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Nuts and Bolts of ^{177}Lu-DOTATATE Administration in the Nuclear Medicine Division: Guidance from a Single Institute's Experience

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Brief title: Nuts and Bolts of ^{177}Lu-DOTATATE PRRT

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Abstract

[Lutetium-177-DOTA(0),Tyr(3)]octreotate (^{177}Lu-DOTATATE) is a radiolabeled somatostatin analog that has been approved by the U.S. Food and Drug Administration for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors in adults. Radionuclide therapies have been administered for many years within nuclear medicine departments in North America. However, in comparison to other radiotherapies, ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) involves more planning, coordination, concomitant medication administration (anti-emetic medications and amino acids) and direct patient care. To date, various methods have been utilized in multiple centers during the Phase 3 trial and the provision of patient care. As participants in the NETTER-1 and subsequent Expanded Access Program for the administration of ^{177}Lu-DOTATATE studies, as well as recently starting post-approval clinical care, we have administered 61 ^{177}Lu-DOTATATE therapies (13 NETTER-1, 39 Expanded Access Program, 9 clinical) at the Dana-Farber Cancer Institute and here share our procedures, personnel training and workflow processes to help other centers establish programs for this Food and Drug Administration-approved ^{177}Lu-DOTATATE PRRT.

Key words: radionuclide therapy, peptide receptor radionuclide therapy (PRRT), nuclear medicine, ^{177}Lu-DOTATATE, neuroendocrine tumor

Neuroendocrine tumors commonly express somatostatin-receptors subtype 2 that can be utilized for both imaging and treatment. While peptide receptor radionuclide therapy (PRRT) has been utilized in other countries for approximately twenty years (*1*), [Lutetium-177-DOTA(0),Tyr(3)]octreotate (^{177}Lu-DOTATATE) became the first agent of its kind approved by the Food and Drug Administration in January 2018 for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (*2,3*). In the NETTER-1 study, treatment with ^{177}Lu-DOTATATE for four administrations administered every 8 weeks along with standard of care 30 milligram (mg)/month long-acting octreotide therapy was associated with an improvement in progression-free survival compared to monthly high dose octreotide therapy in patients with somatostatin receptor-positive mid-gut neuroendocrine tumors whose disease had progressed on standard dose somatostatin analog therapy (*4*). Efficacy of ^{177}Lu-DOTATATE has also been demonstrated in non-randomized studies including patients with other gastrointestinal and pancreatic neuroendocrine tumors (*1*). The delivery of ^{177}Lu-DOTATATE PRRT to patients with gastroenteropancreatic neuroendocrine tumors requires more planning, coordination, concomitant medication administration and direct supervised patient care than most other radionuclide therapies administered in nuclear medicine departments, based on our experience in the phase 3 NETTER-1 clinical trial, subsequent Expanded Access Program, and post-approval clinical care at Dana-Farber Cancer Institute.

Brief Description of ^{177}Lu-DOTATATE Therapy

^{177}Lu-DOTATATE PRRT consists of an intravenous infusion of 7.4 gigabecquerels (GBq) [200 milliCuries (mCi)] of ^{177}Lu-DOTATATE given every 8 weeks for a total of four

infusions. This 8-week interval between PRRT has varied among investigators in other centers. Should the patient experience an adverse reaction during the initial ^{177}Lu-DOTATATE infusion, further adverse reactions can be managed by delaying therapy and reducing the dose depending on the severity and time course of the adverse event. We manage adverse events between treatments by delaying the next treatment, if required. So far, we have not had an adverse event that would lead to a reduced dose. Given that ^{177}Lu-DOTATATE binds to somatostatin receptors, therapy with long-acting somatostatin analogs should be stopped at least 4 weeks prior to ^{177}Lu-DOTATATE administration, but therapy with short-acting somatostatin analogs can continue if necessary for symptom control, until 24 hours prior to ^{177}Lu-DOTATATE administration (*2-4*). We re-administer long-acting octreotide to patients between 4 and 24 hours after each ^{177}Lu-DOTATATE PRRT, usually prior to patient discharge on the treatment day so that the patient doesn't have to travel the next day.

Given the preferential renal excretion of ^{177}Lu-DOTATATE, a co-infusion of amino acids consisting of 18-24 grams (g) each of lysine and arginine is administered to help decrease renal retention and lower the radiation dose delivered to the kidneys. The amino acids' infusion starts at least 30 minutes prior to the ^{177}Lu-DOTATATE infusion and continues after ^{177}Lu-DOTATATE PRRT at a rate of infusion that is dependent on the content and volume of the amino acids' solution (*2*). We typically infuse the post-PRRT amino acids over at least 5 hours and 25 minutes with 2 Liters (L) of commercial amino acids at a rate of 320 milliliters/hour (mL/h). Prophylaxis for amino acids-related nausea and vomiting includes anti-nausea (anti-emetic) medication(s) given at least 30 minutes before the start of the amino acids' infusion (*2*) and as needed throughout the treatment, as well as reduction of the amino acids' infusion rate

(from 500 to 320 mL/h).

Multidisciplinary Team Roles, Responsibilities, Required Resources and Training

Multiple departments (Imaging, Medical Oncology, Pharmacy, and Radiation Safety) and individuals within each department are involved in providing ^{177}Lu-DOTATATE PRRT. These include medical oncologists, nurses/nurse practitioners, Nuclear Medicine physicians and technologists, pharmacists, and the Radiation Safety Officer. Each group of individuals are assigned specific roles and responsibilities that enable us to streamline the process and optimize care delivery. Training and required resources are tailored based on these specific roles and responsibilities. Suggested training, required resources, roles, and responsibilities for each department are provided in Tables 1-2. Since the Food and Drug Administration approval of ^{177}Lu-DOTATATE PRRT, we have established a multidisciplinary bi-monthly tumor board and a nuclear medicine consultation appointment. The bi-monthly tumor board meets to determine patient eligibility, which includes demonstration of somatostatin receptor positive tumor on somatostatin receptor imaging, such as ^{68}Ga-DOTATATE Positron Emission Tomography/Computed Tomography (PET/CT), and the consultation appointment occurs between the patient and a nuclear medicine physician prior to scheduling therapy.

Workflow for Scheduling, Ordering, and Receiving the ^{177}Lu-DOTATATE Dose

Once a patient has been deemed eligible for ^{177}Lu-DOTATATE PRRT, an order is placed with the nuclear medicine division who orders the ^{177}Lu-DOTATATE dose from Advanced Accelerator Applications at least two weeks prior to PRRT delivery. Advanced Accelerator

Applications confirms dose availability for the specified date and time within 24 hours of receiving the dose order. A separate order is also placed for a patient consultation appointment with the nuclear medicine physician prior to PRRT delivery.

Approximately two days before the treatment, a batch release document containing dose product information with the dose batch number, shipment date and time, calibration date, time and activity, expiration date and time, and dose volume for the ^{177}Lu-DOTATATE dose is received from Advanced Accelerator Applications. On the day before the treatment, a nuclear medicine technologist receives the dose and visually checks that it is free of particles.

Patient Treatment Room and Restroom Preparation

A lead-lined patient treatment room and restroom in the Dana-Farber Cancer Institute nuclear medicine division is prepared on the evening before the treatment date by lining the floors and lower walls with plastic-backed kraft paper (Figure 1). Chux are placed over the patient stretcher or chair and then covered by a bedsheet before the patient's arrival. A large sharps' waste bucket is placed in the patient treatment room to collect any waste that might contain ^{177}Lu (alcohol wipes, gauze, emesis basins, IV supplies, etc.). Several pairs of scrubs are also set aside for the patient to use on the treatment day as needed.

Method for Amino Acids' Infusion

An anti-emetic (oral or IV, depending on patient insurance) is administered at least 30 minutes prior to the initiation of the amino acids' infusion. Our pharmacy most often provides either 2 L of the amino acids' infusion Aminosyn II® (Hospira, Inc.) 10%, which we infuse at 320 mL/h via the Alaris™ (BD) infusion pump for at least 50 minutes before starting the ^{177}Lu-

DOTATATE administration to help reduce nausea symptoms, or Clinisol® [Baxter Healthcare Corporation] 15%, which we dilute to a volume of 2.2L and administer for 60 minutes before starting the ^{177}Lu-DOTATATE infusion. This rate and time can be adjusted as needed per the amino acids content.

^{177}Lu-DOTATATE Therapy Dose Preparation

There are multiple options that can be considered for the intravenous administration of ^{177}Lu-DOTATATE, including infusion directly from the vial by infusing saline into the vial either by gravity drip or at a specific rate with an infusion pump that as the saline enters the vial, the ^{177}Lu-DOTATATE exits the vial into the patient's intravenous tubing, or withdrawal of the dose into a syringe. We withdraw the ^{177}Lu-DOTATATE dose into a syringe and administer it via a shielded Graseby™ (Smiths Medical) pump (Figures 2-4). So far, we have not had any problems administering the therapy with this method. The alternative method of dripping or infusing saline into the vial requires close monitoring and can have potential issues related to vial pressure and leakage.

The ^{177}Lu-DOTATATE dose is delivered in a 30 mL vial with an approximate volume of 25 mL. Two nuclear medicine technologists work side-by-side to prepare the dose with one technologist recording the dose preparation and administration information on the technologist worksheet (Figure 5), while the other technologist prepares the actual dose. It is recommended that the nuclear medicine technologist drawing up the dose wears routine personal protective equipment such as scrubs and a lab coat, along with two pairs of gloves and wrist gaiters to cover the gap between gloves and lab coat sleeves, as to protect the technologist from drip or splash as

the syringe needle is withdrawn from the vial septum. As part of the training regimen for nuclear medicine technologists, treatment procedures are simulated using a saline solution to practice drawing up and loading the dose into the Graseby™ (Smiths Medical) pump. To prepare for this training and the delivery of ^{177}Lu-DOTATATE, a graded-Z 30 mL syringe shield was built in-house using an acrylic syringe shield wrapped with lead and covered with CoFlex® (Andover adhesive bandage, Figure 2). The needed supplies are listed in Table 3. The procedure for dose preparation is provided in Table 4 (Technologist Checklist).

^{177}Lu-DOTATATE Administration

The patient is asked to empty his/her bladder and vital signs are checked by the nurse prior to the start of the ^{177}Lu-DOTATATE infusion. Immediately prior to the administration of the ^{177}Lu-DOTATATE, the nuclear medicine physician checks the intravenous line patency and performs a time-out procedure with the patient. The technologist connects the ^{177}Lu-DOTATATE dose microbore tubing into the Alaris™ (BD) pump tubing port closest to the patient's intravenous line and the nuclear medicine physician starts the ^{177}Lu-DOTATATE infusion. The start time is documented by the technologist and the infusion is completed within approximately 30 minutes. Once the infusion is complete, the technologist documents the stop time, fills the syringe with saline and infuses a bolus saline flush at 400 mL/h via the Graseby™ (Smiths Medical) pump. Once this flush completes, the technologist disconnects the patient microbore tubing and brings the dose cart back into the nuclear medicine hot lab to measure the residual radioactivity.

Two nuclear medicine technologists work together to unload the pump and assay the

residual radioactivity in the syringe, while wearing two pairs of gloves in addition to routine personal protective equipment. One technologist covers the pump with chux pads to avoid potential radioactive contamination, removes the dose syringe from the 3-way stopcock, replaces the original needle onto the syringe, and assays the residual of the syringe in the dose calibrator with the appropriate plastic sleeve and channel setting for ^{177}Lu, while the other technologist records the data on the technologist worksheet. The syringe residual is subtracted from the first syringe assay to determine the net injected dose. Both syringe and patient tubing residual assay were measured during the trial and Expanded Access Program, and the tubing residual amounts measured were noted to be negligible.

For treatment documentation, we created amino acid/^{177}Lu-DOTATATE administration worksheets for our nurses and technologists (Figures 5 and 6). The pharmacy phone number is listed on the nurses' worksheet for ease of communication when activating and releasing drug orders. It is also helpful for the nurses to note the start time of the amino acids' infusion to estimate when the technologists would be ready to bring the ^{177}Lu-DOTATATE dose in the patient room for administration, and for the nurses to have an area outside the patient room but contiguous to it (like the hallway) to document vital signs, all medication administrations and any adverse events. The nurses also document every bathroom visit to ensure that the patient voids at least every hour post-^{177}Lu-DOTATATE administration. These forms are saved and referenced during subsequent treatments. The technologist worksheet helps ensure that each step of dose preparation is followed in proper order. The information on the technologist worksheet has been incorporated into our clinical nuclear medicine Quality Management Program worksheet and the nursing worksheet has been reformatted for use in the clinic to contain patient

name and medical record number instead of clinical trial subject identification number.

Further Recommendations for Non-Investigational Treatment with ^{177}Lu-DOTATATE

As with all novel therapeutic agents, the transition from use in clinical trials to routine clinical care requires planning and preparation prior to implementing a ^{177}Lu-DOTATATE PRRT clinical program. The experience acquired during the clinical trial and the Expanded Access Program helped us design standard operating procedures for the delivery of ^{177}Lu-DOTATATE PRRT in routine clinical care, now that the therapy is approved by the Food and Drug Administration. Some of the differences between the protocol therapy and standard therapy include our addition of a multidisciplinary tumor board and a nuclear medicine consultation appointment. Follow-up procedures should be in place that can be similar to what was utilized in the clinical trial to monitor for efficacy and toxicity. Additionally, individualized treatment decision regarding somatostatin analog therapy after treatment needs to be made. As of May 2018, the National Comprehensive Cancer Network also published guidance regarding the principles of PRRT (3).

Proper departmental and institutional preparation and coordination can ensure high quality patient care and safe delivery of ^{177}Lu-DOTATATE PRRT within a nuclear medicine division. Some of the key considerations include processes for patient consent, team coordination, handling of radioactive materials, departmental resources and workflows, and methods for treatment administrations.

Patient Consent

In the clinical trial, a member of the medical oncology team consented the patients for the study and a nuclear medicine technologist reviewed the radiation safety instructions with the patients. Post-Food and Drug Administration approval, we recommend that potential candidates be reviewed in a multi-disciplinary tumor board clinic including an additional consultation with the nuclear medicine physicians. The goals of the nuclear medicine consultation are to confirm patient eligibility and appropriateness for therapy, review the risks and benefits of therapy, as well as post-treatment radiation safety precautions, answer any questions, and obtain informed written consent. These precautions include information about potential radiation risks, myelosuppression, secondary myelodysplastic syndrome and acute leukemia, renal toxicity, hepatotoxicity, neuroendocrine hormonal crises, embryo-fetal toxicity, lactation, and infertility (*2*,*3*). This nuclear medicine consultation is included in the clinical notes in the patient's electronic health record and can be billed separately from the therapeutic procedure.

Team Coordination

We recommend maintaining a list of updated contact information for each team member and communicating with the patient in advance about the schedule and events on the treatment day. We also believe that it is helpful to designate a point-of-contact person in nuclear medicine to coordinate between the multidisciplinary teams (*5*,*6*).

Handling of Radioactive Materials

Additional preparation measures include calibration of the dose calibrator for ^{177}Lu and inclusion of ^{177}Lu in the radioactive materials license. Of note, if not already included, addition of ^{68}Ga to the license may also be very helpful since ^{68}Ga-DOTATATE is approved by

the Food and Drug Administration (*7*) and routinely used to assess patient eligibility for ^{177}Lu-DOTATATE PRRT (*3*). Decay in storage is standard for most nuclear medicine divisions, but confirming that there is adequate room for storage and decay of radioactive waste would be useful because the bulk of the waste can add up quickly if patients vomit or void on something that must be stored for decay. Due to the intrinsic (non-separable) ^{177m}Lu contaminant in the ^{177}Lu-DOTATATE that has a half-life of about 160 days as opposed to 6.647 days for ^{177}Lu, the ultimate disposition as low-level waste has been required for most of our contaminated materials, including some of the kraft paper used for prophylactic protection of floor areas, adding significant bulk to the disposed volume. Retention of the waste materials for management via decay-in-storage procedures was not possible without license amendment. We recommend avoiding mixing or co-mingling these wastes with those from shorter-lived ($T_{1/2}$ < 120 day) materials to minimize resultant waste disposal costs.

Our process to reduce radiation exposure to technologists and nurses includes the ALARA (As Low As Reasonably Achievable) principle, focusing on time, distance, and shielding. All technologists are trained in the procedure and deliver it on a routine rotated schedule. Treatment simulation with saline is provided as a training exercise until the technologist feels comfortable and adequately trained. A dedicated patient treatment room is nearby the dedicated patient restroom, minimizing the length of exposure while attending to the patient. The use of a powered reclining chair allows for the patient to adjust his/her position without close technologist assistance/support. Contamination control is preeminent in handling this material to minimize the risk of skin contamination or impact on the operational capability of the department should contamination occur outside of the shielded/protected patient area.

Shielding includes the lead-lined patient treatment room and restroom, as well as the graded-Z syringe shield, shielded infusion pump, and leaded plastic L-block.

Departmental Resources and Workflows

We designate a nuclear medicine technologist and a radiology nurse to the patient for the entire day, noting that a second technologist is needed to assist during the dose preparation and a second nurse is needed to relieve the first nurse for breaks and to verify medications. In addition to the number of staff and necessary supplies, one will also want to identify the type of training needed for everyone involved. The type of training provided for each team is provided in Tables 1-2 (*5*).

The timing of the sequence of events needed to treat a patient must also be considered. At the present time, the ^{177}Lu-DOTATATE dose needs to be ordered at least two weeks in advance. One will want to determine when to schedule the dose to arrive and the treatment day. We recommend for the dose to arrive the day before the scheduled treatment and for the patient to arrive early (7:00 am) on the treatment day to help avoid potential delays. Standard release criteria, including a 1-meter survey with a Geiger counter, are followed at the end of the amino acids' infusion to discharge the patient. The nuclear medicine physicians assess the well-being of the patient and confirm that he/she complies with the radiation safety precautions prior to discharge. Thus far, all patients have been treated in an outpatient setting. Additional needs include determination of the physical location for the therapy in nuclear medicine and the method for the intravenous administration of ^{177}Lu-DOTATATE PRRT. In the Phase 3 trial, sites had options such as starting the patient in the medical oncology unit for the anti-emetics and

amino acids' infusion, then transporting the patient to nuclear medicine for the ^{177}Lu-DOTATATE infusion, and finally transporting the patient back to the medical oncology unit to complete the amino acids' infusion. At Dana-Farber Cancer Institute, we keep the patient in the nuclear medicine division from start to finish. This avoids requiring the patient to be transported when he/she may not be feeling well and the need for additional personnel support. Also, if radioactive contamination were to occur, we are more comfortable with it happening in nuclear medicine where we know how to handle it and can keep it contained instead of during patient transport or in the medical oncology unit. When identifying the necessary department resources, such as a reserved patient treatment room and restroom on the treatment day, we recommend a restroom close to the treatment room since patients may be drowsy when taking anti-emetics and need assistance walking to the restroom every hour post-^{177}Lu-DOTATATE infusion.

Methods for Treatment Administrations

For the administration of amino acids, the prescribing information states to start the amino acids 30 minutes prior to administering ^{177}Lu-DOTATATE (*2*). We reduce the rate of amino acid infusion from 500 mL/h to 320 mL/h to minimize nausea and vomiting. Because the rate is reduced, we administer the amino acids for a longer duration in order to provide the same amount of amino acids' content prior to starting ^{177}Lu-DOTATATE, i.e., we adjust the infusion from 30 minutes to 50 minutes for AminosynII® [Hospira, Inc.] 10% and to 60 minutes for Clinisol® [Baxter Healthcare Corporation] 15%. This also extends our total duration of amino acids' infusion from 4 hours to more than 6 hours, but we experience fewer emetic events with this method. In May 2018, the National Comprehensive Cancer Network also updated guidelines

for neuroendocrine and adrenal tumors to include principles of PRRT with ^{177}Lu-DOTATATE, which offers options for administering compounded versus commercial amino acids and starting the infusion at a lower rate while increasing every ten minutes (*3*).

It is also important to note that the deadly category 5 hurricane Maria in September 2017 lead to a shortage of intravenous saline products and amino acids due to damaged production sites in Puerto Rico (*8,9*). We recommend checking in advance to ensure that the required amino acids and saline solutions can be procured before scheduling patients for treatment.

As mentioned earlier, one will need to determine which method to use for ^{177}Lu-DOTATATE dose administration. Also, given that we documented negligible residual activity in the microbore tubing and 3-way stopcock following injection during the clinical trial and Expanded Access Program, we now only measure the syringe residual post-administration of ^{177}Lu-DOTATATE PRRT.

Conclusion

New workflows and procedures for the Food and Drug Administration-approved ^{177}Lu-DOTATATE PRRT administration within nuclear medicine can be challenging to introduce, yet can be successfully implemented with proper departmental and institutional preparation.

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Nuclear medicine team members shown in Figure 7 include:

- Back row left to right – Umesh Mukkuzhi, MS, CNMT, RT(N)(CT); Amanda Abbott, MS, CNMT, RT(N)(CT), PET; Lauren Gilbert, CNMT, RT(N)(CT); Timothy Belisle, CNMT, RT(N)(CT)
- Middle row left to right – Michele Iacobucci; Yuji Kuzuhara, MHA, RT(N)(MR)(CT), CNMT; Jennifer Manganella, CNMT, RT(N)(CT); Justin Tremont, CNMT, RT(N)(CT), PET
- Front row left to right – Christopher Sakellis, MD; Annick D. Van den Abbeele, MD, FACR; Eileen Vo, RT(N); Heather Jacene, MD; and Marta Adamkiewicz, CNMT, RT(N)

- Not pictured – Theresa Carroll, RT(N)(CT); Oswaldo Delgado, CNMT; Johnny Madrid, CNMT, NMTCB(CT); James Wellemeyer, RT(N); Aida Arthur, RN; Marianne Castano, MS, RN: Marion Fallon, RN; Leslie Hajjar, RN; Betsy Mele, RN; Mary Jane Murphy, RN

References

1. Brabander T, van der Zan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res.* 2017;23:4617-4624.

2. Lutetium Lu 177 dotatate [package insert]. Colleretto Giacosa (TO), Italy: Advanced Accelerator Applications USA, Inc; 2018.

3. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Neuroendocrine and Adrenal Tumors (Version 2.2018) website. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed May 24, 2018.

4. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med. 2017;*376:125-35.

5. Abbott A, Kuzuhara Y, Jacene H, et al. ^{177}Lu-dotatate therapy for patients with metastatic gastrointestinal neuroendocrine tumors: How to prepare your practice for optimal administration. *J Nucl Med 2016;*57:2681.

6. Abbott A. (2018). Nuclear medicine and ^{177}Lu-dotatate therapy: A guide to success. *Pathways*, 8;5.

7. NETSPOT (kit for the preparation of gallium Ga 68 dotatate injection) [package insert]. Saluggia (Vc), Italy: Gipharma, S.r.l.; 2016.

8. FDA. Statement by FDA Commissioner Scott Gottlieb, M.D., updating on Puerto Rico related medical product shortages [Press release] website.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587290.htm. Accessed February 5, 2018.

9. FDA. Statement by FDA Commissioner Scott Gottlieb, M.D., update on recovery efforts in Puerto Rico, and continued efforts to mitigate IV saline and amino acid drug shortages [Press release] website. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm591391.htm. Accessed February 5, 2018.

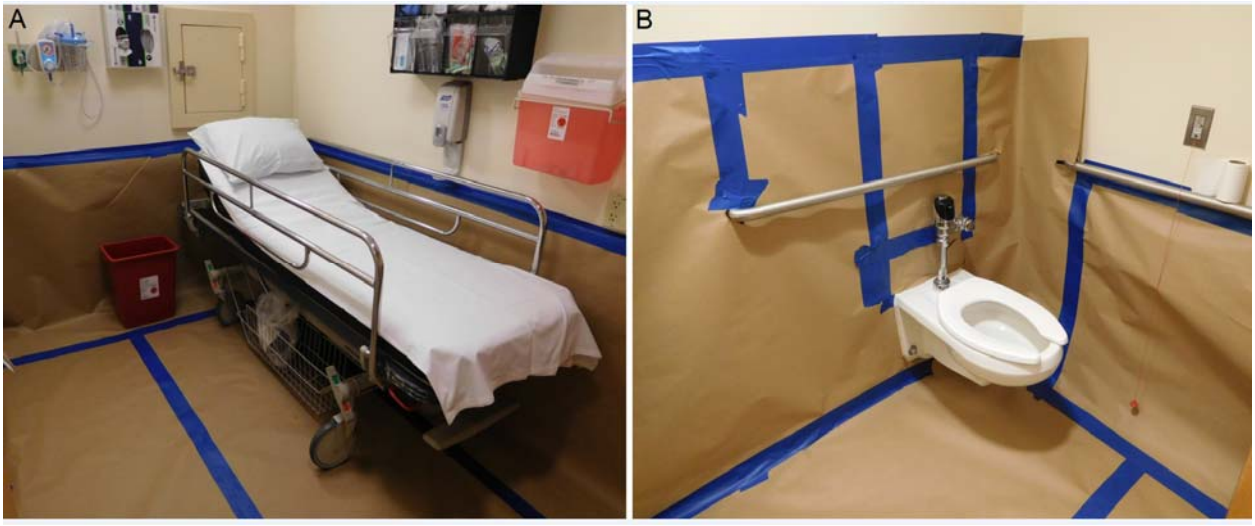

Figure 1. A. Prepared Patient Treatment Room. B. Patient Restroom.

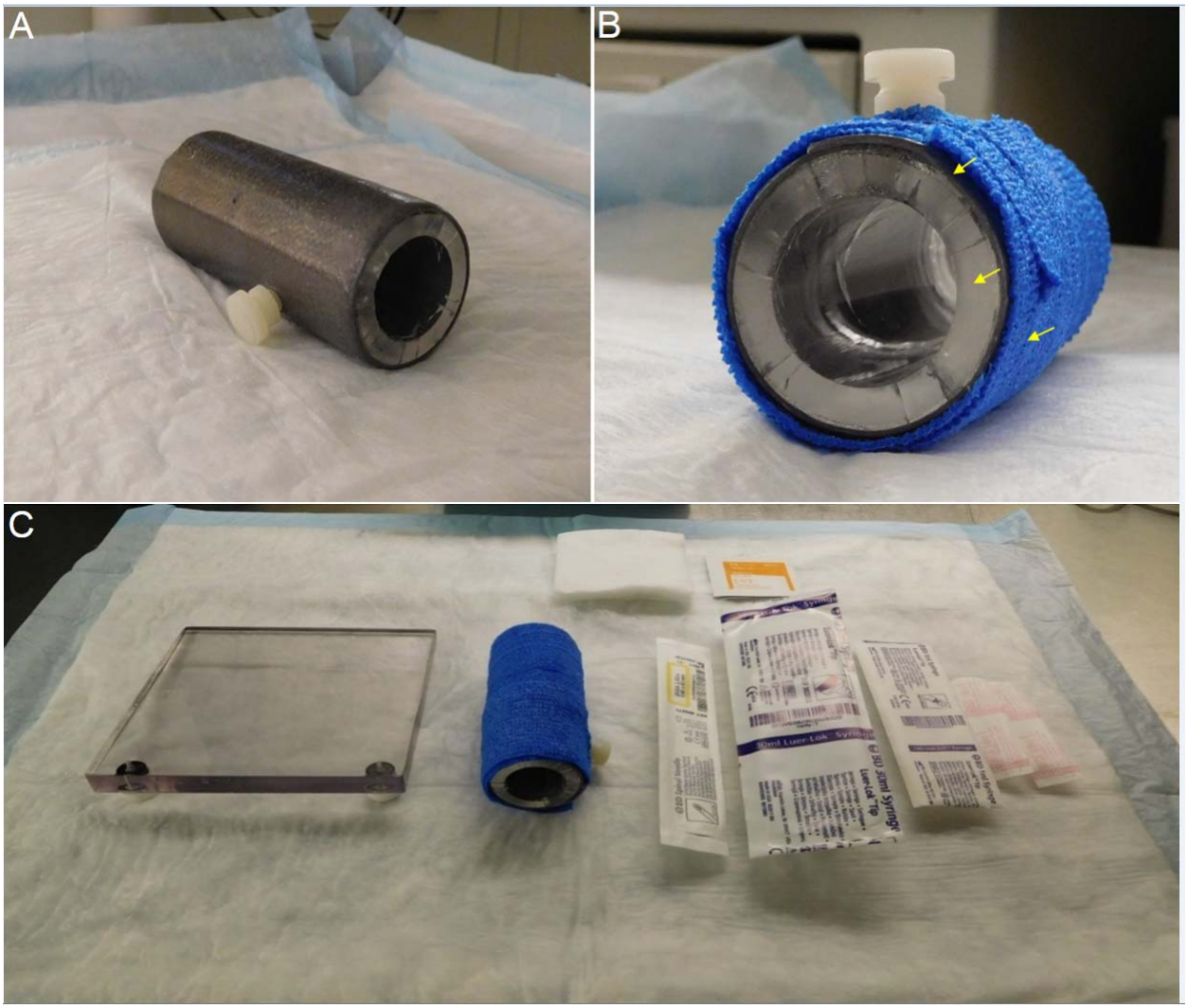

Figure 2 Dose Preparation Supplies. A. In-house fabricated 30-mL syringe shield. B. From outer to inner, arrows represent the covering to prevent contact with lead surface, lead, and acrylic. C. Some supplies needed to draw up the dose (a wedge, 30-mL syringe shield, gauze, alcohol wipes, 30-mL syringe, 3 ½" spinal needle, 1-mL syringe, 20-gauge (g) needles, chux pad).

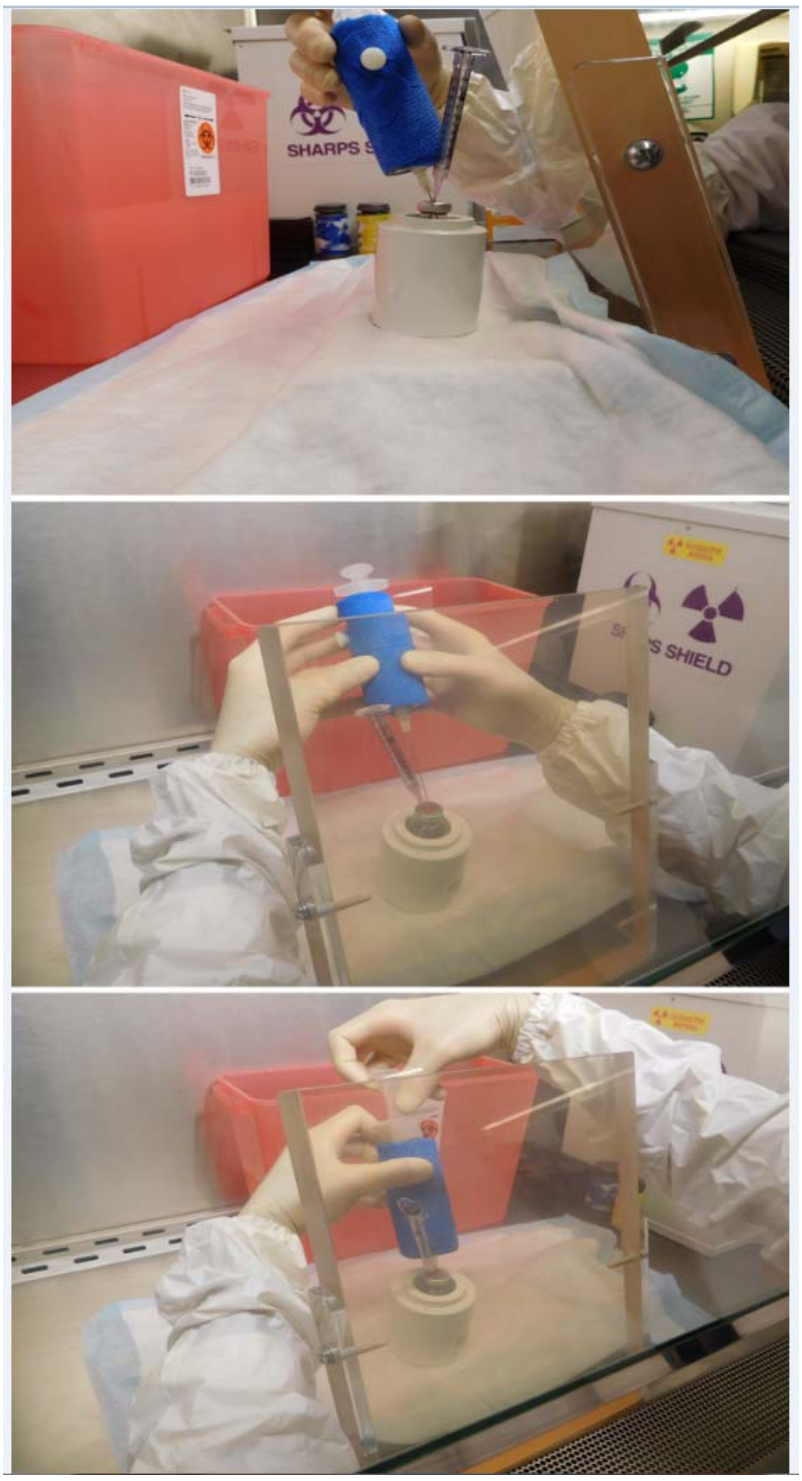

Figure 3. Dose Preparation: Insertion of the vent needle and spinal needle for drawing up the dose with vial tilted on the wedge, behind the L-block in the biological safety cabinet and a dedicated ^{177}Lu waste bucket in the back.

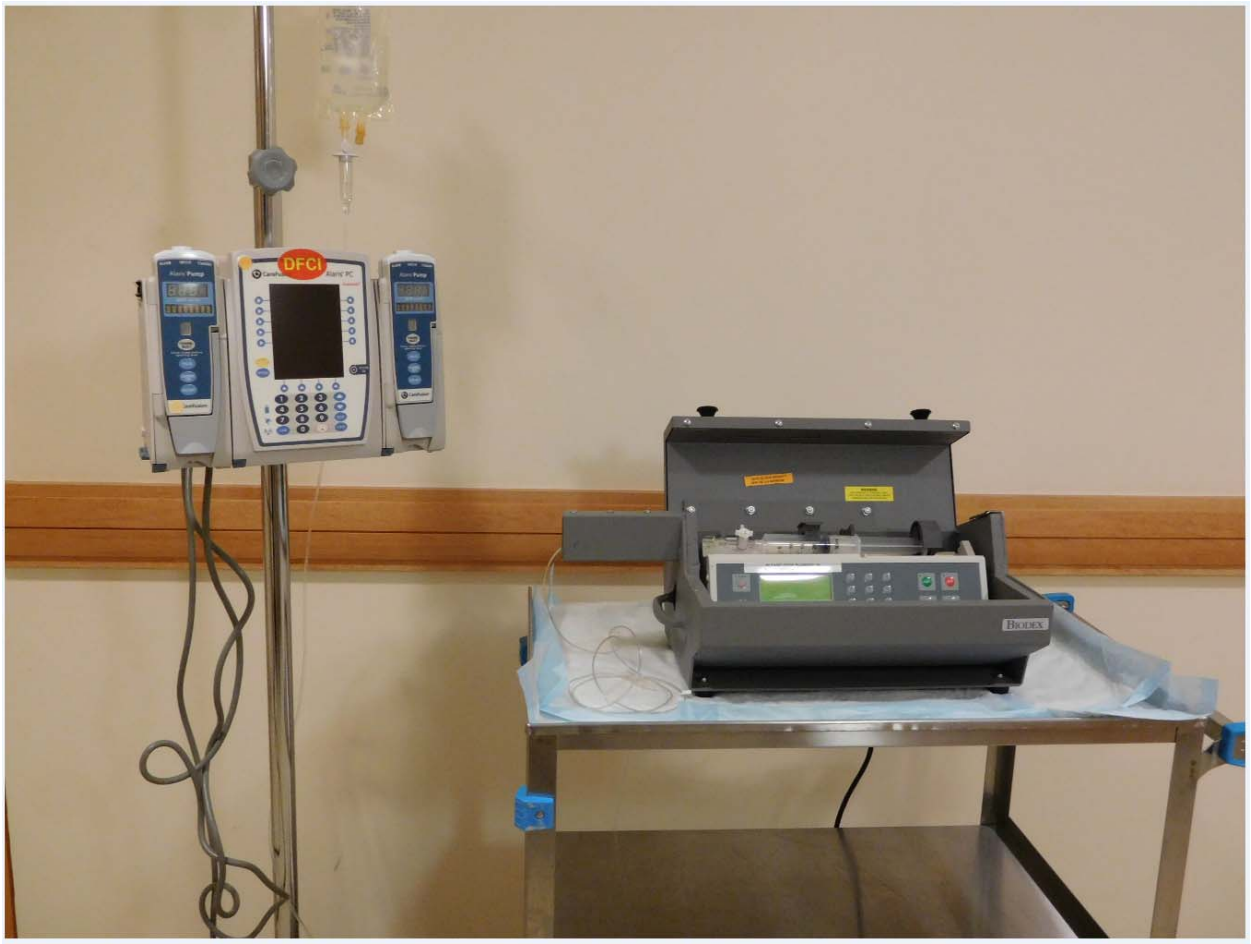

Figure 4. Dose Administration Supplies: Alaris™ (BD) pump with amino acids, saline bag, shielded Graseby™ (Smiths Medical) pump with ^{177}Lu-Dotatate on the chux-covered cart.

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	Tech initials:	
Infusion Date	/ / *(DD / MMM / YYYY)*	
Subject ID #		
IV site(s)		*(for ^{177} Lu-DOTATATE if second IV is placed)*

*Nurse to activate medication orders and call Pharmacy (phone # xxx-xxxx) to ask the pharmacist to process orders

Start time of **amino acids**	:	

Calibration date and **time** of ^{177}Lu-DOTATATE	/ / *(DD / MMM / YYYY)*		:
Volume of ^{177}Lu-DOTATATE		ml	
Flow rate to enter into Graseby™ Pump =		50 ml/hr	
Vial assay and time (^{177}Lu)		mCi	:
Start time of dose prep	:		
(Insert Cal# here) Get M.D. to check assay → **Syringe** assay and time		**mCi**	:
Vial residual assay and time		mCi	:
Time IV patency observed	:		
Time of '**Time-Out**' and physician initials	:		physician initials:
Start time of ^{177}Lu-DOTATATE	:		
End time of ^{177}Lu-DOTATATE	:		
Syringe residual assay and time		**mCi**	:
Tubing residual assay and time		**mCi**	:
Total Residual		**mCi**	
NET Injected Dose	Syringe assay - total residual		**mCi**

1 meter survey prior to patient's departure: mR/hr

Meter/Serial# info:

Notes:

Figure 5 Amino Acid/^{177}Lu-DOTATATE Worksheet for Technologists.

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Nurse initials:	

Infusion Date	/ / *(DD / MMM / YYYY)*	
Subject ID #		
IV site(s)		*(for ^{177} Lu-DOTATATE if second IV is placed)*

*Nurse to activate medication orders and call Pharmacy (phone # xxx-xxxx) to ask the pharmacist to process orders

Start time of **amino acids**	:	
Vital signs pre-^{177}Lu-DOTATATE infusion	:	BP: Pulse rate:
End time of **^{177}Lu-DOTATATE**	:	
Vital signs post-^{177}Lu-DOTATATE infusion	:	BP: Pulse rate:
End time of **amino acids**	:	

Time Patient Released from Nuc Med:	:	Physician Initials:	
Comments about Release:			

Additional meds given:

Medication name	Route / Site of administration	Dose	Time (up/down if applicable)
			:
			:
			:
			:

Bathroom visits, nausea/vomiting episodes, & other (This section on the back of the sheet)	**Time**	**Notes**
	:	
	:	
	:	
	:	
	:	

Figure 6. Amino Acid/^{177}Lu-DOTATATE Worksheet for Nurses.

Figure 7 DFCI Nuclear Medicine Team.

TABLE 1. Resources, Roles/Responsibilities and Required Training for Medical Oncology, Pharmacy, and Radiation Safety Officer

Human Resources	Roles/Responsibilities	Required Training
Medical Oncology Team	• Communicates with the nuclear medicine team regarding eligible patients • Enters the orders in the electronic health record for the ^{177}Lu-DOTATATE procedure and required medications • Evaluates patients within the week prior to each ^{177}Lu-DOTATATE treatment and monitors for adverse events through follow-up visits	• Workflow training • Eligibility training
Pharmacist	• Provides the anti-emetics, amino acids, and post-treatment long-acting somatostatin analog on the treatment day	• Workflow training
Radiation Safety Officer	• Provides ^{177}Lu radiation safety training to nuclear medicine staff • Prepares treatment room and restroom with contamination control measures. Provides radiological survey support as needed. • 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	• Workflow training

TABLE 2. Resources, Roles/Responsibilities and Required Training for Nuclear Medicine

Human Resources	Roles/Responsibilities	Required Training
Nuclear Medicine Nurse	• Checks the medication orders placed in the electronic medical record on the day prior to treatment to ensure that they have been entered correctly and sends them to pharmacy on the treatment day	• Workflow and radiation safety, including for providing patient care and proper waste disposal in the patient treatment room
	• Establishes an intravenous catheter into the patient (or this can also be performed by the nuclear medicine technologist) • Administers anti-emetics, amino acids, and long-acting somatostatin analog • Monitors the patient for adverse events during the amino acids' infusion, administers anti-emetics as needed, measures the patient's vital signs (blood pressure and pulse rate) immediately before and after the ^{177}Lu-DOTATATE infusion, and ensures that the patient voids before the start of the ^{177}Lu-DOTATATE infusion and every hour thereafter to reduce radiation exposure to the bladder	• Medication management and Alaris™ (BD) pump
Nuclear Medicine Physician	• Consents patients and reviews patient radiation safety instructions	• Workflow and radiation safety
	• Confirms the ^{177}Lu-DOTATATE dose assay in the dose calibrator, assesses the IV patency and performs time-out procedure before the ^{177}Lu-DOTATATE infusion, and administers the ^{177}Lu-DOTATATE infusion • Assesses the status and discharges the patient from the nuclear medicine department	• Graseby™ (Smiths Medical) pump
Nuclear Medicine Technologist	• Orders the ^{177}Lu-DOTATATE dose, receives and inspects the dose, prepares the dose for administration, prepares the patient for treatment (or this is performed by the nurse)	• Workflow and radiation safety, including for dose preparation and proper waste disposal
	• Surveys the restroom floor and path of travel to the treatment area with a Geiger counter Contacts the radiation safety officer if contamination is found and restricts access to contaminated areas pending remedial measures • Prints a patient dose administration card; measures exposure rate at 1 meter from the patient and confirms that the measurement is below the level established by the radiation safety officer once all administrations are complete	• Graseby™ (Smiths Medical) pump and ^{177}Lu-DOTATATE dose preparation

TABLE 3. Recommended Supplies

Supplies	Purpose
Separate patient treatment room and restroom	Designated for treatment day
Nuclear Medicine hot lab	^{177}Lu-DOTATATE dose preparation
Workstation	Documentation of medication administration and vital signs
250 mL[1] saline bags	To flush the ^{177}Lu-DOTATATE dose syringe
Extension tubing	To run from saline bags
3-way stopcocks	To connect therapy and saline tubing
Microbore tubing	To attach the ^{177}Lu-DOTATATE dose to the patient IV[2]
10 mL pre-filled saline syringes	To flush IV lines and check IV patency
30 mL vial saline	For training simulation
30 mL syringes	To draw up the ^{177}Lu-DOTATATE dose
1 mL syringes	To vent the ^{177}Lu-DOTATATE vial
2.5-3.5" spinal needles	To draw up the ^{177}Lu-DOTATATE dose
20-gauge needles	For vent and dose syringes
Gauze	To raise the vial inside the shielded pig and use for cleaning
Chux pads	For cleanliness and protection
Alcohol Wipes	To clean the vial
Tongs and tweezers	To pick up and clean the vial
Wedge	To tilt the vial when drawing up the ^{177}Lu-DOTATATE dose
30 mL lead-lined acrylic syringe shield	To draw up the ^{177}Lu-DOTATATE dose
Plastic-backed Kraft paper and masking tape	To line treatment room and bathroom walls and floors
Scrubs for patients and technologists	Standard personal protective equipment
Lab coats for technologists	Standard personal protective equipment
Impermeable gloves	Standard personal protective equipment
Wrist gaiters and goggles or face shield	Personal protective equipment for drawing up the dose
Sharps waste buckets (small and large)	For all waste
Appropriate L-block shield within a Biosafety cabinet	For dose preparation
Radiation detection/survey instrument and personal dosimetry ring/body badges	For monitoring radiation exposure
Appropriate infusion pumps and tubing	For infusion of anti-emetics, amino acids, and ^{177}Lu-DOTATATE
General IV supplies: 22-20 gauge IV, Tourniquet, Chlorohexidine, Tegaderm, CoFlex® (Andover) adhesive bandage	Establishing patient IV line

[1] mL = milliliter

[2] IV = intravenous

TABLE 4. Technologist Checklist for ^{177}Lu-DOTATATE Preparation

Tech Initials	^{177}Lu-DOTATATE Preparation Steps:
	Prepare cart with chux and Graseby™ (Smiths Medical) pump: • Hang a 250 mL[1] saline bag and prime the tubing with saline • Connect this tubing to a 3-way stopcock and prime the 3-way stopcock with saline • Prime the dose microbore extension tubing that will be connected to the dose syringe with saline • Connect the extension tubing into the 3-way stopcock • Load tubing into the Graseby™ (Smiths Medical) pump • Set rate on Graseby™ (Smiths Medical) pump (50 mL/h)[2] and clear the volume. Change dose calibrator setting, sleeve and plunger to those specified for ^{177}Lu • Place label on syringe (patient name, date of birth, medical record number, drug, dose, and date)
	Assay vial – place piece of gauze in bottom of pig while vial is still in the dose calibrator: • If less than 6.66 GBq[3] or 180 mCi[4] (7.4 GBq-10%, or 200 mCi-10%), contact the nuclear medicine physician before proceeding • Record time and assay on technologist worksheet
	Draw up the entire volume of the dose from the vial into the 30-mL syringe: • Insert a 20-gauge needle on a 1 mL syringe with the plunger removed at a tilted angle into the vial to use as a vent system, making sure to insert just enough to puncture the vial • Use a 30-mL syringe attached to a 3 ½" spinal needle with a syringe shield to draw the dose. With the vial tilted on the wedge, insert the spinal needle attached to the 30-mL syringe until the bottom of the vial is reached. A 2 ½" spinal needle can also be used but it will not touch the bottom of the vial. • Slowly draw up all the volume within the vial. If it is difficult to draw, slightly loosen the syringe shield thumbscrew. • Raise the vial using tongs and visually assess if all the volume has been drawn up before removing the syringe • Slowly pull the syringe straight up and out of the vial • Carefully pull back the syringe plunger to ensure that no liquid remains in the hub of the spinal needle. Twist off the spinal needle and attach a regular needle, discarding the spinal needle into the designated sharps waste bucket • Remove extra air from the syringe
	Measure vial residual in the dose calibrator and record the assay/time
	Measure the syringe dose in the dose calibrator and record the assay/time (nuclear medicine physician to confirm assay)
	Load Graseby™ (Smiths Medical) pump: • Connect the syringe dose into the 3-way stopcock and load the syringe into the pump, setting aside the needle to use for the residual assay of the syringe post-infusion

[1] mL = milliliter
[2] h = hour
[3] GBq = Gigabecquerel
[4] mCi = milliCuries