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JNMT continuing education: ^{177}Lu PSMA therapy

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Abstract:

Radiopharmaceutical therapy utilizing ^{177}Lu-PSMA is an effective treatment for prostate cancer which has recently been approved by the United States Food and Drug Administration. This method leverages the success of PSMA targeted PET imaging, enabling the delivery of targeted radiopharmaceutical therapy, This agent 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. In this review, the evidence supporting the use of this agent is highlighted, along with important areas now 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 between referring physicians, nuclear medicine, technologists, radiopharmacy, and nursing, to enable streamlined patient care.

Introduction:

Aside from non-melanoma skin cancer, prostate cancer (PCa) is the most common cancer among men in the United States, with one out of eight men diagnosed during their lifetime (*1*). Although PCa is highly treatable, up to 30% of patients with prostate cancer 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 over-expressed in more than 90% of PCa 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 PCa recurrence and metastasis (*6*). Given the differential expression of PSMA between PCa and normal tissue, small molecule PSMA inhibitors have been developed, such as ^{177}Lu PSMA-617 (Pluvicto®) 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 beta minus or alpha emitters. Over the last decade, significant knowledge about the efficacy of PSMA radioligand therapy has been gained. ^{177}Lu PSMA-617 has now gained widespread acceptance as a viable targeted treatment for mCRPC, with the United States Food and Drug Administration (FDA) approval granted on 3/23/2022 for the treatment of

adult patients with PSMA-positive mCRPC and who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy (*8*). This continuing education article will cover patient selection, clinical considerations, technical considerations, treatment protocols, imaging and response to therapy, dosimetry and future developments, and radiation safety. However, as of the time of publication, billing/coding, payer reimbursement, and regulatory considerations for ^{177}Lu PSMA-617 have not yet been determined and are not discussed in this continuing education review.

Patient Selection

Given a shared target, PSMA PET has been utilized to assess patients eligible for PSMA-targeted radioligand therapy such as ^{177}Lu-PSMA or ^{225}Ac-PSMA (*9,10*). PSMA PET imaging is essential for patients with mCRPC being considered for PSMA RLT to help stage and identify PSMA positive lesions that would respond to PSMA RLT (*11*). The FDA package insert for ^{177}Lu PSMA-617 (Pluvicto®) specifies that patients to be are selected for treatment must use the FDA approved PSMA PET radiopharmaceutical ^{68}Ga PSMA-11 (Illuccix®, Locametz®) (*8*). There are currently two FDA approved PSMA PET radiopharmaceuticals for initial staging and biochemical recurrent mCRPC: ^{68}Ga PSMA-11 (Ga 68 gozezotide, Illuccix®, Locametz®) and ^{18}F DCFPyL (Pifluofolastat F 18, Pylarify®).

Many clinical trials have shown the utility of using PSMA PET to appropriately identify patients with mCRPC that would benefit from PSMA RLT, and to also exclude those that are most likely to be non-responders. Two major multicenter clinical trials, VISION (USA 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

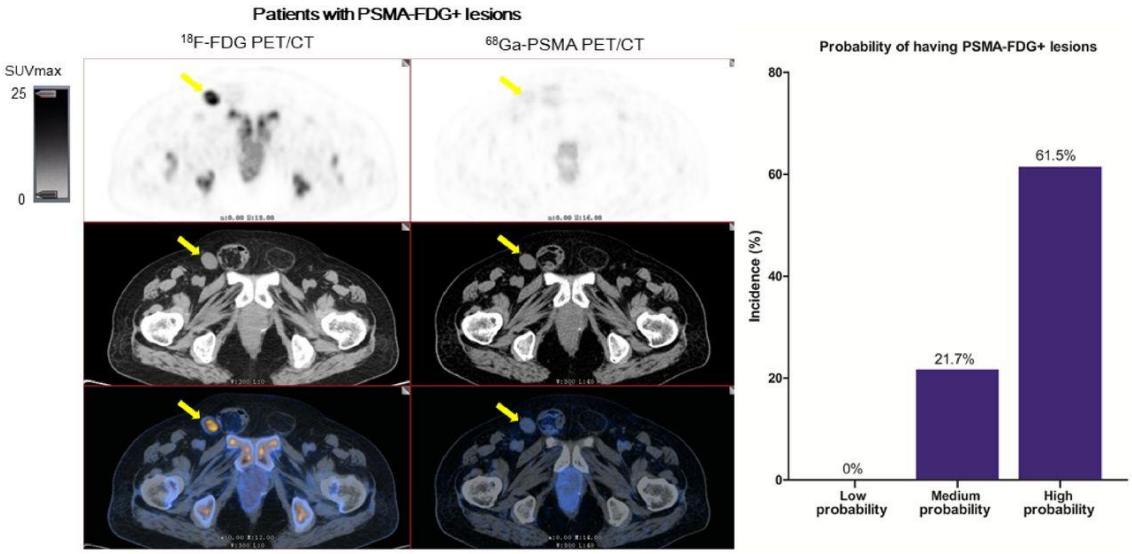
^{177}Lu PSMA-617 RLT plus standard of care (SOC) verses SOC alone. ^{177}Lu PSMA-617 plus SOC significantly prolonged both imaging-based progression-free survival compared with SOC, (median, 8.7 vs. 3.4 months) and OS (median, 15.3 vs. 11.3 months). Additionally, while the incidence of adverse events, grade 3 or above, was higher with ^{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 to SOC cabazitaxel in 200 men with mCRPC. The primary endpoint was Prostate-Specific Antigen (PSA) response defined by a reduction of PSA ≥ 50% from baseline. In contrast to the VISION trial, TheraP set PSMA SUVmax requirements of at least one lesion on ^{68}Ga-PSMA-11 PET with $SUV_{max} > 20$, and the remaining metastatic lesions $SUV_{max} > 10$, and no discordant hypermetabolic disease. PSA responses were more frequent among men in the ^{177}Lu PSMA-617 RLT group verses the cabazitaxel group (66% vs. 37%, respectively). Grade 3 - 4 adverse events occurred in 33% of the ^{177}Lu PSMA-617 RLT group versus 53% of the cabazitaxel group. It is yet to be determined if stratifying by SUVmax can improve patient outcomes and the OS has yet to be reported in the TheraP trial.

Although both trials reported better outcomes for patients who received ^{177}Lu PSMA-617 RLT compared to standard of care chemotherapy, the TheraP trial outcomes are considered superior to the Vision trial. The better outcome is believed to be the result of a more strict exclusion criteria that excluded mCRPC patients with discordant hypermetabolic lesions. The main inclusion criteria for both the VISION and TheraP trials 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. While the VISION trial used conventional imaging to exclude patients with discordant lesions (positive lesions on CT and negative on PSMA PET), the TheraP trial 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 (-)/FDG (+), were excluded.

Many studies with PSMA PET in patients with mCRPC have consistently shown that there is a sizable minority of patients that have at least 1 discordant hypermetabolic lesion (PSMA (-)/FDG (+)) and these patients have worse outcomes. For example, Chen et al. found that in a study of 56 patients, 23.2% had at least 1 PSMA (-)/FDG (+) lesion, and that prostate serum antigen (PSA) and Gleason score with both higher in these patients with discordant hypermetabolic disease (Figure 1) (*14*).

[Figure 1]



Previously published image demonstrating discordant hypermetabolic right inguinal metastatic deposit with high FDG PET uptake and little to no PSMA accumulation. Reprinted from (*13*).

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

Until recently, it was unknown whether the VISION or the TheraP trails inclusion and exclusion criteria 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) verses patients who received ^{177}Lu PSMA-617 RLT which met the VISION eligibility criteria. The outcome for the VISION non-eligible group was found to be significantly worse than that of patients who met the VISION inclusion criteria, with a PSA response rate of 21% vs. 50% ($p = 0.005$), PSA-progression-free survival of 2.1 vs. 4.1 months ($p = 0.023$), and a trend of shorter OS of 9.6 months vs. 14.2 months ($p = 0.16$), respectively (*16*). Several additional similar trials have similarly found significant outcome differences in ^{177}LuPSMA RLT in patients with discordant hypermetabolic disease, compared to those with PSMA matched or 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 has a OS of 6.0 vs 16.0 months for those without discordant disease (*17*). While there it has been shown that patients can develop discordant hypermetabolic disease after ^{177}Lu-PSMA RLT, these patients do not appear to have differences in outcomes when compared to those with FDG concordant disease (*18*). Despite the seemingly clear and consistent evidence that PSMA PET is needed for patient stratification prior to ^{177}Lu-PSMA RLT, there remains debate from both industry and the medical community about the need for pre-therapy PSMA PET/CT. To address this concern, a recent review article summarized their conclusions that, “We hope the prostate cancer medical community will stand up for precision medicine, including by ordering PSMA (and FDG) PET before treating a patient with ^{177}Lu PSMA-617. PSMA radioligand therapy for prostate cancer without PSMA PET should not be accepted” (*19*).

Of note, according to the Center of Medicare and Medicaid Services (CMS), 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 scan to PSMA PET to optimize patient selection for ^{177}Lu PSMA-RLT may be challenging. Alternative PET agents that are approved for biochemical recurrent prostate cancer, such as ^{18}F-Fluciclovine (*20*) and ^{11}C-choline, may potentially be used in the future as an adjunct modality to optimize patient selection and improve outcomes. However, this hypothesis should be evaluated in clinical trials.

Clinical considerations:

With the recent FDA approval of ^{177}Lu PSMA-617 (Pluvicto®) on 3/23/2022, the field of PSMA radioligand therapy is expected to rapidly evolve in the months and years to come. The European Association of Nuclear Medicine (EANM) has published procedure guidelines for ^{177}Lu-PSMA radiotherapies (*21*). Procedure standards from the Society of Nuclear Medicine and Molecular Imaging (SNMMI) are under development. EANM 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 of whether or not other alternative therapies have been exhausted is often beyond the scope of a nuclear medicine/radiology physician. Therefore, the involvement of a multidisciplinary tumor board composed of nuclear medicine/radiology physician, medical oncologist, radiation oncologist, and/or urologist is strongly encouraged. A full discussion as to the benefits and risks of other alternative therapies (including androgen deprivation therapy (ADT), anti-androgens, secondary hormone agents (e.g. abiraterone, enzalutamide), chemotherapy, and other targeted radionuclide therapies (e.g. $^{223}RaCl_2$)) is beyond the scope of this continuing education article.

While the FDA package insert for ^{177}Lu PSMA-617 does not specify any contraindications, the EANM guidelines have published contraindications for PSMA-RLT. For the most part, these

guidelines have mirrored in the inclusions and exclusion criteria of large phase II/III trials such as VISION (*12*) and TheraP (*13*) with some minor variations. These contraindications include: (1) Life expectancy is less than 6 months and ECOG performance status > 2. (2) Unacceptable medical or radiation safety risk. (3) Unmanageable urinary tract obstruction or hydronephrosis. (4) Inadequate organ function (GFR < 30 mL/min or creatinine > 2-fold upper limit of normal (ULN); liver enzymes > 5-fold ULN). (5) Inadequate marrow function (a. Total white cell count less than 2.5×10^9/L b. Platelet count less than 75×10^9/L). (6) Conditions which require timely interventions (radiation therapy, surgery), e.g. spinal cord compression and unstable fractures, PSMA-RLT might be performed afterwards upon patient's condition.

^{177}Lu PSMA-RLT has been shown to have a low rate of adverse events (AE) in several clinical studies. There are, though, some observed risks that the nuclear medicine physician and patient should know. In the phase III VISION study, 52.7% of patients experienced grade 3 or higher AE, greater than the 38.0% of patients with similar events in the control group. Anemia was the most common grade ≥3 AE, observed in 12.9% of subjects. This is somewhat surprising given the relatively low uptake in bone marrow. This anemia is considered a real effect as a recently published meta-analysis of 250 studies with a total of 1192 patients similarly found that while grade 3 and 4 toxicities were uncommon, anemia was the highest reported adverse event for both ^{177}Lu PSMA-617 (0.19 [0.06-0.15]) and ^{177}Lu PSMA—I&T (0.09 [0.05 – 0.16]) (*22*). Other notable AE include the 7.9% and 2.5% of patients in the VISION trial who experienced thrombocytopenia and leukopenia, respectively. Elevated transaminases are 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 the VISION trial experienced fatigue, dry mouth, or nausea, though almost entirely grade ≤ 2 AE (*12*). Adverse event incidence was similar to smaller early-phase studies that preceded the VISION study (*13,23-25*). Of note, quality of life was not adversely affected in the VISION trial, supporting its inclusion into a

treatment plan, with patients reporting a favorable BPI-SF pain intensity score and time to deterioration in the FACT-P score for the ^{177}Lu PSMA-617 arm (*12*). Additionally, the reported mean global health status was similar between the ^{177}Lu PSMA-617 arm and SOC in the TheraP trial.

Technical considerations

Production and quality control (QC) recommendations of the joint International Atomic Energy Agency (IAEA), EANM, and SNMMI guidance on peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors is applicable to ^{177}Lu-PSMA RLT(*26*). ^{177}Lu-PSMA consists of pharmacophore (PSMA) conjugated with the chelating moiety (DOTA) to bind to the ^{177}Lu radiometal (*27*). The DOTA-PSMA precursor is typically manufactured under good manufacturing process (GMP) conditions by a commercial supplier such as ABX (GMP grade; ABX, Radeberg, Germany). The ^{177}Lu is supplied as $^{177}LuCl_3$ and is also manufactured under GMP conditions. This radiosynthesis has previously been described in detail (*28*), consisting of a radiolabeling step, followed by a purification. The radiolabeling is typically carried out in ascorbate buffer, which is used to control the pH of the reaction and also acts as a stabilizer for radiolysis. The reaction is heated, 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, then diluted with saline containing ascorbic acid. The solution is then passed through a cation exchange cartridge (CM) that contains diethylenetriamine pentaacetate (DTPA) and finally passed over a 0.22μm sterilizing filter. A small aliquot (< 1mL) is taken for QC analysis.

QC testing typically consists of seven total tests: radiochemical purity, radiochemical identity, appearance, pH, endotoxin content, filter integrity, and sterility. Radiochemical purity and identity are analyzed by high performance liquid chromatography (HPLC), appearance is

analyzed by visual inspection, pH is analyzed using pH paper strips, endotoxin content is measured using a PTS Endosafe system according to USP<85>, filter integrity is measured using a bubble point test, and sterility testing is performed using direct inoculation of TSB and FTM media according to USP<71>. Typical specifications are shown in Table 1.

Table 1.

Test	**Specification**
Radiochemical purity (HPLC)	>95%
Radiochemical identity (HPLC)	t_R ± 5% reference standard
Appearance (visual inspection)	Clear, colorless, and 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 days

Administration Protocol

The clinical administration of ^{177}Lu-PSMA requires a close collaboration between nuclear medicine physicians, nursing, radiopharmacists, and technologists. The following section details specific roles and responsibilities for each member of the care team. While the responsibilities of each team member may vary depending on the established hospital protocols, the procedure outlined below could be considered a guide that each nuclear medicine team could apply to their institutional practice and radiation safety guidelines.

The FDA package insert for ^{177}Lu PSMA-617 specifies that each patient be treated with up to 6 cycles of 200 mCi (7.4 GBq) every 6 weeks with dose interruption, reduction, or permanent discontinuation due to adverse reactions. The VISION study provided for a +/- 1 week

allowance of treatment dates. On the day of therapy, the patient may work with providers including nursing, a nuclear medicine doctor and nuclear medicine technologist.

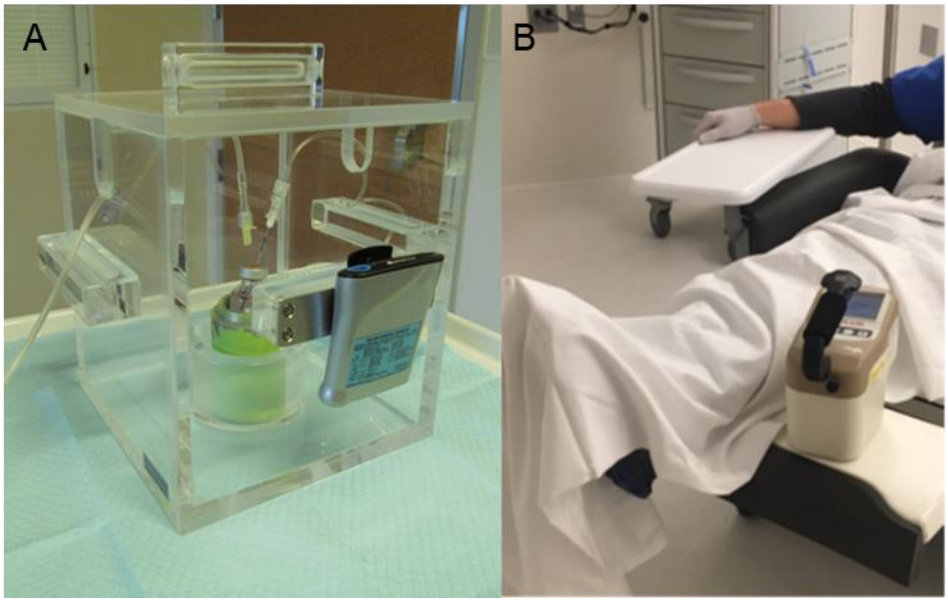
Baseline labs are typically collected prior to therapy. These labs typically include: complete blood count (CBC), Albumin, Creatinine, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Total bilirubin, Alkaline Phosphatase, and PSA. When the patient arrives for their appointment, the nurse orients them to the therapy room, explains radiation safety guidelines to the patient and obtains a set of vitals. The discharge paperwork including expected side effects, what to do in case of mild, moderate or severe unexpected side effects and dates of future appointments, is also reviewed. Patients may have been prescribed a methylprednisolone dose pack to offset any expected increase in bone pain and the patient is asked to bring the prescription to the appointment. The nursing team will go over the instructions and encourage the patient to take their first dose before they leave the appointment.

The nuclear medicine physician consents the patient for the procedure and goes over radiation safety in further detail and according to the institutional radiation safety guidelines. Typical recommendations include minimizing radiation exposure to others by limiting close contact (less than three feet) for two days, and sexual activity for 7 days. It is also advised to sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or pregnant woman for 15 days (*8*). The patient is typically provided a copy of Radiation Safety Precautions for Discharge of ^{177}Lu Therapy Patients and instructed to keep with them for two months. It is explained that this paperwork could be necessary during air travel and should be presented if brought to a hospital.

Patients should be encouraged to drink fluids during the procedure and instructed to void as often as feasible to reduce bladder radiation. The nurse starts an IV or accesses a port

depending on existing access. The nurse collects a PSA pre-infusion and starts saline, with a minimum of 10 mL as recommended by the package label. After saline, the nuclear medicine technologist will infuse the ^{177}Lu PSMA-617, either via the gravity method (with or without an infusion pump) (*29*), the syringe method (disposable syringe fitted with a syringe shield), or the vial method with a peristaltic infusion pump (Figure 2).

[Figure 2]



Gravity method ^{177}Lu PSMA-617 delivery system with in-flow and out-flow needles (A) and plexiglass shielding to reduce radiation dose to the nuclear technologist while maintaining validation of adequate flow. Radiation survey meter utilized during ^{177}Lu PSMA-617 delivery to verify systemic administration of ^{177}Lu PSMA-617 during the infusion (B).

The patient is kept for observation for one hour. During observation the nursing staff and nuclear medicine technologist can check for any AE from treatment. Following administration of ^{177}Lu PSMA-617, depending on the institutional protocols, the patient may undergo whole body imaging with SPECT(±CT) to document radiotracer accumulation within the PSMA avid disease and to allow for dosimetry. Please note that SPECT imaging is not considered an essential

requirement for required for successful administration of ^{177}Lu PSMA-617. If performed, the timing of the SPECT may be performed 24 hours, or at later time points, after administration of ^{177}Lu PSMA-617. The time of the post therapy scan is a good opportunity to discuss side effects, such as increased fatigue, increased bone pain lasting approximately 5 days, and a potential for dry mouth. Three weeks after treatment, the patient will typically get the following labs: CBC, Albumin, Creatinine, AST, ALT, Total bilirubin, ALK Phos and PSA. The labs and SPECT results are reviewed and the next cycle of PSMA can be confirmed. In some cases, based on laboratory abnormalities or clinical outcome, the dose may be reduced, or discontinued.

The method of infusion is important to provide a safe transfer of the radiopharmaceutical (which is typically provided by a radiopharmacy in a vial) to the patient with the least amount of manipulation to decrease exposure to the technologist, lower the chances of contamination, and assure sterility. The manual syringe technique is the most common method in nuclear medicine and is the same technique used for other liquid radiopharmaceuticals in a syringe. The learning curve is lowest for the technologist, this makes it the easiest to adopt in a nuclear medicine department. The syringe is luer-locked to the intravenous line of the patient. The main pitfalls to the manual push are an inconsistent rate and the highest exposure to the technologist.

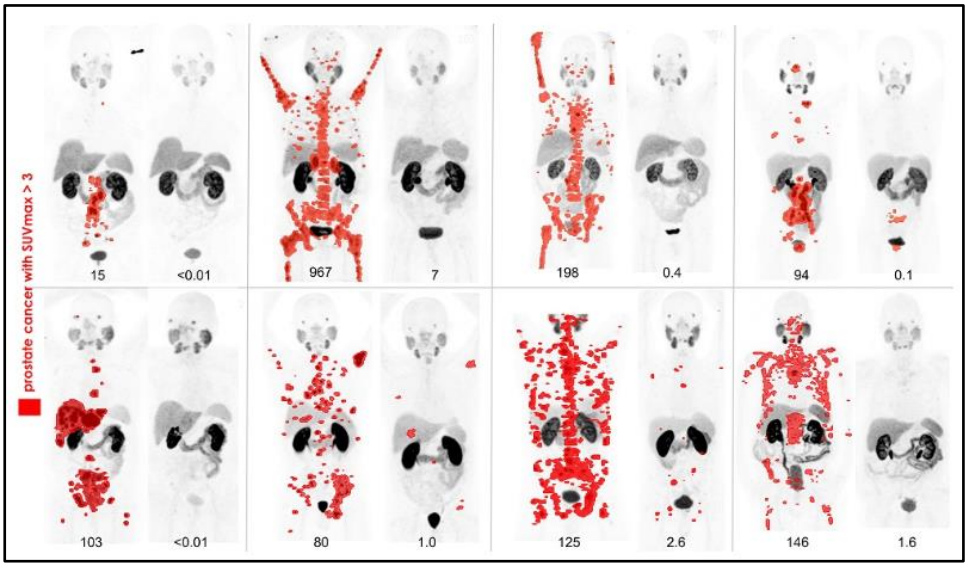
The pump method using the syringe has multiple steps. The pumps are common in hospitals and frequently used by anesthesia. This method has a lower exposure to the technologist, with most of the exposure coming from the set-up of the pump. The rate is consistent and risk for contamination is low. The gravity method uses a 250ml 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 due to the length of 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 utilized as the gravity method may result in an incorrect volume. Medication pumps may include air sensors, pressure sensors, and micro tubing allowing a safe transfer of the radiopharmaceutical to the patient, while 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 performing each infusion technique, it is important to follow ALARA and to decrease technologist exposure, all of the methods discussed can be applied behind an L-block or plexiglas shielding.

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 to the baseline. Although quantification of disease burden by PSMA PET imaging response criteria have not been uniformly established, some academic groups use semiquantitative threshold of residual disease to demonstrate therapeutic effects (Figure 3) (*30*). Post-therapy 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*). The TheraP trial demonstrated that PSA responses were more frequent in men treated with ^{177}Lu PSMA-617 (65%) vs cabazitaxel arm (37%)(*13*). A meta-analysis of 1192 patients found that approximately 46% patients with mCRPC treated with at least 1 cycle of ^{177}Lu-PSMA had PSA reductions of ≥50%(*22*).

[Figure 3]



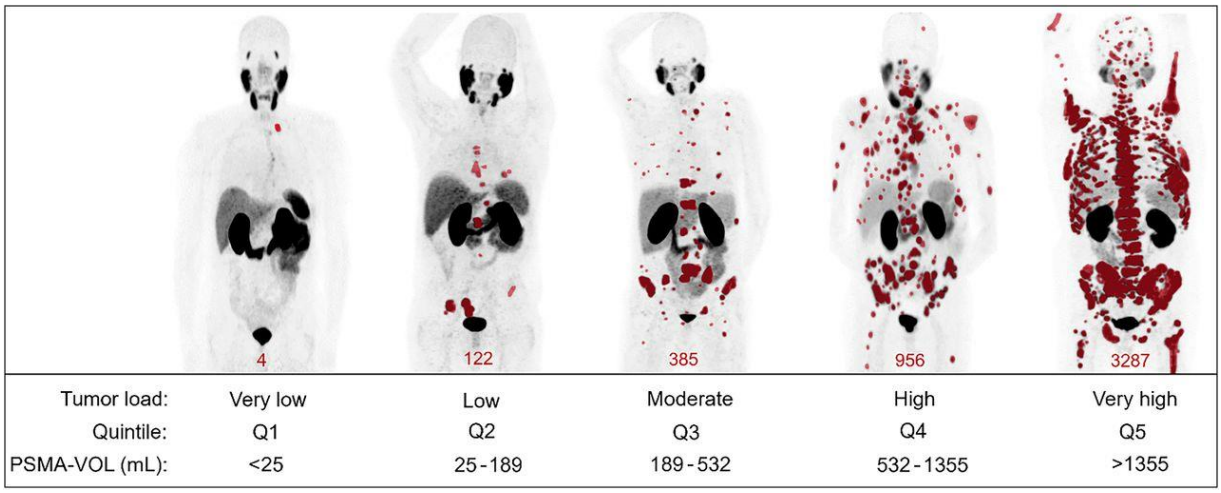
Previously published data showing 6 individual subjects with a good serum PSA response. Paired ^{68}Ga PSMA-11 PET maximum intensity projection images are shown before (left), and 3 months after ^{177}Lu-PSMA therapy (right). Highlighted In red are lesions which have SUV max over 3. The serum PSA values pre-and post- ^{177}Lu-PSMA therapy serum shown below each image, and demonstrate a good response to treatment. Reprinted from (*29*).

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

Dosimetry and future developments

Utilizing dosimetry to tailor dosing to a patient's particular biology has potential to further advance ^{177}Lu PSMA-617 RLT. While the large TheraP (*13*) and VISION (*12*) trials employed a fixed dosing of 200 mCi (7.4 GBq), a small study demonstrated safety of dosing of up to 250 mCi (9.3 GBq) in selected cohorts (*31*). In principle, a more patient-centered dosing scheme could be employed using dosimetry to appropriate calculate 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 >50% PSA decline in pretreatment PSA following therapy. Moreover, recent studies have demonstrated a "tumor sink" effect, where patients with particularly high burden demonstrated reduced delivery of ^{68}Ga-PSMA-11 (*35*) or ^{177}Lu PSMA-617 (*36*) to organs at risk (Figure 4). Taken together, these studies suggest a dosimetry guided strategy of ^{177}Lu PSMA-617, where either pre-therapy PSMA-PET or intercycle ^{177}Lu PSMA-617 SPECT could be utilized to select a more patient centered dose.

[Figure 4]



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

Optimal dosimetry requirements and recommendations for ^{177}Lu-PSMA have been recently been reported and a full description is beyond the scope of this review (*37*). Optimal dosimetry includes imaging over several time points using quantitative 3D techniques such as SPECT/CT. However, outside of clinical trials, this may be difficult to obtain for routine patient care. Delayed time point imaging is the most accurate determinate of the absorbed doses to organs and/or tumors, and ideally scans are performed approximately 4–7 days after ^{177}Lu-PSMA RLT.

While 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 demonstrate ^{177}Lu-PSMA-617 RLT to be effective at improving

clinical outcomes, but ^{177}Lu-PSMA may have more significant benefits earlier if employed earlier in the disease evolution. Several trials are currently underway 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 PCa.

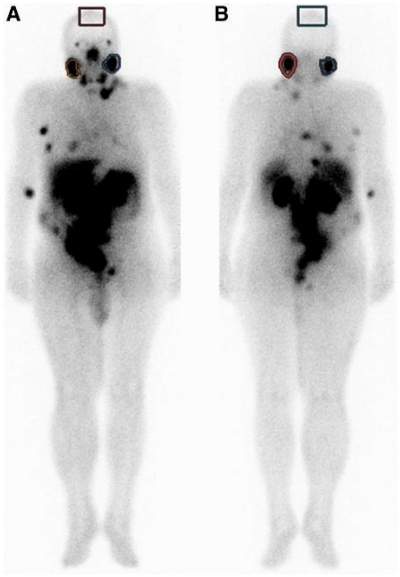
Another area of emerging interest is the use of alpha emitting isotopes such as ^{225}Ac for therapy. Kratochwil et al.(*21*) reported two patients who had complete responses to ^{225}Ac-PSMA-617, including one who had previously progressed after ^{177}Lu PSMA-617 treatment. This initial report has been confirmed in several small case series (*38,39*). Pooling 10 small studies together, a recent meta-analysis found a 62.8% PSA50 response rate (*40*). While the efficacy of ^{225}Ac-PSMA is likely greater than ^{177}Lu-PSMA, the side effect profile also appears to be more significant, including greater incidence of xerostomia (dry mouth). 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 meta-analysis 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 radiation absorbed doses to the lacrimal and salivary glands after 4 cycles of ^{177}Lu PSMA-617 is near the tolerated dose limit whereas the dose to the kidneys is far below the dose tolerance limits. The use of folic acid or external cooling using icepacks has been described to reduce salivary gland uptake, but the results have been inconsistent (Figure 5) (*44,45*). The liver, spleen, and bone marrow receive a relatively lower amount of radiation, but the authors note that dosimetry may underestimate the amount of bone marrow dose in mCRPC patients with extensive bone metastases.

[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 who underwent post treatment SPECT/CT right-sided ice pack. No differences in radioligand uptake were observed when comparing cooled (right) and noncooled (left) sides, with region of interest or volume of interest on images shown. Reprinted from (*44*).

Conclusion

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

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