

REVIEW ARTICLE

Lutetium ¹⁷⁷ PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy

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Abstract

Prostate-specific membrane antigen (PSMA) is a receptor on the surface of prostate cancer cells that is revolutionising the way we image and treat men with prostate cancer. New small molecule peptides with high-binding affinity for the PSMA receptor have allowed high quality, highly specific PET imaging, in addition to the development of targeted radionuclide therapy for men with prostate cancer. This targeted therapy for prostate cancer has, to date, predominately used Lutetium 177 (Lu) labelled PSMA peptides. Early clinical studies evaluating the safety and efficacy of Lu PSMA therapy have demonstrated promising results with a significant proportion of men with metastatic prostate cancer, who have already failed other therapies, responding clinically to Lu PSMA. This review discusses the practical issues of administering Lu PSMA, and gives an overview of the findings from currently published trials in regards to treatment response rates, expected toxicities and safety.

Introduction

Prostate cancer is the most commonly diagnosed cancer among men in the Western world, accounting for about 25% of all new male cancer cases in Australia. Although many patients present with localised or indolent disease, there are still a significant proportion of patients that eventually progress to advanced metastatic disease, for which no curative treatment exists. In men who fail initial therapy of curative intent (radical prostatectomy or primary radiotherapy), treatment options include androgen deprivation therapy followed by chemotherapy if the disease progresses. However, conventional chemotherapy responses are often transient, leaving many men with symptomatic metastatic cancer and few treatment options.

Recent published studies have raised the possibility of targeted radionuclide therapies such as ¹⁷⁷Lutetium-PSMA (prostate-specific membrane antigen) as a viable therapeutic option in men with metastatic prostate cancer.^{1–10} The aim of this review was to discuss practical aspects of Lu PSMA therapy including, radiochemistry, physics dosimetry and radiation safety, in addition to reviewing the current literature and assessing its value in the current clinical setting.

What is PSMA

PSMA is a 750 amino acid type II transmembrane glycoprotein.¹¹ It is thought to have multiple cellular functions, acting as an enzyme involved in nutrient

uptake (folate). It also plays a role in cell migration, cell survival and proliferation.¹¹ While expressed at low levels in normal human prostate epithelium, it is overexpressed (up to 1000 times higher than normal prostate cells) in virtually all prostate cancers (5–10% of prostate cancers appear not to express the PSMA glycoprotein) (Fig. 1).¹² The PSMA receptor has an internalisation process that allows endocytosis of bound proteins on the cell surface into an endosomal compartment, which allows PSMA labelled radioisotopes to be concentrated within the cell.¹³ The density of expression of this transmembrane receptor on prostate cancer cells further increases dependent on the Gleason score of the prostate cancer, and in castrate-resistant prostate cancers, making it the ideal target for radionuclide therapy.¹²

PSMA is not entirely prostate specific and is expressed in other cells including the small intestine, proximal renal

tubules and salivary glands. This means that, although the expression of PSMA on these cells is significantly reduced compared to prostate cancer cells, there is a radiation dose delivered to these target organs when PSMA is used as a target for radionuclide therapy. This has an impact on both the side effect profile of PSMA-targeted therapy, and on the safe dose of radiotherapy that can be delivered to the patient without causing significant radiation damage to non-target organs. In clinical trials to date, the organs that have been identified as most at risk from this are the salivary glands and the lacrimal glands.¹⁴

Prostate cancer is not the only type of cancer that overexpresses PSMA on its cell surface. Clear cell renal cancer has also been reported to express the PSMA receptor, and there are case reports of the use of PSMA as a staging tool for renal cancer.^{15,16} Other cancers may also be visible on PSMA diagnostic imaging, but the cells do not overexpress the PSMA receptor on the cell surface. Instead, there is prominent expression of the PSMA receptor on the endothelial cells of tumour-associated microvessels or in 'neo-angiogenesis'. This has been demonstrated in a number of tumours including glioblastoma multiforme, colorectal and gastric cancers, and in squamous cell cancers of the head and neck.¹⁷

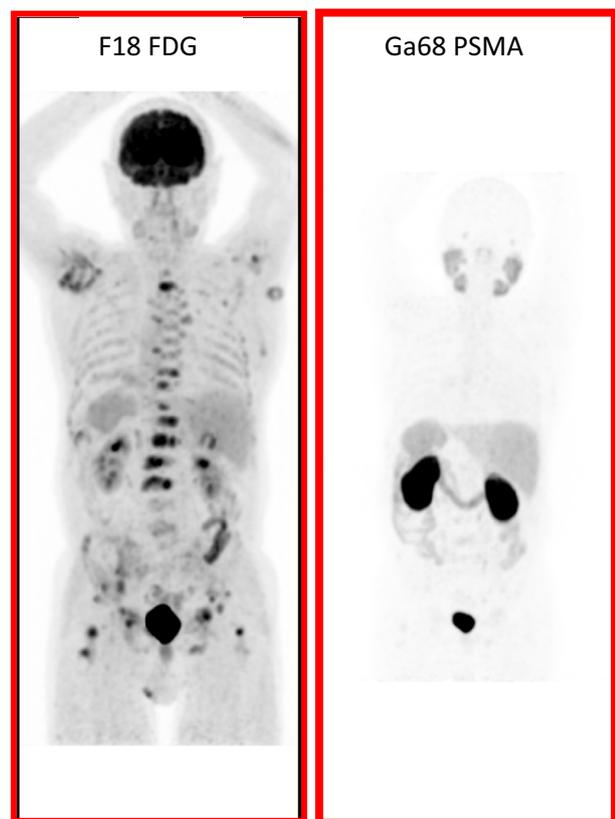


Figure 1. 5–10% of men with prostate cancer do not express PSMA and have negative 68Ga-PSMA imaging. This case is a 72 yo man with metastatic castrate-resistant prostate cancer (mCRPC) who had failed conventional therapy options. He has intensely FDG avid metastatic prostate cancer throughout his bones, with a negative 68Ga-PSMA scan. His lack of PSMA activity precluded Lu PSMA as therapeutic option for him. Up to 20% of men with mCRPC will not be eligible for Lu PSMA due to inadequate expression of PSMA.

Why Lutetium labelled PSMA? The Physical Properties of Lu¹⁷⁷ and Why It Makes A Good Therapy Agent

¹⁷⁷Lutetium (¹⁷⁷Lu) has gained popularity as the therapeutic radionuclide of choice due to its desirable physical properties. Ideally, the emission characteristics of a therapeutic radionuclide should match the lesion size/volume to be treated to ideally focus energy within the tumour rather than in the tissue surrounding the lesion. ¹⁷⁷Lu is a medium-energy β -emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β -range of ¹⁷⁷Lu provides better irradiation of small tumours, in contrast

Table 1. Radionuclides used in targeted therapy.

Radionuclide	Physical $T_{1/2}$ (days)	Radiation type (MeV)	Particle range (mm)
¹³¹ I	8	β (0.6), γ (0.364)	2
⁹⁰ Y	2.67	β (2.28)	12
⁶⁷ Cu	2.58	β (0.54), γ (0.185)	1.8
¹⁸⁶ Re	3.77	β (1.08), γ (0.131)	5
¹⁷⁷ Lu	6.7	β (0.497), γ (0.208)	1.5

The ideal radionuclide for targeted therapy is persistent, short range and powerful. Lu¹⁷⁷ compared favourably to other β emitters.

to the longer β -range of ^{90}Y (Table 1). ^{177}Lu is a reactor produced radiometal that emits low-energy γ -rays at 208 and 113 keV with 10 and 6% abundance respectively. The gamma emission from ^{177}Lu allows for *ex vivo* imaging and consequently the collection of information pertaining to tumour localisation and dosimetry. Furthermore, ^{177}Lu has a relatively long physical half-life of 6.73 days. It is these physical properties that allow for the delivery of high activities of ^{177}Lu PSMA to prostate cancer cells.

Labelling of Lu 177 with PSMA Peptides: Different Available Options

There are a number of different PSMA peptides and antibodies^{9,18} that have been labelled with ^{177}Lu , and which have been utilised in both clinical trials and for clinical use as therapy agents in men with metastatic castrate-resistant prostate cancer (mCRPC).^{4,19–21} These include the compound PSMA-DKFZ-617, with which most patients in the published literature to date have received their therapy. This is a small molecule peptide, rather than an antibody, chemically conjugated with ^{177}Lu lutetium. In an initial study in mice, it has a highly efficient internalisation into prostate cancer cells with approximately 75% of the peptide bound to the cell internalised after 3 h of incubation.²² A similar small molecule PSMA peptide ending with a different chemical conjugation (^{177}Lu PSMA-I&T) also appears effective as a therapeutic agent in a number of published studies.^{3,21} ^{177}Lu -J591, a monoclonal antibody to the PSMA receptor has been used for the therapeutic treatment of prostate cancer, with effective results, but appears to have a more limited treatment response and higher myelosuppression than seen in the studies undertaken using the smaller PSMA labelled peptides^{18,23}

Practical Aspects of Lu-177 PSMA Administration

^{177}Lu PSMA is an easily administered targeted therapy with no significant symptoms at the time of injection. The main safety issues are standard radiation safety precautions that are inherent in all intravenously injected, renally excreted radionuclide therapies.

Dose calculation

Standard administered activity of ^{177}Lu PSMA has been variable across the currently published literature as institutions undertake safety and toxicity trials.^{3,5,7,8,20,21,24–29} Injected doses have ranged from 3 to 8 GBq per single injections with up to six injections given to men, generally at a minimum 6-weekly intervals. Dose

calculations for individual patients have been determined from a combination of disease burden, patient weight and renal function.

Lu PSMA is applied by a slow intravenous injection (30–60 sec) in a volume of 5 mL (diluted with 0.9% sterile sodium chloride solution), followed by a flush of sterile 0.9% sodium chloride. It is recommended that the patients are hydrated pre- and post-administration of ^{177}Lu PSMA with 1–1.5 L of water and encouraged to void as frequently as possible.

Radiation safety

In Australia, the patient-specific radiation doses in a patient undergoing ^{177}Lu PSMA with a standard 6–8 Gbq dose falls within the range which can be administered safely and legally within an outpatient setting. This is not the case in other countries such as Germany, where the therapy must be administered in an inpatient setting with a minimum 3 days hospital admission. General precautions for staff members are to follow the general radiation safety principle of ALARA (As Low As Reasonably Achievable). For patients, the ARPANSA (Australian radiation protection and nuclear safety agency) recommendation are followed which states, “*when patient-specific dose estimates to family members and to members of the general public are not available, the ambient dose equivalent rate at a distance of 1 metre from a patient who is undergoing treatment with a radioactive substance should not exceed 25 $\mu\text{Sv/h}$ at the time of the patient’s discharge from hospital.*”³⁰

^{177}Lu PSMA is renally excreted in the first 48 h following injection, and instructions need to be given to patients, staff and families on managing potential radioactive spills. Given the rapid renal excretion of ^{177}Lu PSMA, patients are required to remain in the department for 2–4 h for observation and for measured radiation levels to decrease. However in our institution, patients were recorded to be below the recommended guideline of 25 $\mu\text{Sv/h}$ by 1 h post-injection and all were recorded to be below 25 $\mu\text{Sv/h}$ at the time of discharge. The safety of ^{177}Lu PSMA administration to staff and caregivers was emphasised in a recent publication.³¹ The authors measured radiation doses delivered both to administering staff and family in 23 patients who received a mean dose of 7500 Mbq ^{177}Lu PSMA per injection. They found that the mean dose rate at 1 m after 4 and 6 h was $23 \pm 6 \mu\text{Sv/h}$ and $15 \pm 4 \mu\text{Sv/h}$ respectively. The effective half-life of blood distribution was 0.4 ± 0.1 h. Mean dose received by close family (measured for 5 days post-injection) was $202.3 \pm 42.7 \mu\text{Sv}$. The radiation dose of the nurse and radiopharmacist was 6 and 4 μSv per patient.

Dosimetry of ^{177}Lu PSMA Therapy

Safety and efficacy of targeted radionuclide therapies can be improved with the use of patient-specific dosimetry, which may guide successful tumour dosing and act as an early indicator of organ toxicity.³² Of particular concern in ^{177}Lu PSMA treatment are the kidney, salivary and lacrimal glands, which suffer from radiation dosing due to the physiological behaviour of the therapeutic peptide. As a result, image-based dosimetry at each cycle of treatment is highly recommended³³(Fig. 2).

Dosimetry requires imaging patients at multiple time points to establish the rate of activity accumulation and depletion in each organ of interest (i.e. at 4, 24 and 96 h post-injection). The more time points that are acquired,

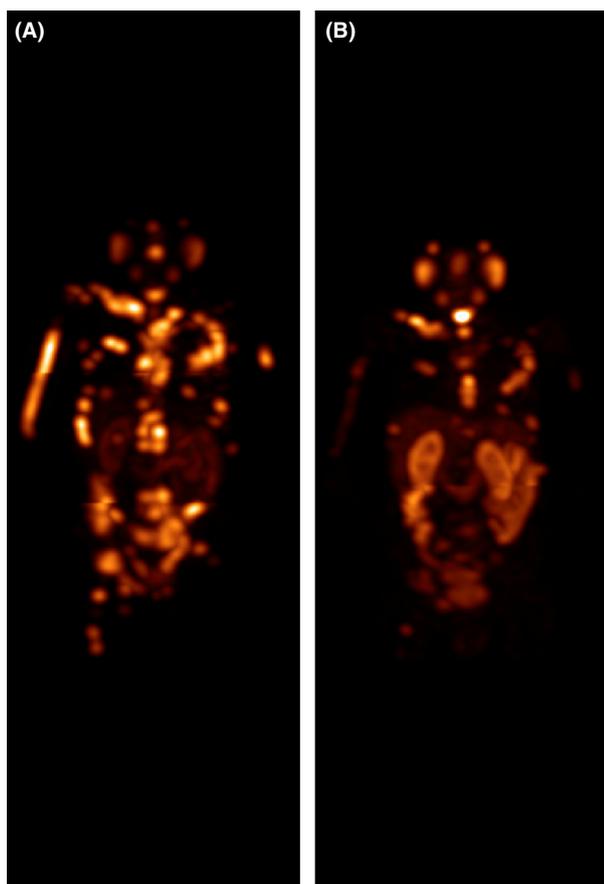


Figure 2. (A) SPECT CT whole body imaging 24 h post-Dose 1. 8.0 Gbq Lu PSMA Images demonstrate Lu PSMA uptake in multiple metastatic foci throughout the axial and appendicular skeleton. Serial time point imaging of the associated gamma emissions allows estimation of tumour dose delivered with each injection. (B) SPECT CT whole body imaging 24 h post-Dose 2. 8.0 Gbq Lu PSMA SPECT CT images show a marked reduction in the intensity and number of Lu PSMA avid metastatic foci, which concurs with the marked reduction in serum PSA in this patient.

the more accurate the dose estimates, however this must be balanced against patient comfort and demand on facilities. The preferential means of performing dosimetry is with 3D imaging, namely quantitative SPECT/CT. Whilst 2D absorbed dose estimates can be made from planar data, limitations do exist, primarily in the form of structure overlap, and will most likely lead to overestimates of absorbed dose.^{34,35} The planar approach to dosimetry is, however, far more readily available without the need for specialised software, and is generally performed on geometric mean whole body data with attenuation and scatter correction, combined with a whole organ MIRD approach (model-based estimate of absorbed dose). Alternatively, SPECT data can avoid issues of overlapping activity, and can also allow estimates to be made even in the presence of organ-specific metastatic disease by excluding tumour in hand-drawn VOIs (volumes of interest). Fully quantitative SPECT should include corrections for scattered and attenuated photons, camera dead time and distant-dependent detector blurring, before application of an energy window- and collimator-specific camera sensitivity factor. Partial volume effects are also likely to be an issue when considering small organs such as kidney or lacrimal and salivary glands, however, with no standardised approach to address these, corrections may be subjective. 3D data also allows for the generation of dose maps through voxel kernel convolution (VKC), which takes into account the range travelled by the emitted ^{177}Lu beta particles as they deposit their dose in the surrounding media. VKC does not rely on a model-average organ volume, and has the advantage of producing 3D dose maps and dose volume histograms allowing sub-organ dose evaluation.

Depending on available facilities and in-house expertise, dosimetry in either form can be used to advise on safety of further treatment cycles with a view to avoiding toxicity. The current critical threshold of kidney absorbed dose is 23 Gy, which has an associated 5% probability of deterministic side effects within 5 years. However, these guidelines are based on evidence from external beam radiotherapy,³⁶ which is unlikely to be comparable to ^{177}Lu PSMA due to stark differences in radiation type, dose rate and heterogeneity of dose, which is thought to allow for higher tissue tolerance.³⁴ More recent kidney toxicity thresholds of 28 and 40 Gy (depending on the presence of additional risk factors) have been proposed,³⁷ and may be more widely adopted after further studies.

Kidney absorbed dose related to targeted radionuclide therapy, and in particular ^{177}Lu PSMA, has generally been reported as being well below the 23 Gy dose-limiting threshold. A recent example from Baum *et al.*³⁸ in 56 metastatic castrate-resistant prostate cancer patients found

an average kidney dose of 0.8 mGy/MBq based on whole body temporal data (approximately 4.6 Gy per cycle based on the reported median administered activity of 5.76 GBq). This compares to an average kidney absorbed dose of 2.2 Gy reported by Delker *et al.*⁴ in a quantitative SPECT/CT study of five patients using the new ¹⁷⁷Lu DFKZ-PSMA-617 ligand. Both groups reported the parotid glands receiving higher doses than kidney, with an average parotid absorbed dose per cycle of 7.5 Gy (based on the reported median injected activity) and 5.1 Gy respectively.

Current Clinical Evidence for the Use of Lu PSMA in Metastatic Prostate Cancer

There are currently a limited number of published trials in the use of Lu PSMA for the treatment of mCRPC (approximately 245 patients).^{2–6,8,9,27,39} These are in the main small, retrospective trials, but they have shown almost uniformly is that a high proportion of men treated with ¹⁷⁷Lu PSMA have a significant treatment response, and that bar a number of low-grade toxicities, the treatment appears well tolerated.

Treatment Efficacy

How effective is Lu PSMA as a therapy agent? In the currently published literature, the number of men who experience a >50% reduction in serum PSA (prostate-specific antigen) levels ranges from 30% to 70%, which compares well to the PSA response rates achieved by chemotherapy agents used in mCRPC (Cabazitaxel and Docetaxel)⁴⁰ (Table 2). Those men with progressive disease who do not respond to ¹⁷⁷Lu PSMA therapy range from 10% to 32%. One of the larger studies, with 56 men enrolled, had 80% of all men enrolled had a PSA response to therapy.³ All currently published studies with ¹⁷⁷Lu PSMA therapy in prostate cancer are retrospective, mostly single arm, and involve a variety of treatment regimens, both in terms of dose given (ranging from 3.5 to 8.0 Gbq/injection of Lu PSMA) and the number of doses administered (ranges from a single injection up to 4–6 injections 6 weeks apart).^{2–6,8,9,27,39} This makes interpretation of the efficacy of the treatment difficult at this stage. Consistent across the trials undertaken to date is that the therapy is effective in a significant proportion of men with metastatic prostate cancer who have extinguished all other treatment alternatives. The next step needs to be prospective analysis of the efficacy of ¹⁷⁷Lu PSMA in randomised trials that are powered to assess overall survival, randomised against treatments already shown to have a survival benefit.

Due to the retrospective and single arm treatment nature of currently published trials there is little information on a possible survival benefit of Lu PSMA therapy in men with mCRPC. A study of 56 patients receiving up to five treatments of Lu PSMA at 6-weekly intervals appeared to suggest there may be a survival benefit. This study found that with a follow-up period of 28 months, 12 patients died (21.4%). Survival after 28 months was 78.6%. Median progression-free survival was 13.7 months.³ Once again, prospective randomised trials will need to confirm any potential survival benefit due to ¹⁷⁷Lu PSMA in men with advanced prostate cancer.

Predictors of Response

Not all men with mCRPC will have a good treatment response to ¹⁷⁷Lu PSMA. Up to a third of those men treated to date show progressive disease despite treatment. This is likely due to a variety of factors. One important factor is whether the tumour cells uniformly express a high density of the PSMA receptor (Fig. 3). Heterogeneity of PSMA receptor activity within the tumour population may mean that some sites will not respond to treatment with ¹⁷⁷Lu PSMA, which will manifest as disease progression, and a rising PSA. Currently PSMA activity is measured by assessing intensity of activity on a ⁶⁸Ga-PSMA staging PET/CT and is a requirement for treatment in all currently published studies. Cutoffs of PSMA intensity on ⁶⁸Ga-PSMA below which ¹⁷⁷Lu PSMA therapy may not be effective have not yet been established. A recent study of 40 patients identified platelet level and the need for pain relief as the most significant predictor of poor response to ¹⁷⁷Lu-PSMA, likely reflective of the burden of metastatic bone disease.²⁶ This same study did not find that intensity of PSMA activity on ⁶⁸Ga-PSMA staging PET/CT was predictive of response, but this is likely because intense PSMA activity on ⁶⁸Ga-PSMA imaging was one of the inclusion criteria for receiving ¹⁷⁷Lu PSMA therapy initially.²⁶ Other studies have commented that bone metastases appear to respond less well than visceral or lymph nodal disease to treatment with Lu PSMA.³

Toxicity

Overall, toxicities related to ¹⁷⁷Lu PSMA therapy have been low grade in all published studies (Table 3). Up to 30% of men report dry mouth or xerostomia following treatment. Fatigue is a common side effect in up to 25% of men treated. Nausea can also be significant and has been reported in up to 10% of men, particularly in the 24–48 h around the time of injection. None of the current studies have reported renal toxicity, although it is

Table 2. Overview of currently published trials.

	PSA fall >50%	CT (RECIST)	PSMA PET (EORTC)	Symptomatic response	Biochemical/radiological PFS	Overall Survival
Zechmann 2014 <i>et al.</i> ³⁹	61% PD 14%	–	–	23% CR, 61% PR	Median BPFS 126 days (62–149) ³	–
Ahmadzadehfar 2015 <i>et al.</i> ²⁵	50% PD 30%	–	–	–	–	–
Ahmadzadehfar 2016 <i>et al.</i> ¹	42% PD 21%	PR 40% SD 55% PD 5%	PR 80% SD 0% PD 20%	–	–	–
Kratochwil 2016 <i>et al.</i> ²⁷	43%–72% ¹ PD 27%	–	–	–	–	–
Baum 2016 <i>et al.</i> ³	59% PD 11%	PR 20%, SD 52%, PD 28%	PR 56% SD 8% PD 36%	33% PR	Median radiological PFS 13.7 months	Median not reached
Rahbar 2016 <i>et al.</i> ²⁹	31% PD 23%	–	–	–	–	–
Rahbar 2016 <i>et al.</i> ⁸	32–50% ² PD 20%	–	–	–	–	29.4 vs. 19.7 weeks
Heck 2016 <i>et al.</i> ⁶	33% PD 32%	PR 11%, SD 56%, PD 33%	'integrated' CR 5%, SD 63%, PD 32%	14% CR, 42% PR	Median PFS 175 days (95% CI 35–315)	–
Yadav 2016 <i>et al.</i> ⁴²	Mean Pre- and post 275/141 PD 20%	–	CR 33%, PR 50%, SD 17% (<i>n</i> = 6)	Analgesic score 2.5 reduced to 1.8	Median PFS 12 months	Median OS 15 months

The limited published studies assessing efficacy of Lu PSMA as a treatment for mCRPC show 30–70% of men have a fall of >50% in their PSA levels with only 10–25% of men showing progressive disease in spite of treatment. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival.

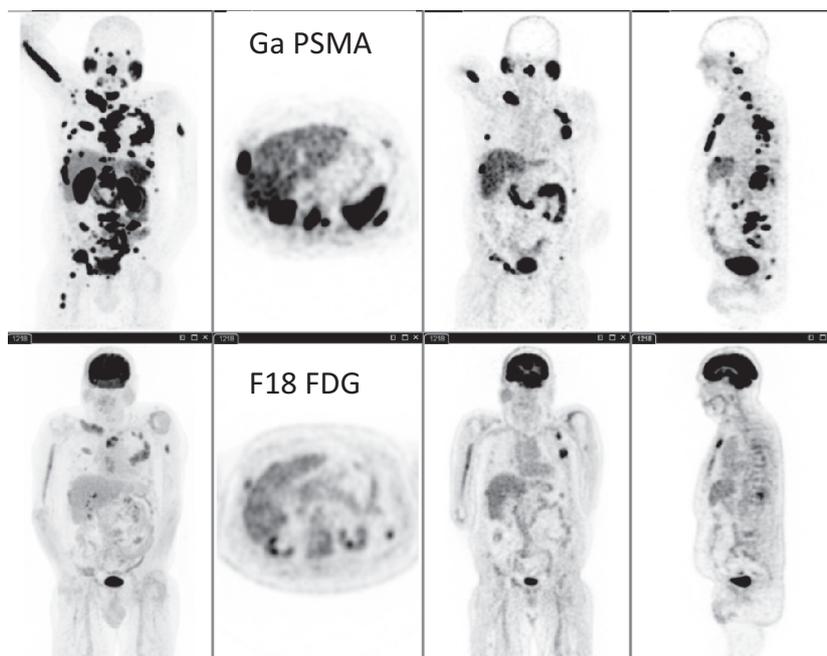


Figure 3. The ideal candidate has intense GaPSMA activity at all sites of metastatic prostate cancer, ensuring a high radiation dose delivered uniformly. This case demonstrates intense Ga PSMA activity compared to minimal FDG activity in metastatic prostate cancer.

Table 3. Toxicity in patients undergoing Lu PSMA therapy.

	Haematological toxicity (G2-3)			Non-haematological toxicity	
	Hb	WCC	Platelets	Salivary	Other
Zechmann 2014 et al. ³⁹	Below 'normal range' 75%	15%	10%	25%	Hypothyroidism 1/28, mucositis 1/28
Ahmadzadehfar 2015 et al. ²⁵	10%	10%	10%	20%	Fatigue 20%, nausea 20%
Ahmadzadehfar 2016 et al. ²	25%	12%	0%	9%	Nausea 12%, fatigue 13–17%, hypogeusia 4%
Kratochwil 2016 et al. ²⁷	10%	7%	7%	7%	Fatigue G1, nausea G1
Baum 2016 et al. ³	5% N/S changes ¹	9% N/S changes ¹	0%	4%	–
Rahbar 2016 et al. ⁸	15% N/S changes	5.4%	3% N/S changes	9%	Nausea G1 1.4%
Rahbar 2016 et al. ²⁹	9–20% ²	0–11% ²	0%	15%	Nausea 14%, nil with routine antiemetic use
Heck 2016 et al. ⁶	32% (G1-2)	Neutropenia 5%	25% (G1-2)	37%	Fatigue 25%, Anorexia 25%,
Yadav 2016 et al. ⁴²	6.5%	3%	0%	Nil reported	–

Fatigue and dry mouth appear most commonly. Haematological problems occur and can be significant in the group of men with borderline marrow function due to extensive bone metastases.

likely that this will be a longer term complication if it is to occur.

Haematological toxicity is the most commonly reported serious side effect related to ¹⁷⁷Lu PSMA therapy. This is predominately an innocent bystander effect in men with a heavy burden of skeletal metastases and borderline marrow function, rather than a direct radiation effect on bone marrow. In men with significant bone metastases, up to 10–25% of men had a Grade 1–2 reduction in haemoglobin or platelets. No significant marrow toxicity is seen in those men who do not have a high burden of skeletal metastases. Because of the longer particle range of ¹⁷⁷Lu, compared to alpha emitters such as radium 223, it is likely that ¹⁷⁷Lu will have a higher radiation dose to surrounding marrow in men with extensive metastatic bone disease, than alpha emitter treatment options. Initial studies using 225 Ac(Actinium) PSMA-617 have confirmed this relative sparing of bone marrow in men with extensive bone metastases using a PSMA labelled alpha emitter.⁴¹

Conclusion

¹⁷⁷Lu PSMA is showing exciting treatment responses in men with mCRPC and almost certainly has an important future role in the treatment of prostate cancer. Preliminary publications suggest it has a low toxicity profile and appears generally well tolerated in men with end stage metastatic disease. Prospective randomised trials are needed to determine its impact on survival, and to rigorously assess its clinical benefit compared to other treatments of prostate cancer, including chemotherapy, external beam radiotherapy and androgen blockade.

Conflict of interest

The authors have no conflict of interest to declare.

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