^{177}Lu-PSMA Therapy

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Radiopharmaceutical therapy using ^{177}Lu-prostate-specific membrane antigen (PSMA) is an effective prostate cancer treatment that was recently approved by the U.S. Food and Drug Administration. This method leverages the success of PSMA-targeted PET imaging, enabling delivery of targeted radiopharmaceutical therapy; has demonstrated a clear benefit in large prospective clinical trials; and promises to become part of the standard armamentarium of treatment for patients with prostate cancer. This review highlights the evidence supporting the use of this agent, along with important areas under investigation. Practical information on technology aspects, dose administration, nursing, and the role of the treating physician is highlighted. Overall, ^{177}Lu-PSMA treatment requires close collaboration among referring physicians, nuclear medicine technologists, radiopharmacists, and nurses to streamline patient care.

Key Words: genitourinary; radiation safety; radionuclide therapy; prostate; radiopharmaceutical therapy; technology

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Aside from nonmelanoma skin cancer, prostate cancer is the most common cancer among men in the United States, with 1 of 8 men diagnosed during their lifetime (*1*). Although prostate cancer is highly treatable, up to 30% of patients will develop metastatic castration-resistant prostate cancer (mCRPC) (*2*). Treatment for mCRPC commonly includes immunotherapy, radionuclide therapy with ^{223}Ra, cytotoxic agents, and androgen deprivation therapy. These treatments have improved overall survival (OS); however, despite advances in systemic therapies, mCRPC remains incurable (*3*).

Prostate-specific membrane antigen (PSMA) has emerged as a valuable target in mCRPC for both diagnosis and therapy. PSMA is highly overexpressed in more than 90% of prostate cancer metastatic lesions and demonstrates higher expression with greater Gleason grades (*4,5*). Furthermore, PSMA PET/CT has been demonstrated to outperform other conventional imaging modalities in the sensitivity and specificity of detecting prostate cancer recurrence and metastasis (*6*). Given the differential expression of PSMA between prostate cancer and normal tissue, small-molecule PSMA inhibitors have been developed, such as ^{177}Lu-PSMA-617 (^{177}Lu-vipivotide tetraxetan; Pluvicto [Novartis]) and ^{177}Lu-PSMA I&T, for therapy of mCRPC. The benefit of this targeted molecular therapy is based on the binding, internalization, and retention of the PSMA ligands within tumor cells (*7*).

Labeling PSMA molecules with a variety of radioisotopes (including ^{18}F, ^{68}Ga, ^{99m}Tc, ^{177}Lu, ^{225}Ac, ^{111}In, and ^{90}Y, among others) allows for PET or SPECT imaging as well as radioligand therapy (RLT) with β^- or α emitters. Over the last decade, significant knowledge about the efficacy of PSMA RLT has been gained. ^{177}Lu-PSMA-617 has now achieved widespread acceptance as a viable targeted treatment for mCRPC, with U.S. Food and Drug Administration (FDA) approval granted on March 23, 2022, for adults who have PSMA-positive mCRPC and have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy (*8*). This continuing education article will cover patient selection, clinical considerations, technical considerations, treatment protocols, imaging, response to therapy, dosimetry, future developments, and radiation safety. However, billing and coding, payer reimbursement, and regulatory considerations for ^{177}Lu-PSMA-617 have not yet been determined as of the time of publication and are not discussed here.

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PATIENT SELECTION

Given a shared target, PSMA PET has been used to assess patients eligible for PSMA-targeted RLT such as ^{177}Lu-PSMA or ^{225}Ac-PSMA (*9,10*). PSMA PET is essential for mCRPC patients being considered for PSMA RLT to help stage and identify PSMA-positive lesions that will respond to PSMA RLT (*11*). The FDA package insert for ^{177}Lu-PSMA-617 (^{177}Lu-vipivotide tetraxetan) specifies that patients to be selected for treatment must use the FDA-approved PSMA PET radiopharmaceutical ^{68}Ga-PSMA-11 (^{68}Ga-gozetotide; Illuccix [Telix Pharmaceuticals] or Locametz [Advanced Accelerator Applications]) (*8*). There are currently 2 FDA-approved PSMA PET radiopharmaceuticals for initial staging and biochemically recurrent mCRPC: ^{68}Ga PSMA-11 (^{68}Ga-gozezotide) and ^{18}F-DCFPyL (^{18}F-piflufolastat; Pylarify [Progenics Pharmaceuticals]).

Many clinical trials have shown the utility of using PSMA PET to identify mCRPC patients who will benefit from PSMA RLT and to exclude those who are most likely to be nonresponders. Two major multicenter clinical trials, VISION (United States and Canada) and TheraP (Australia), investigated the outcome of patients with mCRPC after ablation with ^{177}Lu-PSMA-617 RLT (*12,13*). The phase III VISION trial evaluated ^{177}Lu-PSMA-617 RLT in 831 patients with mCRPC and was the principal justification for FDA approval of ^{177}Lu-PSMA-617 RLT. Primary outcomes measured imaging-based progression-free survival and OS between ^{177}Lu-PSMA-617 RLT plus standard of care (SOC) versus SOC alone. ^{177}Lu-PSMA-617 plus SOC significantly prolonged both imaging-based progression-free survival (median, 8.7 vs. 3.4 mo) and OS (median, 15.3 vs. 11.3 mo), compared with SOC. Additionally, whereas the incidence of adverse events (AEs), grade 3 or above, was higher in the ^{177}Lu-PSMA-617 arm (52.7% vs. 38.0%), quality-of-life measures were not significantly impacted.

The phase II TheraP trial compared ^{177}Lu-PSMA-617 RLT with SOC cabazitaxel in 200 men with mCRPC. The primary endpoint was prostate-specific antigen (PSA) response defined by a reduction in PSA by at least 50% from baseline. In contrast to VISION, TheraP set requirements of at least 1 lesion on ^{68}Ga-PSMA-11 PET with an SUV_{max} of more than 20, the remaining metastatic lesions with an SUV_{max} of more than 10, and no discordant hypermetabolic disease. PSA responses were more frequent in the ^{177}Lu-PSMA-617 RLT group than the cabazitaxel group (66% vs. 37%, respectively). Grade 3–4 AEs occurred in 33% of the ^{177}Lu-PSMA-617 RLT group versus 53% of the cabazitaxel group. It is yet to be determined whether stratifying by SUV_{max} can improve patient outcomes, and the OS of the TheraP trial has yet to be reported.

Although both trials reported better outcomes for patients who received ^{177}Lu-PSMA-617 RLT than for those who received SOC chemotherapy, the TheraP outcome is considered superior to the VISION outcome. The better outcome is believed to result from more strict criteria that excluded mCRPC patients with discordant hypermetabolic lesions. The main criteria for both VISION and TheraP included patients with PSMA-positive metastatic lesions on ^{68}Ga-PSMA-11 PET/CT and excluded patients without PSMA uptake on ^{68}Ga-PSMA-11 PET/CT. Although VISION used conventional imaging to exclude patients with discordant lesions (lesions positive on CT and negative on PSMA PET), TheraP used functional techniques including ^{18}F-FDG PET/CT in conjunction with PSMA PET/CT, and patients with at least 1 discordant hypermetabolic lesion (PSMA-negative or ^{18}F-FDG–positive) were excluded. Many studies using PSMA PET on patients with mCRPC have consistently shown that a sizable minority has at least 1 discordant hypermetabolic lesion and that these patients have worse outcomes. For example, Chen et al., in a study of 56 patients, found that 23.2% had at least 1 discordant lesion and that prostate serum antigen (PSA) and Gleason score were both higher in these patients (Fig. 1) (*14*).

A subanalysis of a single-center phase 2 trial of ^{177}Lu-PSMA-617 RLT similarly found that 16 of 50 patients had at least 1 discordant lesion and were deemed ineligible for ^{177}Lu-PSMA-617 therapy. The OS of these patients was 2.6 mo (compared with 13.5 mo for patients who received ^{177}Lu-PSMA-617) (*15*).

Until recently, it was unknown whether the inclusion and exclusion criteria of VISION and TheraP were appropriate or whether all patients with mCRPC would benefit from ^{177}Lu-PSMA RLT regardless of PSMA PET findings. A recent retrospective analysis compared the outcomes of patients who were treated with ^{177}Lu-PSMA-617 RLT and who would have failed the VISION inclusion criteria (positive metastatic lesions on CT and with low or no PSMA uptake) versus patients who received ^{177}Lu-PSMA-617 RLT

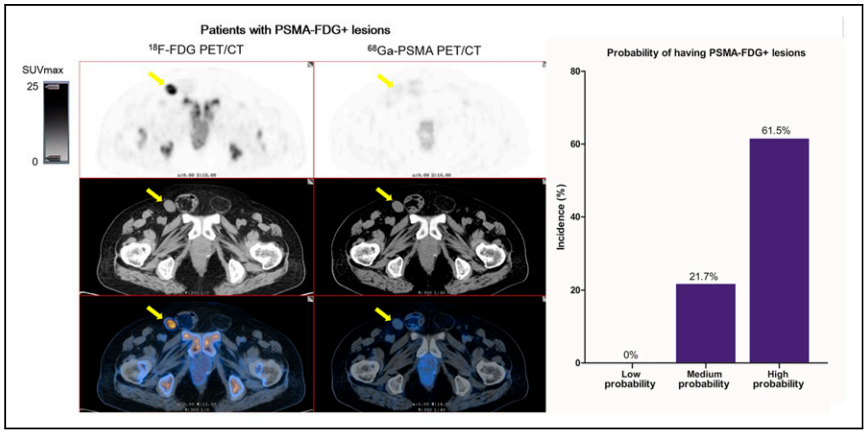

FIGURE 1. Previously published image demonstrating discordant hypermetabolic right inguinal metastatic deposit with high ^{18}F-FDG PET uptake and little to no PSMA accumulation. (Reprinted from (*13*).)

and met the VISION eligibility criteria. The outcome for the VISION-noneligible group was significantly worse than that of patients who met the VISION inclusion criteria, with a PSA response rate of 21% versus 50% ($P = 0.005$), PSA progression-free survival of 2.1 versus 4.1 mo ($P = 0.023$), and a trend toward a shorter OS of 9.6 mo versus 14.2 mo ($P = 0.16$), respectively (*16*). Several additional similar trials have also found significant differences in ^{177}LuPSMA RLT outcome between patients with discordant hypermetabolic disease and those with PSMA-matched or ^{18}F-FDG–negative disease. For example, Michalski et al. demonstrated that in a study with 54 patients who received ^{177}Lu-PSMA RLT and included patients both with and without discordant hypermetabolic disease, patients with discordant hypermetabolic disease had an OS of 6.0, versus 16.0 mo for those without discordant disease (*17*). Although that study showed that patients can develop discordant hypermetabolic disease after ^{177}Lu-PSMA RLT, these patients do not appear to have outcomes different from patients with ^{18}F-FDG–concordant disease (*18*). Despite the seemingly clear and consistent evidence that PSMA PET is needed for patient stratification before ^{177}Lu-PSMA RLT, there remains debate from both industry and the medical community about the need for pretherapy PSMA PET/CT. To address this concern, a recent review article summarized the community's hope that "the prostate cancer medical community will stand up for precision medicine, including by ordering PSMA (and ^{18}F-FDG) PET before treating a patient with ^{177}Lu-PSMA-617," adding, "PSMA RLT for prostate cancer without PSMA PET should not be accepted" (*19*).

According to the Centers for Medicare and Medicaid Services, the use of ^{18}F-FDG PET/CT in the evaluation of patients with prostate cancer is not approved for billing in the United States. Therefore, using ^{18}F-FDG PET/CT as an adjunct to PSMA PET to optimize patient selection for ^{177}Lu-PSMA RLT may be challenging. Alternative PET agents that are approved for biochemically recurrent prostate cancer, such as ^{18}F-fluciclovine (*20*) and ^{11}C-choline, may potentially be used in the future as an adjunct to optimize patient selection and improve outcomes. However, this possibility should be evaluated in clinical trials.

CLINICAL CONSIDERATIONS

With the recent FDA approval of ^{177}Lu-PSMA-617 (^{177}Lu-vipivotide tetraxetan), the field of PSMA RLT is expected to evolve rapidly. The European Association of Nuclear Medicine has published procedure guidelines for ^{177}Lu-PSMA radiotherapies (*21*), and procedure standards from the Society of Nuclear Medicine and Molecular Imaging are under development. The European Association of Nuclear Medicine guidelines promote the use of ^{177}Lu-PSMA radiotherapy for patients with mCRPC "who have exhausted or are ineligible for approved alternative options and with adequate uptake of PSMA ligands on the basis of a pre-therapy imaging." However, the decision on whether alternative therapies have been exhausted is often beyond the scope of a nuclear medicine or radiology physician. Therefore, the involvement of a multidisciplinary tumor board comprising a nuclear medicine or radiology physician, a medical oncologist, a radiation oncologist, and/or a urologist is strongly encouraged. A full discussion of the benefits and risks of alternative therapies (including androgen deprivation therapy, antiandrogens, secondary hormone agents [e.g., abiraterone, enzalutamide], chemotherapy, and other targeted radionuclide therapies [e.g., $^{223}RaCl_2$]) is beyond the scope of this article.

Although the FDA package insert for ^{177}Lu-PSMA-617 does not specify any contraindications, the European Association of Nuclear Medicine guidelines have published contraindications for PSMA RLT. For the most part, these guidelines have mirrored the inclusion and exclusion criteria of large phase II or III trials such as VISION (*12*) and TheraP (*13*), with some minor variations. These contraindications include a life expectancy of less than 6 mo, an Eastern Cooperative Oncology Group performance status of more than 2, an unacceptable medical or radiation safety risk, an unmanageable urinary tract obstruction or hydronephrosis, inadequate organ function (glomerular filtration rate < 30 mL/min or creatinine $>$ 2-fold the upper limit of normal; liver enzymes $>$ 5-fold the upper limit of normal), inadequate marrow function (total white cell count $< 2.5 \times 10^9$/L and platelet count $< 75 \times 10^9$/L), and conditions that require timely interventions (radiation therapy, surgery). For example, for spinal cord compression and unstable fractures, PSMA RLT might be performed afterward depending on the patient's condition.

^{177}Lu-PSMA RLT has been shown to have a low rate of AEs in several clinical studies. There are, though, some observed risks that the nuclear medicine physician and patient should know about. In the phase III VISION study, 52.7% of patients experienced grade 3 or higher AEs, greater than the 38.0% of patients with similar events in the control group. Anemia was the most common AE of grade 3 or higher, observed in 12.9% of subjects. This finding is somewhat surprising given the relatively low uptake in bone marrow. This anemia is considered a real effect, as a recently published metaanalysis of 250 studies with a total of 1,192 patients similarly found that although grade 3 and 4 toxicities were uncommon, anemia was the highest reported AE for both ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA I&T (*22*). Other notable AEs include the 7.9% and 2.5% of patients in VISION who experienced thrombocytopenia and leukopenia, respectively. An elevated transaminase level is often seen; this is somewhat expected, given the moderate amount of ^{177}Lu-PSMA uptake in the liver. Greater than 35% of patients in the treatment group of VISION experienced fatigue, xerostomia (dry mouth), or nausea, though almost all were grade 2 or less (*12*). The AE incidence was similar to that in smaller early-phase studies that preceded VISION (*13,23–25*). Quality of life was not adversely affected in VISION, supporting its inclusion in a treatment plan, with the ^{177}Lu-

PSMA-617 arm reporting a favorable pain intensity score on the short form of the Brief Pain Inventory, as well as a favorable time to deterioration in the Functional Assessment of Cancer Therapy–Prostate questionnaire (*12*). Additionally, the reported mean global health status was similar between the ^{177}Lu-PSMA-617 arm and the SOC arm in TheraP.

TECHNICAL CONSIDERATIONS

The production and quality control recommendations of the joint International Atomic Energy Agency, European Association of Nuclear Medicine, and Society of Nuclear Medicine and Molecular Imaging on peptide receptor radionuclide therapy for neuroendocrine tumors are applicable to ^{177}Lu-PSMA RLT (*26*). ^{177}Lu-PSMA consists of a pharmacophore (PSMA) conjugated with a chelating moiety (DOTA) to bind to the ^{177}Lu radiometal (*27*). The DOTA–PSMA precursor is typically produced under good-manufacturing-practice conditions by a commercial supplier such as ABX. The ^{177}Lu is supplied as $^{177}LuCl_3$ and is also produced under good-manufacturing-practice conditions. This radiosynthesis has previously been described in detail (*28*), consisting of a radiolabeling step followed by purification. The radiolabeling is typically performed in ascorbate buffer, which is used to control the pH of the reaction and to stabilize the radiolysis. The reaction is heated and then purified using a series of solid-phase extraction cartridges. Purification consists of passing a diluted reaction solution through a C18 cartridge, which retains the radiolabeled ^{177}Lu-PSMA and allows any unreacted $^{177}LuCl_3$ to pass through to waste. The C18 is rinsed and eluted with an ethanol–water solution and then diluted with saline containing ascorbic acid. The solution is then passed through a cation-exchange cartridge containing diethylenetriamine pentaacetate and is finally passed over a 0.22-μm sterilizing filter. A small aliquot (<1 mL) is taken for quality control analysis.

Quality control testing typically consists of tests for radiochemical purity, radiochemical identity, appearance, pH, endotoxin content, filter integrity, and sterility. Radiochemical purity and identity are analyzed by high-performance liquid chromatography; appearance, by visual inspection; pH, by pH paper strips; endotoxin content, by a PTS Endosafe (Charles River Laboratories) system according to U.S. Pharmacopeia <85>; filter integrity, by a bubble-point test; and sterility, by direct inoculation of trypticase soy broth and fluid thioglycollate medium according to U.S. Pharmacopeia <71>. Typical specifications are shown in Table 1.

TABLE 1
Typical Specifications for Quality Control Tests

Test	Specification
Radiochemical purity (HPLC)	>95%
Radiochemical identity (HPLC)	t_R ± 5% reference standard
Appearance (visual inspection)	Clear, colorless, particulate-free
pH	4.0–7.0
Endotoxin content (USP <85>)	<175 EU/injected dose
Filter integrity (bubble point)	According to filter manufacturer
Sterility	Sterile after 14 d

EU = endotoxin units; HPLC = high-performance liquid chromatography; t_R = retention time; USP = U.S. Pharmacopeia.

ADMINISTRATION PROTOCOL

Clinical administration of ^{177}Lu-PSMA requires close collaboration between nuclear medicine physicians, nurses, radiopharmacists, and technologists. Although the specific roles and responsibilities of each team member may vary depending on the established hospital protocols, the following section can be considered a guide.

The FDA package insert for ^{177}Lu-PSMA-617 specifies that each patient be treated with up to 6 cycles of 7.4 GBq (200 mCi) every 6 wk, with the dose being interrupted, reduced, or permanently discontinued if there are adverse reactions. VISION provided for a ±1-wk allowance of treatment dates. On the day of therapy, the patient may work with providers such as a nurse, a nuclear medicine physician, and a nuclear medicine technologist.

Baseline laboratory tests are typically performed before therapy. These usually include a complete blood count and testing of albumin, creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, and PSA levels. When patients arrive, the nurse orients them to the therapy room, explains radiation safety guidelines, obtains a set of vital-sign measurements, and reviews with the patient the discharge paperwork, including expected side effects; unexpected mild, moderate, and severe side effects and what to do if they occur; and the dates of future appointments. If patients have been prescribed a methylprednisolone dose pack to offset any expected increase in bone pain, they are asked to bring the medication to the appointment. The nursing team goes over the instructions with patients and encourages them to take their first dose before leaving.

The nuclear medicine physician obtains the patient's consent to undergo the procedure and instructs the patient on radiation safety measures, according to the institutional radiation safety guidelines. The patient is typically given a copy of these instructions and told to bring them along on any air travel during the next 2 mo in case of causing radiation detection alarms. Typical recommendations include minimizing exposure of others to radiation by limiting close contact (<91 cm [3 ft]) for 2 d and limiting sexual activity for 7 d. Patients are also advised to sleep in a separate bedroom for 3 d, increasing this to 7 d if there are children in the household or 15 d if there are pregnant women (*8*).

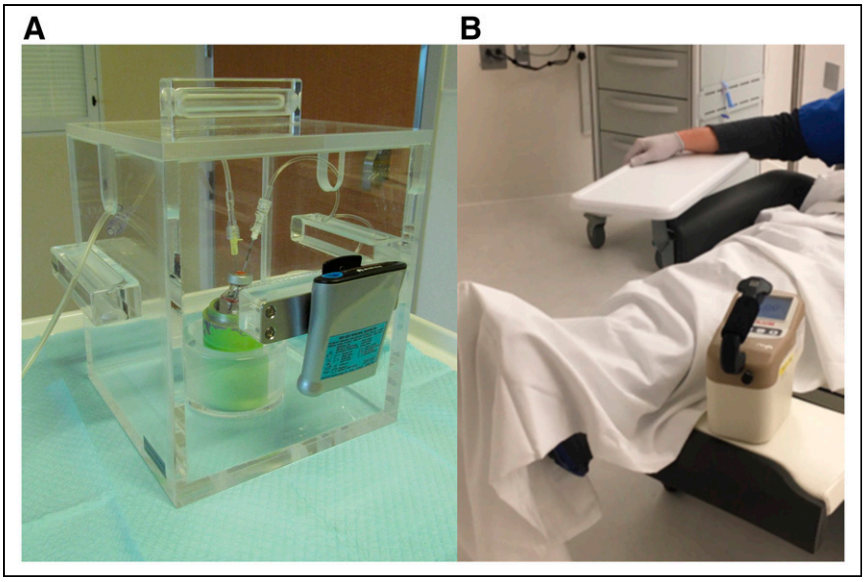

FIGURE 2. Gravity-method ^{177}Lu-PSMA-617 delivery system with inflow and outflow needles (A) and acrylic glass shielding to reduce radiation dose to nuclear technologist while maintaining validation of adequate flow. Radiation survey meter is used during ^{177}Lu-PSMA-617 infusion to verify systemic administration (B).

Patients are encouraged to drink fluids during the procedure and to void as often as feasible to reduce bladder radiation. The nurse establishes an intravenous line or accesses an existing port, collects a preinfusion blood sample for PSA measurement, and starts a saline drip, with a minimum of 10 mL as recommended by the prescribing information. After the saline infusion is complete, the nuclear medicine technologist infuses the ^{177}Lu-PSMA-617 via the syringe method (a disposable syringe fitted with a syringe shield), vial method (with a peristaltic infusion pump), or gravity method (with or without an infusion pump) (*29*) (Fig. 2). It is important that the infusion method be able to transfer the radiopharmaceutical to the patient safely and with the least manipulation to decrease exposure of the technologist to radiation, lower the chances of contamination, and ensure sterility. The radiopharmaceutical is typically provided by a radiopharmacy in a vial.

Syringe Method

The manual-push syringe technique is the most common transfer method in nuclear medicine, is the same technique as used for other liquid radiopharmaceuticals in a syringe, and has the lowest learning curve for the technologist, making it the easiest technique to adopt. The syringe is Luer-locked to the intravenous line of the patient. The main pitfalls of the manual push are an inconsistent rate of infusion and the highest exposure of the technologist to radiation.

Vial Method

Another method using a syringe—the vial method with a peristaltic infusion pump—has multiple steps. Pumps are common in hospitals and are frequently used by anesthesia staff. This method decreases exposure of the technologist, with most of the exposure coming from setting up the pump. The infusion rate is consistent, and risk for contamination is low.

Gravity Method

The gravity method uses a 250-mL saline bag punctured by a line with long and short needles to rinse the vial and a second line to the patient. There are several potential pitfalls to this method. The probability of contamination increases because of multiple punctures to the vial, leading to fluid overfilling the vial. Additionally, the residual is difficult to determine because of the length of the tubing and shielding. The technologist will have to constantly monitor the vial for fluid overfills to prevent contamination. If a reduced dose of ^{177}Lu-PSMA-617 is to be administered, the syringe method or vial method should be used because the gravity method may result in an incorrect volume. Medication pumps may include air sensors, pressure sensors, and microtubing allowing a safe transfer of the radiopharmaceutical to the patient while the patient is being monitored from a distance. This method greatly reduces the risk of infiltration, contamination, and exposure. The downside is the learning curve, and supplies can be costly.

When technologists are performing each infusion technique, they must follow as-low-as-reasonably-achievable principles to decrease radiation exposure; all methods discussed here can be applied behind an L-block or acrylic glass shielding.

The patient is kept for observation for 1 h. During observation, the nursing staff and nuclear medicine technologist check for any AEs from treatment. After administration of the ^{177}Lu-PSMA-617 the patient may—depending on the institutional protocols—undergo whole-body imaging with SPECT (with or without CT) to document radiotracer accumulation within the PSMA-avid disease and to allow for dosimetry. SPECT is not considered essential for successful administration of ^{177}Lu-PSMA-617. If used, SPECT may be performed 24 h or later after administration of ^{177}Lu-PSMA-617. The visit for the posttherapy scan is a good opportunity to again review potential side effects, such as increased fatigue, increased bone pain lasting approximately 5 d, and xerostomia. Three weeks after treatment, a complete blood count will typically be obtained, along with measurement of albumin, creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, and PSA levels. The laboratory and SPECT results are reviewed, and the next cycle of PSMA is confirmed. If there are abnormalities in the laboratory test results or clinical outcome, the dose may be reduced or discontinued in some cases.

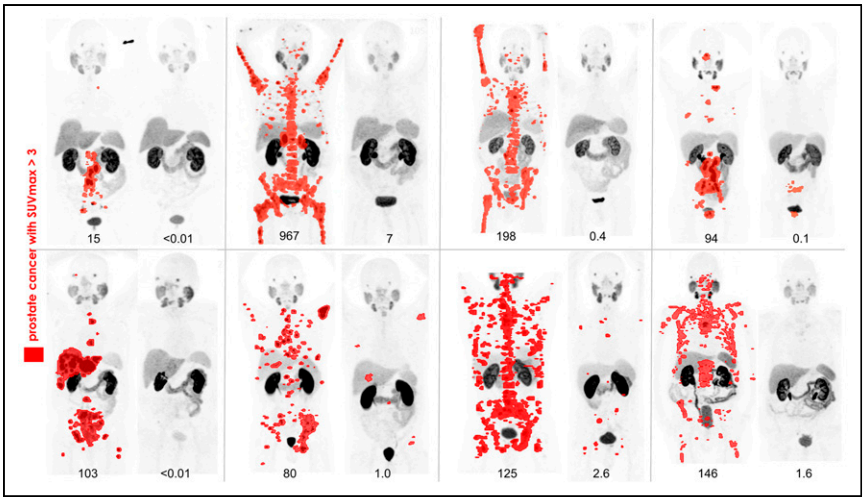

FIGURE 3. Previously published data showing 6 individual subjects with good serum PSA response. Paired ^{68}Ga PSMA-11 PET maximum-intensity projections are shown before (left) and 3 mo after (right) ^{177}Lu-PSMA therapy. Highlighted in red are lesions that have SUV_{max} over 3. Serum PSA values before and after ^{177}Lu-PSMA therapy serum are shown below each image and demonstrate good response to treatment. (Reprinted from (*29*).)

IMAGING AND RESPONSE TO THERAPY

In clinical trials, the most commonly accepted primary metrics of response to therapy include serum PSA response (*12,13,24*), radiographic progression-free survival by RECIST 1.1, and OS (*12,13*). A PSA response in clinical trials is commonly defined as a decrease in serum PSA of 50% or greater compared with baseline. Although quantification of disease burden by PSMA PET imaging response criteria has not been uniformly established, some academic groups use a semiquantitative threshold of residual disease to demonstrate therapeutic effects (Fig. 3) (*30*). Posttherapy SPECT imaging may also be used for this purpose. Standardized quality-of-life and symptom metrics, such as pain scores, may also be used to assess clinical benefit (*12,13,24*). TheraP demonstrated that PSA responses were more frequent in the ^{177}Lu-PSMA-617 arm (65%) than in the cabazitaxel arm (37%) (*13*). A metaanalysis of 1,192 patients found that approximately 46% patients with mCRPC treated with at least 1 cycle of ^{177}Lu-PSMA had PSA reductions of at least 50% (*22*).

In clinical practice, physicians and patients typically make treatment decisions based on the currently available clinical data. Because PSA response in clinical trials frequently correlates with radiographic progression-free survival outcomes, PSA response provides a practical metric of disease response. Overall, the serum PSA level is typically a sensitive and early biomarker of disease recurrence or progression. Imaging-based assessments commonly include CT and bone scanning. Other potential tests include PSMA or ^{18}F-FDG PET/CT. The FDG PET/CT may identify more glycolytically active, clinically aggressive disease and support the rationale to change therapy or perform a biopsy.

DOSIMETRY AND FUTURE DEVELOPMENTS

Using dosimetry to tailor dosing to a patient's particular biology has potential to advance ^{177}Lu-PSMA-617 RLT. Although the large TheraP (*13*) and VISION (*12*) trials used a fixed dose of 7.4 GBq (200 mCi), a small study demonstrated the safety of up to a 9.3-GBq (250 mCi) dose in selected cohorts (*31*). In principle, a more patient-centered dosing scheme could be applied, using dosimetry to calculate the safe dose to the organs at risk (maximum tolerated activity) or to deliver predictable radiation doses to tumors (lesional dosimetry) (*32,33*). One piece of evidence supporting a lesional dosimetry-based approach is the study of Violet et al. (*34*), which demonstrated that patients receiving less than 10 Gy to tumors were unlikely to achieve a PSA response, defined as more than a 50% decline in pretreatment PSA level after therapy. Moreover, recent studies have demonstrated a tumor sink effect, in which patients with a particularly high tumor burden demonstrated reduced delivery of ^{68}Ga-PSMA-11 (*35*) or ^{177}Lu-PSMA-617 (*36*) to organs at risk (Fig. 4). Taken together, these studies suggest a dosimetry-guided strategy for ^{177}Lu-PSMA-617 in which either pretherapy PSMA PET or intercycle ^{177}Lu-PSMA-617 SPECT might be used to select a more patient-centered dose.

Optimal dosimetry requirements and recommendations for ^{177}Lu-PSMA have recently been reported, and a full description is beyond the scope of this review (*37*). Optimal dosimetry includes imaging over several time points using

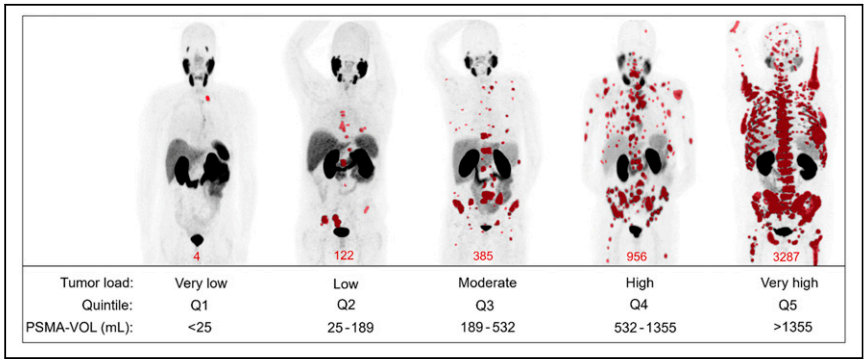

FIGURE 4. Previously published image providing examples of maximum-intensity projections of PSMA PET for each tumor load group. PSMA-positive tumor segmentation is highlighted in red. (Reprinted from (*34*).)

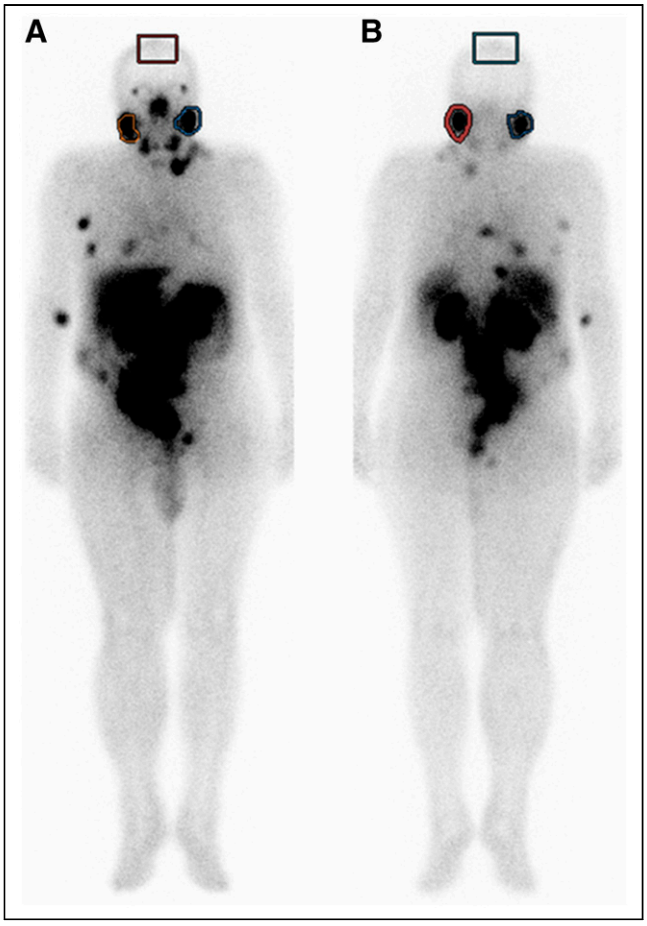

FIGURE 5. Previously published region-of-interest measurements on ^{177}Lu-PSMA-617 uptake (anterior [A]; posterior [B]) in both parotid glands and cranium in patient on whom right-sided ice pack was used during posttreatment SPECT/CT. No differences in radioligand uptake were observed between cooled (right) and noncooled (left) sides, with region of interest or volume of interest on images shown. (Reprinted from (*44*).)

quantitative 3-dimensional techniques such as SPECT/CT. However, outside of clinical trials, this recommendation may be difficult to achieve for routine patient care. Delayed imaging is the most accurate determinant of the absorbed doses to organs or tumors, with the ideal timing being approximately 4–7 d after ^{177}Lu-PSMA RLT.

Although strong evidence has emerged to support the use of ^{177}Lu-PSMA in men with mCRPC, there are several open questions and innovations that promise to further extend the role of theranostics in prostate cancer. For example, the synergistic effects from combination therapies, as well as appropriate sequencing of the treatment in the disease course, remain uncertain. Both VISION and TheraP were deployed late in mCRPC disease, when patients have limited therapy options remaining. Both trials demonstrated ^{177}Lu-PSMA-617 RLT to be effective at improving clinical outcomes, but ^{177}Lu-PSMA may have more significant benefits if used earlier in the disease evolution. Several trials are under way in hopes of answering this question. The UpFrontPSMA and PSMAddition trials seek to determine the efficacy and safety of ^{177}Lu-PSMA-617 in men with metastatic hormone-sensitive prostate cancer. Other trials are assessing ^{177}Lu-PSMA-617 as first-line therapy for mCRPC. In addition, ^{177}Lu-PSMA-617 is being tested as neoadjuvant therapy for localized prostate cancer.

Another area of emerging interest is the use of α-emitting isotopes such as ^{225}Ac for therapy. Kratochwil et al. (*21*) reported 2 patients who had a complete response to ^{225}Ac-PSMA-617, including one who had previously progressed after ^{177}Lu-PSMA-617 treatment. This initial report has been confirmed in several small case series (*38,39*). Pooling 10 small studies together, a recent metaanalysis found a 62.8% response rate for a PSA decline of more than 50% (*40*). Although the efficacy of ^{225}Ac-PSMA is likely greater than that of ^{177}Lu-PSMA, the side effect profile also appears to be more significant, including a greater incidence of xerostomia. In recognition of these effects, small trials of a tandem therapy strategy incorporating small doses of ^{225}Ac-PSMA together with ^{177}Lu-PSMA have been reported, with promising results (*41*). However, an additional major current challenge in the clinical use of ^{225}Ac-PSMA is the limited availability of the isotope itself. Nevertheless, the clinical future for ^{225}Ac-PSMA appears highly promising.

RADIATION SAFETY

General radiation safety precautions should be followed with ^{177}Lu-PSMA, with local and national guidelines dictating specific clinical practice. Radiation safety precautions may be modeled after ^{177}Lu-DOTATATE therapy for neuroendocrine tumors given a shared radionuclide (*9,42*). A recent metaanalysis of ^{177}Lu-PSMA-617 dosimetry found that the lacrimal and salivary glands are the critical organs, with the kidneys also receiving a significant radiation dose (*43*). The calculated absorbed radiation doses to the lacrimal and salivary glands after 4 cycles of ^{177}Lu-PSMA-617 are near the tolerated dose limit, whereas the dose to the kidneys is far below the dose tolerance limit. The use of polyglutamate or external cooling through ice packs has been described as reducing salivary gland uptake, with the studies reporting a reduction in salivary gland uptake induced by polyglutamate uptake, but no change in salivary gland uptake induced by cooling (Fig. 5) (*44,45*). The liver, spleen, and bone marrow received a relatively lower amount of radiation, but the authors of those studies noted that dosimetry may underestimate the bone marrow dose in mCRPC patients with extensive bone metastases.

CONCLUSION

With the recent FDA approval of ^{177}Lu-PSMA-617, and the emerging promising data on the use of other PSMA RLT agents, radiopharmaceutical therapy is expected to become part of the SOC for treatment of prostate cancer. Routine incorporation of this treatment in nuclear medicine departments will require collaboration between referring

physicians, nuclear medicine physicians, nurses, and nuclear medicine technologists.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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