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Molecular Targeted Radionuclide Therapy for Prostate Cancer

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Abstract: According to the American Cancer Society, prostate cancer affects 1 in 8 men. This chapter reviews the molecular targeted radionuclide therapy for prostate cancer, including pretherapy imaging and evaluation, considerations during the course of therapy, and follow-up. Dosimetry and alpha-particle therapies are also discussed.

Keywords: molecular targeted radionuclide therapy; prostate cancer; PSMA-targeting radiotracers; radioligand therapy; theranostics

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancers among men globally and has the second highest mortality rate in western countries (1). The 5-year relative survival rate for localized prostate cancer is 100%; however, the survival

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rate for metastatic prostate cancer (mPCa) drops to 30% (2). Biochemical recurrence is frequently seen after initial therapy; therefore, it is extremely important to have tools for timely detection, accurate staging of primary, metastatic and relapsed PCa for prognostication and appropriate management of the disease. The prognosis correlates with tumor stage and Gleason score (3). The treatment options for early localized PCa include radical prostatectomy or external radiation therapy. For advanced or metastatic hormone-sensitive PCa, androgen deprivation therapy (ADT) is considered the standard of care with > 95% of patients responding to ADT until they progress to the castration-resistant phase. Metastatic castrate-resistant prostate cancer (mCRPC) is the final stage of the disease and is the leading cause of death. In mCRPC, the treatment options include cytotoxic chemotherapy, abiraterone acetate, enzalutamide, SiPuleucel-T, ^{223}Radium-dichoride or PARP inhibitors which can help prolong survival (4, 5). However, these therapies are associated with poor tolerance due to high systemic toxicity, poor tissue selectivity, and drug resistance. The survival benefit of these therapies is generally less than 6 months (6).

PROSTATE SPECIFIC MEMBRANE ANTIGEN RADIOLIGAND THERAPY

In recent years, significant progress has been made in PCa treatment based on prostate-specific membrane antigen (PSMA), and this led to recent Food and Drug Administration approval (FDA) of Lu-177 PSMA-617 (Pluvicto), a PSMA-based radioligand therapy (RLT). RLT is a type of treatment which involves injecting therapeutic doses of radionuclide-labeled ligand into the body. Therapeutic radiolabeled ligands bind to target cells and release alpha (α) particles, beta (β) particles or Auger electrons, which induce the break of single or double stranded DNA, leading to aging, necrosis, or apoptosis of target cells. DNA damage caused by low linear energy transfer such as beta particles is through indirect action of radiation with water molecules in the cell to form free radicals which in turn damage DNA strands. Most DNA damage by high energy transfer such as alpha particles or fast electrons produced by photons in Compton and photoelectric interactions is via direct DNA damage usually through double strand DNA breaks. RLT is different from conventional external radiation therapy; RLT targets disease at the cellular level, while external radiotherapy generally targets disease at a gross anatomical level (7).

Prostate-specific membrane antigen (PSMA) theranostics

PSMA is a transmembrane type II glycoprotein, consists of 750 amino acids located in three domains; these include the intracellular domain that contains 19 amino acids, the transmembrane domain that consists of 24 amino acids, and the extracellular domain that contains 707 amino acids (8). PSMA is present in the cytosol in normal prostate cells; this switches to a membrane-bound protein in prostate cancer cells. PSMA is expressed by prostate cancer tumors at nearly all stages of the disease (9). PSMA expression has been found to be correlated with

an increased tumor grade, pathologic stage, aneuploidy, and/or biochemical recurrence (10, 11). However, the term PSMA is a misnomer as low level of PSMA expression is seen in the brain, kidneys, salivary glands, and small intestine. The level of PSMA expression increases in PCa with increasing tumor dedifferentiation, and in metastatic and hormone-refractory cancers (12). This makes PSMA an excellent target for both PCa imaging and therapy. Ultrasound-guided biopsy is considered the standard of care in the initial diagnosis of PCa, however it can miss 21% to 28% of prostate cancer and under-grade 14% to 17% (13). The widely used multiparametric magnetic resonance imaging (MRI) has a combined sensitivity of 89% and a specificity of 73% for the identification of PCa (14). Current guidelines recommend MRI and positron emission tomography/computed tomography (PET/CT) for evaluation of patients with high-risk disease (15).

PSMA-targeting radiotracers

Recently, two PSMA-targeting molecular imaging agents Gallium-68 prostate specific membrane antigen (^{68}Ga-PSMA-11) and fluorine-18 piflufolastat (^{18}F-DCFPYL) received FDA approval after the completion of two landmark clinical trials, VISION and TheraP, which evaluated their safety and efficacy in treating metastatic castrate-resistant prostate cancer. These two agents have superior sensitivity and specificity profiles for recurrent or metastatic prostate cancer than the earlier approved PET molecular imaging agents (i.e., ^{18}F-fluciclovine [Axumin] and ^{11}C-choline). PSMA-targeting diagnostic imaging is critical in identifying eligible patients who can benefit from ^{177}Lu-PSMA therapy (Figure 1) and serves as a diagnostic component in ^{177}Lu- PSMA theranostics. At present, there is no definitive consensus on what amount of PSMA uptake in a metastatic lesion is considered sufficient for a patient to derive significant benefit from ^{177}Lu-PSMA therapy. Following the example of neuroendocrine tumor theranostics, adequate uptake is generally considered when most metastatic lesions show uptake higher

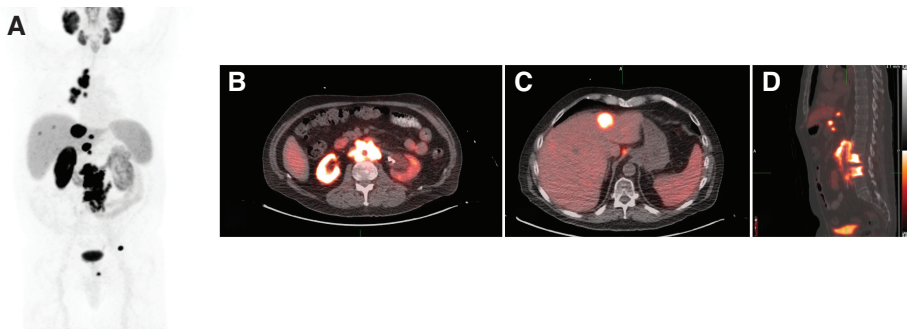

Figure 1. An 89-year-old male with mCRPC eligible for 177Lu-PSMA-617. A, Maximum intensity projection (MIP) image from a PSMA PET scan showing intensely PSMA-avid mediastinal and retroperitoneal lymphadenopathy, as well as intensely PSMA-avid metastatic lesions in the liver and lumbar spine. **B**, Fused axial image more clearly demonstrating extensive PSMA-avid retroperitoneal lymphadenopathy. **C**, Fused axial image more clearly demonstrating intensely PSMA-avid liver metastases. **D**, Fused sagittal image showing PSMA-avid osseous metastases in the lumbar spine.

than that of normal organs such as the liver. For example, the inclusion criteria of the TheraP phase 2 trial of ^{177}Lu-PSMA-617 required SUVmax values at dominant sites of metastatic disease to be least 1.5 times the SUVmean value of the liver on baseline ^{68}Ga-PSMA-11 PET imaging and excluded patients with FDG-avid metastatic lesions that lacked PSMA expression (16).

The VISION trial

This was a multicenter international open-label phase 3 trial, which compared the standard of care with standard of care plus ^{177}Lu- PSMA-617 in patients with mCRPC who had progressed after both taxane and novel androgen axis therapy. All patients enrolled in the trial had PSMA-positive ^{68}Ga-PSMA-11 PET-CT scan. PSMA positive lesions were defined as ^{68}Ga-PSMA-11 uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system. Patients with PSMA-negative lesions defined in the trial protocol as PSMA uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft tissue component of at least 1.0 cm in the short axis. The median follow-up was 20.9 months; the ^{177}Lu- PSMA-617 arm demonstrated superior progression-free survival (8.7 months vs. 3.4 months) and overall survival (15.3 months vs. 11.3 months) (17).

The TheraP trial

This was a multicenter, randomized, unblinded phase 2 trial in 11 centers in Australia. The trial recruited men with mCRPC patients for whom cabazitaxel was considered the next appropriate standard treatment and compared ^{177}Lu- PSMA-617 versus cabazitaxel. Previous treatment with androgen receptor-directed therapy was allowed. Participants underwent ^{68}Ga-PSMA-11 and ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET-CT scans. The PET eligibility criteria for the trial were PSMA-positive disease, and no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings. Men were randomly assigned (1:1) to ^{177}Lu- PSMA-617 (6·0–8·5 GBq intravenously every 6 weeks for up to six cycles) or cabazitaxel (20 mg/m2 intravenously every 3 weeks for up to ten cycles). The primary endpoint was prostate-specific antigen (PSA) response defined by a reduction of at least 50% from baseline. The results of the trial showed that ^{177}Lu- PSMA-617 compared to cabazitaxel in men with metastatic castration resistant prostate cancer led to a higher PSA response (66% vs 37%) and fewer grade 3 or 4 adverse events (16).

Comparison of VISION and Thera P trials

If we compare the VISION and Thera P trials, the PSA response rates were higher in the Thera P trial compared to the VISION trial (64% vs 46%), probably attributed to superior patient selection by FDG PET-CT. Table 1 summarizes the differences between the two trials.

TABLE 1 A Comparison of the VISION and TheraP trials

	VISION Trial	Thera P Trial
Type	**Phase 3**	**Phase 2**
PSMA PET imaging-based eligibility Criteria	PSMA SUVmax 1.5 times more than liver	PSMA SUVmax ≥20
FDG PET imaging-based eligibility criteria	Not performed	PSMA-positive disease, and no discordant FDG-positive and PSMA-negative findings
LU-psma-617	7.5 GBq per cycle up to 6 cycles ±2 cycles	8.5 GBq per cycle up to 6 cycles
Posttherapy emission scan	No	Yes
Control arm	Protocol defined SOC, excluding systemic therapies	Cabazitaxel
Excluded	12%	28%
Primary endpoint	OS, rPFS	PSA decline ≥50%
PSA 50% response	46%	66%

PSA: Prostate specific antigen, rPFS: radiographic progression free survival, OS: overall survival

Referral stream for PSMA RLT

Clinicians seeking to start a PSMA RLT program will, in most cases, need to advocate to their healthcare organization's leadership for the required resources. This can be a difficult task, as there may be significant upfront costs required, including but not limited to, acquiring and maintaining the required Nuclear Regulatory Commission (NRC) licenses for handling radioactive materials for medical use, hiring key support staff, staff training in radiation safety, radioactive waste disposal methods, and radiation safety administration. (18, 19) These infrastructure requirements for administering PSMA RLT are greater than for other types of RLT therapies such as ^{223}Radium-dichloride. For example, centers without nuclear medicine imaging equipment and staff will need to assess the financial feasibility of adding these capabilities, or if nuclear medicine imaging cannot be performed, a referral plan to imaging centers that have these capabilities will need to be established, as patient eligibility for PSMA RLT requires an assessment by PSMA PET. Guidance on these topics published by a variety of sources exists and should be used to help implement a new PSMA RLT program (20–22).

Other key operational requirements to plan for include revenue cycle management, identifying and addressing bottlenecks to maximize facility treatment capacity, establishing clear communication channels between patient care teams for consultation and management, and most importantly, creating an accessible and effective patient navigation system that provides individualized assistance that reduces systemic barriers to PSMA RLT. Lastly, effective PSMA RLT treatment

programs require coordinated input from multiple disciplines before, during and after treatment. The specialties include medical oncology, urology, nuclear medicine, radiation oncology, and pharmacy, as well as each group's administrative staff. Even large medical centers that have all the necessary capital resources will need to spend additional time and financial investment to establish efficient workflows to perform appropriate patient selection and administer PSMA RLT safely.

Consultation and patient selection

As with any medical intervention, it is important to determine whether a patient is an appropriate candidate for PSMA RLT before deciding to proceed with treatment. This can quickly become a difficult decision-making process, as patients who are referred for PSMA RLT frequently have complex medical comorbidities, as well as differing treatment goals. Thus, a multidisciplinary approach is required to reach a shared decision that balances the risks and benefits of PSMA RLT with alternative treatment options.

After a patient is first referred for potential PSMA RLT, one of the initial objectives is to confirm that the necessary indications are present. This determination requires a thorough review of the patient's clinical notes, recent imaging studies, and pertinent laboratory results. Currently, PSMA RLT treatment is only considered for patients with a confirmed diagnosis of mCRPC, who have received prior treatment with an AR pathway inhibitor and taxane-based chemotherapy, and who have PSMA-positive disease confirmed by a recent PSMA PET/CT (optimally within 6 months prior to consultation). As the request is initially being reviewed, it is important to note any potential inconsistencies, errors, or omissions in the patient's medical record, and clarification should be sought from the referring physician if present.

The consultation visit provides an opportunity to establish a clear understanding of the patient's treatment goals and to have a comprehensive discussion on the rationale, potential benefits, contraindications, and the individual risk of adverse events. Special emphasis should be placed on obtaining a detailed social history. Unique concerns such as the need for translation services, the patient's situation at home, travel plans, and other health needs (such as incontinence or dialysis) should be documented in the consultation, as these aspects can significantly affect the patient's ability to follow the radiation safety precautions and logistical requirements required by PSMA RLT. A detailed copy of treatment instructions and radiation safety precautions should be provided for the patient to review and refer to after the consultation visit.

Once the patient's candidacy for PSMA RLT has been established, recommendations should be communicated to the referring physician and other members of the patient's treatment team. In the event that the patient has been referred by a physician who works in a different hospital, it is recommended to communicate the results of the consultation to ensure continuity of care. If a decision is made to proceed with PSMA RLT, a written directive must be produced and informed consent must be obtained. Copies of the written directive, informed consent, and other relevant clinical data should be collected and organized into one source that can be referred to on days of scheduled PSMA RLT. In cases with borderline indications, the individual benefit-to-risk ratio should be evaluated and discussed with a multidisciplinary tumor board.

ROLE OF PSMA PET IMAGING

Lesion-specific PSMA expression is evaluated with PSMA PET imaging and is a key determinant for PSMA RLT eligibility. For PSMA RLT to be beneficial, metastatic lesions must demonstrate sufficient expression of PSMA (Figure 1). Patients whose metastatic lesions lack significant PSMA expression should not be considered for PSMA RLT, as PSMA receptor expression is required for treatment target localization (Figure 2). Pretreatment PSMA PET may also contain important prognostic information that has been shown to correlate with the degree of response and overall benefit of PSMA RLT. However, there are different definitions of what constitutes PSMA-positive and PSMA-negative disease in currently published PSMA RLT trials (Tables 1 and 2).

To identify potential PSMA-negative disease, patients should undergo contrast-enhanced CT or MRI of the abdomen and pelvis within a reasonable timeframe surrounding PSMA PET imaging. Treatment may be appropriate for patients with heterogeneous disease on PSMA PET, especially if most of the disease is PSMA positive and the patient has exhausted all other therapeutic options.

In addition to determining eligibility for PSMA RLT, another purpose of PSMA PET is to evaluate the current state of metastatic disease. Ideally, PSMA PET imaging should be performed within three months prior to starting RLT treatment, and only after it has been confirmed that disease progression has occurred on the most recent line of therapy.

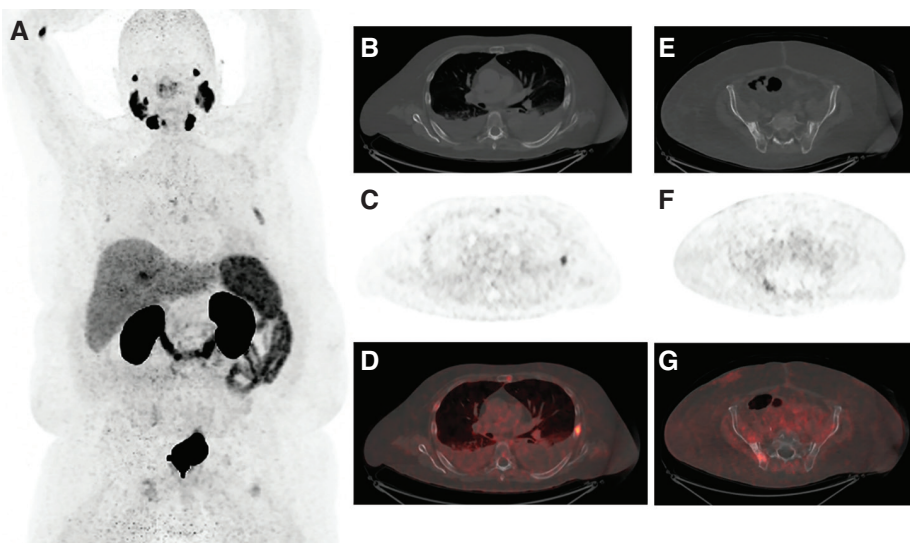

Figure 2. An 82-year-old man with metastatic prostate cancer, but with limited PSMA expression of disease, ineligible for 177Lu- PSMA-617 RLT. A. Maximum intensity projection image of ^{18}F-PyL PSMA PET/CT; **B.** axial CT image of the chest demonstrating one osteoblastic rib lesion and mild uptake in the sternal body and a right-sided rib; **C.** axial PSMA PET image demonstrating uptake related to the osteoblastic rib lesion and mild uptake in the sternal body and a right-sided rib; **D.** fused PET/CT images of B and C; **E.** axial CT image demonstrating an osteoblastic right iliac bone lesion; **F.** PSMA PET image demonstrating limited uptake associated with the osteoblastic lesion; **G.** fused images of E and F.

TABLE 2 **Comparison of PSMA PET positive and negative disease criteria used in the TheraP and VISION randomized clinical trials**

	PSMA PET Positive Disease (PSMA PET Eligibility Criteria)	PSMA PET Negative Disease (Sufficient for Trial Exclusion)
TheraP	≥1 metastatic lesion with maximum SUV >20 *AND* Maximum SUV >10 at all sites of disease measuring ≥1.0 cm in diameter*	A metastatic lesion with FDG maximum SUV > PSMA maximum SUV *OR* A PSMA-avid lesion with maximum SUV <10
VISION	≥1 metastatic lesion with PSMA uptake > normal liver parenchyma.	≥1 lesion with PSMA uptake < normal liver parenchyma, in the following organ systems: • Lymph node (≥2.5 cm) • Solid-organ (≥1.0 cm) • Bone lesion with soft-tissue component (≥1.0 cm)

*Excluding lesions with falsely decreased PSMA uptake caused by an imaging artifact

PSMA PET imaging protocol

PSMA PET/CT imaging should be performed in accordance with institutional protocols and published procedure guidelines (23). In general, once the patient arrives at the nuclear medicine department, a PET technologist begins the preparation by gathering relevant medical history and test results. The indication for imaging, prostate cancer history, and other relevant comorbidities such as the presence of other nonprostate malignancies must be reviewed and confirmed. A nuclear medicine physician is consulted for guidance if concerns are identified.

Once pre-procedure screening is complete, the PSMA PET dose is administered intravenously, followed by a resting uptake period of about 60 minutes. Around 30–60 minutes before image acquisition, the patient is given an oral contrast mixture. The patient is then placed in the supine position with both arms raised above the head. CT is performed first, covering the skull base to mid-thigh and in accordance with institutional protocols. If planned, contrast-enhanced CT should be performed in the portal venous phase.

Following the CT scan, PET images are acquired in an identical anatomic range starting at the mid-thigh and proceeding towards the skull base. PET scans are acquired in 3D mode with an acquisition time of usually 2–4 min per bed position. PET/CT image reconstruction is performed with any necessary data corrections and finally transferred for archiving and interpretation. Upon completion, patients are advised to void as soon as possible and drink ample fluids to assist with urinary and gastrointestinal radiotracer excretion. Occasionally, PET/MRI may be performed and can be done with MRI sequences based on the clinical question.

Technical considerations on the day of therapy

Before scheduled therapy, patients are encouraged to maintain adequate hydration, beginning two days beforehand. On the day of therapy, the consultation (including scan results), recent lab results, and the patient's medications must be verified, paying special attention to any new contraindications that may have occurred since the initial consultation.

Multiple safety checkpoints must be completed while preparing and administering a PSMA RLT dose to minimize the risk of medical error. These steps include dose quality control, confirming that a signed consent form is on file, confirming that the patient has received post-treatment instructions, and confirming the correct patient, therapeutic dose, prescribed activity, and intravenous patency before beginning the treatment infusion.

PSMA RLT is administered intravenously as an injection or infusion for approximately 10 minutes. When managing the treatment dose, it is essential to employ both the aseptic technique and radiation shielding to prevent contamination and reduce radiation exposure to the patient and healthcare staff. There are multiple methods that can be used to administer PSMA RLT. A commonly used approach, known as the 'gravity method', is reliable, cost-effective, and safe for both the patient and staff. Alternative options for dose administration include the use of a peristaltic infusion pump or intravenous injection through a shielded syringe. Regardless of the method chosen, it is essential to follow the detailed procedural descriptions provided by the manufacturer of the radiopharmaceutical (24, 25).

Post-administration considerations

Radiation safety precautions should be discussed with patients at the time of initial consultation, well before treatment is initiated. Additionally, after each treatment administration, patients should be reminded of these safety measures to help reduce radiation exposure to themselves and others around them.

General recommendations include that patients increase their posttreatment fluid intake and void as often as possible, as the bladder wall receives some of the highest doses of absorbed radiation. There are also several instructions regarding the interactions of a patient with other members of their household, and details of the current living situation should be collected at the time of initial consultation, as they can significantly affect a patient's ability to properly follow if they have smaller living spaces or share them with several people. Table 3 provides a detailed list of radiation instructions given to patients which should be always easily accessible to the patient during PSMA RLT treatment.

MANAGING TREATMENT-RELATED ADVERSE EVENTS

PSMA RLT therapy is not without risks, and there are several posttreatment adverse events that require subsequent dose modification. These dose modifications fall into one of the three categories:

TABLE 3 **Radiation safety precautions provided after ^{177}Lu-PSMA-617 administration**

	Instructions
Close Contact with Others	Limit close contact (<3 feet) with household contacts for 2 days post-treatment.
	Limit contact with children (<10 years) and pregnant women for 7 days post-treatment.
Toilet Use	Drink plenty of fluids and attempt to urinate every hour on every treatment day
	Strive for daily bowel movements
	Use toilets in a seated position.
	Always use toilet paper
	Flush the toilet twice after every use
	Flush wipes for at least two days after every treatment.
	Place non-flushable items (pads, bandages) in specified plastic trash bags. Keep these trash bags separate and away from children and animals for six weeks. After six weeks, they can be disposed with other normal household waste.
	Wash hands after every toilet use.
Personal Hygiene	Shower daily for at least the first 7 days following every treatment.
Laundry	Wash items containing your body fluids separately and wash them two or three times before allowing others to use them again.
Sleep	Sleep separately from household contacts for 3 days after treatment
	Sleep separately from children for 7 days after treatment
	Sleep separately from pregnant women for 15 days post-treatment.
Sexual Activity	Avoid sexual activity for 7 days post-treatment.
	Male patients must use effective contraception while undergoing treatment and continue to do so for 14 weeks after completing treatment.
Patients Who Receive Extra Assistance	Care providers assisting patients should wear disposable gloves for 2–3 days post-administration.
	Patients with urinary incontinence should use incontinence pads. Dispose in specified plastic bag.
	Empty and clean any special medical equipment (catheters, colostomy bags, etc.) immediately after use.
Medical Care	Notify your oncologist about any unplanned hospitalization.
	Carry your discharge letter for at least 3 months post-treatment. Inform emergency medical providers about treatment during the first week.
Travel	Carry your discharge letter when travelling for at least 3 months post-treatment.

i. Withholding treatment until the system in question returns to baseline function or another specified criterion.
ii. Reducing the next scheduled treatment dose by 20% (i.e., 160 mCi).
iii. Permanently discontinuing PSMA RLT.

Although the FDA package insert (24) should be directly consulted when managing any treatment-related adverse event, special attention should be paid to the following scenarios that require PSMA RLT to be permanently discontinued:

- Any Grade 3 or 4 adverse reaction that recurs after a previous dose reduction.
- Any Grade ≥3 renal toxicity.
- Any renal toxicity that recurs after a dose reduction for previous renal toxicity.
- If there are no liver metastases, an AST or ALT elevation > 5 times the upper limit of normal (ULN) after PSMA RLT administration.
- Any serious adverse reaction that requires delaying treatment longer than 4 weeks.
- Any treatment-related toxicity that a patient is unable to tolerate.

DOSIMETRY AND POST-THERAPY SCINTIGRAPHY

Post-therapy scintigraphy can allow for quantitative estimation of absorbed radiation doses to normal organs and tumor lesions after ^{177}Lu-PSMA administration using a process known as internal dosimetry. Internal dosimetry uses variables such as the accumulation and clearance of radionuclide activity over time in specific regions or volumes of interest in conjunction with standard methods such as the Medical Internal Radiation Dose (MIRD) model and accurate radionuclide biodistribution data to estimate absorbed dose in an organ- or lesion-specific manner (26, 27).

There is growing evidence that patient-specific dosimetry measurements can significantly improve the efficacy of radionuclide therapies while reducing toxicity by allowing more individualized dosing strategies. For example, dosimetry measurements obtained from post-treatment ^{177}Lu-PSMA scintigraphy have been found to correlate with the likelihood of subsequent PSA response and occurrence of tumor sink effect. Additionally, dosimetry studies have shown an association between overall PSMA-avid tumor burden and organ absorbed doses (28–30).

Post-therapy scintigraphy can be performed at a single time point after ^{177}Lu-PSMA RLT administration or at multiple points in a serial fashion, typically ranging from 120 minutes to 8 days post-injection (Figure 3). Post-therapy scintigraphy can be performed by planar imaging or single photon emission computed tomography (SPECT). A significant disadvantage of planar imaging compared to SPECT/CT is its inaccuracy in distinguishing between overlapping areas of radiotracer uptake present in more than one organ, which most likely results in dose overestimation.

^{177}Lu-177 PSMA dose modifications found in current PSMA RLT treatment protocols reflect the findings of previous dosimetry studies (24). ^{177}Lu-PSMA dosimetry studies have shown that the salivary glands, lacrimal glands, and kidneys consistently receive the highest absorbed radiation dose after administration (29, 31–34). Other organs that receive significant absorbed dose include the small intestine and colon.

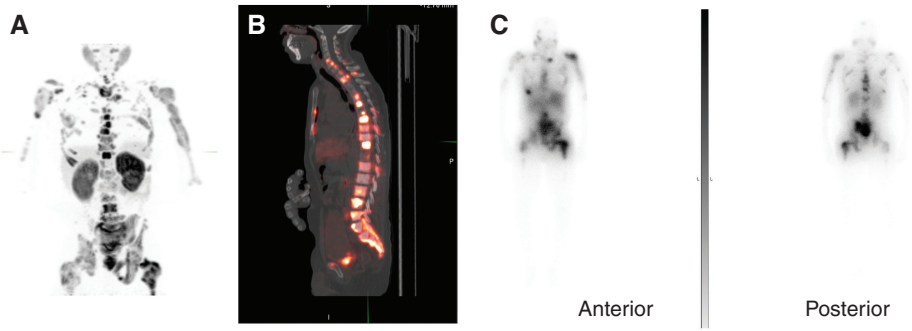

Figure 3. A 57-year-old male with mCRPC. A, ^{68}Ga-PSMA PET-CT Maximum intensity projection (MIP) image shows widespread intensely PSMA avid osseous lesions in the axial and appendicular skeleton. **B,** Fused sagittal image showing multiple intensely PSMA avid sclerotic lesions in the spine. **C,** PSMA post-therapy emission planar images (anterior and posterior) acquired 7 days after the therapy show PSMA-avid osseous lesions in the axial and appendicular skeleton with a distribution similar to the PSMA PET/CT.

CONCLUSION

In the current treatment schema, ^{177}Lu-177 PSMA therapy is considered in the late stages of prostate cancer, and not in the early stages of the disease. The application of ^{177}Lu-177 PSMA therapy earlier in the course of the disease has demonstrated prolonged survival in prostate cancer (35).

Certain patients who are nearing the end of their six cycles of ^{177}Lu-177 PSMA therapy, especially those who are responding well to therapy, may desire to continue with treatment. There are centers outside the United States that are considering additional cycles after demonstrating an additional favorable response with limited toxicity (36). At Stanford, certain patients are beginning to receive additional therapies based on dosimetry performed on their final cycle post-therapy scan. Currently, only two additional cycles are planned, whereas in Europe a patient may receive six or more additional cycles.

Some patients are pursuing alpha-PSMA therapies in other countries. Alpha-PSMA therapy is performed with ^{213}Bi or ^{223}Ac. Alpha particles have significantly larger mass than the beta particles emitted from ^{177}Lu-PSMA-617, and thus have significantly shorter penetration distances and deposit higher energy in a more localized space. Some published reports demonstrate marked treatment responses on posttreatment imaging; however, side effects such as salivary gland toxicity may be significantly greater than with ^{177}Lu-PSMA-617 (37, 38).

PSMA RLT has been shown to improve patient-centered outcomes in mCRPC and is becoming increasingly incorporated into a multi-modality treatment approach. An area that warrants further investigation is determining if administering PSMA RLT earlier in the disease course of mCRPC could provide additional therapeutic benefit.

Conflict of Interest: The authors declare that they have no potential conflict of interest with respect to research, authorship, and / or publication of this chapter.

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