PSMA Theranostics in advanced prostate cancer: an evolving option

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ABSTRACT:

Prostate-specific membrane antigen (PSMA) has significantly altered the global landscape of prostate cancer imaging in recent years due to its reported high sensitivity and specificity. Evidence for the use of PSMA PET at both the staging and restaging settings is promising, and novel applications such as radio-guided surgery add further value to this exciting imaging modality. However, PSMA has yet wider applications that extend away from diagnostics and into therapeutics: the so-called “theranostic” approach.

- Radioligand therapy (RLT) with PSMA is an exciting therapeutic alternative to the existing management options already in use for patients with metastatic castrate-resistant prostate cancer (mCRPC).
- To date, most evidence exists regarding small-molecule PSMA inhibitors bound to beta-emitting radioisotopes such as ^{177}Lu (Lu-PSMA)
- Small prospective phase II data supports the safety and efficacy of Lu-PSMA in men with heavily pre-treated progressive mCRPC
- Several late-phase randomised trials of Lu-PSMA are underway, with many more in the pipeline.
- Early results are encouraging, indicating that the theranostic approach may play a vital role in management of advanced prostate cancer and perhaps even in much earlier disease states.

This review provides an update for multidisciplinary teams on the current and potential future applications of theranostics in prostate cancer.

1. Introduction

Since the mid-2000s, researchers have been investigating prostate-specific membrane antigen (PSMA) as a target for imaging prostate cancer(1, 2). In the last five years, the introduction of PSMA positron emission tomography/computed tomography (PET/CT) has drastically altered the global landscape of prostate cancer staging, due its reported high sensitivity and specificity compared to conventional imaging (3). PSMA has yet wider applications that extend away from diagnostics and into therapeutics: the so-called “theranostic” approach. Encouraging data is emerging on the use of radiolabelled PSMA ligands in heavily pre-treated metastatic castrate-resistant prostate cancer (mCRPC) patients, indicating that the theranostic approach confers a promising oncological benefit, with a promising side-effect profile (4-6). As we have seen with other novel agents in mCRPC, the strategy of bringing novel life-prolonging therapies (LPTs) forward into earlier disease stages, usually confers a considerable survival benefit for patients(7). As this exciting research area advances, the role of PSMA-based theranostics will be defined more clearly, including its potential role in earlier disease states. In this review, we provide an update for urologists, uro-oncologists and uro-imaging specialists on the current and potential future applications of theranostics in prostate cancer.

2. What is theranostics?

The fundamental principal of theranostics lies in combining a **therapeutic** agent with a **diagnostic** radiotracer. The concept is by no means a novel one in the setting of cancer management. Indeed, the use of radioiodine as a tracer was described in 1938(8) followed by its use in higher, therapeutic doses to result in “arrest, if not regression” of a metastatic thyroid carcinoma (9). Over 70 years later, this approach is still common practice for management of both benign (10) and malignant (11)

thyroid disease. A diagnostic scan occurs using a radioactive isotope of iodine before therapy is administered with high-activity Iodine-131 (^{131}I) capable of DNA damage through particle emission. Similar approaches are used in pheochromocytoma and neuroblastoma where the radiopharmaceutical used to image and then treat is radiolabelled iodine-131 meta-iodobenzylguanidine (^{131}I MIBG) (12). The most recent success story in theranostics comes in its application to midgut neuroendocrine tumours (NETs) as demonstrated in the NETTER-1 trial (13). This landmark randomised controlled trial enrolled 229 patients with advanced somatostatin-receptor positive midgut NETs, randomising patients to either theranostic management with ^{177}Lu -DOTATATE or current standard of care treatment with somatostatin analogues. Estimated progression-free survival at 20 months was 65.2% in the ^{177}Lu -DOTATATE group, compared to 10.8% in the control group. This was the first multinational phase III RCT in the field, which validated over 17 years of research into peptide-receptor radionuclide therapy, and subsequently led to both FDA and EMA approval in the following months.

In genitourinary (GU) oncology, theranostics is now being harnessed for the management of prostate cancer, particularly in the high-risk group of men in the mCRPC population. This emerging option hinges on the use of PSMA as a target. PSMA is a class II transmembranous glycoprotein, also known as glutamate carboxypeptidase II and encoded by folate hydrolase I (FOLH1) (14), that is expressed on the cell surface of prostatic epithelial cells. It is overexpressed 100 to 1000-fold on over 90% of prostate cancer cells (15), making it an ideal target for molecular imaging and radioligand therapy (RLT). Furthermore, PSMA expression is associated with more aggressive prostate cancers, androgen independence (16) and acts a predictor of poorer prognosis (17). However, despite its name PSMA is not 100% specific to the prostate, and is also expressed in other cancers such as various subtypes of bladder cancer(18), renal cell carcinoma and papillary thyroid carcinoma (19, 20), for all of which it is undergoing research as a target for imaging (21-23) with the potential for theranostic management. Furthermore, PSMA is found in select normal tissue including the salivary and lacrimal glands, duodenum and kidneys amongst others (24) which has posed issues with toxicity in its theranostic application that will be outlined later.

3. PSMA in Imaging of Prostate Cancer

The staging of prostate cancer has traditionally relied on conventional imaging methods such as CT and bone scintigraphy to characterise distant disease.

However, a 2008 meta-analysis from Hovels et al (25) highlighted the shortcomings of conventional imaging in primary staging, with the pooled sensitivity and specificity of CT reported at 42% and 82% respectively. For staging after biochemical recurrence (BCR), the conventional imaging modalities employed are abdomino-pelvic CT to detect regional lymph node disease and skeletal scintigraphy for bone metastases, yet the yield of these techniques at low PSA levels is very poor indeed (26). Bone scintigraphy, for example, has been shown to be positive on less than 5% of scans at PSA values of <7ng/ml (27). The recognised limitations of conventional imaging prompted investigation into functional imaging with PET/CT using fluorodeoxyglucose (FDG) or choline-based tracers (for example ^{11}C -choline or ^{18}F -FCH), but these methods have limitations of their own. FDG-based PET imaging can be of limited value due to the low glucose metabolism of prostate cancer (28), and ^{11}C -choline has a half-life of only 20 minutes, limiting its use to centres with their own cyclotron (29). The amino acid tracer ^{18}F -FACBC (fluciclovine), has been shown to be vastly inferior to PSMA in a prospective study of men with BCR, with a detection rate of 26% compared to 56% in the same set of 50 men (OR 4.8 [95% CI 1.6-19.2; $p=0.0026$]). (30).

More recently, there has been a surge of data published on the superior diagnostic performance of PSMA-based PET imaging (31). The most widely studied agents are comprised of small-molecule ligands radiolabelled with ^{68}Ga or ^{18}F that bind to PSMA and are subsequently internalised by the target cell. Such ligands not only bind with great affinity to the PSMA receptor, but have rapid plasma clearance, leading to images with high tumour-to-background contrast (32). Of these, ^{68}Ga -PSMA-11 (also known as ^{68}Ga -PSMA-Glu-urea-Lys-(Ahx)-HBED-CC and ^{68}Ga -HBED-CC-PSMA) is most widely used and there is a growing body of evidence to support its use in various disease states.

The two key PET radioisotopes used for labelling are ^{68}Ga and ^{18}F . Most clinical experience to date has been with ^{68}Ga -labelled PSMA tracers. ^{18}F radioisotopes are

short-lived and as a result necessitate an onsite cyclotron. ^{68}Ga tracers rely on a $^{68}\text{Ge}/^{68}\text{Ga}$ generator and radio-pharmacy, allowing independent production. Furthermore, ^{68}Ga has a physical half-life of 67.71 min and is therefore compatible with the pharmacokinetics of a number of radiopharmaceuticals(33).

3.1. *Primary Staging*

In the setting of primary staging, there are few studies reporting the accuracy of functional imaging using ^{68}Ga -PSMA-11, particularly those with adequate histopathological reference. However, Maurer et al's 2015 prospective cohort of 130 patients with intermediate to high-risk prostate cancer reported a sensitivity of 66% and specificity of 99% for ^{68}Ga -PSMA-11 PET imaging in detecting nodal metastases on a per-patient analysis (34). Furthermore, there was significant discordance between morphological imaging findings versus those from ^{68}Ga -PSMA-11 PET. Large retrospective series have compared the performance of PSMA PET/CT against mpMRI and radical prostatectomy histopathology, reporting high accuracy for PSMA PET/CT as a "one stop" staging scan for the primary in the prostate, along with regional and distant disease(35, 36). An updated meta-analysis from Perera et al (3) earlier this year evaluated the use of ^{68}Ga -PSMA-11 PET/CT and reported a sensitivity and specificity of 75% and 99% respectively in primary staging in a per-patient analysis. However, considerable heterogeneity existed amongst the five included studies used to generate these data, three of which were retrospective. Since these data were published, the largest retrospective analysis of the use ^{68}Ga -PSMA-11 PET imaging in primary staging of prostate cancer was published in the BJUI by Yaxley et al, which detected metastases in 12% of 1253 men of varying disease grades (37). The study provides compelling evidence in favour of PSMA-based imaging in primary staging, but suffers similar shortfalls to previous series in that it is retrospective in nature. A further retrospective series from Australia comparing mpMRI, PSMA PET/CT and final pathology, demonstrated high accuracy for both mpMRI and PSMA PET/CT in identifying index lesions within the prostate(38). These results and those from other meta-analyses (39, 40) are encouraging, but we await definitive results from the proPSMA trial (41), a multicentre prospective study of ^{68}Ga -PSMA-11 PET/CT vs conventional imaging in the setting of primary staging. This randomised crossover trial includes 300 men with high risk disease (International Society of Urological Pathology [ISUP] grade group 3

and higher, PSA >20ng/ml or clinical stage T3 and above) and aims to provide the most robust, high-level data on the diagnostic accuracy of PSMA-PET/CT for detecting both nodal and metastatic disease to date. Importantly, it will also report management impact. Ultimately, it may well provide validation for a new gold standard in primary staging of prostate cancer.

3.2. *Biochemical Recurrence and Restaging*

PSMA PET is increasingly being recognised as a useful imaging modality to guide salvage treatment in patients with biochemical recurrence (BCR), see example in Figure 1, and it is in this setting that the most extensive research has taken place. For example, Van Leeuwen et al (42) provided early data on the utility of ^{68}Ga -PSMA PET in a cohort of 70 patients with BCR after radical prostatectomy (RP). It is recognised that salvage radiotherapy (RT), the only curative option post-RP, is most effective at low PSA levels (43). The median PSA in this cohort was 0.2ng/ml, in patients with no evidence of recurrence on conventional imaging. 38 patients (54%) had pathological PSMA uptake, with 24 (34%) deemed “definitely positive” lesions and 14 (20%) as “probably positive”, indicating the superiority of PSMA-based imaging. Furthermore, a large retrospective analysis of 1007 patients who had undergone various primary treatment approaches (including RT, RP, chemotherapy, androgen deprivation therapy, high intensity focused ultrasound [HIFU] and combinations of these) reported pathological ^{68}Ga -PSMA-11 PET scans at PSA values of <0.2, 0.2-0.5, 0.5-1 and 1-2ng/ml of 46%, 46%, 73% and 80% respectively (44). Various meta-analyses (3, 45, 46) have added to the evidence in favour of ^{68}Ga -PSMA-11 PET scanning for BCR. Perera et al’s (3) predominantly retrospective meta-analysis reported positivity rates of 33%, 45%, 59%, 75% and 95% for PSA levels of <0.2, 0.2-0.49, 0.5-0.99, 1-1.99 and >2ng/ml respectively in the BCR group (combined post-RP and post-RT). Subsequently, the 2019 European Association of Urology guidelines (43) have been updated to reflect this, recommending PSMA PET/CT for PSA values of >0.2ng/ml in those having undergone treatment with curative intent (RP or RT). These changes have been supported by the recent results of a prospective, single-centre, single-arm, comparative study in which patients underwent both ^{18}F -fluciclovine and ^{68}Ga -PSMA which demonstrated that the latter tracer was superior (30). Disease was detected by PSMA in 56% of patients but only 26% by ^{18}F -fluciclovine. By improving the diagnosis of previously

unseen local or oligometastatic disease, ^{68}Ga -PSMA-11 PET/CT is no doubt impacting management, as demonstrated by Han et al (45) who reported that 54% of patients underwent a change in management secondary to PSMA-based imaging findings. As with findings in other meta-analyses, it must be noted that substantial heterogeneity was present and 10 of the 15 studies included were retrospective in nature. Despite this, the data are promising and highlight the importance of PSMA-based imaging in the management of BCR patients, and further research will determine the impact on patient outcomes and prognoses.

3.3. Novel Applications

3.3.1. Radio-guided Surgery

Despite the improved detection offered by ^{68}Ga -PSMA-11 PET/CT, surgical detection and resection of small metastatic lesions, especially sub-centimetre lymph nodes, continues to present a major challenge. In an attempt at combating this challenge, radio-guided surgery (RGS) has been developed at the Technical University of Munich (47). This novel technique, dependent on a positive preoperative ^{68}Ga -PSMA-11 PET/CT, uses weakly-radiolabelled PSMA ligands such as ^{111}In -PSMA-I&T or $^{99\text{m}}\text{Tc}$ -PSMA-I&S that allow for preoperative SPECT imaging followed by intraoperative surgical guidance with the aid of a gamma probe. $^{99\text{m}}\text{Tc}$ -PSMA-I&S has proven the most suitable agent due to its lower cost and greater availability, and initial feasibility trials have provided encouraging results (48) with extremely high rates of intraoperative tumour detection, significant PSA reduction and increased BCR-free survival rates. Horn et al (47) report a retrospective analysis of 121 patients who underwent PSMA-RGS after BCR (median PSA: 1.13 ng/ml) post-RP and positive PSMA-PET imaging for metastatic lymph nodes or avidity in the former region of the seminal vesicles, wherein there was a complete biochemical response (PSA <0.2ng/dl) for 66% of patients, and a PSA decline of >50% in 77% patients. Of the 121 patients, metastatic tissue was removed in 120. Longer-term follow-up and prospective data are necessary to definitively determine the impact of metastasis-directed therapy such as this. Indeed, the first prospective clinical trial, the TRACE study (NCT03857113), is now underway. Overall, RGS is feasible and

may represent a useful weapon in the armoury for treating biochemical recurrence at its earliest stage.

3.3.2. Early detection of prostate cancer

Recent evidence from high-profile randomised trials (49-51) has confirmed multiparametric MRI as the gold standard imaging modality for initial prostate cancer workup prior to biopsy. The PRECISION trial (50) showed that it was possible to reduce the detection of clinically insignificant cancers, with 22% detected in the standard of care arm (12-core TRUS biopsy) vs just 9% in the mpMRI arm. Not only does mpMRI help to reduce overdiagnosis, but it increases the likelihood of detecting clinically significant cancers (38% in mpMRI group vs 26% in TRUS biopsy group). By reducing the number of biopsies performed, mpMRI triage is currently the safest and most cost-effective option, as well as the most accurate. However, the negative predictive value of mpMRI is only 76%, indicating that up to 1 in 4 men will have a clinically significant cancer despite a negative MRI. Little research has been performed to evaluate the impact that PSMA-PET/CT may have in the initial diagnosis of prostate cancer, particularly in the group of men with a negative MRI but with a clinical suspicion of cancer, though there is early evidence that PSMA PET/CT may be of use in this subset of patients (52). While the evidence is currently on the side of mpMRI, the PRIMARY trial (ACTRN12618001640291) aims to compare the accuracy of PSMA-PET/CT to MRI in the biopsy-naïve setting to aid localisation of prostate cancer.

3.3.3. PSMA PET/CT in Theranostics

In their recent review, Farolfi et al aptly describe PSMA-based imaging as “the gatekeeper for PSMA-based radioligand therapy (RLT)” (53). A key principle in theranostics is that of theranostic pairs; in the setting of prostate cancer management, a positron-emitter (e.g. ^{68}Ga) labelled to a PSMA-based ligand allows detection of a lesion and determines suitability for therapy via PET imaging, before a beta- (e.g. ^{177}Lu) or an alpha-emitter (e.g. ^{225}Ac) is labelled to the same/similar ligand with theranostic intent. A direct analogy can be made with the use of Herceptin in the management of breast cancer, where the monoclonal antibody to HER2 is only administered upon diagnosing a patient with HER2 receptor-positive cancer; in

prostate cancer, PSMA-based RLT is administered only to those with positive PSMA-based imaging. The importance of PSMA-PET/CT is highlighted by its use in ongoing clinical trials, whereby it plays a vital role in identifying patients with PSMA-avid lesions that are suitable for theranostic management.

4. Limitations of PSMA Imaging

While ^{68}Ga -PSMA-11 PET/CT has demonstrated superiority in identifying metastatic disease in patients in the BCR setting compared to conventional imaging (3), it is not without limitations. Absent or low PSMA expression in a proportion of prostate cancers means that discordance may occur between PSMA-based PET imaging and FDG PET/CT imaging (54), which may present difficulties in selecting patients for theranostic intervention. As will be discussed, the phase II Lu-PSMA trial (6) provided some of the first prospective data in favour of ^{177}Lu -PSMA RLT, demonstrating that the theranostic approach has a high response rate with low associated toxicity in mCRPC patients. As part of the trial protocol, patients with advanced PSMA-avid prostate cancer were included in the study, but those with low or absent PSMA expression on ^{68}Ga PSMA PET, or discordant expression on FDG PET/CT, were excluded. Thang et al (54) report on the poor outcomes of the 16 patients excluded from the trial, with a median OS of 2.5 months compared to 13.5 months in those managed with RLT. The theory of excluding patients with low PSMA expression originates from experience of theranostics in neuroendocrine tumours whereby low somatostatin receptor expression or discordant FDG uptake indicates more aggressive and higher-grade clones, predictive of poor response. Whether this subset of patients may still benefit from PSMA RLT, for example, in order to manage tumour-related pain or in combination approaches with existing management options, remains to be seen.

Furthermore, the interplay between systemic treatments and PSMA expression has not been fully elucidated. The effect of androgen deprivation therapy (ADT) on PSMA expression is still a topic of contention, and more studies are warranted to determine the factors that may influence PSMA expression (55). In a retrospective study, of the 31 lesions that were visible in 10 men about to commence ADT, only 14 lesions were visible in eight patients following treatment with ADT. Average duration

of treatment was 229 days (range 42-369 days, median 230 days). The uptake of tracer decreased in 71%. Further research will be required in this area, especially as systemic treatment is being utilised earlier in the disease course.

Vapiwala et al (56) voice concern that the “appetite has outpaced the guidance” when it comes to adopting novel radiotracers in the quest for greater accuracy, and warn about the danger in adopting new imaging techniques without clear evidence. There is clearly a need for well-designed randomised clinical trials to lend credence to the use of PSMA-based imaging in prostate cancer in order to create standardised guidelines. Furthermore, the question arises as to where these novel imaging modalities fit in the paradigm of prostate cancer management, and whether clinicians should be using them alongside existing imaging methods or simply adopting them as a new gold standard. Ultimately, a data-driven response is essential in guiding adoption, and international cross-speciality collaboration is likely to help answer some of the key questions still facing these novel imaging methods.

5. Future Developments in PSMA—based Imaging

5.1. Monitoring

With more accurate molecular imaging modalities, it is possible to standardise and quantitatively measure treatment response. PSMA-PET imaging allows assessment of whole-body tumour burden and a direct volumetric analysis can be made. As a result, solely morphology-based criteria such as the Response Evaluation Criteria in Solid Tumours (RECIST) (57) are being rendered obsolete. Already, new staging frameworks are being developed (58), and it may only be a matter of time before the RECIST criteria are replaced by molecular-based evaluation systems. For example, Bieth et al's early work in producing a combined quantitative index that incorporates anatomic information from CT and functional information from PSMA-PET/CT in determining osseous tumour burden from prostate metastases has shown great promise(59).

5.2. Fluorine-18-labelled Tracers

Tracers radiolabelled with fluorine-18 (^{18}F) are undergoing early phase trials as ^{18}F is of greater clinical availability and has the advantage of eliminating the need for

onsite radiolabelling (53). Results of ^{18}F -labelled small-molecule inhibitors of PSMA such as DCFPyL and PSMA-1007 have shown excellent image quality (60). One particular advantage of ^{18}F -PSMA-1007 is its delayed urinary excretion meaning it may be superior to ^{68}Ga -PSMA-11 in detecting lesions close to the bladder or ureters (61). On balance, current experience suggests these PSMA radiotracers have minor differences and are all suitable for clinical imaging. Availability and cost may ultimately guide selection.

6. PSMA in Theranostics

PSMA-based radiopharmaceuticals have proven their utility as a tool for diagnostics, and are now leading the way in guiding therapeutics. A proportion of men who undergo treatment with curative intent go on to develop advanced disease which can initially be controlled by ADT, but eventually progress into castrate-resistant disease. EAU Guidelines (43) recommend a number of agents based on the presence or absence of metastases including abiraterone acetate, cabazitaxel, docetaxel, enzalutamide, apalutamide, radium-223 and sipuleucel-T. While these therapeutic options have proven to prolong overall survival (OS) (43), there is still room for improvement. Radioligand therapy (RLT) with PSMA is an exciting novel therapeutic alternative that may well play a significant role in the setting of advanced prostate cancer.

The first agents developed to target PSMA through RLT were monoclonal antibodies such as J591 which can be radiolabelled with either ^{90}Y or ^{177}Lu . However, despite promising early results (62), high rates of haematotoxicity were described, likely secondary to the size of antibodies, which are large molecules and therefore undergo slow glomerular clearance, resulting in a longer circulatory half-life and greater radiation exposure to bone marrow (4). Tagawa et al (63) report a Phase II clinical trial in which 47 mCRPC patients received a single dose of ^{177}Lu -J591, 60% of which experienced any PSA decline, and five patients (10.6%) >50% PSA decline, yet grade 4 thrombocytopenia occurred in 47%, and nearly 30% of patients required platelet transfusion.

As a result, small-molecule PSMA inhibitors such as PSMA-617 and PSMA-I&T have since been developed as alternate ligands, offering encouraging early results, with high rates of PSA decline and lower toxicity rates (5, 6). The majority of this early research has focused on PSMA-617 radiolabelled with the beta-emitter ^{177}Lu , which has proven the most favourable radionuclide due to its short maximal tissue penetration depth and long half-life (53). As a result, ^{177}Lu -PSMA-617 not only demonstrates high affinity for PSMA, it is also taken up and retained for prolonged time periods by the target cells, accumulating in the perinuclear location and causing direct DNA damage. Calopedos et al (4) conducted a meta-analysis including 10 studies made up of 369 patients, the majority of which had docetaxel-refractory disease and had failed post-chemotherapy ADT with abiraterone and enzalutamide, who underwent RLT with J591, PSMA-617 or PSMA-I&T on a compassionate use basis. In a subgroup analysis of the small-molecule radioligands (^{177}Lu -PSMA-617 or PSMA-I&T), the pooled proportion of patients experiencing a >50% PSA decline was 51%, and 165 of 238 (69%) patients experienced any PSA decline. Despite this, prospective data was still lacking until very recently, as well as data on hard endpoints such as overall survival and patient-centred outcomes.

The prospective ^{177}Lu -PSMA trial (6) aimed to provide meaningful data on the efficacy of ^{177}Lu -PSMA-617 by reporting not just on rates of PSA decline, but OS, progression-free survival (PFS) and impact on quality of life. This single-arm, single-centre, prospective phase II trial included 30 mCRPC patients, the majority of whom had progressed after taxane-based chemotherapy and second-generation antiandrogens. All patients were screened with a ^{68}Ga -PSMA-11 PET/CT and ^{18}F -FDG PET/CT, and were excluded if sites of FDG-positive disease without high PSMA expression were identified. Patients received up to four cycles of ^{177}Lu -PSMA-617, with 29 patients experiencing any PSA decline (97%) and 57% achieving a >50% PSA decline. Grade 3-4 thrombocytopenia occurred in only 27% of patients, 13% of this attributable to marrow progression of skeletal metastases. Grade 1-2 xerostomia (87%), nausea (53%) and fatigue (53%) were the most commonly reported adverse effects attributed to ^{177}Lu -PSMA. Notably, 37% of patients described an improvement of pain. The biochemical PFS was 7.6 months and median OS was 13.5 months. Moreover, an extension cohort of 50 patients with longer follow-up from

this prospective phase II study, confirmed the safety and efficacy of Lu-PSMA, with PSA decline $\geq 50\%$ achieved in 32 of 50 patients (64%, 95% CI 50-77%)(64). At a median follow-up of 31.4 months, median OS was 13.3 months (95% CI 10.5-18.7) with a significantly longer survival of 18.4 months (95% CI 13.8-23.8) in patients achieving a PSA decline $\geq 50\%$. At progression following prior response, further Lu-PSMA was administered to 15 (30%) patients with PSA decline $\geq 50\%$ in 11 patients (73%). See figure 2 for an example of a typical patient course in a patient from the phase II trial at Peter MacCallum Cancer Centre. These results certainly promote Lu-PSMA-617 as an efficacious treatment option for those with mCRPC, and have laid the basis for RCTs comparing standard of care therapy to a theranostic approach with RLT, as well as RLT as part of combination therapies.

Heck et al (5) also reported results for 100 heavily pre-treated patients treated with ^{177}Lu -labelled PSMA-I&T. Patient characteristics were similar to Lu-PSMA study population, but a significantly higher proportion of patients with visceral metastases were included (35% vs 13%). It should be noted that Heck et al did not perform FDG PET scans in order to exclude patients with FDG/PSMA-PET discordant disease. This study reported a PSA decline of $>50\%$ in 38 of the 100 patients, median clinical PFS was 4.1 months and median OS was 12.9 months. In general, treatment-related toxicity was low, and no patients stopped treatment due to adverse effects. The common toxicities experienced included transient xerostomia (24%) and fatigue (20%). Grade 3-4 haemato-toxicity was minimal, with anaemia in 9%, neutropenia in 6% and thrombocytopenia in 4% of patients. The presence of visceral metastases was associated with poorer PSA response as well as shorter clinical PFS [HR 1.7, 95% CI 1.1-2.6] and OS [HR 2.1, 95% CI 1.2-3.5]. While prospective studies into Lu-PSMA-I&T will give a clearer picture of where this radioligand fits into the paradigm of advanced prostate cancer management, the existing data suggest that, whether PSMA-I&T or PSMA-617, small-molecule RLT is well-tolerated and demonstrates encouraging efficacy. A summary of ongoing LuPSMA trials are listed in Table 1.

A further aspect of theranostic therapy is not just the targeting of a PET-imaged molecule such as PSMA for theranostic benefit, but also the ability of PET imaging and post-treatment dosimetry to assess received dose and to predict responses. We have prospectively assessed dosimetry in our phase II LuPSMA trial and observed

very high doses of radiation within tissues with high PSMA expression/high SUVmax(65), and also that prognostic biomarkers could be identified using PET imaging. We demonstrated that high FDG expression was a poor predictor of overall survival, whereas high PSMA expression was a favourable predictor(66).

It should be noted that a proportion of patients treated with ^{177}Lu -PSMA in the aforementioned studies did not respond to treatment. The molecular mechanisms of resistance to lutetium-based RLT are not fully understood (67) and future studies are needed to investigate this. ^{225}Ac , an alpha-emitter, radiolabelled to PSMA-617 was initially shown by Kratchowil et al (68) to be effective in one patient in whom treatment with beta-emitters was contraindicated and in one patient resistant to ^{177}Lu -PSMA-617. In the case of resistance to prior RLT, the patient's PSA dropped from over 400ng/dl to <0.1ng/dl after three cycles of ^{225}Ac -PSMA-617. In a further retrospective analysis of 40 patients (69), the promising anti-tumour activity of ^{225}Ac -PSMA-617 has been demonstrated. Of the 38 patients surviving at least eight weeks, 24 (63%) had a PSA decline of more than 50%, and 33 (87%) had a PSA response of any degree. PFS was 9.0 months and five patients had an enduring response of more than two years. These results in the context of patients with such advanced tumour characteristics are remarkable. Dry mouth was a significant adverse effect, however, with four patients discontinuing therapy due to intolerable xerostomia, indicating co-radiation to the salivary glands may hinder the development of ^{225}Ac -PSMA-617.

Moreover, Sathekge et al (70) published results of a retrospective analysis including 73 less heavily pre-treated mCRPC patients who received treatment with ^{225}Ac -PSMA-617. Fifty-one patients (70%) presented with a PSA decline of >50% and 60 patients (83%) with any decline in PSA. While the majority of patients (85%) reported grade 1-2 xerostomia, none complained of grade 3 dry mouth and no patients discontinued treatment due to this side effect. Furthermore, no patients suffered grade 4 haematotoxicity. Estimated median OS was 18 months and PFS was 15.2 months. On multivariate analysis, PSA decline >50% was demonstrated to be an independent predictor of OS ($p=0.025$) and PFS ($p<0.001$). If prospective-designed studies can replicate these findings then the future of alpha-emitting RLT looks favourable.

7. Future Directions for PSMA Theranostics

Through a series of retrospective trials (53) and some early phase prospective studies (6), PSMA theranostics has shown a great deal of promise in the management of advanced prostate cancer. The LuPSMA study has paved the way for randomised trials such as the TheraP (71) and the VISION (NCT03511664) studies. The Phase II TheraP trial has completed randomisation of 200 patients in Australia and will assess PSA response after randomising patients to either RLT with ¹⁷⁷Lu-PSMA-617 or cabazitaxel. Aiming to recruit 750 patients, the primary objective of VISION (phase III) is to compare overall survival in patients receiving treatment with ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.

With early data suggesting that PSMA-based RLT may prolong life expectancy more than rival therapeutic strategies, much discussion has been held about its position in the paradigm of advanced prostate cancer and even whether patient outcomes may benefit from the use of RLT at an earlier stage, perhaps in earlier mCRPC prior to hormone therapies or chemotherapy, or even in mHSPC. There is now substantial evidence of the benefit of numerous combination approaches in mHSPC(72, 73), and it is certainly worth exploring the value of using RLT earlier in the prostate cancer landscape. A clinical trial from Radboud University (NCT03828838) has begun recruiting subjects with low volume disease that are prior to the CRPC state. Theoretically, RLT could be more effective in low volume disease because of the very high tumour uptake of radioligands in small lesions. Investigators in Australia are developing a Lu-PSMA trial in men with high-volume mHSPC in a multicentre randomised trial (UpFront PSMA trial) as part of a prostate cancer research alliance co-funded by the Movember Foundation, Cancer Australia and the US Department of Defense. Furthermore, they are also evaluating Lu-PSMA in a neoadjuvant trial in men with high-risk localised prostate cancer, prior to radical prostatectomy (the LuTectomy trial; personal correspondence – DG Murphy). This is based on high response rates within the prostate seen on dosimetry in men undergoing Lu-PSMA as part of the phase II trial in Melbourne (see figure 3)(6).

Furthermore, the question arises as to whether RLT may be effective in combination approaches as an adjuvant or neoadjuvant strategy. A number of trials have been registered, some of which have begun recruiting (Table 1), that combine Lu-PSMA-617 with immune checkpoint inhibitors such as pembrolizumab (NCT03805594, NCT03658447) or targeted therapy with PARP inhibitors (NCT03874884). Furthermore, one study will evaluate the dose-limiting toxicity and efficacy of Lu-PSMA-617 alongside the antibody-based radioligand Lu-PSMA-J591 (NCT03545165). The high recurrence rate of prostate cancer and poor long-term survival rates in these patients means that such combinations are worth exploring and may well represent feasible and effective treatment options at various disease states.

Finally, whilst the most widely used radioligands show great promise, there are yet more alternatives and adjustments in the pipeline. A group in China recently showed greater tumour accumulation and retention of Lu-PSMA-617 by conjugating it to the albumin-binding molecule Evans Blue (74), and recruitment for two Phase I studies (NCT03403595, NCT03780075) is now underway to evaluate this potentially improved ligand in larger cohorts. Furthermore, BAY 2315497, an investigational PSMA monoclonal antibody that can be bound to the alpha-emitter thorium-227, will be administered to patients for the first time in an upcoming clinical trial (NCT03724747). ¹⁷⁷Lu-PSMA-R2 is yet another novel small-molecule ligand undergoing Phase I testing in patients with mCRPC in the PROter trial (NCT03490838).

8. Conclusion

Despite the introduction of numerous management options in the past decade for men with advanced prostate cancer, the disease often progresses rapidly. Theranostics based on PSMA may be the addition to the armamentarium that is so desperately required to manage this complex, heterogeneous group of patients, and our nuclear medicine colleagues clearly have a role to play in multidisciplinary care(75). Already, Phase III trials are underway, meaning it may only be a matter of time before PSMA theranostics gains validation as a key treatment option for men

with advanced prostate cancer, and we look forward to its evaluation in earlier stage disease.

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Legends for figures

Figure 1: Patient with intermediate risk prostate cancer, treated with 74Gy EBRT. Biochemical recurrence 10 years later with PSA doubling time of 4 years. PSMA PET/CT demonstrates recurrence limited to the prostate bed with no evidence of locoregional nodal or distant metastatic disease. Calculations of tumour volume and dosimetry as per Violet et al(65).

Figure 2 Progressive metastatic castration-resistant prostate cancer with rapidly progressive and symptomatic nodal and bone metastases following docetaxel, enzalutamide, abiraterone and cabazitaxel chemotherapy. There was a rapid clinical response following Lutetium-177 PSMA-617 (LuPSMA, red stars) with resolution of pain, PSA becoming undetectable and complete anatomic response on CT. Dosimetry demonstrated delivery of 175Gy to the dominant retroperitoneal node

from the 1st cycle of LuPSMA. Upon progression, further LuPSMA was given, each with favourable response. The patient remains asymptomatic 3.5 years after commencing LuPSMA therapy.

Figure 3: The patient in Figure 2 had residual active disease within the prostate gland at the time of first Lutetium-177 PSMA-617 (LuPSMA) therapy. Post therapy and dosimetry demonstrated focal targeting of prostate disease with delivery of 75 Gy after the first cycle of LuPSMA. Follow-up imaging demonstrated a complete response on PSMA PET.

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Table 1. Ongoing theranostic trials

	Size	Phase	Status	Registration
Combinations / Different Doses				
¹⁷⁷ Lu-PSMA-617 + Olaparib (LuPARP)	52	I	Recruiting	NCT03874884
¹⁷⁷ Lu-PSMA-617 + Pembrolizumab	30	I	Recruiting	NCT03805594
¹⁷⁷ Lu-PSMA-617 + Pembrolizumab (PRINCE)	37	I/II	Recruiting	NCT03658447
¹⁷⁷ Lu-J591 + ¹⁷⁷ Lu-PSMA-617	48	I/II	Recruiting	NCT03545165
Fractionated ¹⁷⁷ Lu-PSMA-617	46	I	Recruiting	NCT03042468
Randomised				
¹⁷⁷ Lu-PSMA-617 vs best supportive/standard of care (VISION)	750	III	Recruitment complete	NCT03511664
¹⁷⁷ Lu-PSMA-617 vs Cabazitaxel (TheraP)	200	II	Recruitment complete	NCT03392428
Earlier in Disease Course				
¹⁷⁷ Lu-PSMA in mHSPC (UpFront PSMA trial)	180	I/II	Recruiting	NCT03828838
¹⁷⁷ Lu-PSMA prior to radical prostatectomy (LuTectomy trial)	20	I	Open 2020	
Novel / Next Generation Ligands				
¹⁷⁷ Lu-EB-PSMA-617: Albumin-binding molecule	30	I	Recruiting	NCT03780075
¹⁷⁷ Lu-EB-PSMA-617: Albumin-binding molecule	30	I	Recruiting	NCT03403595
Thorium-227-BAY 2315497: Monoclonal antibody	111	I	Recruiting	NCT03724747

¹⁷⁷ Lu-PSMA-R2: New small-molecule ligand (PROter)	96	I/II	Recruiting	NCT03490838
²²⁵ Ac-J591: Monoclonal antibody	42	I	Recruiting	NCT03276572
I-131-1095 + Enzalutamide: New small-molecule ligand	175	II	Recruiting	NCT03939689
¹⁷⁷ Lu CTT1403: Novel molecule with albumin-binding moiety	40	I	Recruiting	NCT03822871
Phase II Lu-177-PSMA Trials				
¹⁷⁷ Lu-PSMA-617 (RESIST-PC)	72	II	Recruitment complete	NCT03042312
¹⁷⁷ Lu-PSMA-617 (LU-PSMA)	210	II	Recruiting	NCT03454750

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baseline PSMA PET

voxel dosimetry

post ^{177}Lu -PSMA₆₁₇ PSMA PET

bju_15143_f3.tif

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