^{68}Ga-PSMA-11 over ^{18}F-PSMA-1007 due to the latter's higher uptake in benign bone lesions. Overall, there was not enough evidence to differentiating the radiotracers based on their clinical impact.[46]

Prognostication Factors

Reports are now starting to emerge on patients that have survived for longer than 2 years, and even up to 5 years post-targeted alpha therapy.[6] How can we then predict which eligible patients are most likely to respond well to targeted alpha therapy to best make use of the limited supply and access to actinium-225? A 2019 study by Sathekge et al., evaluated factors that are predictive of progression-free and overall survival in 73 patients with metastatic castrate-resistant prostate cancer that received ^{225}Ac-PSMA.[19]

Baseline PSA, any PSA decline and PSA decline of at least 50% were statistically significantly associated with longer PFS and OS. Prior chemotherapy or radiation therapy, and a normal baseline hemoglobin level were associated with longer PFS and OS in univariate analysis. Of these, only a PSA decline of at least 50% remained significantly associated with overall survival on multivariate analyses. Multivariate analyses demonstrated a negative association between prior ^{177}Lu-PSMA therapy and PFS.[19]

In a study that included 63 patients with metastatic prostate cancer with resistance to conventional forms of therapy and who had received at least 2 cycles of ^{225}Ac-PSMA-617, the researchers highlight the following statistically significant poor prognostic indicators for overall survival: a less than 50% decline in s-PSA ($P = 0.031$), an ECOG performance status of 2 or higher ($P = 0.048$), and radiological progression (rPD) ($P < 0.001$). Interestingly, in multivariate analysis, only rPD remained as an independent prognostic factor with a hazard ratio (HR) of 8.264 ($P = 0.004$). The researchers conducted the radiological tumor response assessment making use of a combination of soft tissue assessment as per RECIST 1.1 criteria and bone lesion assessment according to PCWG3 criteria using a comprehensive criterion "PCWG-modified RECIST 1.1".[47]

PSMA-based imaging, over and above its crucial role in the assessment of treatment eligibility, also provides several clues with regards to prognosis. The Standard Uptake Value (SUV) represents a familiar quantitative tool, which is easily reproduced, and has been used in various studies to select eligibility prior to PSMA-based therapy.[48-50]A range of cut-off values for SUV mean has been proposed, in order to predict treatment response, which of course has to be used cognisant of differences in imaging protocols, software and cameras. Other quantitative measures which has been used in related settings to predict treatment response include the whole-body tumor volume (wbPSMA-TV and wbPSMA-TL).[51]

Resistance to Targeted Alpha Therapy

Part of the attraction of targeted alpha therapy, is found in its suggested ability to overcome resistance to radiation therapy. This has been demonstrated successfully in patients who were initiated on ^{177}Lu-PSMA therapy and subsequently switched to ^{225}Ac-PSMA treatment upon lack of sufficient response or progression of disease. Various tandem approaches[52,53] followed, leading to more unresolved clinical issues related to optimal timing, sequencing and combinations were other treatment modalities, such as PARP-inhibitors.[54,55] The schema in Figure 2 provides a representation of the various tools and available options that help to optimize patient management at various stages during the disease process, and hints at the multi-disciplinary approach needed for optimal patient management and outcomes.[56]

Dosimetry

Dosimetry remains essential to treatment individualization and crucial to informing patient management decisions regarding additional treatment cycles or therapy termination. Imaging without the need for invasive and cumbersome urine-and blood sample collections, are clearly preferable and has worked well with the Lu-177-based therapies. The ^{225}Ac decay chain demonstrates noticeable gamma emission (440 keV, 25.9%; 218 keV, 11.4%), which is unfortunately hampered by the low activity (4-8 MBq) administered during patient treatment. The poor abundance of gamma emissions from daughter radionuclides further complicates imaging.[57]

A recent feasibility study by Delker et al.,[58] demonstrated how a combination of 1000 MBq ^{177}Lu-PSMA-I&T and 8 MBq ^{225}Ac-PSMA-I&T could be used to achieve quantitative SPECT imaging for patient dosimetry purposes. Eight patients with prostate cancer underwent an hour-long single-bed quantitative ^{177}Lu/^{225}Ac SPECT/CT acquisition at 24 h post treatment. A high-energy collimator was used to image the 440 keV peak, with 16 projections per camera head and a 128 × 128 matrix. The authors presented comparative quantitative SPECT/CT images of both ^{177}Lu-PSMA-I&T and ^{225}Ac-PSMA-I&T which was compared to ^{18}F-PSMA-1007 PET/CT. This approach seems feasible and practical and will certainly work well in departments that have adopted a tandem treatment approach.[58]

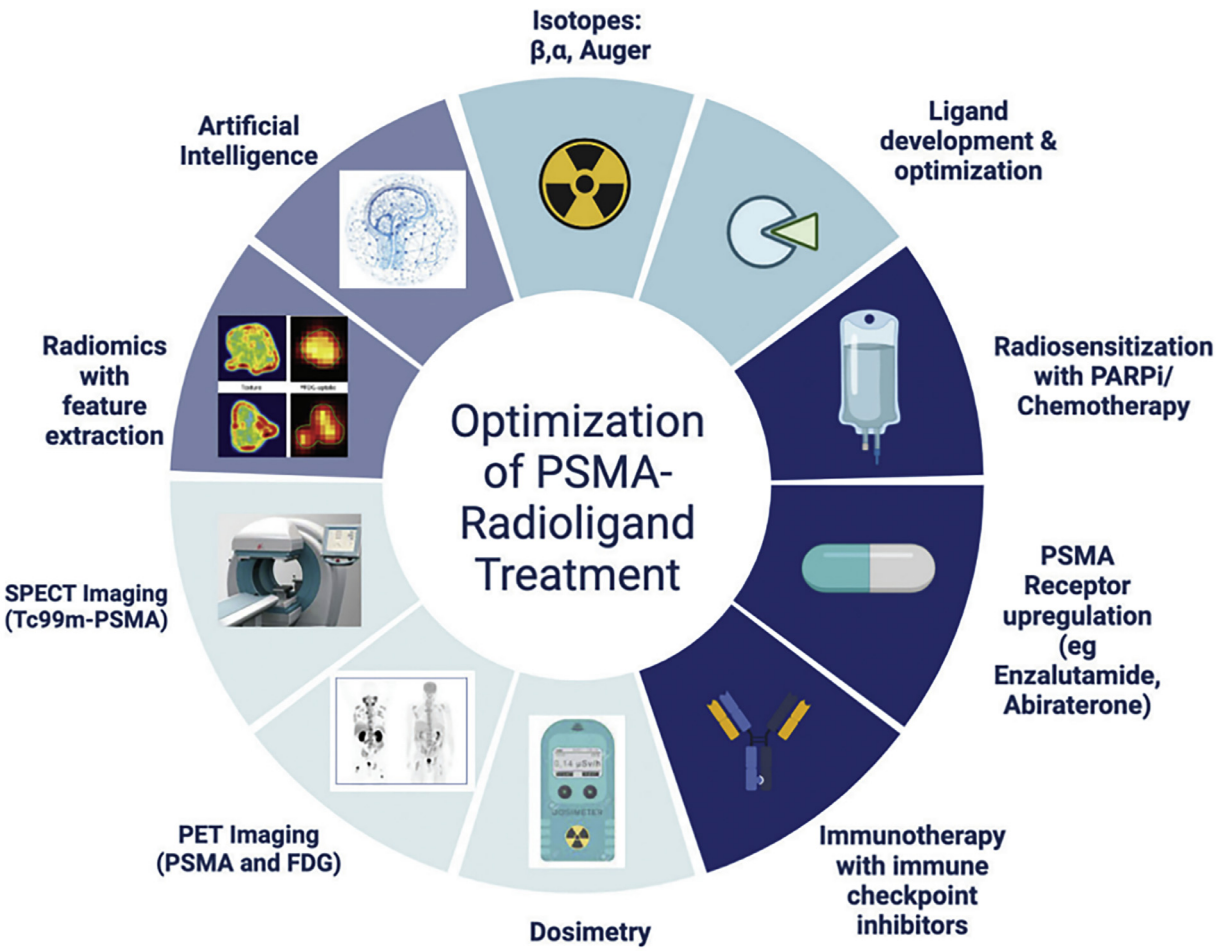

Figure 2 Some of the tools and strategies available for the optimization of prostate cancer management (with permission Vorster & Sathekge, 2021 Theranostics in mCRPC).[56]

Gosewish and colleagues[59] in an "Image of the month" demonstrated a similar approach using only Ac-225 images with a high-energy general-purpose collimator centered around the 440 keV peak with a 20% window. A comparison with the pre-therapy ^{18}F-PSMA-I&T PET/CT was done and effective half-life information that was determined from a previous ^{177}Lu-PSMA-I&T imaging sequence was used in the calculations.[59] (See Fig. 3 for a similar imaging approach followed at the department of Nuclear Medicine at the Inkosi Albert Luthuli Central Hospital in KwaZulu-Natal, South Africa and compared to pre-therapy ^{68}Ga-PSMA PET/CT images.)

Alternative Alphas

In light of the limited global actinium-225 supply and the production difficulties, it would be important to consider feasible alternatives.[60] Radium-223 dichloride was of course the first FDA-approved alpha used in prostate cancer, but is limited to treatment of skeletal metastases only.[61] It may play a role in combined therapy regimes, though. Other alpha emitters that have demonstrated potential include astatine-211, Pb-212, thorium-227, terbium-149 and bismuth-213. The aforementioned have all been complexed to PSMA inhibitors and evaluated in preclinical and clinical studies for their efficacy and safety in the treatment of mCRPC. ^{225}Ac and its short-lived daughter radionuclide ^{213}Bi, have been most extensively studied in clinical settings.[62] Terbium-149, despite its ideal properties and versatility presents multiple challenges regarding supply, production and chemical separation, and as such may not provide a solution to the challenges already presented by Ac-225 supply. Terbium-161 with its combination of auger and beta emission, represents another interesting possibility.[63]

Ongoing Clinical Trials

Dawson and colleagues[64] recently compiled a comprehensive summary of clinical trials (as registered on ClinicalTRials.gov) with active recruitment that involve diagnostic and/or therapeutic PSMA-based approaches. They found 210 ongoing trials (45 outside of prostate cancer indications) with

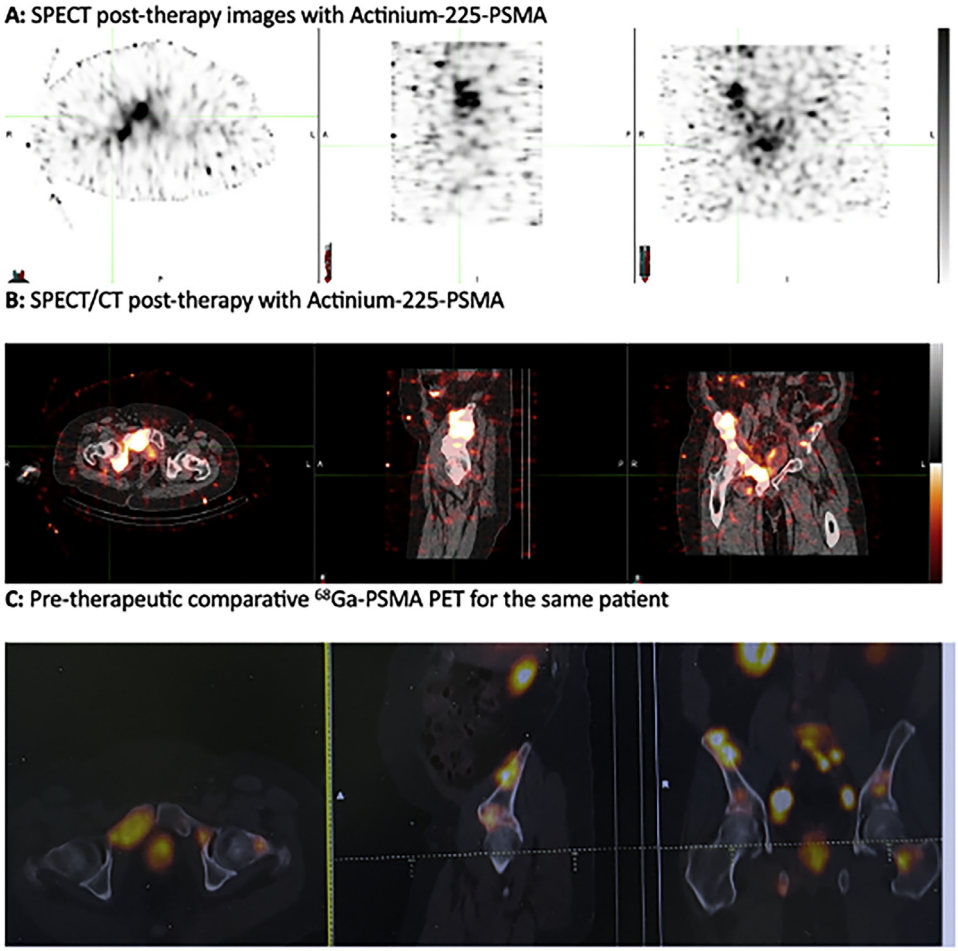

Figure 3 Imaging for dosimetry purposes with a high energy collimator (440keV) at 24 hours post-injection of 8 MBq ^{225}Ac-PSMA-617.

results anticipated by 2030, and suggest that PSMA PET will become an integral part of the work-up of prostate cancer patients to determine the most appropriate treatment approach.

The authors highlighted several ongoing phase 1 and 2 trials that are focused on exploring novel diagnostic PSMA-targeting radioligands and the influence that this is likely to have on treatment decision-making in all stages of prostate cancer management. These include PSMA-targeting T-cell/antibody therapies, which may serve as proof of concept for PSMA-targeted immunotherapy. Randomized phase 3 trials include several that evaluate clinical outcomes with PSMA-PET directed therapy as compared to standard of care management strategies, which should provide valuable clinical information.

Additional phase three trials aim to evaluate radioligand therapy in the settings of hormone sensitive and castrate resistant metastatic prostate cancer. These trials are expected to provide valuable information on the ideal sequencing of and combinations with existing therapies such as androgen deprivation therapy, androgen receptor signaling inhibitors, and chemotherapy. Novel radioligand treatments and dose optimization will also be explored in various randomized phase 2 trials.[64]

Standardization of PSMA-PET reporting, response assessment, quantitative metrics and personalized dosimetry is required to optimize knowledge translation and future trial imaging outcomes.

Conclusion

The evidence to date strongly supports the use of ^{225}Ac-PSMA radioligand therapy as an alternative treatment strategy in patients who have exhausted (or are ineligible for) conventional therapies. The side effect profile of this treatment modality has consistently been shown to be acceptable, consisting mainly of lower grades of xerostomia and hematological side effects. Emerging data, however, suggests that the impact of ^{225}Ac-PSMA radioligand therapy may be even greater if it is introduced earlier in the treatment landscape and possibly in combination with other treatment modalities.

It is imperative that such treatment decision-making take place within a multi-disciplinary team that includes urologists, oncologists, nuclear physicians, radiologists, palliative care physicians, pathologists (and preferably a dietician, and a psychologist) to truly achieve holistic, personalized, precision prostate cancer treatment.

The many unresolved issues that relate to patient selection criteria, standardization of treatment protocols, minimization of side effects, dosimetry, determination of the optimal radiopharmaceutical formulation (best alpha emitter, PSMA type, chelator, delivery system) could potentially be addressed by compilation of an international treatment guideline and from the results of the myriad of ongoing clinical trials designed to address these issues.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Mariza Vorster: Methodology, Validation, Writing – original draft, Writing – review & editing. **Mike Sathekge:** Conceptualization, Visualization, Writing – review & editing.

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