



Incorporating radioligand therapy in clinical practice in the United States for patients with prostate cancer[☆]

Jeremie Calais^{a,*}, Stephen M. Eulau^b, Linda Gardner^c, Ralph J. Hauke^d, Ayse T. Kendi^e, Neal D. Shore^f, Song Zhao^b

^a Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California Los Angeles, 650 Charles E. Young Drive South, Los Angeles, CA 90095, USA

^b Swedish Cancer Institute at Swedish Medical Center, 1221 Madison Street, Seattle, WA, USA

^c Department of Nuclear Medicine, University of California, Los Angeles, 650 Charles E. Young Drive South, Los Angeles, CA 90095, USA

^d Nebraska Cancer Specialists, 17201 Wright Street, Suite 200, Omaha, NE 68130, USA

^e Department of Radiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

^f Carolina Urologic Research Center/GenesisCare, US, Myrtle Beach, SC 29572, USA

ARTICLE INFO

Keywords:

Radioligand therapy
Prostate cancer
Lutetium-177
Multidisciplinary team

ABSTRACT

Prostate cancer (PC) is the second most commonly diagnosed cancer in the United States. Advanced PC evolves to metastatic castration-resistant PC (mCRPC). Theranostics combining prostate-specific membrane antigen-targeted positron emission tomography imaging and radioligand therapy (RLT) represents a precision medicine approach to PC treatment. With the recent approval of lutetium Lu 177 (¹⁷⁷Lu) vipivotide tetraxetan for men with mCRPC, the utilization of RLT will increase. In this review, we suggest a framework for incorporating RLT for PC into clinical practice. A search of PubMed and Google Scholar was performed using keywords related to PC, RLT, prostate-specific membrane antigen, and novel RLT centers. The authors also provided opinions based on their clinical experience.

The setup and operation of an RLT center requires the diligence and cooperation of a well-trained multidisciplinary team committed to patient safety and clinical efficacy. Administrative systems should ensure that treatment scheduling, reimbursement, and patient monitoring are efficient. For optimal outcomes, the clinical care team must have an organizational plan that delineates the full range of required tasks. Establishing new RLT centers for treatment of PC is possible with appropriate multidisciplinary planning. We provide an overview of the key elements to consider when establishing a safe, efficient, and high-quality RLT center.

Introduction

In 2022, there will be approximately 268,490 newly diagnosed PC patients and 34,500 deaths [1]. Advanced PC evolves to metastatic castration-resistant PC (mCRPC) [2,3], a lethal phenotype, which results in prostate cancer-specific mortality [4–14]. The 5-year survival rate for men diagnosed with metastatic PC between 2011 and 2017 was 31 % [1], indicating that the development of therapies with novel mechanisms of action demonstrating an overall survival benefit and an acceptable safety profile is needed [5].

Theranostics uses specific molecular targets on cancer cells for

imaging and therapy. Theranostics based on prostate-specific membrane antigen (PSMA)-targeted positron emission tomography (PET) imaging and radioligand therapy (RLT) is an established precision medicine approach that was clinically validated by the approval of lutetium Lu 177 (¹⁷⁷Lu) vipivotide tetraxetan (formerly ¹⁷⁷Lu-PSMA-617) to treat men with progressive, PSMA-positive mCRPC [15]. ¹⁷⁷Lu vipivotide tetraxetan combines a PSMA-targeting ligand (vipivotide tetraxetan) with radionuclide ¹⁷⁷Lu, a β -particle emitter that delivers cytotoxic radiation to PC cells [13,15].

This RLT was approved based on results from the phase 3 VISION trial, which evaluated the addition of ¹⁷⁷Lu vipivotide tetraxetan to

[☆] Authorship: Authors confirm that they meet ICMJE authorship criteria and that no one who would qualify for authorship has been excluded.

^{*} Corresponding author.

E-mail addresses: jcalais@mednet.ucla.edu (J. Calais), Stephen.Eulau@swedish.org (S.M. Eulau), lgardner@mednet.ucla.edu (L. Gardner), rhaue@nebraskacancer.com (R.J. Hauke), Kendi.Ayse@mayo.edu (A.T. Kendi), nshore@auclinics.com (N.D. Shore), Song.Zhao@swedish.org (S. Zhao).

<https://doi.org/10.1016/j.ctrv.2023.102524>

Received 21 November 2022; Received in revised form 8 February 2023; Accepted 10 February 2023

Available online 11 February 2023

0305-7372/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

standard of care for the treatment of men with mCRPC who had demonstrated progression after having received at least 1 prior androgen-receptor pathway inhibitor and 1 or 2 prior taxane regimens [13]. The addition of ^{177}Lu vipivotide tetraxetan to standard of care led to statistically significant improvements in radiographic progression-free survival (rPFS) (median rPFS, 8.7 vs 3.4 months; hazard ratio [HR], 0.40; 99.2 % confidence interval [CI], 0.29–0.57; $p < 0.001$) and overall survival (median, 15.3 vs 11.3 months; HR, 0.62; 95 % CI, 0.52–0.74; $p < 0.001$) compared with best supportive care alone [13]. Median time to worsening health-related quality of life on the Functional Assessment of Cancer Therapy–Prostate questionnaire (5.7 vs 2.2 months; HR, 0.54; 95 % CI, 0.45–0.66) and pain intensity on the Brief Pain Inventory–Short Form (5.9 vs 2.2 months; HR, 0.52; 95 % CI, 0.43–0.63) also favored the ^{177}Lu vipivotide tetraxetan group [13].

The demand for RLT is anticipated to increase as ^{177}Lu vipivotide tetraxetan becomes available for more men with mCRPC and at earlier stages of disease [16], pending the results of trials. Other RLT modalities for PC—such as PSMA ligands conjugated to other radionuclides, particularly α -emitters like actinium-225—are currently in clinical development and may also achieve regulatory approval [17,18]. At the extreme, an estimated 34,000 patients with end-stage PC progressing after chemotherapy could be eligible for PSMA-targeted RLT, which would require approximately 120,000 treatment cycles per year [19]. Approximately 115 centers would be required to meet this demand, assuming each site delivers 4 cycles per day [19]. Thus, new RLT centers need to be established to offer effective, safe, and high-quality services.

In this review, we suggest a framework for incorporating RLT for PC into clinical practice. Our insight is based on experience in the real-world and clinical trial settings and is informed by the rollout of RLT applications for patients with neuroendocrine tumors by other institutions [20,21].

Advocating for the incorporation of RLT in clinical practice

An important first step in starting a new RLT program is advocating for patient accessibility (Fig. 1). High upfront costs associated with starting a new RLT program will be a barrier for many centers; these costs include licensing for radioactive materials, implementing infrastructure and dedicated spaces for RLT, training and deploying staff to allow the safe and efficient delivery of RLT, and disposing of radioactive waste. Additional costs for obtaining imaging equipment and administering an accredited radiation safety team should also be considered.

Despite these upfront costs, offering RLT can be lucrative for centers once programs are established. Clinicians can affect change by conveying the potential long-term efficacy and patient-centered benefits of RLT (Table 1). RLT provides patients with individualized treatment targeted to the unique characteristics of their cancer (e.g., PSMA expression) [22]. Incorporation of RLT into a practice will lead to clinical patient benefits, such as improved survival and quality of life. In addition to the positive results from the VISION trial, the phase 2 TheraP trial showed ^{177}Lu vipivotide tetraxetan provided similar overall survival compared with cabazitaxel but yielded better response rates, superior rPFS, improved quality of life, and a lower incidence of grade 3/4 adverse events [12,23]. The superior clinical efficacy of RLT coupled with fewer high-grade adverse events translated into improved scores for pain and other patient-reported outcomes [12,13].

Planning

A systematic approach to implementing an RLT program is needed to address the regulatory, clinical, and technical components, including facility safety requirements and patient treatment plans [16]. These tasks are relatively straightforward for established nuclear medicine, radiology, or radiation oncology centers, which are well-versed in the

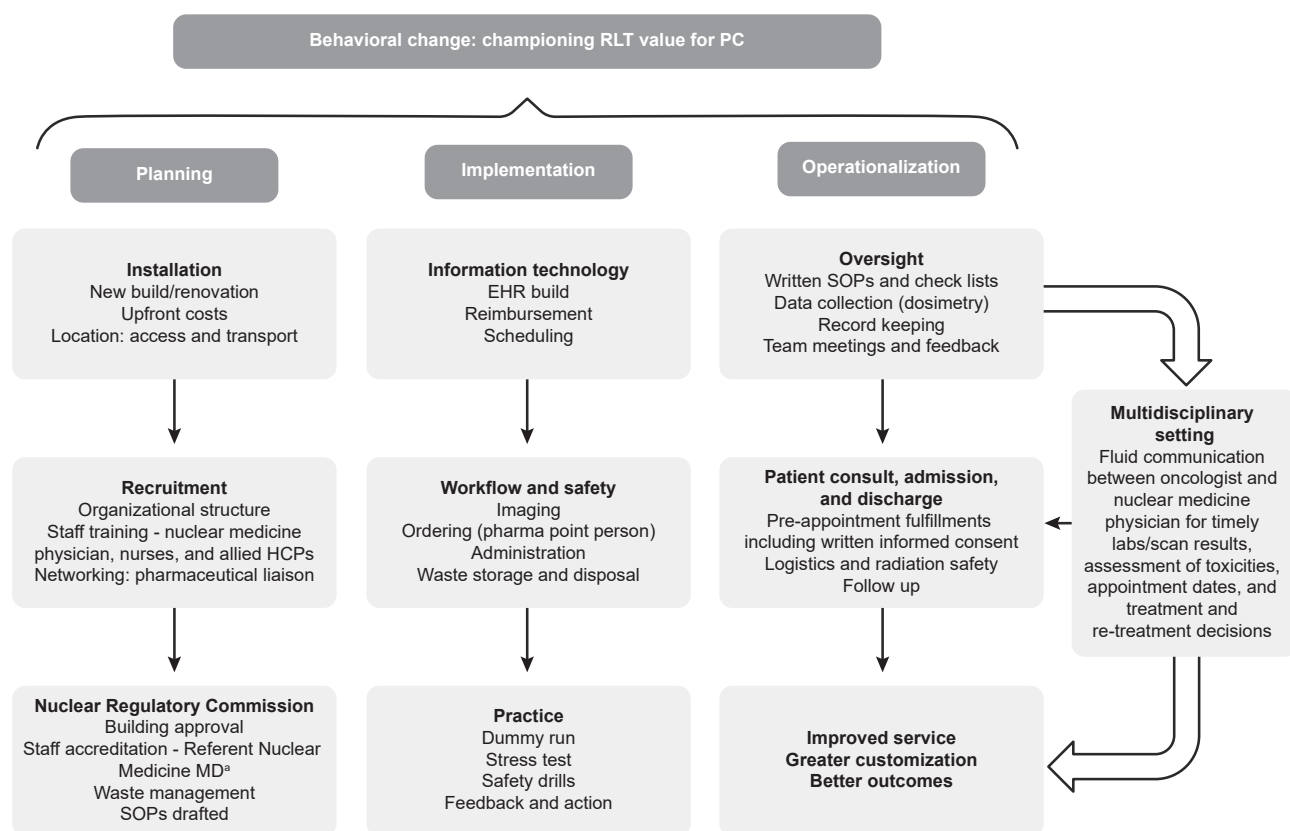


Fig. 1. Development and deployment of a new RLT program. EHR, electronic health record; HCP, healthcare professional; PC, prostate cancer; RLT, radioligand therapy; SOP, standard operating procedure. ^aSee Table 3 for more information on the role of the nuclear medicine physician.

Table 1
Selected clinical experience with RLT in PC.

PUBLISHED STUDIES								
Study, design	N (Type of patients)	Intervention, N	PSA 50 response, %	PFS		OS		PROs
				Median, mo	HR	Median, mo	HR	
Violet 2020 [56], single-center, phase 2 study	50 (mCRPC)	¹⁷⁷ Lu vipivotide tetraxetan	64			13.3		BPI-SF pain intensity and interference scores declined at all time points
Hofman 2021 (TheraP) [12], multicenter (single-country), randomized, open-label, phase 2 study	200 (mCRPC after docetaxel and a novel anti-androgen)	¹⁷⁷ Lu vipivotide tetraxetan, 99 Cabazitaxel,101	66 vs 37 <i>p</i> < 0.0001	5.1 vs 5.1	0.63 95% CI 0.46–0.86 <i>p</i> = 0.0028	—	—	PPI, EORTC QLQ-C30, and DATA favored ¹⁷⁷ Lu vipivotide tetraxetan
Sartor 2021 (VISION) [13], international, randomized, open-label, phase 3 study	581 ^a (mCRPC after AR–pathway inhibitor and 1 or 2 taxane regimens)	¹⁷⁷ Lu vipivotide tetraxetan + SOC, 385 SOC alone, 196	46 vs 7.1	8.7 vs 3.4	0.40 99.2% CI 0.29–0.57 <i>p</i> < 0.001	15.3 vs 11.3	0.62 95% CI 0.52–0.74 <i>p</i> < 0.001	FACT-P total score and BPI-SF pain intensity score favored ¹⁷⁷ Lu vipivotide tetraxetan
Calais 2021 (RESIST PC) [57,58], bicentric, phase 2 study	71 ^b (mCRPC after AR–pathway inhibitor)	¹⁷⁷ Lu vipivotide tetraxetan (6.0 or 7.4 GBq)	28 ^c	—	—	14.0	—	On the BPI-SF, 12 of 18 (67%) had pain improvement, and median pain PFS was 8.2 months
Rathke 2019 [59], single-center, prospective, case series	11 (mCRPC after exhausting approved therapies)	⁹⁰ Y-PSMA-617	45	—	—	—	—	—
Sathekge 2020 [60], single-center, retrospective, case series	73 (mCRPC)	²⁵⁵ Ac-PSMA-617	70	15.2	—	18.0	—	—
Kratochwil 2017 [61], single-center, retrospective, dose-finding study	14 (advanced mCRPC)	²⁵⁵ Ac-PSMA-617 (50–200 KBq)	—	—	—	—	—	—
Zechmann 2014 [62], compassionate use program	28 (mCRPC)	¹³¹ I-labelled PSMA ligand (single cycle)	61	—	—	—	—	Of men with bone pain, 85% showed complete or moderate reduction in pain
Afshar-Oromieh 2017 [63], prospective, interventional study	34 (mCRPC after exhausting approved therapies)	¹³¹ I-IMP-1095	71 ^d	—	—	17.0 ^d	—	Most patients who presented with bone pain reported a reduction of analgesics or improved well-being
ONGOING STUDIES								
Trial	Type of patients	Intervention	Phase	Primary outcome measure				
NCT04430192 (LuTectomy)	High-risk PC	¹⁷⁷ Lu vipivotide tetraxetan	1/2	Radiation absorbed dose in the prostate and involved lymph nodes				
NCT05146973 (ProstACT TARGET)	Oligometastatic PC	¹⁷⁷ Lu-DOTA-TLX591	2	PSA PFS				
mHSPC								
NCT04443062 (Bullseye)	mHSPC	¹⁷⁷ Lu vipivotide tetraxetan	2	Disease progression within 6 months				
NCT04343885 (UpFrontPSMA)	mHSPC	Sequential ¹⁷⁷ Lu vipivotide tetraxetan + docetaxel vs docetaxel	2	Undetectable PSA rate at 12 months				
NCT04720157 (PSMAddition)	mHSPC	¹⁷⁷ Lu vipivotide tetraxetan + SOC vs SOC	3	Radiographic PFS				
mCRPC								
NCT03805594	mCRPC	¹⁷⁷ Lu vipivotide tetraxetan + pembrolizumab	1	Determination of recommended dose/schedule and objective response rate				
NCT03874884 (LuPARP)	mCRPC	¹⁷⁷ Lu vipivotide tetraxetan + olaparib	1	Dose-limiting toxicity and maximum tolerated dose				
NCT04786847 (ProstACT Select)	mCRPC	¹⁷⁷ Lu-DOTA-TLX591 + best standard of care	1	Safety and tolerability (treatment-related adverse events)				
NCT03403595	mCRPC	¹⁷⁷ Lu-EB-PSMA-617	1	Standardized uptake values in normal organs and mCRPC				
NCT04597411 (AcTION)	mCRPC	²²⁵ Ac-PSMA-617	1	RP2D				
NCT03276572	mCRPC	²²⁵ Ac-J591	1	Dose-limiting toxicities and maximum tolerated dose				
NCT03724747	mCRPC	²²⁷ Th-PSMA-TTC	1	Maximum tolerated dose				

(continued on next page)

Table 1 (continued)

PUBLISHED STUDIES				
NCT05113537 (UPLIFT)	mCRPC	¹⁷⁷ Lu vipivotide tetraxetan + abemaciclib	1/2	Recommended phase 2 dose, dose-limiting toxicity, change in maximum standard uptake value
NCT05340374 (LuCAB)	mCRPC	¹⁷⁷ Lu vipivotide tetraxetan + cabazitaxel	1/2	Recommended phase 2 dose, dose-limiting toxicity, maximum tolerated dose
NCT03658447 (PRINCE)	mCRPC	¹⁷⁷ Lu vipivotide tetraxetan + pembrolizumab	1/2	PSA50 response rate and safety
NCT05383079 (AlphaBet)	mCRPC	¹⁷⁷ Lu-PSMA-I&T + ²²³ Ra	1/2	Dose-limiting toxicity, maximum tolerated dose, recommended phase 2 dose, PSA50 response rate
NCT04886986	mCRPC	²²⁵ Ac-J591 + ¹⁷⁷ Lu-PSMA-I&T	1/2	Dose-limiting toxicity, maximum tolerated dose, recommended phase 2 dose, PSA50 response rate
NCT04946370	mCRPC	²²⁵ Ac-J591 + ARPI + pembrolizumab	1/2	Dose-limiting toxicity, determination of optimal dose, change in composite response rate
NCT04506567	mCRPC	²²⁵ Ac-J591 antibody	1/2	Dose-limiting toxicity and cumulative maximum tolerated dose
NCT05521412 (VIOLET)	mCRPC	¹⁶¹ Tb-PSMA-I&T	1/2	Dose-limiting toxicity, maximum tolerated dose, recommended phase 2 dose, safety
NCT04868604 (SECURE)	mCRPC	⁶⁷ Cu-SAR-bisPSMA	1/2a	Biodistribution, dosimetry, maximum tolerated dose, recommended dose, efficacy (PSA response and radiographic response), safety
NCT04419402 (ENZA-p)	mCRPC	Enzalutamide + ¹⁷⁷ Lu vipivotide tetraxetan vs enzalutamide	2	PSA PFS
NCT05150236 (EVOLUTION)	mCRPC	¹⁷⁷ Lu vipivotide tetraxetan vs. ¹⁷⁷ Lu vipivotide tetraxetan + ipilimumab + nivolumab	2	PSA PFS
NCT05219500 (TATCIST)	mCRPC	²²⁵ Ac-PSMA-I&T	2	Efficacy (PSA response) and safety
NCT03939689 (ARROW)	mCRPC	¹³¹ I-MIP-1095 + enzalutamide	2	PSA50 response rate
NCT04689828 (PSMAfore)	mCRPC	¹⁷⁷ Lu vipivotide tetraxetan vs. change in ARPI	3	Radiographic PFS
NCT05204927 (ECLIPSE)	mCRPC	¹⁷⁷ Lu-PSMA-I&T vs. standard of care hormone therapy	3	Radiographic PFS
NCT04647526 (SPLASH)	mCRPC	¹⁷⁷ Lu-PSMA-I&T vs ARAT	3	Radiographic PFS
NCT04876651 (ProstACT GLOBAL)	mCRPC	¹⁷⁷ Lu-DOTA-rosopatamab + standard of care vs. standard of care	3	Radiographic PFS

AR, androgen receptor; ARAT, androgen receptor axis-targeted therapy; BPI-SF, brief pain inventory–short form; DATA, Patient Disease and Treatment Assessment Form; CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer core quality of life questionnaire; FACT-P, Functional Assessment of Cancer Therapy–Prostate; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; mo, month; OS, overall survival; PC, prostate cancer; PPI, McGill-Melzack scale for present pain intensity; PFS, progression-free survival; PRO, patient-reported outcome; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; RLT, radioligand therapy; RP2D, recommended phase 2 dose; SOC, standard of care.

^aAnalysis set for imaging-based PFS. ^bEvaluable from University of California, Los Angeles, cohort. ^cAfter 2 cycles. ^dAfter first therapy.

principles and practices of anticancer radiopharmaceutical therapies and thus can incorporate new RLT programs as a natural extension of an existing service. Nevertheless, even these centers must customize their workflows and update or increase their radiation protection protocols for specific types of RLT delivery.

Radiation oncology community practices can draw on their experiences with the α -particle emitter radium 223 (^{223}Ra) dichloride; however, the infrastructure, staffing level, expertise, workflows, and oversight required to administer ^{223}Ra dichloride are insufficient for RLT. Expanding the scope of an existing program beyond delivery of traditional therapeutics at these centers, or initiating an RLT program at a new center, requires a comprehensive plan that addresses all program elements (Fig. 1). In particular, centers that do not offer nuclear medicine imaging techniques, such as PET/computed tomography (CT) and single-photon emission CT (SPECT), will need to determine whether it is feasible to begin offering these imaging modalities or whether they can create a plan to refer patients to other centers, because patient eligibility for most RLTs, including PSMA-targeted RLTs, is determined in part by a patient's tumor target expression as assessed by PSMA PET [24]. The Nuclear Regulatory Commission (NRC) and state radiation safety and licensing offices require different licenses for different types of radioactive sources, which can impact the feasibility of offering imaging services [25]. These requirements are particularly important if a radiation oncologist plans to deliver RLT. While radiation oncologists may be approved to use external sources of radiation, additional training may be required for approval to use nuclear medicine tracers and obtain theranostic compounds. In some states, different training requirements exist for using imaging tracers versus therapeutic radionuclides [26].

The planning process requires coordinated input from medical oncology, urology, nuclear medicine, radiation oncology, pharmacy, nurse practitioners, and administrative staff. They consult on a range of factors, including: (1) building and licensing the appropriate infrastructure; (2) medical physics, radionuclide imaging, and dosimetry; (3) radiation safety; (4) patient access and referral; (5) reimbursement; (6) capacity planning and efficient workflow streams; (7) established rapid communication between medical oncologists and nuclear medicine physicians; and (8) patient education and discharge.

Regulation and accreditation

In the United States, the use of RLT requires a license issued by the Nuclear Regulatory Commission (NRC), which approves the facility, accredits staff, and regulates all workflow pertaining to the manipulation of radiopharmaceuticals [26]. The NRC sets minimum standards for radiation safety and protection, but some states, known as "agreement states," have agreements with the NRC authorizing them to regulate radioactive materials. Facilities located in agreement states have regulations that are at least as strict as NRC standards. If an institution has not used radioactive materials previously, a new license application will be required; institutions that currently use radioactive materials for other purposes will need to determine if their licenses must be amended to allow use of additional radioisotopes or to increase quantities of radioisotopes currently in use [26]. The NRC has provided detailed information on licensing procedures and for contacting state radiation control officers in agreement states [27,28].

All radioactive materials license applications must define: (1) an authorized user (AU) of the radioactive material, (2) a dedicated space for handling radioactive material, and (3) a radiation safety and waste management program that conforms to all applicable federal regulations [26]. Although federal regulations define who can be an AU, state-level regulations vary regarding how they can operate. For example, many states differ in their requirements for the degree of proximity between the AU and the treated patient (e.g., whether the AU must be in the same room as the patient during therapy).

Title 10 of the U.S. Code of Federal Regulations details requirements for the use of radiopharmaceuticals, including who can be an AU [26].

Table 2

Radiation safety requirements for radionuclides used in prostate cancer treatment [15,18,29–32,37].

Element	Tissue penetration, mm	Radionuclide half-life	Specific material-handling needs required to minimize radiation exposure
α-emitting			
²²³ Radium	< 0.1	11.4 d	Standard personal protection equipment, including mask, gloves, laboratory coat, safety glasses/goggles
²²⁵ Actinium ^a	0.05–0.08	10.0 d	
²²⁷ Thorium ^a	0.05–0.08	18.7 d	
²¹¹ Astatine ^a	0.05	7.2 h	
²¹² Lead ^a	0.06–0.09	10.6 h	
β-emitting			
¹³¹ Iodine	0.8	8.0 d	Shielding with an appropriate thickness of low atomic number (Z < 14) materials (e.g., Plexiglas) or aluminum
¹⁷⁷ Lutetium	0.67	6.6 d	
¹⁵³ Samarium ^b	0.40	46.5 h	
⁹⁰ Yttrium	5.30	64.1 h	
⁶⁷ Copper ^a	0.6	2.6 d	
¹⁶¹ Terbium ^a	0.29	6.9 d	Standard personal protection equipment, including gloves, laboratory coat, safety glasses/goggles

d, day; h, hour; Z, atomic number.

^a Investigational use only.

^b Commercial production discontinued.

To become an AU, board-certified physicians must complete training and specific experience requirements [26]. To start a new RLT service, they must apply to the NRC or their state (for facilities within agreement states) for a license. Only AUs are permitted to administer RLT and oversee all other technical support involved in delivering and using RLT [26]. The AU is usually a nuclear medicine physician or a radiation oncologist, but it can be another specialized physician as long as the training and experience requirements defined by the NRC are met.

Installation

The planned facility should contain enough chairs to meet anticipated patient volume and all relevant features and equipment to ensure patient safety (Table 2). Based on our experience with chair breakdown, radiation monitoring, and preparation steps, chair use is limited to about 3 infusions per day. The safety features are designed to contain radioactivity and depend on the type of therapy given and the radionuclides selected. For example, α -particle emitters such as ^{223}Ra dichloride are relatively simple to administer owing to the very short path length of the α -particles (<100 μm) in most materials (Table 2) [29–32]. Thus, the amount of shielding and personal protective equipment required to administer an α -emitting radionuclide therapy or RLT is minimal, allowing delivery in a clinic (office) setting if desired [33,34].

However, β -emitting RLTs, such as ^{177}Lu vipivotide tetraxetan for PC or iodine-131 for thyroid cancer, which also emit γ -photons, require more complex facility considerations. The combination of the emission of β -particles and low-energy γ -photons, mandates additional radiation safety precautions [20,35,36], particularly for medical staff at risk of daily exposure. Adequate space for storage and manipulation of ^{177}Lu vipivotide tetraxetan doses before administration (i.e., a hot lab) must be available, and appropriate rooms for delivering therapy must be defined. Although some nuclear medicine clinics are equipped with infusion chairs enclosed in lead-shielded private compartments to provide optimized radiation protection, shielded patient rooms for ^{177}Lu vipivotide tetraxetan administrations are not required. However, patients receiving ^{177}Lu vipivotide tetraxetan need to be separated from other patients, staff, and visitors.

Table 3

Duties of key personnel involved in running an RLT treatment center.

Position	Duties	Training
Medical oncologist/ radiation oncologist ^a	- Manages entire patient journey by liaising with nuclear medicine/clinical care team regarding eligibility, RLT ordering, concomitant medication entry in EHR, post-treatment scans, and AE monitoring - Prioritizes communication with clinical care team, including provision of scans/results to colleagues to ensure continuity of patient care, trust, and communication	Potentially an NRC Authorized User on completion of CFR part 35 [26] Workflow, eligibility, and safety training
Nuclear medicine physician ^a	- PSMA PET image analysis - Obtains consent from patients and reviews patient radiation safety instructions - Confirms RLT dose assay - Assesses IV patency and performs time-out procedure before RLT - Administers RLT - Monitors patient's status during and immediately after RLT - Discharges the patient - Follows up with the patient - Prioritizes communication with medical oncology team and referring provider to ensure continuity of patient care, trust, and communication	NRC Authorized User The theranostics specialist, defined as a qualified Nuclear Medicine Specialist trained in the practice of theranostics by the appropriate medical regulatory body. Accreditation in theranostics requires deep knowledge and experience in PET and SPECT interpretation, dosimetry, and response assessment for theranostics practice. Advanced training is essential in the RLT services medical subspecialties [64]
Nuclear medicine nurse	- Checks EHR and orders medication from pharmacy the day before treatment - Reviews patient laboratory values - Establishes IV catheter^b - Administers co-medications - Monitors the patient's vital signs, looks for AEs during infusion, and administers anti-emetics - Ensures that the patient voids when necessary to avoid radiation accumulation in bladder - May perform radiation measurements prior to discharge - Provides patients with detailed discharge instructions after treatment, including treatment wallet card and radiation safety instructions - Coordinates follow-up phone calls, visits, and laboratory work	- Workflow - Ordering - Radiation safety - Providing patient care - Providing patient education - Waste disposal in the treatment room - Medication management - Infusion pump
Nuclear medicine technologist	- Orders, receives, and inspects the RLT dose - Prepares the dose for administration and the patient for treatment - Monitors the restroom floor and path of travel to the treatment area with a Geiger counter (alerts the radiation safety officer if contamination is found and restricts access pending neutralization) - Prints a patient dose administration card - Measures exposure rate at 1 m (3 ft) from the patient and confirms that the measurement is below the level established by the radiation safety officer once all administrations are complete	- Workflow - NRC radiation safety credentialed - Dose preparation - Waste disposal - Syringe pumps and medication infusion accessories
Radiation safety officer	- Provides RLT safety training to nuclear medicine staff - Prepares treatment room and restroom with contamination control measures - Provides radiological survey support - May perform radiation measurements prior to patient discharge - Collects residual or unused doses and associated contaminated materials and manages inventory of those items for ultimate disposal - Reviews each record of therapeutic administration - Develops and maintains the basis for release of patients following treatment	- NRC radiation safety credentialed - Workflow training
Pharmacist Radiopharmacist	- Provide comedications on treatment day - Prepares radiopharmaceuticals requiring manipulation before administration - Ensures quality, safety, and efficacy of radiopharmaceuticals	- Workflow training - Radiopharmacists must be NRC-credentialed - Aseptic conditions/techniques - Analytical techniques for quality control - Workflow training

AE, adverse event; CFR, Code of Federal Regulations; EHR, electronic health record; ft, feet; IV, intravenous; m, meter; NRC, Nuclear Regulatory Commission; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; QC, quality control; RLT, radioligand therapy; SPECT, single-photon emission computerized tomography.

^a Physicians administering RLT may differ among centers: they could be radiation oncologists in some centers and nuclear medicine physicians in others.

^b Can also be performed by the nuclear medicine technologist.

Table 4

Principles of ALARA in radiation protection.

Principle	Examples
Time	- Staff are well trained in aseptic techniques and specific RLT administration procedures, which minimizes the time they spend near the radioactive source [20] - Staff deliver RLT on a routine schedule dependent on personal dosimetry to minimize accumulation of radiation exposure [20]
Distance	- Handling vials and syringes with tongs [20] - Ensure the radiation dose rate at 1 m (3 ft) from the patient is below certain levels before discharge [20]
Shielding	Staff are protected from the radiation source by use of personal protection equipment and effective shielding (plexiglass, lead), which depends on what kind of radiation the source is emitting [20]

ALARA, as low as reasonably achievable; ft, feet; m, meter; RLT, radioligand therapy.

Institutional radiation safety and waste management program

The NRC operationalizes training specifications for key personnel who are tasked with specific roles and responsibilities (Table 3) [38]. This process starts by providing a training and education program for staff that focuses on the principle of ALARA (as low as reasonably achievable) (Table 4) [39]. In-house staff training is also required to handle all eventualities (e.g., spills). In addition, a system that monitors the radiation dose received by all personnel is needed [26]. Most medical centers in the United States contract with outside vendors to provide personal dosimetry for staff. The Washington State Department of Health maintains a list of vendors providing these services [40].

The radiation safety officer is mandated with collecting and disposing residual and unused doses as well as contaminated materials, all of which are logged in an inventory [20]. Radioactive waste generated during an RLT infusion includes all paraphernalia used in the administration procedure (e.g., vials, needles and tubing, swabs, gloves, and gowns). Radioactive waste disposal procedures are based on the specific isotopes being used in an RLT program. The handling and disposal of radioactive waste associated with ^{177}Lu depends on which isotope it is prepared from, lutetium Lu 176 (“carrier added”) or ytterbium Yb 176 (“non-carrier added”) [15]. ^{177}Lu vipivotide tetraxetan is prepared using ytterbium Yb 176 unless the product batch release certificate states otherwise [15,20]. Thus, waste resulting from its use can be “decayed in storage” on-site and then disposed of as regulated medical waste because of its short physical half-life (6.6 days). ^{177}Lu -containing radiopharmaceuticals that are prepared using lutetium Lu 176 (“carrier added”) may contain an intrinsic contaminant, lutetium Lu 177 metastable ($^{177\text{m}}\text{Lu}$), which has a half-life of 161 days and cannot be “decayed in storage” without license amendments. This waste must be removed from the site and disposed of as low-level radioactive waste [20], which is costly and usually requires an outside vendor to provide the service.

Implementation and operationalization

Precise and efficient logistics processes are invaluable in the day-to-day running of an RLT program, as they reduce the need for ad hoc decision-making. In the following sections, we will highlight logistical considerations that may arise during each step of the treatment journey and provide suggestions for proactively addressing each concern as a center implements an RLT program. These suggestions can form the basis of detailed standard operating procedures for RLT programs that incorporate logistical and clinical considerations, an example of which is shown in the online supplement containing the 2022 standard operating procedures for ^{177}Lu vipivotide tetraxetan treatment used at the University of California, Los Angeles.

Patient selection

^{177}Lu vipivotide tetraxetan is indicated for the treatment of adult patients with PSMA-positive mCRPC who have already been treated with androgen receptor pathway inhibitors and taxane-based chemotherapy [15]. An example of detailed patient eligibility criteria at a typical RLT center are listed in the [Supplementary Materials](#) (Appendix A, page 5). Prior to initiating therapy, the presence of PSMA-positive mCRPC should be confirmed by PSMA-targeted PET imaging [15]. While obtaining these types of functional imaging studies may be straightforward at larger medical centers that perform PET imaging regularly, some smaller community-based centers may not have PET scanners available. In these cases, establishing a robust referral pathway that allows patients to undergo PSMA-targeted PET imaging at a larger center would be advantageous.

Complete blood counts should also be performed within 2 weeks of initiating RLT with ^{177}Lu vipivotide tetraxetan [41]. Efficient scheduling processes should be created to ensure that these laboratory results are

obtained and reviewed in a timely manner, thereby reducing the potential for treatment delays or cancellations.

In current real-world practice, the process of ordering a PSMA-targeted PET scan, consulting with the radiation oncologist or nuclear medicine physician, and the initiation of ^{177}Lu vipivotide tetraxetan treatment may take months. Thus, it is imperative that treating oncologists anticipate the need for RLT and make timely referrals for potentially eligible patients. This waiting time may be reduced in the future, with improvements in production and the distribution infrastructure.

Finally, many clinical questions remain regarding patient selection for RLT. In the absence of prospective data, patient selection for RLT often relies on clinician judgment. An externally validated risk calculator is available as a prognostic tool before treatment initiation with ^{177}Lu vipivotide tetraxetan in patients with mCRPC, which may help individual clinical decision-making (<https://www.uclahealth.org/medical-services/nuclear-medicine/research/prostate-cancer-nomogram>) [52], but treatment decision-making must rely first on the clinical judgment of the RLT treatment team for each individual case.

Consultation

At the initial consult, the uro-oncologist, the medical oncologist, the nuclear medicine physician, or the radiation oncologist discusses with the patient the rationale of RLT and the possible requirements for specific imaging to determine eligibility.

Efficient communication regarding the results of the screening PET/CT is key to the theranostics concept and builds success for the RLT program. Urgent provision of any patient-related information, including scans, imaging interpretation, laboratory results, treatment decisions, or adverse event management decisions ensures continuity of patient care as well as a streamlined workflow. For patients eligible for RLT, ongoing case review to assess additional dosing will require follow-up clinic consults to explain the treatment schedule/duration, blood work schedule, and potential side effects (emphasizing those requiring immediate medical attention).

Reimbursement policies

Accurate reimbursement policies for RLT are essential for the ongoing sustainability of the service. As soon as patient eligibility is confirmed, insurance pre-authorization should be requested at the initial nuclear medicine consult [20,21]. Designated patient financial advocates are tasked with pre-authorization, and administrative members specializing in the claim process can manage and follow cases. For example, to obtain maximum reimbursement for administration of ^{177}Lu vipivotide tetraxetan, the administrative staff requires familiarity with relevant Current Procedural Terminology codes (79101 Radiopharmaceutical therapy, by intravenous administration), Healthcare Common Procedure Coding System codes (A9699 Radiopharmaceutical, therapeutic, not otherwise specified), and pharmacy costs (\$42,500 per 200 mCi dose) [42]. Support can be sought from other centers and representatives from pharmaceutical companies to set up the necessary software systems and to educate on claims implementation.

Patient scheduling: Logistical considerations

Patients undergoing RLT should be informed of the potential for treatment delays. Receiving timely blood work for appropriate RLT administration, for example, is important as a treatment may need to be cancelled because of myelosuppression, resulting in wasted doses and delays that cause a ripple effect on future schedules. The time-sensitive decay profile of radioactive material and fixed treatment intervals associated with RLT add additional complexity. Finally, supply chain disruptions for radiopharmaceuticals, which cannot be manufactured far in advance, can also lead to treatment delays.

These challenges can be mitigated by setting expectations about therapy with patients so that they are aware that adjustments to their planned treatment schedule may be required because of adverse events or supply chain disruptions. Providing the appropriate logistic support will foster optimal patient scheduling and allow for greater access to RLT. The medical management plan incorporating RLT is typical of an oncology therapy plan in that patients return to the center for multiple procedures (including imaging, treatment, and blood work), must be followed up, and require scheduling for additional appointments. To ensure RLT can proceed as scheduled, the prescribing clinician will oversee the patient's treatment. During these visits, laboratory studies (complete blood count and comprehensive metabolic panel), history, and physical examination are undertaken. In the event that treatment parameters are not met or high-grade adverse events are noted, treatment can be postponed, avoiding generation of radioactive waste. Advanced Practice Providers (nurse practitioners and physician assistants) can play an important role in the management of RLT schedules by coordinating appointments and following up with patients regarding laboratory results and clinical progress. In particular, close follow-up of transfusion-dependent patients receiving RLT requires dialog between the oncology team and the transfusion facility. Computerized workflow applications can optimize scheduling, prevent the center from becoming overwhelmed, and allow the staff to follow each patient's care plan to reduce wastage and inefficiencies [20,21]. With accurate forecasting, the requisite number of staff can be assigned each week.

Radiopharmaceutical ordering and supply

Centers performing imaging and RLT require an adequate, consistent supply of radiopharmaceutical agents [43]. Most medical radioisotopes are formed in a small number of facilities, including cyclotrons and nuclear reactors, which emphasizes the need for clear lines of communication with suppliers. For some radioisotopes, orders can be submitted a few days before injection date [20]. These orders are typically made earlier in the week for administration later in the same week. However, for ^{177}Lu -based RLTs, the order must be placed with the supplier 2 weeks before the proposed date of treatment [20,21]. These ordering considerations introduce complexity into the supply chain, and additional staff

may be needed to handle RLT orders in a timely manner by inputting ordering information into the Novartis Advanced Accelerator Applications Radiopharmaceutical Order Management Environment scheduling platform [44] as soon as the patient is approved and scheduled for RLT. This system reduces waste, ensures the patient can be treated quickly, and mitigates the likelihood of rescheduling. Regarding ^{177}Lu vipivotide tetraxetan, RLT centers base their ordering and supply on the approved dosage regimen of 7.4 GBq (200 mCi) administered by intravenous (IV) infusion every 6 weeks for a maximum of 6 cycles [15].

Patient admission

Nurses should confirm the treatment day and discuss the planned procedures with the patient well ahead of time. The patient should be educated and prepared so that the RLT treatment can run smoothly on treatment day. Any incontinence needs (e.g., self-catheterization, incontinence pads) can be addressed at this time, as failure to do so can pose a radiation safety risk. Travel to the center can be arranged on this call; some centers offer assistance with hotel stays the night before and/or the night following treatment.

A streamlined workflow is needed to ensure the safety of the staff and patients and enhance the patient's journey through treatment (Fig. 2). Dedicated staff members should be assigned to each patient receiving RLT to ensure proper education, treatment delivery, and monitoring. The patient should be oriented to the therapy room and instructed to use the separate, designated restroom when needed. All radiation safety protocols should be explained to the patient, and all questions answered.

Radioligand preparation

Before administration, the radioligand preparation is inspected by a nuclear medicine technologist to ensure it is clear of particulate matter. The technologist then uses a dose calibrator to measure the activity to ensure the patient receives the correct dose and prepares the radioligand for administration. Radioligands that are delivered in a vial must be prepared for administration in a hot lab and can be transferred to a shielded syringe when choosing the syringe method of administration [15]. For ^{177}Lu vipivotide tetraxetan, the approved activity of 7.4 GBq is

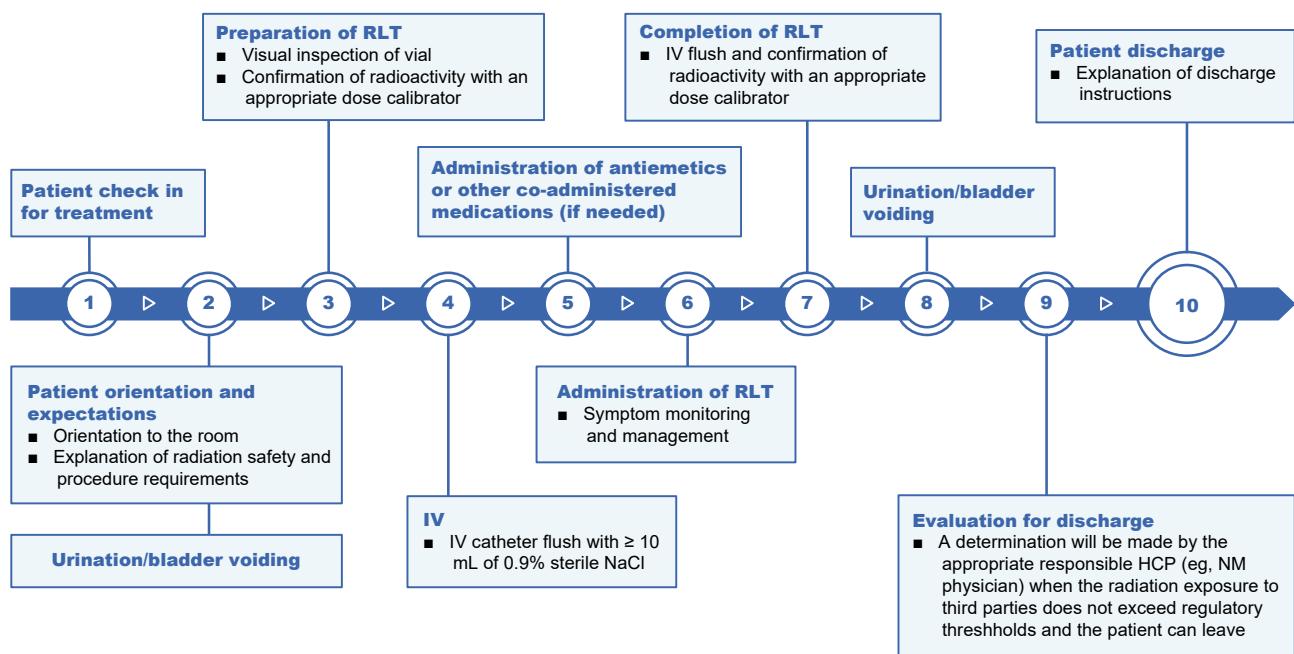


Fig. 2. Patient's journey on treatment day.^a HCP, healthcare provider; IV, intravenous; NaCl, sodium chloride; NM, nuclear medicine; RLT, radioligand therapy.
^aAdvise patients to remain well hydrated and to urinate.

administered to most patients [15]; however, this dose can be modified if risk factors for toxicity are present [35,45].

Administration

Prior to administration, appropriate imaging studies, complete blood counts, and kidney function testing should be performed.

RLT administration methods differ based on the specific RLT involved. Equipment that is readily available to perform RLT in accordance with radiation safety standards includes tongs, shielded barriers with leaded glass, syringe shields, radioactive material spill kits, and Geiger counters [20]. A treatment room with a dedicated patient rest-room should be available for the duration of treatment as the patient will need to void frequently. Caution should be used with patients who may be incontinent as excreta must be treated as radioactive waste in accordance with institutional guidelines.

Any pre-medications and concomitant medications should also be available. For ¹⁷⁷Lu vipivotide tetraxetan, an antiemetic such as oral ondansetron may be given 30–60 min before infusion and on days 2 and 3 of each treatment cycle [45]. The European Association of Nuclear Medicine guidelines state corticosteroids can also be administered 1 day before and up to several days after treatment in patients with cerebral, spinal, or other metastases that present the risk of painful or obstructive swelling after RLT [45,46]. Unlike ¹⁷⁷Lu DOTATATE for neuroendocrine tumors, ¹⁷⁷Lu vipivotide tetraxetan treatment does not require administration of amino acids for renal protection [15,47].

When administering RLT, adequate venous access should be established. ¹⁷⁷Lu vipivotide tetraxetan is usually administered to the patient by slow IV push within approximately 1–10 min via an IV catheter pre-filled with 0.9% sterile sodium chloride solution; other methods of administration are the gravity method or the vial method [15]. A ≥ 10-mL saline flush is needed before and after the infusion to minimize extravasation [15]. These methods are detailed in the [Supplementary Materials](#).

Patients undergoing treatment with ¹⁷⁷Lu vipivotide tetraxetan should be monitored by a nurse with oversight by the supervising physician so that any adverse events can be handled appropriately. ¹⁷⁷Lu vipivotide tetraxetan treatment effects can occur more than 3–4 weeks following therapy [47]. The most common adverse reactions (incidence, ≥ 20%) are fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation. The most common laboratory abnormalities (incidence, ≥ 30%) are decrease in lymphocytes, hemoglobin, leukocytes, platelets, calcium, and sodium [15]. Other common adverse events include vomiting and diarrhea. Patients with extensive bone metastases may encounter bone marrow toxicity [47]. Clinically significant cytopenia after ¹⁷⁷Lu vipivotide tetraxetan treatment can be managed by transfusion, and the next treatment cycle may be postponed until blood counts recover. If a patient has symptomatic bone metastasis, they may experience a transient increase in pain for 3–7 days, which can be treated with pain medication, steroids, and/or non-steroidal anti-inflammatory drugs. RLT-specific patient-reported outcomes measures, such as the recently developed Functional Assessment of Cancer Therapy – Radionuclide Therapy (FACT-RNT), may help nurses and physicians to monitor these symptoms and toxicities among patients with PC undergoing RLT ([Supplementary Materials](#), Appendix C) [48].

Patient discharge

In the United States, treatment with ¹⁷⁷Lu vipivotide tetraxetan is an outpatient procedure, and release criteria are based on regulations set by the NRC. After completion of treatment, the nuclear medicine technologists should measure the radiation dose at 1 m (3 feet) from the patient. The NRC permits release of patients who have been administered radioactive materials if the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 500 mrem (5 mSv) [49]. Demir et al analyzed the dose rate from

23 patients receiving ¹⁷⁷Lu vipivotide tetraxetan and found that the mean dose rate at 1 m after 4 h and 6 h was 23 ± 6 μSv/h and 15 ± 4 μSv/h, respectively [50]. Although ¹⁷⁷Lu produces low levels of γ-radiation, the levels emitted and excreted by the patient after therapy are relatively low; therefore, the radiation protection guidelines for ¹⁷⁷Lu are less extreme than those for therapies with more abundant γ-emission (e.g., iodine-131) [51].

Patients, as well as caregivers and public/healthcare workers, must be provided with guidance on contamination control measures at the clinic and at home upon discharge (detailed example shown in the on-line supplement, appendix E and H). The patient should be reminded that they are a potential source of radioactive contamination via bodily secretions. After RLT with ¹⁷⁷Lu vipivotide tetraxetan, approximately 50% of the total administered activity is excreted in the urine within the first 4 h [52]. As patients are usually discharged within 1–3 h after injection, they should be instructed to use good bathroom hygiene at home and maintain adequate hydration to assist in clearance of ¹⁷⁷Lu vipivotide tetraxetan [45]. Patients should also limit close contact (<3 feet) with adults for 2 days or with children and pregnant women for 7 days, sleep in a separate bedroom from children for 7 days and from pregnant women for 15 days, and refrain from sexual activity for 7 days [15]. There are no specific guidelines for interaction with pets.

Patients should report any signs of significant post-treatment adverse events, such as signs of myelosuppression, to the clinic and inform any providers they see outside of the oncology care team that they are being treated with RLT. Coordinated care questions should be directed to the oncology care team. Not all patients can be expected to acknowledge serious adverse events, emphasizing the importance of a routine post-therapy follow-up call by the assigned healthcare provider.

Discussion and future perspective

Establishing new RLT centers for patients with PC is possible with appropriate planning. In this review, we have provided guidance in regard to logistical and organizational considerations to assist with the implementation of new RLT programs based on the current standards of

Table 5
Current clinical questions surrounding RLT treatment.

Topic	Clinical Questions
Patient selection for RLT	• Minimum bone marrow function parameters for RLT eligibility are not clearly defined • Minimum renal function parameters for RLT eligibility are not defined • New biomarkers for patient selection are under investigation • Alternative radiotracers for image-based patient selection are under investigation
Administration of RLT	• The utility of RLT dose reduction in patients with impaired renal function is unknown • The optimal number of RLT treatments to administer and the time interval between treatments has not been fully elucidated • The value of providing treatment holidays to patients with a complete/near to complete response to RLT is not known • The effectiveness of retreatment with RLT is still under investigation • Studies are underway to determine the value of performing individualized dosimetry for patients undergoing RLT
Treatment sequencing	• The optimal time for RLT in the PC treatment sequence is currently based on the treatment team's clinical judgment
Monitoring treatment response	• The role of PSMA PET, FDG PET, and bone scans in assessing treatment response after RLT is not defined • Criteria defining tumor progression and tumor response via PSMA PET must be established

FDG, fluorodeoxyglucose; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

care. The preparation and running of an RLT center requires the cooperation of a well-trained multidisciplinary team committed to a culture of radiation safety. A computerized system to facilitate the processes of treatment scheduling, reimbursement, and patient monitoring will maximize efficiencies. For optimal outcomes, the clinical care team must develop an organizational structure that delineates the full range of tasks with clarity. Surrounding the take-down and set-up of each treatment chair, meticulous clearance and swipe testing for treatment areas and bathrooms is critical to control contamination and unnecessary exposure. Providing patient education on RLT, particularly with respect to efficacy and basic health physics, will be empowering and lead to a successful RLT program.

While we can provide logistical guidance for program implementation that will be applicable to many centers wishing to incorporate RLT into clinical practice, we acknowledge that at this time, many clinical questions surrounding RLT remain unanswered. Currently, research on RLT focuses on refining patient selection, testing novel administration, individualizing image-based dosimetry and follow-up, and assessing treatment response (Table 5) [51–63]. The identification of biomarkers and the development of additional radiotracers for imaging will improve patient selection for RLT [54,55]. Many patients inquire about differential response rates from one RLT recipient to another, as well as the potential for additional cycles of treatment and re-treatment. There is also interest in the use of RLT administered at earlier stages of PC, concomitantly with radiosensitizers, and with new radioligands [55]. Until additional prospective data are obtained, we cannot provide definitive guidance on these clinical questions and how the answers may impact the logistical and organizational pathways of effective RLT programs.

In conclusion, we have provided guidance based on real-world experience for effectively incorporating RLT into current PC clinical practice. Current standard operating procedures for RLT treatment at our institutions reflect this guidance, as illustrated by the example shown in the online supplement. In the future, robust RLT programs will have to adapt the guidance presented here as the field of RLT rapidly evolves.

Funding

Editorial support for this manuscript was provided by Novartis Pharmaceuticals.

CRediT authorship contribution statement

Jeremie Calais: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Stephen M. Eulau:** Conceptualization, Writing – original draft, Writing – review & editing. **Linda Gardner:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Ralph J. Hauke:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Ayşe T. Kendi:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Neal D. Shore:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Song Zhao:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: Dr. Calais reports grants from Lantheus, Novartis, and POINT biopharma, honoraria payments from Advanced Accelerator Applications, Astellas, Bayer, Curium Pharma, DS Pharma, GE Healthcare, Isoray, IBA RadioPharma, Janssen Pharmaceuticals, Lightpointmedical, Lantheus, Novartis, POINT biopharma, Progenics, Radiomedix, Sanofi, Telix

Pharmaceuticals.

Dr. Eulau reports no interests.

Ms. Gardner reports no interests.

Dr. Hauke reports payment for expert testimony from TeleDoc and leadership or fiduciary roles with Nebraska Oncology Society, Midwest Private Practice Associates ACO and ASCO.

Dr. Kendi reports investigator fees from the VISION and PSMAfore studies at Mayo Clinic Rochester, Novartis Studies.

Dr. Shore reports consulting fees from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Boston Scientific, Clarity, Clovis Oncology, Cold Genesys, Dendreon, Exact Imaging, Exact Sciences, FerGene, Foundation Medicine, Genesis Care, Invitae, Janssen, Lantheus, Lilly, MDxhealth, Merck, Myovant, Myriad, Nymox, Pacific Edge, Pfizer, Phosphorous, Photocure, Propella, PreView, Sanofi Genzyme, Sema4, Speciality Networks, Sesen Bio, Telix, Tempus, Tolmar, Urogen, Vaxijon, and payment for expert testimony from Ferring.

Dr. Zhao reports consulting fees from AstraZeneca, EMD Serono, Exelixis, Janssen, Pfizer, Sanofi, and Seagen.

Acknowledgements

Medical writing and editorial support for development of this manuscript was provided by Malcolm Darkes, PhD, Jennifer Olson, PhD, Andrew Gomes, PhD, and Frederique H. Evans, MBS, of Ashfield Med-Comms, an Inizio company. The UCLA SOP document provided as Supplementary Material was developed by Martin Allen-Auerbach, MD, Magnus Dahlbom, PhD, Anthony Euril Daley, NMT, Linda Gardner, RN, and John Williams, NMT.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctrv.2023.102524>.

References

- [1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022;72(1):7–33. <https://doi.org/10.3322/caac.21708>.
- [2] Slawin KM, Ohori M, Dilliogluligil O, Scardino PT. Screening for prostate cancer: An analysis of the early experience. *CA Cancer J Clin* 1995;45(3):134–47. <https://doi.org/10.3322/canjclin.45.3.134>.
- [3] Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol* 2016;34(12):1402–18. <https://doi.org/10.1200/JCO.2015.64.2702>.
- [4] Lowrance WT, Breaux RH, Chou R, Chapin BF, Crispino T, Dreicer R, et al. Advanced prostate cancer: AUA/ASTRO/SUO guideline Part I. *J Urol* 2021;205(1):14–21. <https://doi.org/10.1097/JU.0000000000001375>.
- [5] Nuhn P, De Bono JS, Fizazi K, Freedland SJ, Grilli M, Kantoff PW, et al. Update on systemic prostate cancer therapies: Management of metastatic castration-resistant prostate cancer in the era of precision oncology. *Eur Urol* 2019;75(1):88–99. <https://doi.org/10.1016/j.eururo.2018.03.028>.
- [6] Sartor O, de Bono JS. Metastatic prostate cancer. *N Engl J Med* 2018;378(7):645–57. <https://doi.org/10.1056/NEJMra1701695>.
- [7] de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364(21):1995–2005. <https://doi.org/10.1056/NEJMoa1014618>.
- [8] de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet* 2010;376(9747):1147–54. [https://doi.org/10.1016/S0140-6736\(10\)61389-X](https://doi.org/10.1016/S0140-6736(10)61389-X).
- [9] de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wulfing C, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med* 2019;381(26):2506–18. <https://doi.org/10.1056/NEJMoa1911206>.
- [10] Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367(13):1187–97. <https://doi.org/10.1056/NEJMoa1207506>.
- [11] Nussbaum N, George DJ, Abernethy AP, Dolan CM, Oestreich N, Flanders S, et al. Patient experience in the treatment of metastatic castration-resistant prostate cancer: State of the science. *Prostate Cancer Prostatic Dis* 2016;19(2):111–21. <https://doi.org/10.1038/pcan.2015.42>.
- [12] Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [(177)Lu] Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant

- prostate cancer (TheraP): A randomised, open-label, phase 2 trial. *Lancet* 2021;397(10276):797–804. [https://doi.org/10.1016/S0140-6736\(21\)00237-3](https://doi.org/10.1016/S0140-6736(21)00237-3).
- [13] Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med* 2021;385(12):1091–103. <https://doi.org/10.1056/NEJMoa2107322>.
 - [14] Gillissen S, Attard G, Beer TM, Beltran H, Bjartell A, Bossi A, et al. Management of patients with advanced prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur Urol* 2020;77(4):508–47. <https://doi.org/10.1016/j.eururo.2020.01.012>.
 - [15] PLUVICTO (lutetium Lu 177 vipivotide tetraxetan) injection for intravenous use. Prescribing information. Novartis AG; 2022.
 - [16] The Health Policy Partnership. Health system readiness for radioligand therapy in the US. Situation analysis report. 2021. Available at: <https://www.radioligandtherapy.com/> [Accessed February 26, 2022].
 - [17] Sandhu S, Guo C, Hofman MS. Radionuclide therapy in prostate cancer: From standalone to combination PSMA theranostics. *J Nucl Med* 2021;62(12):1660–8. <https://doi.org/10.2967/jnumed.120.243295>.
 - [18] Sgouros G, Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: Clinical advances and challenges. *Nat Rev Drug Discov* 2020;19(9):589–608. <https://doi.org/10.1038/s41573-020-0073-9>.
 - [19] Czernin J, Calais J. How many theranostics centers will we need in the United States? *J Nucl Med* 2022;63(6):805–6. <https://doi.org/10.2967/jnumed.122.264144>.
 - [20] Abbott A, Sakellis CG, Andersen E, Kuzuhara Y, Gilbert L, Boyle K, et al. Guidance on (177)Lu-DOTATATE peptide receptor radionuclide therapy from the experience of a single nuclear medicine division. *J Nucl Med Technol* 2018;46(3):237–44. <https://doi.org/10.2967/jnmt.118.209148>.
 - [21] Burkett BJ, Dundar A, Young JR, Packard AT, Johnson GB, Halfdanarson TR, et al. How we do it: A multidisciplinary approach to (177)Lu DOTATATE peptide receptor radionuclide therapy. *Radiology* 2021;298(2):261–74. <https://doi.org/10.1148/radiol.2020201745>.
 - [22] Duan H, Iagaru A, Aparici CM. Radiotheranostics - Precision medicine in nuclear medicine and molecular imaging. *Nanotheranostics* 2022;6(1):103–17. <https://doi.org/10.7150/ntno.64141>.
 - [23] Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. TheraP: 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—Overall survival after median follow-up of 3 years (ANZUP 1603). *J Clin Oncol* 2022;40(16 suppl):5000. https://doi.org/10.1200/JCO.2022.40.16_suppl.5000.
 - [24] Herrmann K, Giovannella L, Santos A, Gear J, Kiratli PO, Kurth J, et al. Joint EANM, SNMMI and IAEA enabling guide: How to set up a theranostics centre. *J Nucl Med* 2022. <https://doi.org/10.2967/jnumed.122.264321>.
 - [25] Burkhardt M, Cockerham A, Cook J, Daibes S, Forster S, Gabriel S, et al. NUREG-1556 consolidated guidance about materials licenses: Program-specific guidance about medical use licenses. Washington, D.C.: United States Nuclear Regulatory Commission; 2019.
 - [26] Baldwin JA, Bag AK, White SL, Palot-Manzil FF, O'Malley JP. All you need to know as an authorized user. *AJR Am J Roentgenol* 2015;205(2):251–8. <https://doi.org/10.2214/AJR.14.13283>.
 - [27] U.S. NRC. Licensing of medical, industrial, and academic uses of nuclear materials. Washington, D.C.: United States Nuclear Regulatory Commission; 2022. Available at: <https://www.nrc.gov/materials/miaul/licensing.html> [accessed July 26, 2022].
 - [28] U.S. NRC. Agreement states. Washington, D.C.: United States Nuclear Regulatory Commission; 2022. Available at: <https://www.nrc.gov/agreement-states.html> [accessed July 27, 2022].
 - [29] XOFIGO (radium Ra 223 dichloride) injection for intravenous use. Prescribing information. Bayer; 2021.
 - [30] Eckerman K, Endo A. ICRP Publication 107: Nuclear decay data for dosimetric calculations. *Ann ICRP* 2007;38:7–96. <https://www.icrp.org/publication.asp?id=ICRP%620Publication%20107>.
 - [31] Chhabra A, Thakur ML. Theragnostic Radionuclide Pairs for Prostate Cancer Management: 64Cu/67Cu, Can Be a Budding Hot Duo. *Biomedicine* 2022;10(11):2787. <https://doi.org/10.3390/biomedicine10112787>.
 - [32] Vaidyanathan G, Zalutsky MR. Targeted therapy using alpha emitters. *Phys Med Biol* 1996;41(10):1915–31.
 - [33] Deshayes E, Roumiguie M, Thibault C, Beuzebec P, Cachin F, Hennequin C, et al. Radium 223 dichloride for prostate cancer treatment. *Drug Des Devel Ther* 2017;11:2643–51. <https://doi.org/10.2147/DDDT.S122417>.
 - [34] Du Y, Carrio I, De Vincentis G, Fanti S, Ilhan H, Mommsen C, et al. Practical recommendations for radium-223 treatment of metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging* 2017;44(10):1671–8. <https://doi.org/10.1007/s00259-017-3756-7>.
 - [35] Kratochwil C, Haberkorn U, Giesel FL. Radionuclide therapy of metastatic prostate cancer. *Semin Nucl Med* 2019;49(4):313–25. <https://doi.org/10.1053/j.semnucmed.2019.02.003>.
 - [36] Dash A, Chakraborty S, Pillai MR, Knapp Jr FF. Peptide receptor radionuclide therapy: An overview. *Cancer Biother Radiopharm* 2015;30(2):47–71. <https://doi.org/10.1089/cbr.2014.1741>.
 - [37] Haller S, Pellegrini G, Vermeulen C, van der Meulen NP, Köster U, Bernhardt P, et al. Contribution of Auger/conversion electrons to renal side effects after radionuclide therapy: preclinical comparison of 161 Tb-folate and 177 Lu-folate. *EJNMMI Res* 2016;6(13). <https://doi.org/10.1186/s13550-016-0171-1>.
 - [38] The Health Policy Partnership. Health system readiness for radioligand therapy in the US - Regulation and reimbursement. Working paper; 2021. Available at: <https://www.radioligandtherapy.com/app/uploads/Health-system-readiness-for-radioligand-therapy-in-the-US-Regulation-and-reimbursement.pdf> [accessed March 10, 2022].
 - [39] Centers for Disease Control. ALARA - As low as reasonably achievable. Available at: <https://www.cdc.gov/nceh/radiation/alara.html> [accessed March 18, 2022].
 - [40] Washington State Department of Health. Dosimetry service providers. Available at: <https://doh.wa.gov/community-and-environment/radiation/x-ray/x-ray-equipment-registration/x-ray-facility-plan-review/dosimetry-service-providers> [accessed August 18, 2022].
 - [41] Kratochwil C, Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, et al. EANM procedure guidelines for radionuclide therapy with (177)Lu-labelled PSMA-ligands ((177)Lu-PSMA-RLT). *Eur J Nucl Med Mol Imaging* 2019;46(12):2536–44. <https://doi.org/10.1007/s00259-019-04485-3>.
 - [42] Applications AA. PLUVICTO (lutetium Lu 177 vipivotide tetraxetan). Millburn, NJ USA: Advanced Accelerator Applications, a Novartis company; 2022. Available at: https://aaapatientconnect.com/assets/pdfs/150177_PLUVICTO_Pricing_Visual_Aid.pdf [accessed October 28, 2022].
 - [43] Merkel C, Whicher CH, Bomanji J, Herrmann K, Cwikla J, Jervis N, et al. Realising the potential of radioligand therapy: Policy solutions for the barriers to implementation across Europe. *Eur J Nucl Med Mol Imaging* 2020;47(6):1335–9. <https://doi.org/10.1007/s00259-020-04745-7>.
 - [44] AAA Radiopharmaceutical Order Management Environment (ROME). Millburn, NJ USA: Advanced Accelerator Applications, a Novartis company; 2022. Available at: <https://rome.adacap.com/login/en> [accessed October 28, 2022].
 - [45] Sanli Y, Simsek DH, Sanli O, Subramaniam RM, Kendi AT. (177)Lu-PSMA therapy in metastatic castration-resistant prostate cancer. *Biomedicine* 2021;9(4). <https://doi.org/10.3390/biomedicine9040430>.
 - [46] LUTATHERA (lutetium Lu 177 dotatate) injection for intravenous use. Prescribing information. Novartis AG; 2022.
 - [47] Groener D, Nguyen CT, Baumgarten J, Bockisch B, Davis K, Happel C, et al. Hematologic safety of (177)Lu-PSMA-617 radioligand therapy in patients with metastatic castration-resistant prostate cancer. *EJNMMI Res* 2021;11(1):61. <https://doi.org/10.1186/s13550-021-00805-7>.
 - [48] Gudenkauf L, Chavez M, Maconi M, Geiss C, Seyedroudbari A, et al. Developing a novel patient reported outcomes measure for prostate cancer patients receiving radionuclide therapy. *J Nucl Med* 2023. <https://doi.org/10.2867/jnumed.122.264946>.
 - [49] Federal Register: Nuclear Regulatory Commission. Release of patients administered radioactive material - Draft regulatory guide DG-8057. 2019. Available at: <https://www.federalregister.gov/documents/2019/07/26/2019-15868/release-of-patient-s-administered-radioactive-material> [accessed October 28, 2022].
 - [50] Demir M, Abuqbeith M, Uslu-Beşli L, Yıldırım Ö, Yeyin N, Çavdar İ, et al. Evaluation of radiation safety in (177)Lu-PSMA therapy and development of outpatient treatment protocol. *J Radiol Prot* 2016;36(2):269–78. <https://doi.org/10.1088/0952-4746/36/2/269>.
 - [51] Mitra ES. Neuroendocrine tumor therapy: (177)Lu-DOTATATE. *AJR Am J Roentgenol* 2018;211(2):278–85. <https://doi.org/10.2214/AJR.18.19953>.
 - [52] Kurth J, Krause BJ, Schwarzenbock SM, Stegger L, Schäfers M, Rahbar K. External radiation exposure, excretion, and effective half-life in (177)Lu-PSMA-targeted therapies. *EJNMMI Res* 2018;8(1):32. <https://doi.org/10.1186/s13550-018-0386-4>.
 - [53] Gafita A, Calais J, Grogan TR, Hadaschik B, Wang H, Weber M, et al. Nomograms to predict outcomes after (177)Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: An international, multicentre, retrospective study. *Lancet Oncol* 2021;22(8):1115–25. [https://doi.org/10.1016/S1470-2045\(21\)00274-6](https://doi.org/10.1016/S1470-2045(21)00274-6).
 - [54] Gafita A, Rauscher I, Weber M, Hadaschik B, Wang H, Armstrong WR, et al. Novel framework for treatment response evaluation using PSMA-PET/CT in patients with metastatic castration-resistant prostate cancer (RECIP 1.0): An international multicenter study. *J Nucl Med* 2022. <https://doi.org/10.2967/jnumed.121.263072>.
 - [55] Zhang H, Koumna S, Pouliot F, Beauregard JM, Kolinsky M. PSMA Theranostics: Current landscape and future outlook. *Cancers (Basel)* 2021;13(16). <https://doi.org/10.3390/cancers13164023>.
 - [56] Violet J, Sandhu S, Iravani A, Ferdinandus J, Thang SP, Kong G, et al. Long-term follow-up and outcomes of retreatment in an expanded 50-patient single-center phase II prospective trial of (177)Lu-PSMA-617 theranostics in metastatic castration-resistant prostate cancer. *J Nucl Med* 2020;61(6):857–65. <https://doi.org/10.2967/jnumed.119.236414>.
 - [57] Calais J, Czernin J, Thin P, Gartmann J, Nguyen K, Armstrong WR, et al. Safety of PSMA-targeted molecular radioligand therapy with (177)Lu-PSMA-617: Results from the prospective multicenter phase 2 trial RESIST-PC (NCT03042312). *J Nucl Med* 2021;62(10):1447–56. <https://doi.org/10.2967/jnumed.121.262543>.
 - [58] Calais J, Gafita A, Eiber M, Armstrong WR, Gartmann J, Thin P, et al. Prospective phase 2 trial of PSMA-targeted molecular Radiotherapy with (177)Lu-PSMA-617 for metastatic castration-resistant Prostate Cancer (RESIST-PC): Efficacy results of the UCLA cohort. *J Nucl Med* 2021;62(10):1440–6. <https://doi.org/10.2967/jnumed.121.261982>.
 - [59] Rathke H, Flechsig P, Mier W, Bronzel M, Mavriopoulou E, Hohenfellner M, et al. Dosimetry estimate and initial clinical experience with (90)Y-PSMA-617. *J Nucl Med* 2019;60(6):806–11. <https://doi.org/10.2967/jnumed.118.218917>.
 - [60] Sathekge M, Bruchertseifer F, Vorster M, Lawal IO, Knoesen O, Mahapane J, et al. Predictors of overall and disease-free survival in metastatic castration-resistant prostate cancer patients receiving 225Ac-PSMA-617 radioligand therapy. *J Nucl Med* 2020;61:62–9. <https://doi.org/10.1007/s00259-021-05434-9>.
 - [61] Kratochwil C, Bruchertseifer F, Rathke H, Bronzel M, Apostolidis C, Weichert W, et al. Targeted alpha-therapy of metastatic castration-resistant prostate cancer with

- (225)Ac-PSMA-617: Dosimetry estimate and empiric dose finding. *J Nucl Med* 2017;58(10):1624–31. <https://doi.org/10.2967/jnumed.117.191395>.
- [62] Zechmann CM, Afshar-Oromieh A, Armor T, Stubbs JB, Mier W, Hadaschik B, et al. Radiation dosimetry and first therapy results with a (124)I/(131)I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. *Eur J Nucl Med Mol Imaging* 2014;41(7):1280–92. <https://doi.org/10.1007/s00259-014-2713-y>.
- [63] Afshar-Oromieh A, Haberkorn U, Zechmann C, Armor T, Mier W, Spohn F, et al. Repeated PSMA-targeting radioligand therapy of metastatic prostate cancer with (131)I-MIP-1095. *Eur J Nucl Med Mol Imaging* 2017;44(6):950–9. <https://doi.org/10.1007/s00259-017-3665-9>.
- [64] Lee ST, Emmett LM, Pattison DA, Hofman MS, Bailey DL, Latter MJ, et al. The importance of training, accreditation, and guidelines for the practice of theranostics: The Australian perspective. *J Nucl Med* 2022;63(6):819–22. <https://doi.org/10.2967/jnumed.122.263996>.