EUROPEAN ASSOCIATION OF NUCLEAR MEDICINE

RADIONUCLIDE THERAPY MANAGEMENT

A TECHNOLOGISTS' GUIDE

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FOREWORD

Foreword

Nuclear medicine is a discipline that encompasses both diagnostic and therapeutic fields. Although the diagnostic field is the more widespread, radionuclide therapy is clearly undergoing a period of rapid evolution, with the results of the latest research trials providing evidence of its importance. With the emergence of the theranostic concept, the two fields of radionuclide therapy and diagnostics have become inseparably linked for many procedures. The need for sustainable development therefore applies to both fields.

The evolution of radionuclide therapy is directly linked to great advances in the field of radiopharmacy, but the sciences of physics and radiobiology also need to be an integral part of these complex procedures. The clinical impact of radionuclide therapy on the course of disease in patients is greatly enhanced by well-applied techniques with the focus on personalised medicine.

Nuclear medicine technologists are part of the multiprofessional team that makes use of these sciences in the application of radionuclide therapies. These therapies need to be managed by specialists with an advanced skillset, and the need for well-trained professionals is unquestionable when it comes to quality of service.

Over the years, the European Association of Nuclear Medicine's (EANM) Technologists' Committee (TC) has dedicated itself to the ongoing professional development of nuclear medicine technologists. A book entitled "Radionuclide Metabolic Therapy" was already published in 2013. Now, almost a decade later, the advances have been immense, which has inspired the committee to revisit the topic with the publication of "Radionuclide Therapy Management – a Technologists' Guide".

A large number of renowned authors have contributed to this publication, and I am very thankful for the knowledge and expertise they have gifted to this project. Gratitude is also due to the other participating EANM committees for their support and input, as well as to our overseas colleagues from the SNMMI-TS. Many thanks to you all.

I would also like to acknowledge and thank Christelle Terwinghe and Agata Pietrzak, my fellow members of the editorial team – your resilience and dedication are much appreciated!

Additionally, I express my gratitude to the staff of the EANM Office – Núria Serra and Sophie Karsai, many thanks for your constant support. My sincere thanks also to Angela Parker for your professionalism in the language review of this publication.

Last but not least, I thank the EANM Technologists Committee and also the EANM Board for their support and for believing in this publication from the very outset.

Each and every individual mentioned above was indispensable in making this publication a reality. Many thanks to you all!

Andrea Santos
Chair, EANM Technologists Committee

INTRODUCTION

Introduction

The specific management of radionuclide therapies requires the nuclear medicine technologist to venture into new fields of expertise and deal with specific needs in daily practice.
Besides the daily routine in dealing with diagnostic procedures, some additional procedures are required and necessary when entering the field of radionuclide therapy.

In view of the increased use of radionuclide therapies, we are convinced that this guide will provide valuable support for technologists who are starting out in the specific area of radionuclide therapy. The use of radionuclide therapies is revolutionising nuclear medicine, and it is time to expand our knowledge and expertise in this area to meet the need for well- trained staff. To aid colleagues in facing the challenges ahead, we have opted to prioritise the management of radionuclide therapies over describing the specific use and applications of the relevant radiopharmaceuticals.

When initiating the Technologists' Guide 2022 and assigning the individual chapters, we decided to devote more attention to the management of radionuclide therapy and to those specific tasks that do not feature so prominently in the diagnostic setting.

In therapeutic settings we are more involved in the care of patients. For the patient it is important to be well informed about the procedure, the measures that need to be taken to protect the patient and the public environment, the logistics and the costs of the therapy. Depending on the local legislation, patients sometimes need to be hospitalised because of the high exposure to the immediate environment. During hospitalisation patients have specific needs which require more attention on our part. There is a higher risk of unexpected incidents, and risk assessment is required to put adequate procedures in place. We also address some specific radiation protection measures relating to the different characteristics of the radionuclides used. Finally, when dealing with radioactive waste, handling radionuclides and managing the hospitalisation of patients we need specific procedures to ensure that the waste can be released according to the local requirements.

The Technologists' Guide 2022 brings together experts from the fields of dosimetry, imaging, radiation protection, patient care and waste management, including physicians, medical and health physicists, radiographers and nuclear medicine technologists. We would like to express our gratitude to all the authors who shared their knowledge and expertise with us. We very much appreciate their willingness to accept the invitation to volunteer and make time for writing alongside their existing daily workload.

We do hope the Technologists' Guide 2022 will provide you with new insights and supply useful information to facilitate the management of radionuclide therapies.

Andrea Santos, Agata Pietrzak and Christelle Terwinghe
Editorial Team

1

RADIATION PROTECTION

by Søren Holm

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TYPES OF RADIATION: PARTICLES AND PHOTONS

Ionising radiation can be defined as a transfer of energy where the individual parts in the transfer have enough energy to ionise atoms. The "individual parts" can either be particles, which have a certain mass, energy and momentum, or photons, which are electromagnetic radiation that can be described in terms of wavelength, frequency and energy. However, in the context of nuclear medicine we usually think of photons as a special kind of particle that moves at the speed of light, has no mass, and yet carries a certain energy and momentum. Ionising radiation can have different origins; here we are concerned with radiation that is emitted from radioactive material.

All matter consists of atoms with nuclei composed of protons (positive) and neutrons (neutral), and with a balancing number of negative electrons arranged in shells or orbits around the nucleus. The nuclear chart [1] (Figure 1) shows all the different nuclei arranged in a coordinate system with the number of neutrons on the horizontal axis and the number of protons on the vertical axis. Every horizontal line in the diagram contains nuclei with an equal number of protons and hence electrons. Since this defines an element, all the nuclei on a single line are isotopes of the same element. Obviously, the range of possible combinations of protons and neutrons is limited.

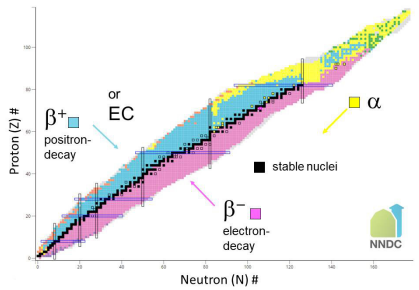

Figure 1. The nuclear chart (based on NuDat3 [1] with permission). EC = electron capture decay. See main text for further description.

ORIGIN OF THE RADIATION TYPES

In Figure 1, the black points are stable nuclei, of which there are 257. Moving away from the "stability curve", we find nuclei that possess an excess of energy that makes them unstable. Each such nucleus will tend to decay into a daughter nucleus with less energy, and thus closer to stability. The process is stochastic, meaning that for a given sample we can only predict an average number per time unit with some uncertainty. We characterise the "instability" using the decay constant, i.e. the fraction of a sample that will decay within a certain time unit, or the half-life, i.e. the time it takes for half of the nuclei to decay. In general, the further we move away from the stability curve, the higher the excess energy and the shorter the half-life. The mode of decay and the half-life are characteristics of each nuclide.

In Figure 1, the nuclei are colour coded according to their most likely decay mode. The original interactive chart on the internet [1] allows users to select an alternative colour coding showing the half-lives. By clicking on these charts one can also access data on the results of all radioactive decay processes. The three dominant decay modes are:

Alpha decay (yellow), where an alpha particle corresponding to a helium nucleus is released. This is the dominant decay mode for the heavier nuclei.

Beta-minus decay (magenta), where the emitted particle is a negative electron, for nuclides with excess neutrons (to the right of the stability curve)

Beta-plus decay (light blue), emitting a positron (positive electron), for nuclides with an excess of protons (positive charge). The beta-plus decay competes with another process not explicitly shown in the diagram: that of electron capture (EC), where one orbital electron is included in the nucleus, leaving a vacancy in the electron system of the atom.

Although this looks simple, the final combined result of the decay process may be quite complex. This is summarised in Figure 2.

Having expelled a particle, the resulting daughter nucleus in most cases still possesses excess energy that must be released before a stable condition is reached. This can be attained by the emission from the nucleus of one or more

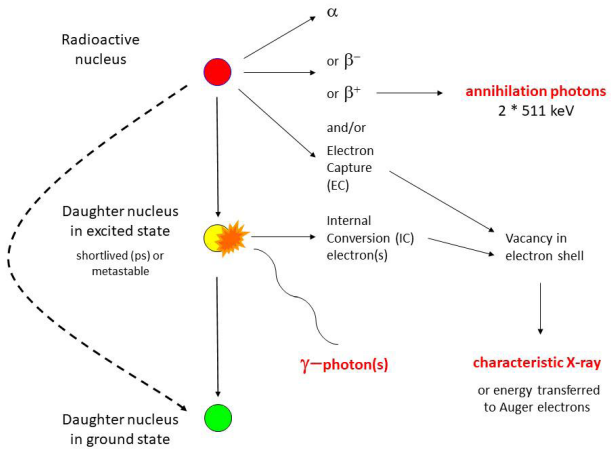

Figure 2. The processes following the initial decay can be quite complicated. The details are explained in the main text.

gamma photons, which can result in a rather complicated gamma spectrum, particularly for the heavier nuclei. It is also possible for part of the excess energy to be transferred to electrons via so-called internal conversion (IC). Following beta-plus decay, the positron (after slowing down) will annihilate with an electron and create annihilation photons with energy of 511 keV each (the basis of PET). Finally, when a vacancy in the electron system is created by EC or IC, this will trigger a cascade of events where holes in the inner shell are filled from outer shells with excess energy, the latter being emitted as characteristic x-ray radiation (photons) or – in a further step – transferred to so-called Auger electrons.

Due to all these steps and processes, almost all beta or alpha emissions are also accompanied by a certain amount of photons.

In some cases (notably ^{223}Ra) the first decay process results in a nucleus that is itself radioactive, with a stable nucleus only being attained via a radioactive chain (i.e. a number of decay steps, each providing more particles and photons).

RANGE OF THE RADIATION COMPONENTS

Particles (alpha or beta) and photons have very different properties as regards their energy and their interaction with matter (tissue), and this is reflected in their penetration range and energy deposition. These properties are summarised in Figure 3.

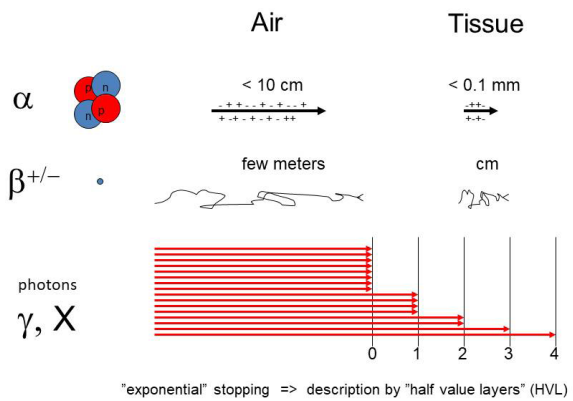

Figure 3. Alpha and beta particles have a maximum range R in a given medium, dependent on its composition and density. Photons do not have a range, but must be described using attenuation coefficients or half-value layers (HVL).

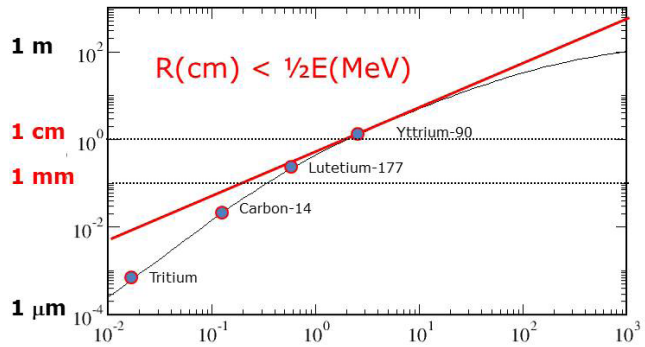

Figure 4. For protection purposes the range R of beta particles can be approximated by a simple and easily remembered inequality: R (cm) < ½ E (MeV), where E is the (maximum) energy of the particles. Adapted from NIST, e-star [3].

Alpha particles initially have a well-defined energy, most often in the range of 2–10 MeV. Being heavy as they consist of 4 elementary masses (2 protons + 2 neutrons), they produce a very dense but short ionisation track in a straight line. In tissue, even the highest energy alpha particles will not exceed a range of 0.1 mm.

Beta particles show a continuous energy spectrum with a certain maximum energy that depends on the nuclide but can vary between a few keV (^{3}H) and several MeV (^{90}Y). The average energy is typically around one third of the maximum. Beta particles are slowed down through many interactions in which they may change direction and even be "backscattered". Their range is higher than that of alpha particles, but still with an (energy-dependent) upper limit. As a reasonably safe rule of thumb, the range of beta particles in tissue (in cm) will not exceed half their maximum energy in MeV. This rule (straight line in Figure 4) greatly overestimates the range for low-energy beta particles (e.g. for ^{3}H and ^{14}C).

The interaction of photons with matter is entirely different. The ionisation is indirect, meaning that energy is first transferred to electrons through processes known as "photo-absorption", "Compton scattering" or "pair production", and then these "secondary electrons" lose their energy through direct ionisation. Unlike the particles, photons cannot be assigned a "range", but must instead be described by means of an attenuation coefficient or a half-value layer (HVL), the distance it takes to stop half of the photons. This also varies with photon energy, but in the relevant energy interval not nearly as much as the particle range does: in soft tissue, the HVL at 50 keV is about 3 cm, increasing to 10 cm at 1 MeV [2].

CHOICE OF RADIATION TYPES FOR DIAGNOSTIC IMAGING VERSUS THERAPY

In order to produce **images** (gamma camera, SPECT or PET) we need radiation to escape from the body to obtain information from the inside. From Figure 3 it is evident that no particles will be useful for this purpose. We therefore need **photons**. The higher the energy, the more photons will escape. But we also need to be able to stop the photons in our detectors, and that limits the practical window of energy to the order of 50–300 keV. The highest gamma energy in practical use for nuclear medicine imaging is that of ^{131}I (364 keV). In PET we also use the annihilation photons (511 keV) following beta-plus decay; this is feasible despite the higher energy because the image defining process is based on electronic coincidence detection and does not depend on the use of lead collimators.

External beam therapy with linear accelerators also makes use of photons with high energy. This makes it possible to reach a target deep inside the body. The radiation is only present for a short exposure window, and a given target can be covered precisely from several directions so that a high local concentration can be applied without too much detriment to surrounding healthy tissue or, in particular, to organs at risk.

In **radionuclide therapy** the situation is different. To kill cancer cells we need a high local exposure, which is provided by **alpha or beta particles** that deposit their entire kinetic energy over short distances. The strength of targeted radionuclide therapy is the ability to perform very localised irradiation of disseminated disease, e.g. directly from the surface into the interior of certain cancer cell types; the weakness lies in the often limited specificity of the uptake and the duration of uptake time, during which most radiation may hit healthy tissue rather than the target.

As mentioned above, almost no nuclides have exclusively particles in their decay scheme (^{210}Po being one notable exception that comes close). There will always be a certain amount of photons accompanying the decay. This is well known from the "oldest" therapy nuclide, ^{131}I, which emits a 364 keV photon in 82% of decays. Such a high yield of photons has consequences for imaging as well as for radiation protection. The activity of ^{131}I used in the treatment of cancers is usually more than gamma cameras are capable of handling, and the high radiation around the patient requires much attention to be given to isolation of the patient and dose considerations for caregivers and comforters. The nuclide ^{177}Lu compares favourably to ^{131}I in that the two primary gamma lines (113 keV, 6% and 208 keV, 10%) are more practical for gamma camera imaging and less demanding in terms of protection. The nuclides ^{90}Y (high-energy beta) and ^{223}Ra (alpha) cause low exposure to the surroundings, but are accordingly difficult to image. Alpha emitter ^{211}At has accompanying x-rays that allow gamma camera imaging.

RADIATION PROTECTION

ICRP

When using radionuclides we must be sure to protect not only patients, but also staff, comforters and carers, members of the public, and the environment itself. The fundamental protection rules derive from the ICRP, the International Commission on Radiological Protection, who describe themselves as an "independent, international organisation that advances for the public benefit the science of radiological protection, in particular by providing recommendations and guidance on all aspects of protection against ionising radiation". Most of their publications are available free of charge on the webpage www.icrp.org.

The most recent basic recommendations date from 2007 (ICRP Publication 103 [4]). In Europe, these recommendations formed the basis for an EU directive [5] that has subsequently been implemented in the national legislation of the different EU member states. The implementation at local level unfortunately means that some rules do differ between countries, making it difficult to provide detailed guidelines that are universally applicable. The recommendations are based on the concepts of justification, optimisation and dose limits.

All use of ionising radiation must be justified. Nuclear medicine in general is an accepted practice with great benefits to mankind, and is thus justified as such. At the next level, a given use (in casu a specific radionuclide therapy) must be documented as safe and effective. And finally, at the third level, patients must be individually evaluated and assigned for treatment.

Optimisation means that the activity administered to a patient should be sufficient to provide the wanted effect, without unnecessary risks of side effects. No dose limits exist for medical use in patients. However, in the planning of a treatment, dose constraints should be evaluated for staff, comforters and carers, and members of the public. This is a task for a medical physics or radiation protection expert.

In ICRP Publication 119 [6] the ICRP has also published extensive tables of dose factors, providing values of effective dose per unit of activity (Sv/Bq) for inhalation or ingestion of radionuclides. Most recently, ICRP Publication 140 [7] presents a thorough description of radiation protection in radionuclide therapy.

Modes of exposure

Alpha particles, due to their short range, are not of concern for external irradiation. Even in the case of skin contamination (of intact skin), the risk of receiving any harmful dose is very limited. However, if ingested, inhaled or taken up through wounds etc., the dose received can indeed be very high, as reflected in the dose factors [6]. The dose factor for ingestion of ^{223}Ra is 1*10-7 Sv/Bq (i.e. 0.1 mSv/kBq) and may, dependent on chemical form, be even higher for inhalation. The very high energy deposited per decay combined with a larger effect per energy unit deposited also means

that a therapeutic activity may consist of only a few MBq.

Beta particles likewise have no direct importance as sources of external radiation. They can, however, give rise to large extremity doses during handling, particularly in the case of skin contamination [8]. High-energy beta particles are also of concern for dose to the eye lens, and eye protection with plexiglass is recommended. With high-energy beta emitters like ^{90}Y, the risk of creating bremsstrahlung yielding photons with high penetration should also be taken into consideration. Bremsstrahlung is the source of photons in an x-ray tube where the anode is bombarded with accelerated electrons. It is always created to some extent when electrons (in casu beta particles) are stopped in a material, but the maximum energy in the spectrum equals the maximum beta energy, and the percentage of the energy that is transferred to photons increases with the product of electron energy and the atomic number (Z) of the shield material. Therefore, a nuclide like ^{90}Y should always be shielded with plastic materials (mean atomic number Z=7) as an inner shield and then optionally lead (Z=82) around this. Dose factors for beta emitters are in general much lower than for alpha, and typical therapeutic amounts of activity are in the range of GBq.

Photons (with energies above 10 keV) will penetrate into the body and irradiate internal organs, contributing to an effective dose. The exposure from an unshielded (point) source can be predicted using values of the "gamma factor" [8], which for a given nuclide provides a dose rate value (Sv/h) per activity unit (GBq) for a point source at a distance of 1 m. A dose value can be estimated by scaling for activity and time, using the inverse square distance law, and taking the shield material into account as appropriate.

Tools and shielding

The basic concepts for protection in radionuclide therapy are the same as in any other use of radioactive material: time, distance and shielding.

When planning a new treatment, practise critical steps "cold" in order to reduce handling times and make sure that the intended procedures actually work. As always, reduce the time spent near injected patients to the absolute minimum necessary. However, the dose rate around therapy patients is very dependent on the type of treatment. It is not necessarily higher than in typical diagnostic examinations such as bone scintigraphies or PET FDG scans, and sometimes much lower than that.

Keep a distance from injected patients. Although patients are not point sources, backing off even by a short distance still has a considerable effect. In general it is better (for protection as well as communication) to stand at the patient's feet if no physical interaction is required. Distance is also very important during preparation to avoid exposure of extremities, particularly fingers. Use (double) gloves and be very observant of spills. Change gloves quickly in the event of a suspected spill, since even small drops of a highly concentrated beta emitter can deliver a significant skin dose in a short time through a glove. Besides, the radiopharmaceutical may penetrate the material and cause direct skin contamination. Use tools, forceps and tongs, whenever possible.

Use appropriate syringe shields, but note that such shielding may give a false impression of safety. Handling time should still be kept to a minimum. The type of shielding will depend on the nuclide. Photons require shielding with dense, high-Z materials (lead or tungsten), but particularly with ^{90}Y it may be better to use 1 cm of perspex next to the source rather than a lead shield to avoid bremsstrahlung. For injections that should be carried out over a certain time interval, consider using an infusion pump or place the (shielded) syringe securely fastened on a table or injection board next to the patient and perform the injection in small steps, removing the hands in between.

In general it is advisable to handle the radiopharmaceutical preparations in a laminar flow bench or a glove box. This is of course particularly important in the event of a spill if the radiopharmaceutical could be airborne by any means, but even the simple routine process of removing a needle from a rubber seal can create an aerosol. Partial inhalation of this could lead to internal contamination, and with some alpha emitters this could result in a very significant internal dose.

Working with therapeutic amounts of activity always requires external personal dosimetry using appropriate measures, e.g. TLD (thermoluminescent dosimetry) or OSL (optically stimulated luminescence). Depending on the type and amount of activity handled, a system for monitoring extremity dose or dose to the eye lens may also be required. In addition to the passive dose meters, active (electronic) personal dose meters with alarms may also be useful/required, as well as area monitors. Similarly, a system may have to be set up for monitoring of internal doses in the event of inhalation or ingestion (see e.g. Appendix 1 in [9] for guidance).

REFERENCES

1. NUDAT 3.0 NNDC database. https://www.nndc.bnl.gov/nudat3/ Accessed 16. February 2022
2. NIST Table of X-ray mass attenuation coefficients. https://physics.nist.gov/PhysRefData/XrayMassCoef/tab4.html Accessed 16. February 2022
3. NIST ESTAR Stopping power and range tables of electrons. https://physics.nist.gov/PhysRefData/Star/Text/ESTAR.html Accessed 16. February 2022
4. ICRP Publication 103. The 2007 recommendations of the International Commission of Radiological Protection. Ann ICRP. 2007;37(2-4):1-335.
5. European Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom. OJ of the EU 2014. L13;57:1-73.
6. ICRP Publication 119. Compendium of dose coefficients based on ICRP Publication 60. Ann ICRP. 2012;41 Suppl. 1:1-130.
7. ICRP Publication 140: Radiological protection in therapy with radiopharmaceuticals. Ann ICRP. 2019;48(1);5-95.
8. Delacroix et al., Radionuclide And Radiation Protection Data Handbook 2002, Radiation Protection Dosimetry 2002;98(1).
9. International Atomic Energy Agency. Assesment of occupational exposure due to intake of radionuclides. Safety Standards Series No. RS-G-1.2, IAEA, Vienna (1999).

2

TIPS AND TRICKS FOR DOSIMETRY ASSESSMENT

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INTRODUCTION

The use of radionuclides for therapy is a well-established discipline for treating a wide range of benign and malignant disorders. The first clinical therapeutic use of a radioisotope was in 1936 using ^{32}P phosphate for the treatment of chronic myeloid leukaemia. ^{89}Sr was later used in 1941 for pain palliation from bone metastases, followed by ^{130}I and ^{131}I in 1942 for treatment of Graves' disease (1, 2). ^{131}I soon became the radioisotope of choice for the treatment of thyroid disease and has proven to be a safe and effective method for remnant ablation of differentiated thyroid cancer (3). Since then the use of targeted radionuclide therapy (TRT) has become more widespread and now utilises the ionising effects of over 20 different radioisotopes labelled to a variety of pharmaceuticals.

The common approach is to administer fixed levels of activity. Typical activities vary from a few megabequerel (MBq) to tens of gigabecquerel (GBq) depending on the therapy, each being delivered across a number of cycles. Other radiation therapies such as external beam radiotherapy (EBRT) and brachytherapy have shown a strong relationship between the effectiveness of a treatment and the absorbed dose (4). The absorbed dose depends on the distribution of the activity in the source and the period of irradiation. With targeted therapies these factors are determined from the biokinetics of the pharmaceutical within the body and the physical decay of the isotope. It is therefore very unlikely that any correlation of response or toxicity will ever be seen by considering the injected activity alone.

Tips and tricks *- A potentially better approach is to tailor the administered activity specifically to the patient, based on a pre-therapy study, or in some instances a previous therapeutic administration. Ideally the administered activity would be selected to deliver a sufficient radiation dose to tumour cells while avoiding toxicity in normal tissue. It is therefore necessary to measure the absorbed radiation dose to both tumour and organs at risk. Only once this is achieved can the correct activity be prescribed and the efficacy of the treatment optimised.*

Dosimetry is the discipline which aims to measure the absorbed dose D following exposure to ionising radiation. The absorbed dose is defined as:

$$D = \frac{dE}{dm},$$

where *dE* is the mean energy imparted to matter of mass *dm*, so that the unit of absorbed dose, the gray (Gy), is equivalent to 1 joule per kilogram.

During the 1960s the Medical Internal Radiation Dosimetry (MIRD) committee proposed a generalised schema for absorbed dose calculation that provides an approach to facilitate dosimetry using methods achievable in a nuclear medicine setting. The schema uses a compartmental approach of source and target regions, usually defined by the organs of the body. The mean absorbed dose D (r_T) to a target region r_T is expressed as the sum of the energy absorbed in the target region from that emitted from all potential source regions, r_S, per unit mass of the target. This can be expressed as:

$$D\,(r_T) = \sum_{r_S} \tilde{A}(r_S)\,\frac{1}{m(r_T)} \sum_i E_i\,Y_i\;\phi(r_T \leftarrow r_S, E_i)$$

where

$\tilde{A}(r_S)$ is the time-integrated activity in source region r_S

E_i is the mean energy emitted per emission of type *i*,

Y_i is the probability of an emission of type *i* per nuclear decay,

$\Phi(r_T \leftarrow r_S, E_i)$ is the fraction of energy E_i which is absorbed in target region r_T, and

$m(r_T)$ is the mass of target region r_T.

The time-integrated activity is the total number of disintegrations that take place within the source and is measured as the integral of the time varying activity function:

$$\tilde{A}(r_S) = \int_0^T A(r_S, t)\,dt.$$

Therefore, for each source region the activity must be consecutively measured from the period that the radiopharmaceutical is administered until the time it is released. In most cases the pharmaceutical kinetics can be described by an uptake phase followed by a retention phase, which in turn may be described by a number of exponential decays (see Figure 1).

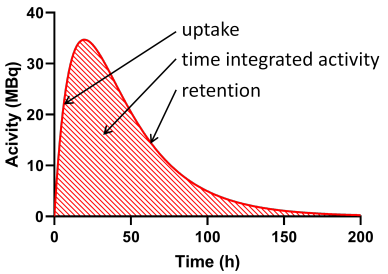

Figure 1: Typical shape of a time-activity curve showing both retention and uptake phases. The time-integrated activity is defined as the shaded area under the curve.

The other parameters in the MIRD equation rely on knowledge of the radionuclide decay data, geometry, tissue and radiation transport. They are therefore often grouped into a single parameter, the S-value, $S(r_T \leftarrow r_S)$, which represents the mean absorbed dose to target region r_T per nuclear transformation in source region r_S:

$$S(r_T \leftarrow r_S) = \frac{1}{m(r_T)} \sum_i E_i\,Y_i\;\phi(r_T \leftarrow r_S, E_i)$$

In many situations, the source and target region are the same region *r* and the MIRD equation simplifies to:

$$D\,(r) = \tilde{A}(r)\,S(r \leftarrow r)$$

With this simplification the dosimetry calculation can be approached by solving two discrete and potentially independent problems – calculating *S* and measuring *A* at different points in time. In the following we review some of the main approaches

to dosimetry calculations and highlight some of the practical considerations in implementing clinical dosimetry.

WHOLE-BODY DOSIMETRY – MIBG THERAPY

Introduction

Potentially the greatest advantage of the MIRD schema is its inherent flexibility and its application in a wide range of scenarios, from the very simple to the highly complex. One of the simplest applications of dosimetry is whole-body dosimetry. In this situation no measure of the in-vivo activity distribution is made, and the radiopharmaceutical distribution is assumed to be uniform throughout the body. Whilst this assumption may seem simplistic, whole-body dosimetry has been successfully applied in a variety of clinical applications and shown to correlate very well with measurable response and toxicity. One of the most successful is in the use of ^{131}I miBG for the treatment of paediatric neuroblastoma. A phase I/II study in the early 1990s reported a clear relationship between haemotoxicity and the absorbed dose averaged over the whole body (5). An absorbed dose threshold of 2.5 Gy was reported, beyond which eighty per cent of patients presented with grade 3 or 4 haemotoxicity. This methodology led to further studies over the coming years, demonstrating that treatments could be optimised and safely delivered when treating to a whole-body absorbed dose (6-8), and is today the subject of a large multicentre European clinical trial (https://clinicaltrials.gov/ct2/show/NCT03165292).

Equipment

As activity is assumed to be uniformly distributed, it is unnecessary to perform a complex calculation to ascertain a value for the *S*-value ; rather it is sufficient to use a pre- calculated value based on a model and scale according to patient mass. *S*-values are available from a number of sources including MIRD, RADAR and ICRP.

$$S_{patient} = S_{model} \frac{m_{model}}{m_{patient}}$$

Tips and tricks – *There are many models available with published S-values, including different ages and genders. Try to select a model that has a similar mass to your patient as this will reduce the uncertainty in the mass scaling correction. This is particularly important when considering a paediatric population.*

The only real challenge for whole-body dosimetry is therefore the estimation of time- integrated activity. To determine this, the activity remaining within the patient should be measured periodically post administration. There is no requirement for imaging, and the most straightforward approach is to measure the activity using a simple radiation detector such as a Geiger-Muller counter, sodium iodide gamma probe or dose-rate meter. This has the added advantage that a large number of data points may be acquired without imposition on a busy nuclear medicine department. Some systems can be automated or connected to PCs for easy implementation, which allows any member of staff, including ward nurses or carers, to perform these measurements.

Tips and tricks – *A monitor to measure low activities of ^{223}Ra will not necessarily be suitable for measuring high activities of ^{131}I. Also ensure that the detector provides a sufficiently precise output for the expected range. Analogue displays will cover a wide range but can sometimes be difficult to read. A digital output is easier to read provided the output does not fluctuate. However, this can be overcome with a system that can average or integrate over a period of time.*

Method

The approach recommended is to monitor the count rate from the patient at a good distance from the patient (≥2 metres is ideal). Measurements taken at too close a distance are very sensitive to positional discrepancies and will affect accuracy. Ceiling-mounted counters are useful as they enable the patient to lie down in a reproducible position, as described by Chittenden et al. (9).

The steps required to perform accurate whole-body dosimetry are as follows:

- Before treatment and prior to any radioactive sources are taken into the room record a background reading from the detector.
- Immediately after administration perform a baseline measurement from the patient. If possible take anterior and posterior measurements.
- Subsequent readings should ideally be taken as often as possible, depending on the biological half-life.
- Ensure the patient empties their bladder prior to any measurement (except the first!).
- As a general rule, a minimum of 3 measurements are required to characterise an exponential function. However, the more measurements taken, the lower the uncertainty in the dose calculation. Taking 4 to 5 measurements per day is not unfeasible.
- The timing of each measurement should also be chosen to cover a period of 3 biological half-lives. For mIBG this can usually be between 5 and 7 days, whilst the patient is in hospital.

Tips and tricks – *If a ceiling monitor is not available, position patients using a spacer, against a wall or with feet positions drawn on the floor, as this can help improve reproducibility. The first measurement is a baseline, and is used with the known administered activity to scale all subsequent measurements. It is therefore vital that this acquisition is made carefully, precisely and before the patient has been to the toilet!*

BLOOD-BASED DOSIMETRY

Introduction

Whole-body dosimetry is very useful in predicting haemotoxicity and works particularly well when the disease burden is very low. This is because it assumes the uptake in disease and organs of the body is negligible compared to that circulating within the blood or extracellular space. For patients with bulky disease or where significant uptake is observed in large organs such as the liver, more direct measurements of bone marrow dose are required.

Bone marrow is the absorbed dose-limiting organ in radioimmunotherapies such as ibritumomab tiuxetan (Zevalin), tositumomab (Bexxar) and more recently lutetium (^{177}Lu) lilotomab satetraxetan (Betalutin). Estimates of bone-marrow absorbed dose from blood measurements assume that the radiolabelled antibody is distributed within the blood and the extracellular space of the red marrow and that it does not bind to any marrow or bone component (10). When this is the case, a ratio conversion between the blood time-activity curve and that of the marrow can be used and the blood kinetics assumed to represent red marrow kinetics (11). The most frequent radionuclides for which blood-based dosimetry is performed are ^{131}I and ^{177}Lu.

Equipment

A well-type NaI(Tl) detector, known as a gamma counter, is commonly used for the measurement of activity in blood samples. For departments that carry out glomerular filtration rate (GFR) measurements this is a common piece of equipment, and the staff who operate the machine can also measure samples for dosimetry purposes. Gamma counters are often well characterised for standard radionuclides, with inbuilt geometry, sensitivity and dead time corrections. However, it is important to validate these corrections when applying them for therapeutic isotopes such as ^{90}Y, ^{177}Lu and ^{131}I, paying particular attention to the activity concentrations expected during the therapy. In most cases, it is recommended to count a standard with a known amount of activity and of the same volume as the blood samples. The results for the standard can then be applied to convert the count rate of the blood samples into activity.

Tips and tricks – *To avoid multiple dilutions and an excess of aqueous waste, prepare the standard days (or weeks) in advance if possible and let it decay to the required activity for measuring with the samples. This allows the standard to be measured directly in a dose calibrator and reduces the likelihood of mistakes during dilution. Also ensure that the activity in the standard is of a similar order of magnitude to that in the samples.*

The acquisition time for measuring the activity should ideally be chosen so that the acquired background-corrected number of counts is higher than 10k, so that the statistical inaccuracy is less than 1%.

Care should be taken when measuring therapeutic blood samples, so that their presence does not interfere with any other measurements being made on the gamma counter. Many well-type counters have insufficient shielding for high activities of ^{131}I, and the presence of such samples on the rack can inadvertently increase the background measurements of any ^{99m}Tc samples.

Tips and tricks – *Because of the long half-life of most therapeutic radiopharmaceuticals it is often possible to delay sample counting to a more convenient time so as not to disrupt a busy department that performs GFR tests.*

Method

Blood samples should be drawn from the arm opposite the injection site to avoid risk of contamination. The timing and total number of withdrawals will depend on the pharmacokinetics (10). Cannulation may be less uncomfortable for the patient when multiple withdrawals are planned, and will help reduce exposure for the operator. Elimination from the blood is often very rapid over the first few hours and increased sampling may be necessary on the first day, e.g. 5 minutes, 30 minutes, 1 hour, 2 hours and 4 hours. After this period, sampling may be reduced to daily or bi-daily extractions, depending on the requirements of the study.

For new radiopharmaceuticals the absence of specific uptake in any component of the blood should first be ascertained. The activity concentration in the blood and plasma should therefore be measured, which can be achieved by separating the blood cells from the plasma by centrifugation. It is vital that both activity and sample volume are measured accurately. Volume can be determined either by careful weighing of empty and full specimen tubes or by pipetting an exact pre-set amount.

The blood-based method assumes that the activity concentration in the extracellular space within the marrow equals the activity concentration in the plasma. The activity concentration in the bone marrow is thus calculated by multiplying the plasma activity concentration by a red marrow extracellular fluid fraction, assumed to be equal to 0.19 (12):

$$D_{marrow} = [\tilde{A}_{plasma}] \cdot RMECFF \cdot m_{marrow} \cdot S_{marrow \leftarrow marrow}$$

Absorbed dose is then determined using:

where [$\tilde{A}plasma$] is the time-integrated activity concentration, m_{marrow} is the marrow mass and $S_{(marrow \leftarrow marrow)}$ is the marrow S-value for activity contained within the extracellular space of the marrow.

Tips and tricks – *Because we are working in units of concentration, there is an additional mass term in the equation for the absorbed dose. This will cancel out the mass term in the*

S-value and we can therefore use phantom data for these values without having to determine patient-specific values.

If there is no specific uptake in blood cells, then this should also be accounted for. In this case the blood sample should be measured without separation of the plasma and the activity concentration in the bone marrow determined using the red marrow-to-blood activity concentration ratio (RMBLR):

$$\frac{[A_{marrow}]}{[A_{blood}]} = \text{RMBLR}$$

such that

$$D_{marrow} = [\tilde{A}_{blood}] \cdot \text{RMBLR} \cdot m_{marrow} \cdot S_{marrow \leftarrow marrow}$$

For radiolabelled monoclonal antibodies, a RMBLR value of 0.36 was recommended (12), whereas for the case of ^{131}I NaI and ^{177}Lu peptides RMBLR =1.

THYROID UPTAKE DOSIMETRY

Introduction

In patients suffering from hyperthyroidism, the thyroid gland produces and secretes excessive amounts of the thyroid hormones. The most common causes of hyperthyroidism are Graves' disease, multi-nodular goitre and autonomous adenoma.

The options for treating hyperthyroidism include: the administration of anti-thyroid drugs which block the formation of thyroid hormones; the administration of radioiodine; and surgery (13). The basis for the treatment with radioiodine is that the thyroid takes up iodine from blood, concentrating it in thyroid follicular cells against an electrochemical gradient over the basal membrane of these cells via the protein NIS (14) to produce the thyroid hormones T3 and T4.

The objective of the treatment with radioiodine is that patient becomes euthyroid, but sometimes the patient becomes hypothyroid or the treatment has to be repeated because the patient remains hyperthyroid (15). In these treatments, a fixed activity or a calculated activity of ^{131}I-NaI is administered in order to deliver a prescribed absorbed dose to the thyroid gland. In the latter approach, the activity will depend on the mass of the gland, its ability to accumulate ^{131}I-NaI and the effective half-life of ^{131}I-NaI in the gland (13). Thyroid uptake dosimetry after administering a tracer activity of ^{131}I-NaI (a few MBq) allows determination of the three parameters and thus the activity to administer for the treatment (16).

Equipment

Thyroid uptake dosimetry can be performed by means of measurements of radioiodine uptake with a probe or gamma camera (17-19) (Figure 2). Unlike gamma cameras, thyroid uptake probes are only counting devices and no positioning information or images are produced.

The thyroid uptake probe consists of a sodium iodide crystal. The crystal is usually 5 cm thick and has a diameter of 5 cm fitted with a cylindrical lead collimator approximately 2 cm thick. The hole of the collimator will define a circular field of view in the patient's neck with a diameter of about 20 cm (18, 20). The electronics of the probe consist of a photomultiplier tube, preamplifier, amplifier and pulse analyser. The pulse analyser enables an energy spectrum to be measured, ensuring that only the primary ^{131}I emissions are recorded.

Alternatively, a gamma camera can be used to acquire thyroid images to quantify the radioiodine uptake in the thyroid. The detection of the ^{131}I photons in the gamma camera is also performed with a non-radioactive thallium-activated sodium iodide crystal. Most gamma cameras have a crystal thickness of 9.5 mm, which aims to optimise detection of the photons of the ^{99m}Tc photopeak. Detection of the ^{131}I photons of the photopeak would be improved by using a crystal 15.9 mm thick. A high-energy general purpose parallel-hole collimator is recommended (20). The electronics of the gamma camera are similar to those of the probe, but with a higher number of devices (21). Gamma cameras can also be used to image the thyroid after ^{99m}Tc-pertechnetate administration in order to determine the thyroid volume and thus the thyroid mass (22). An alternative to determine the thyroid volume is the use of ultrasound imaging. However, for the latter technique the measured volume may not correspond to the metabolically active thyroid tissue, and the ultrasound images should be compared with the ^{99m}Tc-pertechnetate images (20).

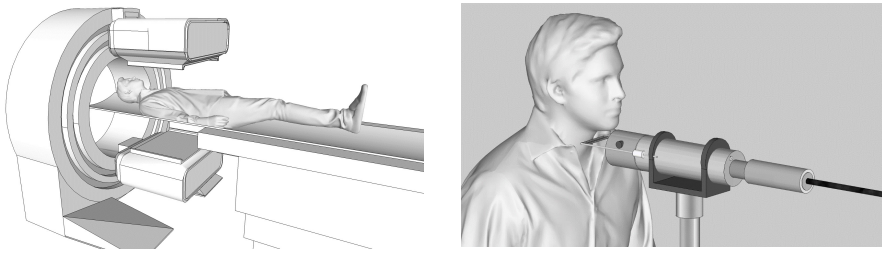

Figure 2: Thyroid uptake measurements can be acquired using either a gamma camera (left) or a dedicated thyroid probe (right).

The use of a phantom mimicking a thyroid in a neck is usually necessary to determine the activity in the thyroid from the count rate obtained in patient measurements (with the thyroid uptake probe or the gamma camera) (23).

Methods

The aim of thyroid uptake dosimetry is to determine the activity to administer to deliver a given absorbed dose. In patients with Graves' disease, the absorbed dose to achieve a euthyroid status is 150 Gy, but if the aim is to achieve complete ablation an absorbed dose in the range 200–300 Gy is recommended. In either toxic or non-toxic multinodular goitre, absorbed doses ranging between 100 and 150 Gy are recommended. Lastly, in patients with autonomous adenoma the recommended absorbed dose is in the range of 300–400 Gy (24).

The activity A_a necessary to deliver an absorbed dose D to a thyroid of mass *M* can be written as (20):

$$A_a = \frac{1}{\bar{E}} \frac{M \cdot D}{\int_0^\infty RIU(t)dt}$$

$\bar{E}$ represents the mean energy deposited in the thyroid per decay of ^{131}I. It has a value of 2.808 Gy g / MBq d for a thyroid with a mass of 20 g, but can be used for thyroid masses ≤90 g with an introduced error ≤ 5%.

RIU(t) is the radioiodine uptake, i.e. the fraction of the administered activity taken up by the thyroid. The curve for *RIU(t)* can be obtained from the patient measurements at different acquisition times. For each time point, *RIU(t)* can be obtained as:

$$RIU(t) = \frac{CR_T(t)}{CR_P}$$

where $CR_T(t)$ is the net count rate in the thyroid at time t and CR_P is the net count rate measured for the tracer activity in the neck phantom before administration. The activity source should be placed in the phantom at a depth of about 2–2.5 cm, which is approximately the depth of the thyroid in the neck.

Tips and tricks – *Count rates can be determined using the thyroid uptake probe or the gamma camera. In both cases, all the measurements should be reproducible and performed at the same source-to-detector distance. For the probe a small spacer can be fitted to the front of the detector to maintain accurate positioning.*

The EANM guidelines on dosimetry prior to radioiodine therapy of benign thyroid disease (20) summarise the different methods to determine A_a from a different number of time acquisitions. In this chapter, as a compromise between the use of a high number of time points (three or more) and the use of only one time point, the methodology described for two acquisitions is shown. The first time point t_1 has to be acquired at 1 or 2 days post administration and the second time point t_2 at 4 to 8 days post administration, with a time interval between the two time points > 3 days. The activity A_a is then given by:

$$A_a[MBq] = \frac{0.714}{\bar{E}} \frac{M[g] \cdot D[Gy]}{RIU(t_1) \cdot 2^{t_2[d]/T_{eff}[d]} \cdot T_{eff}[d]}$$

where

$$T_{eff}[d] = \frac{(t_2[d] - t_1[d]) \cdot \ln(2)}{\ln(RIU(t_1)) - \ln(RIU(t_2))}$$

The volume can be obtained from ultrasound imaging by approximating each thyroid lobe or the autonomous nodule to an ellipsoid with volume π·A·B·C/6, A, B and C being the long axes of the ellipsoid. As mentioned above, the volume can also be obtained by means of scintigraphy with ^{99m}Tc-pertechnetate. The more accurate way would be to delineate the metabolically active thyroid volume using SPECT/CT imaging. However, planar imaging is faster than SPECT imaging and can likewise be used. The volume *V* (in cm^3) as a function of the area of the AP image of the thyroid *S* (in cm^2) is empirically estimated as (25):

$$V = (0.33 \pm 0.06) \cdot S^{3/2}$$

Tips and tricks – *For autonomous nodules with a near spherical shape the volume can be estimated from the formula for the volume of a sphere, obtaining the sphere diameter from the image of the nodule. Once the volume is determined, the mass M can be obtained by multiplying the volume by thyroid mass density (1.05 g/cm^3).*

SPECT-BASED DOSIMETRY

Introduction

In treatments with radiopharmaceuticals, SPECT imaging facilitates the three-dimensional activity distribution within the body to be determined. Among the most common uses of SPECT for dosimetry is renal dosimetry in treatments with [^{177}Lu] Lu-DOTATATE (Lutathera), as kidneys are generally considered the absorbed dose- limiting organs due to uptake in proximal tubular cells (26). Nephrotoxicity can manifest up to one year after therapy. Dosimetry-guided therapies have been undertaken (27) applying renal absorbed dose constraints derived from EBRT. Treatments have been applied that tailor the number of therapy cycles or the administered activity per cycle to the renal absorbed dose, the intent being to achieve the maximum possible absorbed dose to tumours while respecting constraints for the kidneys. Absorbed dose constraints of 27 Gy have been proposed, with up to 40 Gy for patients without risk factors (28).

Equipment

Kidney dosimetry is performed using image-based activity quantification, for which ^{177}Lu is one of the less challenging radiotherapeutic isotopes. Methods of quantitative SPECT/CT are summarised in MIRD pamphlet 23 (29), with specific reference made to ^{177}Lu SPECT in the EANM/MIRD guideline (30). More detailed guidance

for ^{177}Lu-based dosimetry is given in the EANM guidelines (31).

Tips and tricks – *Although ^{177}Lu has two photopeaks (113 keV and 208 keV), commonly only the 208 keV photopeak-imaged with a medium-energy collimator- is used for quantitative imaging as the image obtained with this peak contains considerably less scatter and septal penetration than that obtained with the 113 keV window.*

Prior to use in a dosimetry study, the gamma camera should be calibrated and characterised such that the count rate measured during a patient SPECT acquisition can be converted to activity. This will usually involve the determination of a calibration factor by imaging a source of known activity within a reference geometry such as a large uniform cylinder. The SPECT calibration factor Q is then defined as the reconstructed count rate per unit activity in the phantom.

Tips and tricks – *Some commercial systems now perform quantitative reconstruction algorithms outputting images with voxel units of activity concentration. Verification should be carried out whichever system of calibration is used, in a similar way to regular SUV validation in PET/CT.*

Even with the best reconstruction and resolution recovery technique system, calibration does not fully characterise the activity due to "spill out" of counts resulting from partial volume effects. Assessment of and subsequent corrections for partial volume effects (PVE) are therefore done by means of further phantom studies, using a set of inserts covering a range of clinically relevant volumes. The recovery coefficient R(v) of an insert of volume v is calculated according to

$$R(v) = \frac{C_{\mathrm{R}}(v)}{Q_{sp} \cdot A_{\mathrm{R}}(v)},$$

where $C_R(v)$ is the count rate measured in a VOI of volume v, and $A_R(v)$ is the ^{177}Lu activity contained in the insert at the time of measurement. A value for $R(v)$ should then be selected appropriate to the mass of the patient kidney.

Tips and tricks – *If using quantitative reconstruction, equation 9 can be simplified and expressed as the ratio of the mean measured activity concentration to the prepared insert activity concentration.*

It is recommended to use the same SPECT/CT system for the entirety of the dosimetry study. Some quantitative parameters, such as recovery coefficients, have shown to be very similar across gamma cameras, particularly for the same manufacturer and model. However, this does depend on the reconstructions used, so be wary of using published data and always obtain your own measurements where possible.

Method

Image acquisitions made using SPECT/CT should be centred over the kidneys. A single SPECT FOV should be sufficient to include the liver and spleen as well, although additional FOVs may be required if absorbed doses to distant lesions are also of interest.

Tips and tricks – *If SPECT acquisitions are too time demanding (particularly if multiple FOV need to be covered) an alternative approach is to acquire SPECT/CT acquisition at one time point complemented by planar imaging – see EANM guidelines for more details.*

CT-based corrections for attenuation, scatter and geometric collimator-response modelling are recommended. The time per projection should be chosen locally and may need to be increased at later time points. Typical times are in the order of 30 s and 60 s. Between 60 and 120 angles are generally recommended.

For reconstruction, the number of iterations and subsets is generally higher than may be necessary for diagnostic interpretation. The reconstruction protocol for activity quantification should be optimised using phantom data and reassessed after the first few patients have been scanned.

At the first therapy cycle, a minimum of three acquisitions between 24 h and 168 h post administration is suggested. In the majority of patients, the biodistribution is characterised by a fast initial plasma phase commencing at infusion and lasting a few hours after administration, followed by exponential washout (32) (see Figure 3).

Tips and tricks – *Do not image too early. If you do, you may catch the initial perfusion plasma washout, which can adversely affect the estimate of the time-integrated activity. A single exponential function is generally acceptable to characterise the washout phase, which is the phase that contributes the most significant proportion of absorbed dose to the kidney.*

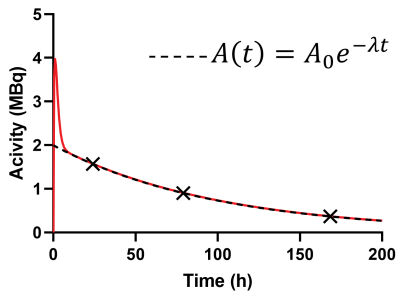

Figure 3. A typical time-activity curve for the kidneys, which can be approximated as a single exponential function.

The kidney should be outlined on the SPECT/CT images, using the CT to aid anatomical definition. The VOI should encompass the entire cortex and medulla, but exclude the renal pelvis. It is often easier to outline on the sagittal or coronal images rather than using the axial images.

Tips and tricks – *Manually outlining on CT can be tedious and time consuming. If the SPECT images are not too noisy a threshold outline can be drawn directly on the SPECT data set. The threshold can then be adjusted until the outline matches the anatomical boundary of the kidney as shown on the fused SPECT/CT image.*

Tips and tricks – *The effective half-life has been shown to be fairly consistent between cycles, provided there are no clinical reasons to expect changes in the patient's renal function. It is therefore possible to use the half-life from cycle 1 in the dosimetry calculations for subsequent cycles and thus reduce the burden of multiple scans.*

Once the kidneys have been outlined on each SPECT scan, the count rate or activity information can be extracted and the time-activity curve generated. A function should be fitted to the data that best represent the observed data. For a single exponential function, the time-integrated activity can be expressed as:

$$\tilde{A} = \frac{A_0}{\lambda}$$

where A_0 is the activity within the kidney at time t=0, extrapolated from the fitted function, and λ is the effective decay constant determined from the fitted function (Figure 3).

A patient-specific quantity of the *S*-value for kidneys can be determined by scaling a published model S-value by the volume determined by the outline and a tissue density ρ=1.05 g/cm³ giving

$$S_{patient} = S_{model} \frac{m_{model}}{v_{patient} \cdot \rho}$$

Staff

The Basic Safety Standard (33) states that the medical physics expert should take responsibility for dosimetry, including physical measurements for evaluation of absorbed doses delivered to the patient. However, for some steps of the process to determine the absorbed dose, such as whole-body retention measurements or activity measurements in the gamma counter, the workload can be split across a range of staffing groups including technologists. The absorbed dose calculation is also fairly easy to implement once all the measurements have been obtained, and can be performed using a simple spreadsheet. However, if using absorbed doses based on a pre-therapy study or a previous therapeutic administration (e.g. whole-body absorbed doses in neuroblastoma treatments) to determine an administered activity, it is especially important to have a double-check and quality assurance system in place.

REFERENCES

1. Thomas SR. Options for radionuclide therapy: From fixed activity to patient-specific treatment planning. Cancer Biother Radio. 2002;17(1):71-82.
2. Sawin CT, Becker DV. Radioiodine and the treatment of hyperthyroidism: the early history. Thyroid. 1997;7(2):163-76.
3. Brans B, Bodei L, Giammarile F, Linden O, Luster M, Oyen WJG, et al. Clinical radionuclide therapy dosimetry: the quest for the "Holy Gray". Eur J Nucl Med Mol I. 2007;34(5):772-86.
4. Bentzen SM. Dose-response relationships in radiotherapy. In: Steel GG, editor. Basic Clinical Radiobiology. New York: Oxford University Press; 1997.
5. Lashford LS, Lewis IJ, Fielding SL, Flower MA, Meller S, Kemshead JT, et al. Phase I/Ii Study of I-131 Metaiodobenzylguanidine in Chemoresistant Neuroblastoma - a United-Kingdom Childrens Cancer Study-Group Investigation. J Clin Oncol. 1992;10(12):1889-96.
6. Genolla J, Rodriguez T, Minguez P, Lopez-Almaraz R, Llorens V, Echebarria A. Dosimetry-based high-activity therapy with I-131-metaiodobenzylguanidine (I-131-mIBG) and topotecan for the treatment of high-risk refractory neuroblastoma. Eur J Nucl Med Mol I. 2019;46(7):1567-75.
7. Buckley SE, Chittenden SJ, Saran FH, Meller ST, Flux GD. Whole-Body Dosimetry for Individualized Treatment Planning of I-131-MIBG Radionuclide Therapy for Neuroblastoma. Journal of Nuclear Medicine. 2009;50(9):1518-24.
8. Gaze MN, Chang YC, Flux GD, Mairs RJ, Saran FH, Meller ST. Feasibility of dosimetry-based high-dose (131)I-meta-iodobenzylguanidine with topotecan as a radiosensitizer in children with metastatic neuroblastoma. Cancer Biother Radio. 2005;20(2):195-9.
9. Chittenden SJ, Pratt BE, Pomeroy K, Black P, Long C, Smith N, et al. Optimization of equipment and methodology for whole-body activity retention measurements in children undergoing targeted radionuclide therapy. Cancer Biother Radio. 2007;22(2):243-9.
10. Hindorf C, Glatting G, Chiesa C, Linden O, Flux G. EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry. Eur J Nucl Med Mol I. 2010;37(6):1238-50.
11. Sgouros G. Bone-Marrow Dosimetry for Radioimmunotherapy - Theoretical Derivation of the Red Marrow to Blood Activity Concentration Ratio. J Nucl Med. 1993;34(5):P160-P.
12. Sgouros G. Bone-Marrow Dosimetry for Radioimmunotherapy - Theoretical Considerations. J Nucl Med. 1993;34(4):689-94.
13. Nyström E, Berg GEB, Jansson SKG, Tørring O, Valdemarsson SV. Thyroid Disease in Adults. Berlin Heidelberg: Springer-Verlag; 2011.
14. Spitzweg C, Harrington KJ, Pinke LA, Vile RG, Morris JC. Clinical review 132: The sodium iodide symporter and its potential role in cancer therapy. J Clin Endocrinol Metab. 2001;86(7):3327-35.
15. McDougall IR. Management of Thyroid Cancer and Related Nodular Disease. London: Springer Verlag; 2006.
16. Hänscheid H, Lassmann M, Reiners C. Dosimetry prior to I-131-therapy of benign thyroid disease. Z Med Phys. 2011;21(4):250-7.
17. Robeson WR, Ellwood JE, Castronuovo JJ, Margouleff D. A new method to measure thyroid uptake with a gamma camera without routine use of a standard source. Clin Nucl Med. 2002;27(5):324-9.
18. Menon BK, Rao RD, Abhyankar A, Rajan MG, Basu S. Comparative evaluation of 24-hour thyroid 131I uptake between γ camera-based method using medium-energy collimator and standard uptake probe-based method. J Nucl Med Technol. 2014;42(3):194-7.
19. Menon BK, Uday AS, Singh BN. Gamma camera based method for. J Nucl Med Technol. 2017.
20. Hanscheid H, Canzi C, Eschner W, Flux G, Luster M, Strigari L, et al. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases. Eur J Nucl Med Mol Imaging. 2013;40(7):1126-34.
21. Zimmerman RE. Gamma cameras--state of the art. Med Instrum. 1979;13(3):161-4.
22. Spencer RP, Scholl RJ, Erbay N. Tc-99m pertechnetate thyroid images in hyperthyroidism. Size, distribution, and presence of a pyramidal lobe. Clin Nucl Med. 1997;22(8):519-22.
23. Menon BK, Basu S. Relevance of a thyroid phantom in estimating thyroid radioiodine uptake values using a gamma camera. Nucl Med Commun. 2015;36(9):962-4.

24. Stokkel MP, Handkiewicz Junak D, Lassmann M, Dietlein M, Luster M. EANM procedure guidelines for therapy of benign thyroid disease. Eur J Nucl Med Mol Imaging. 2010;37(11):2218-28.
25. HIMANKA E, LARSSON LG. Estimation of thyroid volume; an anatomic study of the correlation between the frontal silhouette and the volume of the gland. Acta radiol. 1955;43(2):125-31.
26. Vegt E, de Jong M, Wetzels JF, Masereeuw R, Melis M, Oyen WJ, et al. Renal toxicity of radiolabeled peptides and antibody fragments: mechanisms, impact on radionuclide therapy, and strategies for prevention. J Nucl Med. 2010;51(7):1049-58.
27. Garske-Roman U, Sandstrom M, Fross Baron K, Lundin L, Hellman P, Welin S, et al. Prospective observational study of (^{177})Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. Eur J Nucl Med Mol Imaging. 2018;45(6):970-88.
28. Bodei L, Cremonesi M, Grana C, Rocca P, Bartolomei M, Chinol M, et al. Receptor radionuclide therapy with 90Y-[DOTA]0-Tyr3-octreotide ([90Y]Y-DOTATOC) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2004;31(7):1038-46.
29. Dewaraja YK, Frey EC, Sgouros G, Brill AB, Roberson P, Zanzonico PB, et al. MIRD pamphlet No. 23: quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy. J Nucl Med.53(8):1310-25.
30. Ljungberg M, Celler A, Konijnenberg MW, Eckerman KF, Dewaraja YK, Sjogreen-Gleisner K, et al. MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative ^{177}Lu SPECT Applied for Dosimetry of Radiopharmaceutical Therapy. J Nucl Med. 2016;57(1):151-62.
31. Gleisner KS, Chouin N, Gabina PM, Cicone F, Gnesin S, Stokke C, et al. EANM Dosimetry Committee recommendations for dosimetry of ^{177}Lu-labelled somatostatin-receptor- and PSMA-targeting ligands. Eur J Nucl Med Mol I. 2020;in press.
32. Delker A, Ilhan H, Zach C, Brosch J, Gildehaus FJ, Lehner S, et al. The Influence of Early Measurements Onto the Estimated Kidney Dose in [Lu-^{177}][DOTA(0),Tyr(3)]Octreotate Peptide Receptor Radiotherapy of Neuroendocrine Tumors. Mol Imaging Biol. 2015;17(5):726-34.
33. Council Directive 2013/59/Euratom. . Official Journal of the European Union. 2013;56.

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CALIBRATION OF INSTRUMENTATION

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INTRODUCTION

According to the International Vocabulary of Metrology (VIM) of the International Bureau of Weights and Measures (BIPM), metrological traceability is a property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty (1). Calibration is an operation under specified conditions that, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication. Both steps together facilitate in a practical way the demonstration of metrological traceability of measurement results (measured values and associated measurement uncertainty) obtained when using the measuring instrument after it has been calibrated. Therefore, ensuring robust calibration of all instrumentation is the first key step towards traceability of measurements in nuclear medicine (2). Calibration should not be confused with verification or adjustment. Calibration is a prerequisite for verification, which provides confirmation that specified requirements (often maximum permissible errors) are met. Calibration is also a prerequisite for adjustment, which is the set of operations carried out on a measuring system such that the system provides prescribed indications corresponding to given values of quantities to be measured, typically obtained from measurement standards. A calibration may be expressed by a statement, calibration function, calibration diagram, calibration curve, or calibration table. In some cases, it may consist of an additive or multiplicative correction of the indication with associated measurement uncertainty.

CALIBRATION OF RADIONUCLIDE CALIBRATORS

Radionuclide calibrators are commonly used in nuclear medicine to measure the activity administered to a patient for diagnostic and therapeutic procedures. Radionuclide calibrators are also used to measure activity dispensed to phantoms for quality control (QC) processes, for calibration of imaging systems such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) and for calibration of well counters, in both the clinical and pre-clinical settings.

Recent advances in nuclear medicine diagnostic and therapeutic procedures have introduced novel radionuclides to clinical and pre-clinical practice. Measurement challenges can arise if instruments have not been previously calibrated for these radionuclides.

The calibration of radionuclide calibrators can be divided into three categories: initial calibration (provided by the manufacturer); subsidiary calibrations, i.e. calibration of the radionuclide calibrator for additional geometries and volumes; and re-calibration, which is recommended by the manufacturers to maintain a reliable system (3). In this guideline, only subsidiary calibrations for additional geometries and novel radionuclides will be discussed in more detail. The principles of operation and quality control (QC) and quality assurance (QA) programs are not described in this document (3-6).

Measurement geometry

Activity calibration factors or calibration coefficients correspond to the conversion between the ionisation chamber measurement current to an activity, these are usually in pA MBq^{-1}. In commercially available radionuclide calibrators, calibration factors are applied within the system and an activity is displayed – usually this is performed by selecting a button or dial setting, therefore these are commonly called dial settings or calibration settings.

Manufacturers of commercially available radionuclide calibrators provide calibration factors/dial settings for common radionuclides, for a specific measurement geometry and one position within the radionuclide calibrator (3). The dial settings provided by the manufacturer are usually determined for a limited number of traceable standards for a master chamber. For the radionuclides that have not been measured, a response-energy curve is available to estimate dial settings using information on the decay schemes (3). The use of the response-energy curve increases the uncertainty associated with the estimated dial settings and does not take account of differences in the manufacturing processes of the radionuclide calibrators.

It is important to note that calibration factors/dial settings from the manufacturer are for a specific measurement geometry (one container type, one container volume) and one position within the radionuclide calibrator (3). Radiopharmaceuticals, medical devices and radionuclides are supplied in a variety of vials and dispensed to phantoms and injected to the patient using a variety of syringe sizes and brands, therefore there might be a need to calibrate the radionuclide calibrator for a specific geometry or if a new radionuclide is being measured. Calibrations performed in addition to those provided by the manufacturer are commonly called subsidiary calibrations, and these are usually associated with calibration for additional geometries (e.g. for a different container, different volumes of solution) (3-5).

To estimate dial settings for novel radionuclides or additional geometries, a series of factors should be taken in account. Most geometries can be used for calibration, but the most important factor is that the dial setting is for a useful geometry, i.e. the calibration should be performed for the geometry that will be used for measurements.

Differences in the radionuclide calibrator response are associated with differences in the source measurement geometry. The impact on the radionuclide calibrator response associated with the wall thickness of the container, type of container (with special emphasis on the differences between glass vials and plastic syringes), volume of solution in the container, position of the source at the time of measurement and adsorption of solution to the walls of the container has previously been described in some detail in other publications (3, 4). Recent work has also shown the impact of solution density on the radionuclide calibrator for ^{90}Y (7). Difficulties in measuring pure beta emitters such as ^{90}Y have also been highlighted (4). The impact of the presence of radionuclide impurities and radionuclide equilibrium at the time of measurement have also been discussed previously (4). These aspects will not be included in this guideline, but should be taken into consideration when proceeding with the calibration of radionuclide calibrators for additional geometries and/or novel radionuclides.

The calibration of radionuclide calibrators for new isotopes and geometries can be challenging, and different methodologies can be used to ensure field instruments are calibrated and traceable to standards. National legislation should always be followed to ensure compliance when choosing a method to calibrate a radionuclide calibrator, and national legislation must also be consulted before proceeding with adjustment of dial settings or deriving dial settings for new radionuclides.

In the series report IAEA TR454 (5), the equipment necessary for the calibration of a radionuclide calibrator is briefly described and includes: balance with an accuracy of at least ± 0.1 %; calibrated volumetric dispensers with an accuracy of at least 1 %; glass vials and plastic syringes with well-known wall thickness and chemical composition; calibrated clock and long-lived radioactive check sources for quality control (5). Higher accuracy can be achieved when dispensing gravimetrically; however, volumetric dispensing is acceptable when calibrating a field instrument (5).

Subsidiary calibration – additional geometries

As previously described, the radionuclide calibrator response is dependent on the type of container used, therefore dial settings and respective uncertainties should be estimated for different geometries used for measurement. If a dial setting previously determined and traceable to primary standards is available for the radionuclide of interest, dial settings and respective uncertainties can be estimated for additional geometries, e.g. for syringes or other vial types.

The process for performing subsidiary calibrations is briefly described in the GPG93 (4) and includes measurement of solution in a standard vial (i.e. geometry for which there is an existing dial setting) and transfer of a known amount of solution to the new geometry and respective measurement. The total activity in the new geometry can be calculated using radionuclide calibrator measurements (measurement of standard vial full and empty, measurement of new geometry full and empty) or gravimetrically if a balance is available (3, 4). To ensure that the dial setting estimated for the new geometry is traceable to national standards, the user must know activity per unit mass (or activity concentration) of the solution or the total mass or volume in the new geometry source along with the total activity (5).

Novel radionuclides

Determination of dial settings and respective uncertainties for novel radionuclides relies on the measurement of a radioactive sample in a field instrument (the system being calibrated) and a system previously calibrated for the same radionuclide. There should be evidence that the systems used for the calibration are traceable for the radionuclide being measured.

Use a secondary standard radionuclide calibrator (SSRC), secondary standard ionisation chamber (SSIC) or reference radionuclide calibrator (RRC) – SSRC and SSIC correspond to radionuclide calibrators/ionisation chambers that have been directly calibrated against national standards (3). SSRC are available commercially and usually have a link to a national measurement institute, therefore when a new primary standard becomes available, it is transferred to SSRC and SSRI. RRC correspond to radionuclide calibrators that have been calibrated using traceable sources that were calibrated using a secondary standard (3). It has been suggested that the tolerances for an RRC should be stricter than those for a field instrument (4).

Send a sample to a national measurement institute (NMI) or designated institute (DI) (4) – the NMI and DI must be able to demonstrate traceability for the radionuclide being measured. In this method a radioactive source is prepared in a clinical suitable measurement geometry and measured on a radionuclide calibrator in an estimated dial setting (usually from the energy-response curve or available literature) if it is a new radionuclide. The radioactive source is then sent to an NMI/DI to be standardised by means of a secondary standard ionisation chamber, SSRC or other equipment traceable to national standards. The NMI- or DI-certified measured value is then compared with the field instrument measured value and adjustments to the dial setting can be made if deemed necessary.

It is recommended that the vial be measured in a series of dial settings, which can then be used to estimate the dial setting with the corresponding difference.

Receive a calibrated sample from an NMI, DI or radiopharmaceutical manufacturer (3, 4) – the NMI, DI and manufacturer

must be able to demonstrate traceability to national standards. In addition to this, the uncertainties reported in the activity should be kept to the same uncertainty level achieved by a secondary standard radionuclide calibrator (SSRC) or reference radionuclide calibrator (3). For this method a standardised source traceable to standards is supplied to the hospital in a standard geometry. The sample is measured in the radionuclide calibrator and the dial setting can be adjusted until the measured activity reading on the field instrument matches the certified activity provided by the NMI/DI/manufacturer. However, it is important to note that the vial geometry sent by the NMI or DI might not be the most applicable clinical geometry, therefore transfer measurements might be necessary – this is described in the "Subsidiary calibration" section. If transfer measurements are necessary, the sample should be measured and a dial setting determined for the standard geometry before proceeding with the transfer measurements.

Participate in intercomparison exercises – NMI or DI organise intercomparison exercises to assess measurement capability for certain radionuclides. In this process, the participant receives a sample and measures it on the radionuclide calibrator; participants can also calibrate for other geometries by means of transfer measurements (described in the "Subsidiary calibration" section). A calibration certificate is received following submission of the measurement results and respective uncertainties. The participant can then compare the measured values with the certified values – this process and respective adjustment of the dial setting if deemed necessary is performed retrospectively.

Other methods can be used to determine a dial setting for a radionuclide calibrator; however, traceability might not be achieved and often geometries do not correspond to those used clinically. To estimate dial settings for a new radionuclide, the energy-response curve and nuclear data can be used. However, the energy-response curve is only valid for photons and it is geometry dependent, therefore the estimated dial setting is only valid for the geometry chosen by the radionuclide calibrator manufacturer (5). Alternatively, a calibrated gamma spectrometer can be used; however, traceability can only be achieved if the radionuclide being measured was used in the calibration process for the gamma spectrometer (5). Furthermore, the same source cannot be measured on the gamma spectrometer and the radionuclide calibrator, therefore a diluted source might need to be prepared.

CALIBRATION OF WELL COUNTERS

Well counters are instruments used in clinical and pre-clinical nuclear medicine for the measurement of low activity samples, up to 37 kBq (8). These instruments can be used clinically and pre-clinically for different applications, such as e.g. for measurement of glomerular filtration rate (GFR) using ^{51}Cr and for biodistribution studies (8).

The principles of operation and the advantages and disadvantages of using well counters are described in a previous EANM Technologists' Guide and hence will not be presented here (8). The recommended quality control (QC) process is described in the same publication (8).

The previous EANM Guide recommends that well counters are calibrated at the time of installation, annually and after any major repair or change (8). The calibration should be performed for each radionuclide of interest.

The calibration factors for well counters are defined in cpm/Bq (counts per minute per unit of activity), and this corresponds to the efficiency. For each radionuclide of interest an efficiency should be calculated for a well-defined specific geometry.

Well counters can be calibrated using:

a. Calibrated source of long-lived surrogate for the radionuclides of interest (e.g. ^{57}Co instead of ^{99m}Tc), although with this method traceability will not be achieved for the corresponding short-lived radionuclide, but only for the radionuclide being measured.

b. A radionuclide calibrator previously calibrated for the radionuclide of interest.

The most common process is to cross-calibrate the well counter with the radionuclide calibrator previously calibrated for the radionuclide of interest. For this process a sample is prepared and measured in the radionuclide calibrator with a dial setting previously determined for a well-defined and controlled geometry. Due to the nature of well counters, measured activities are in the order of kBq, i.e. a factor of hundreds lower than activities measured on the radionuclide calibrator, therefore a diluted sample must be accurately prepared for measurement in the well counter at a suitable activity level and traceable to the radionuclide calibrator measurement.

A diluted sample can be prepared from the sample measured on the radionuclide calibrator, or a stock solution can be made to prepare both the sample for measurement on the radionuclide calibrator and a diluted sample to be measured on the well counter. Irrespective of the method used, the activity per unit mass or activity concentration of the sample measured on the radionuclide calibrator must be known accurately, so that the total activity dispensed either gravimetrically or volumetrically to the diluted sample will be known and traceable to the activity measured on the radionuclide calibrator.

The most accurate method of preparing a diluted sample is gravimetrically, i.e. using a balance with sufficient accuracy to weigh the sample. The total mass of active solution and carrier solution dispensed to the diluted sample will thus be known, therefore the total activity and activity per unit mass in the diluted sample will be known accurately and be traceable to the radionuclide calibrator measurement and hence to national standards. Alternatively, if a balance is not available, the solution can be dispensed volumetrically. However, this method will result in higher uncertainties associated with the measured activities. Alternatively, and depending on the half-life of the radionuclide, the sample measured on the radionuclide calibrator – once decayed to an activity measurable on a well counter – can be gravimetrically transferred to an appropriate container to be measured on the well counter. In this case a diluted sample will not be necessary.

CALIBRATION OF IMAGING INSTRUMENTATION

Nuclear medicine imaging plays a key role in the assessment of the spatial and temporal distributions of a radiopharmaceutical for treatment planning, treatment verification and follow-up in radionuclide therapy. Image formation depends on the individual modality and manufacturer, but in general for SPECT, PET and X-ray computed tomography (CT) the signals generated are processed by electronic hardware components and software algorithms to determine the energy, position and timing of a given detected event. This information is then processed to generate the images, and typically includes various calibrations and corrections that ensure correct functioning of the instrument, quantitative accuracy, and good image quality. A robust calibration, quality assurance and control programmes are key to ensure that all imaging instrumentation performs to specifications for daily clinical use, and its implementation should follow international or national guidelines and take account of relevant legislation as well as the manufacturer's recommendations (8-22). QA is required after installation of a new system, to confirm the performance parameters provided by the manufacturer and the baseline parameters for comparison with follow-up QC measurements. Routine QC protocols test the system's performance to detect potential malfunctions and changes in constancy of the expected functionality. If the deviations found are beyond the tolerance levels established at baseline, re-calibration and/or maintenance should be performed as required, therefore all calibrations of imaging instrumentation are maintained through implementation of a robust and regular QC programme. The frequency and procedures for testing depend on the imaging modality and manufacturer, and most systems are equipped with some form of automated or semi-automated procedure. In addition to the calibrations that ensure the performance of the instrumentation and acceptable image quality for clinical use, the intensity in each pixel or voxel, usually in counts or counts per second, needs to be calibrated for absolute image quantification and dosimetry purposes using sources of known activity traceable to primary standards.

This chapter considers the main aspects of calibrating the three main imaging instruments used in radionuclide therapy: gamma camera/SPECT, PET and CT scanners. Further corrections for quantification purposes, such as attenuation, scatter, dead time or partial volume corrections, will be addressed in the next chapter.

Planar and SPECT

A gamma camera is often used following radionuclide therapy with beta- or alpha-emitting radiopharmaceuticals to calculate and verify the absorbed doses delivered to the targets and organs at risk by means of planar scintigraphy and/or SPECT. A typical gamma camera comprises two detector heads, though this can vary, and three-head systems are also available. In general terms, each head comprises: (i) a large scintillation detector (commonly sodium iodide crystal doped with thallium NaI(Tl)); (ii) a collimator, which is a large slab made of a highly attenuating material with an array of typically parallel holes that sits in front of the crystal and limits the acceptance angles of the incoming photons, and (iii) an array of photomultiplier tubes (PMTs) optically coupled with the crystal that converts the visible light produced by the scintillator into measurable signals which are used to provide the spatial position and energy on an event-by-event basis. Two-dimensional (2D) voxelised images representing the accumulation of the individual events per pixel are finally generated, and multiple views can be acquired at different angles and reconstructed into a 3D image.

Multiple calibrations are needed to correct the inherently non-uniform signal outputs of a gamma camera. Uniformity can be evaluated and corrected either intrinsically, when correcting for the performance of the crystal, PMTs and electronics without the collimator, or extrinsically when the collimator is in place. The first step is to correct for differences in the gains between PMTs and potential drifts over time. An energy calibration is needed to correct for the differences between the local energy spectra by applying spatially dependent factors to align the photopeaks. The linearity calibration corrects the image for geometric non-uniformities related to the position-dependent differences in the efficiency of light collection from the scintillation crystal by the PMTs (higher/lower efficiency close to/between the PMTs). Even though linearity has the largest impact on uniformity, it does not require frequent updating and is usually performed by the service engineer. Any leftover non-uniformity is corrected by acquiring a high-count flood image intrinsically and/or extrinsically to create

a pixel-by-pixel correction to address the variations in intensity across the image. For tomographic SPECT, the transaxial alignment of the images with the mechanical centre of rotation (COR) and the axial alignment of the individual heads are key to accurate image reconstruction, as non-alignment can result in image-blurring artefacts.

Several methods have been proposed to calculate the calibration factor to translate detected count rate into activity for absolute image quantification (23, 24). The simplest and most practical methods involve planar imaging of a small point source, a small syringe volume or a petri dish to measure the calibration factor in air. However, this can lead to inaccuracies if perfect scatter and attenuation corrections are not applied to the patient scans. Tomographic imaging of large phantoms has also been proposed for absolute calibration. Despite the added complexity and time required, in particular for long-lived radionuclides, this geometry better represents the attenuation and scatter characteristics of a patient scan. This absolute calibration is specific to the measurement conditions in which it has been derived, therefore new calibration factors must be determined for each combination of radionuclide, camera, collimator, energy window settings, correction methods, and image reconstruction settings. The calibration must be performed under the same conditions as subsequent patient studies. EARL are presently developing a new accreditation programme for the harmonisation of SPECT imaging across multi-centre studies (25).

PET

PET uses positron-emitting radiopharmaceuticals and plays an important role in theragnostics. It is based on the detection of two 511-keV photons in coincidence resulting from the annihilation of a positron and an electron. Each detected photon is time-stamped, and a true coincidence event is defined as a pair of annihilation photons counted by the coincidence detectors within a time interval called the coincidence timing window. Other types of events can also occur which degrade image quality and quantitative accuracy, such as random or scattered coincidences. Most modern systems also have time of flight (TOF) capabilities, measuring the time difference between the arrival of both photons, which in turn is proportional to the difference in distances travelled and can be used to better estimate the position of the event along the line of response. Typical PET scanners are composed of detector blocks consisting of a large crystal that is divided into an array of detector elements, organised in several adjacent coaxial rings, with several individual detectors connected in coincidence, which typically results in tens of thousands of detectors and several million lines of response. Most PET scanners use scintillation materials such as lutetium oxyorthosilicate (LSO) or lutetium yttrium oxyorthosilicate (LYSO), which are coupled to position-sensitive photodetectors like PMTs or silicon photomultipliers in more modern systems. Due to the complexity of PET systems, users do not have access to the calibration utilities and the re-calibration of the system is generally only performed by the manufacturer. The frequency of calibration will be dependent on the manufacturer's recommendations and the need for retuning following QC protocols. The methodology varies between manufacturers, but very broadly the calibration of a PET scanner includes setting the gains of the PMTs to provide suitable 511-keV signals within an energy window, timing calibrations to ensure that coincidence time windows between detectors and blocks are aligned, uniformity of response across all the detectors as well as an absolute calibration for activity quantification.

Events are assigned to individual detector elements in the block based on comparison of the signal output from corresponding PMTs. The gains must be adjusted such that the signal amplitude from the PMTs is comparable on average, by exposing the detectors to a flood source of 511-keV photons. Detector flood histograms are acquired to ensure that each detector element in each block can be identified, and a look-up table is generated to assign a particular combination of positions in both directions to a particular element. The location of the photopeak in the energy spectra of individual detectors in a block will vary depending on the light collection efficiency, and the amplitude of the signal will depend on its location with respect to the PMTs, therefore an energy calibration is needed to correct the location of the photopeak. Energy spectra are acquired for each detector element, where it is assumed that the photopeak corresponds to 511 keV. Coincidence events are accepted within a narrow time window, therefore it is important to have a common reference time. Timing spectra between detectors are acquired by recording differences in the time of detection of annihilation photon pairs. The time delay is measured for each detector, and time adjustments are introduced such that the centroid of all timing spectra is aligned, accounting for variations in the time characteristic of individual scintillators, electronics, time delays in PMTs, cables, etc. Following these calibrations, there will be a significant residual non-uniform response due to non-perfect calibrations, geometrical variations, imperfections in manufacturing, electronics performance, etc. The correction for these effects is comparable to the uniformity calibration in SPECT, whereas in PET the detector pairs are exposed to a uniform source of 511-keV photons to generate a multiplicative correction matrix that is applied to the acquired sinograms. This is usually known as the normalisation. As with SPECT, the system calibration factor for absolute quantification is derived by scanning a calibrated source with a known uniform activity concentration traceable to primary standards. If a patient study uses a different positron emitter to that used to determine the activity calibration factor, the branching ratios of both radionuclides should be taken into account.

For PET, the EARL accreditation programme provides protocols to ensure correct calibration of the systems for multi-centre studies. The sites are required to perform activity calibration and image quality measurements and submit the image data in DICOM format and the results to EARL (25).

CT

The addition of CT to emission tomography with SPECT and PET is vital, not only for anatomical localisation purposes, but also to improve quantification by enabling correction for attenuation of the photons emitted by radionuclides. A CT scanner uses a polyenergetic X-ray fan beam rotated around the patient, with the attenuated X-rays being recorded in an array of detectors on the opposite side of the scanner gantry. The raw CT data is normalised to represent tissue type rather than the measured linear attenuation coefficient by calculating each pixel value in terms of Hounsfield units (HU).

An important aspect of hybrid SPECT/CT and PET/CT systems is that they rely on a calibration to establish the co-registration of both imaging modalities for accurate quantification and image quality. Co-registration in SPECT/CT is considered more complex due to the rotating nature of the detector heads and variation in the centre of rotation for different collimators, which can result in a higher degree of misalignment compared to PET/CT rings, which are in fixed positions.

As with the other imaging modalities, several calibrations are required to ensure correct functioning of the instrument (detector gains, uniformity, dosimetry, geometry, etc.) and should follow guidelines and manufacturer's recommendations. The polyenergetic nature of the X-ray beam results in beam-hardening artefacts caused by the higher attenuation of the lower-energy photons as they travel through the attenuating material. Since the attenuation coefficients depend on the material and beam energy, the same tissue in the middle of the patient has a lower attenuation coefficient. A calibration using phantoms in a range of sizes can be used to correct for spectral changes due to object thickness. In terms of the main role of CT in radionuclide therapy, CT scans provide patient-specific measurements of the linear attenuation coefficient. However, these are for the energies of typical X-ray energy spectra, which on average are considerably lower than the photon energies emitted by most radionuclides. In PET, all pairs of photons detected are attenuated by the same probability, therefore the raw data in terms of counts obtained for that line of response can be corrected by a well-defined factor before reconstruction. A calibration curve can be generated where measured CT numbers are plotted against the known attenuation coefficients at the photon energy of a given radionuclide of interest in SPECT, typically using a phantom with tissue-equivalent materials with known chemical compositions. The methods developed to convert CT units to linear attenuation coefficients at specific energies enables a single CT scan to be used for correcting a variety of different radiopharmaceuticals. These calibration curves must be generated for each tube voltage used. The administration of oral or intravenous contrast media can result in incorrect attenuation maps and should also be taken into consideration.

FINAL REMARKS

Absolute quantification of SPECT and PET imaging systems is needed to estimate the absorbed doses delivered to tumours and organs at risk. This relies heavily on the calibration of the imaging systems to ensure the correct functioning of the instruments and to convert counts into activity, as well as on cross-calibration with a radionuclide calibrator using radioactive sources prepared with a known activity and associated uncertainties that are traceable to primary standards (6).

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REFERENCES

1. Joint Committee for Guides in Metrology. JCM 200 - International Vocabulary of Metrology – Basic and General Concepts and Associated Terms (VIM 3rd edition). BIPM. 2012.
2. Fenwick AJ, Wevrett JL, Ferreira KM, Denis-Bacelar AM, Robinson AP. Quantitative imaging, dosimetry and metrology; Where do National Metrology Institutes fit in? Appl Radiat Isot. 2018;134:74-8.
3. Carey J, Byrne P, DeWerd L, Lieto R, Petry N. The Selection, Use, Calibration, and Quality Assurance of Radionuclide Calibrators Used in Nuclear Medicine2012.
4. Gadd R, Baker M, Nijran KS, Owens S, Thomas W, Woods MJ, et al. Protocol for establishing and maintaining the calibration of medical radionuclide calibrators and their quality control. Measurement Good Practice Guide. 2006.
5. IAEA. Quality assurance for radioactivity measurement in nuclear medicine. Vienna: Internation Atomic Energy Agency; 2006.
6. Ferreira KM, Fenwick AJ, Heetun W, Denis-Bacelar AM, Deidda D, Robinson AP, et al. Guide on the preparation of radioactive phantoms with an activity traceable to national standards. In preparation. 2022.
7. Ferreira KM, Fenwick AJ, Arinc A, Johansson LC. Standardisation of 90Y and determination of calibration factors for 90Y microspheres (resin) for the NPL secondary ionisation chamber and a Capintec CRC-25R. Applied Radiation and Isotopes. 2016;109:226-
8. European Association of Nuclear Medicine. Quality control of nuclear medicine instrumentation and protocol standardisation: EANM Technologists Guide. 2017.
9. EANM Physics Committee, Busemann Sokole E, Plachcinska A, Britten A, Eanm Working Group on Nuclear Medicine Instrumentation Quality Control, Lyra Georgosopoulou M, et al. Routine quality control recommendations for nuclear medicine instrumentation. Eur J Nucl Med Mol Imaging. 2010;37(3):662-71.
10. Busemann Sokole E, Plachcinska A, Britten A, Committee EP. Acceptance testing for nuclear medicine instrumentation. Eur J Nucl Med Mol Imaging. 2010;37(3):672-81.
11. Quality Assurance for SPECT Systems. 2009.
12. International Atomic Energy Agency. SPECT/CT atlas of quality control and image artefacts. IAEA HUMAN HEALTH SERIES No 36. 2019.
13. International Atomic Energy Agency. Quality assurance for PET and PET/CT systems. Viennna,: IAEA; 2009.
14. International Atomic Energy Agency. Quality Assurance Programme for Computed Tomography: Diagnostic and Therapy Applications. Vienna: INTERNATIONAL ATOMIC ENERGY AGENCY; 2012.
15. National Electrical Manufacturers Association. NEMA NU 2-2018 - Performance Measurements of Positron Emission Tomographs (PET). 2018.
16. National Electrical Manufacturers Association. NEMA NU 1-2018 - Performance measurements of gamma cameras. 2018.
17. International Atomic Energy Agency. PET/CT atlas on quality control and image artefacts. Vienna: IAEA; 2014.
18. American Association of Physicists in Medicine. Report No. 177 - Acceptance Testing and Annual Physics Survey Recommendations for Gamma Camera, SPECT, and SPECT/CT Systems. 2019.
19. American Association of Physicists in Medicine. Report No. 126 - PET/CT Acceptance Testing and Quality Assurance (2019). 2019.
20. Zanzonico P. Routine Quality Control of Clinical Nuclear Medicine Instrumentation: A Brief Review. Journal of Nuclear Medicine. 2008;49(7):1114-31.
21. Lawson RS. The gamma camera : a comprehensive guide. : Institute of Physics and Engineering in Medicine; 2013.
22. Cherry SR, Phelps ME, Sorenson JA. Physics in nuclear medicine. 2012.
23. Dewaraja YK, Frey EC, Sgouros G, Brill AB, Roberson P, Zanzonico PB, et al. MIRD pamphlet No. 23: quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy. J Nucl Med. 2012;53(8):1310-25.
24 . Ljungberg M, Celler A, Konijnenberg MW, Eckerman KF, Dewaraja YK, Sjogreen-Gleisner K, et al. MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative 177Lu SPECT Applied for Dosimetry of Radiopharmaceutical Therapy. J Nucl Med. 2016;57(1):151-62.
25. EANM Forschungs GmbH (EARL). EARL accreditation. Vienna: EANM; 2022 [https://earl.eanm.org/.

4

QUANTITATIVE IMAGING

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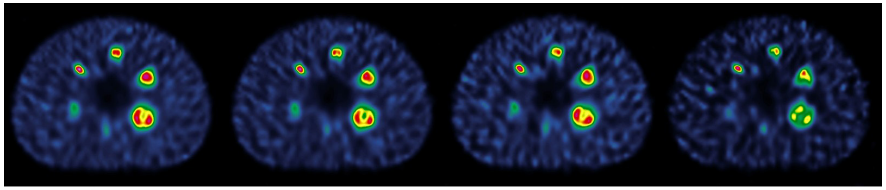
Quantitative imaging aims to produce a SPECT or PET image with voxel values representing activity concentration. For radionuclide therapy, this can allow the absolute activity within a delineated volume or organ to be extracted for dosimetry purposes. This chapter will discuss the technical factors and considerations associated with performing quantitative SPECT and PET.

PHANTOM INVENTORY

Before undertaking quantitative imaging in either SPECT or PET, it is important to ensure access to appropriate phantoms in order to perform system calibration, characterisation and quality control. The minimum requirements are a large-volume phantom to measure activity concentration for calibration purposes and a phantom such as the NEMA IEC image quality phantom to characterise the activity concentration as a function of object size [1–4]. This characterisation allows "recovery curves" to be generated, which should allow multi-centre harmonisation for both SPECT [5] and PET [6]. It is quite likely that these phantoms will be available for PET users, but less so for SPECT, where quantitative volumetric assessment has not traditionally been a focus.

IMAGE ACQUISITION

In SPECT and PET, gamma-ray emissions from the patient are detected by the imaging system and stored in projections. For SPECT these are the planar projections acquired at a series of angles around the patient, while in PET sinograms represent the position and angle of the line of response formed by the two 511 keV gamma rays. These images can then be reconstructed into transaxial images reflecting the activity concentration. The quality of the acquired data will determine the quantitative accuracy of the reconstructed images. As in all nuclear medicine applications, this is based around an image quality trade-off between spatial resolution and statistical noise. One of the main determinants of statistical noise is the combination of administered activity and acquisition time, and Figure 1 shows the impact of reduced counts on image quality; the quantitative impact will be described later. However, assuming that these are determined by protocol to balance radiation exposure and the logistics of patient comfort and throughput, then it remains to evaluate the influence of other technical acquisition factors on quality and accuracy. These are predominantly applicable to SPECT, as most technical factors in PET are defined during the reconstruction process.



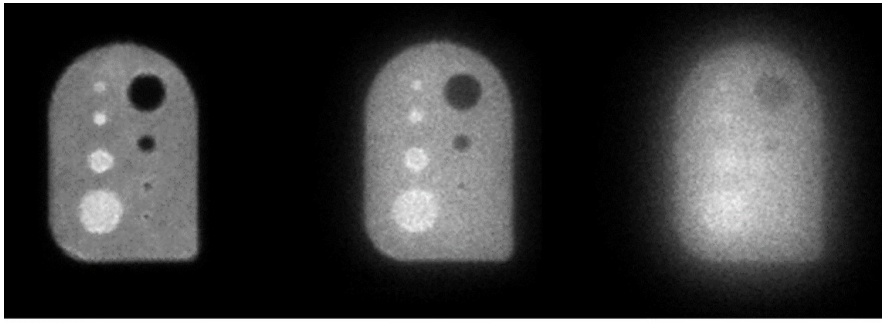
100% 75% 50% 25%

Figure 1: Demonstration of the visual impact of reducing image counts in SPECT. In these phantom images, the gamma camera projection counts were resampled from the 100% count image (left) to the values shown underneath each image.

Collimator

A gamma camera collimator absorbs oblique gamma rays with metal septa. The required thickness of the septa is determined by the radionuclide gamma-ray energy. If the septa are too thin, septal penetration will occur, resulting in a loss of image contrast. It is therefore essential that the appropriate collimator is used. Figure 2 shows the consequences of acquiring indium-111 with 171- and 245-keV emissions on a range of collimators with different septal thickness.

Lutetium-177 is a common radionuclide used for therapeutic applications. It has gamma-ray emissions at 208 keV, hence medium-energy collimators are required for SPECT [2].



Medium energy 1.0 mm septa | "Extended" low energy 0.4 mm septa | Low energy 0.2 mm septa

Figure 2: Planar images of a phantom filled with In-111 (171- and 245-keV gamma rays) acquired with a series of collimators of different septal thickness. The loss of contrast is apparent as septal penetration occurs.

Pixel size

The projection pixel size will impact on the image noise due to the count density per pixel. Secondly, pixel size will likewise influence the fineness, and ultimately the accuracy, of spatial sampling of the system's spatial response. For SPECT, the voxel dimensions in the reconstructed image volume are equal to the 2D pixel dimensions in the projections, while in PET the voxel dimensions are usually determined during the reconstruction. Figure 3 shows the impact of acquiring a NEMA IEC image quality phantom with various projection pixel sizes for SPECT.

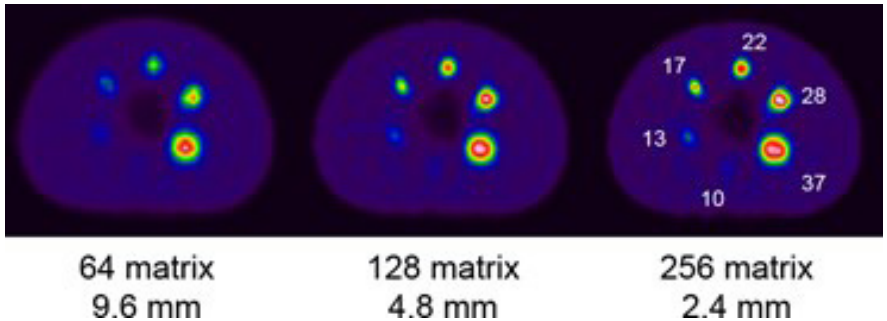


Figure 3: SPECT transaxial image slice of NEMA IEC image quality phantom acquired with three different projection pixel sizes, as indicated below each image. The right-hand image has the sphere diameters, in mm, superimposed.

Quality control

It is essential that regular quality control is performed on imaging equipment to ensure the uniformity of detector response across the field of view. For gamma cameras, planar uniformity should be assessed using long-lived sheet sources or radionuclide point sources with the collimator removed. PET uniformity will be assessed using a long-lived uniform volumetric phantom. These processes do not differ from the routine QC steps. However, additional quantitative quality control should be performed to ensure reliable image quantification. This involves the calibration and verification of volumetric activity concentration measurements for all radionuclides that are to be used.

Calibration

The initial step in the calibration process for quantitative imaging is to establish a reliable cross-calibration factor between a radionuclide calibrator and the imaging system. A range of calibration techniques are available for SPECT systems, including planar petri-dish source measurement, a long-lived sealed point source planar measurement, or volumetric measurements from a large uniformly filled phantom. Due to the nature of the imaging system, the calibration process for PET is always this latter volumetric technique. The exact technique for calibration will be set out by the system manufacturer and should be performed accordingly. Prior to calibration imaging, it is important to employ a good technique for measuring activity in the radionuclide calibrator. The process should mirror the measurement approach used for patients, i.e. if patient injections are performed with specific syringe sizes and diluted to a given volume, this should be replicated when measuring the activity for the calibration scan.

Once the imaging system has been calibrated, it must be verified before clinical use. As stated above, multiple calibration methods are available for gamma cameras, including some planar techniques, but the verification should be performed using a large uniformly filled volumetric phantom as this will most closely replicate the clinical scenario.

If a volumetric phantom is used for calibration (always in PET and occasionally in SPECT), then the verification scan should not be performed immediately after calibration using the same phantom. This would simply result in any errors in the activity measurement or phantom filling transferring across to the verification scan, which would give a false impression of the calibration. The verification should be performed with a freshly filled phantom to allow testing of the entire process of activity measurement, phantom filling and image acquisition. For long-lived radionuclides, this should be taken into consideration during planning. For verification, the precise volume of the phantom should be known together with the activity that was injected, taking into account any residual activity in the syringe. Following data acquisition and reconstruction, large regions of interest should be placed on several transaxial slices and the mean activity concentration should be measured. This should then be compared with the true activity concentration in the phantom. It is recommended that verification scans are performed at least quarterly to check the cross-calibration factor.

IMAGE RECONSTRUCTION

From a user perspective, there are two definable reconstruction variables that will influence the quantitative accuracy of an image. These are the number of reconstruction updates and the application of a post-reconstruction smoothing filter. In addition, there are data corrections that can be applied, and these will be discussed later.

Reconstruction updates

It is recommended that iterative reconstruction is used for both SPECT and PET, as this allows accurate incorporation of data corrections. For ordered subset expectation maximisation (OSEM), increasing the number of updates, defined by the product of the number of iterations and subsets, will converge towards an image that is more accurate quantitatively, as the estimate of the image shifts closer to the ground truth [7]. The number of updates should preferably be obtained from phantom measurements in which the convergence of activity concentration is studied.

One aim of quantitative imaging is to have consistent quantification of activity in an organ or lesion, irrespective of the size, local contrast and position within the patient. If the number of updates is too low, then the images will not be reliable. In SPECT in particular, variations may be observed in the accuracy of quantification across the transaxial field of view, even when attenuation correction has been applied, hence it is important to assess variable phantom configurations and positions when characterising a system [8, 9].

Post-reconstruction filters

In addition to adjusting the number of updates, the user can also vary the strength of a post-reconstruction smoothing filter. This is performed on the reconstructed image volume after the reconstruction has been completed.

A smoothing filter will inevitably degrade the spatial resolution and exaggerate partial volume effects [10], therefore it is argued that filtering should not be applied to images for quantitative applications. However, the application of a post-filter is intended to control the degree of noise in the image and hence the potential positive bias that may arise from noise in certain types of measurements.

In dosimetry situations such as organ delineation, where large regions are drawn and the mean activity concentration measurements are derived from all voxels, a post-filter is unlikely to be beneficial.

However, as objects become smaller and the number of voxels being averaged reduces, noise can become a more significant influence. Here a post-filter can be helpful in ensuring a greater level of consistency.

IMAGE CORRECTIONS

Attenuation correction

Attenuation is an exponential process and the single largest cause of quantitative errors in both SPECT and PET, hence it must be addressed. For Tc-99m, only 30% of 140-keV gamma rays are emitted from a depth of 10 cm in soft tissue. This is even more significant in PET, despite the higher gamma-ray energy, as both gamma rays must be detected in order to form the line of response.

On modern hybrid systems, CT images are used to correct for attenuation in both SPECT/CT and PET/CT. The CT image is converted to an attenuation map for the appropriate radionuclide energy and incorporated into the iterative reconstruction process. This conversion process involves translation of the CT Hounsfield units into attenuation coefficients, changing the CT voxel dimensions to match the SPECT or CT image and, usually, applying some smoothing to compensate for the differences in spatial resolution between CT and either SPECT or PET.

To calculate the required attenuation correction factor, the full path length of the gamma ray is required, from the point source to the patient boundary on the attenuation map. Note that for PET, this is the path length of both gamma rays forming the line of response. If the attenuation map is truncated, either by a large patient or an inadequate CT field of view, then the attenuation correction may not be fully accurate and quantitative errors can occur. Care should therefore be taken when positioning the patient to minimise the likelihood of truncation, e.g. by raising the arms up if possible.

Scatter correction

Scattered gamma rays will result in quantitative errors within the photopeak window due to incorrect placement of detected events resulting from scatter in the patient. Gamma rays lose energy as they undergo scatter, hence additional scatter windows are usually acquired at a lower energy relative to the photopeak. It is important to validate scatter correction techniques using appropriate phantoms containing areas of no activity surrounded by uniform activity, to demonstrate that the algorithms do not overcorrect the final images.

SEGMENTATION

Image-derived quantification requires the extraction of voxel values using segmentation of organs or lesions by defining regions on the images. The inclusion criteria for voxels will impact on the overall value [10]. There are two methods of defining regions to delineate an organ or lesion, according to the base image that is used. Anatomical segmentation is when regions are drawn on organs or lesions using the anatomical image (CT or MR) as the base image, irrespective of the voxel values in the

overlying functional (SPECT or PET) image. Typically, all voxels on the functional image within this region will be included and the mean of these calculated. Dosimetry almost always employs anatomical segmentation, with regions manually drawn on organs or cancerous deposits based on the anatomical image. Anatomical segmentation will typically produce relatively robust measurements due to the large number of voxels being averaged.

Functional segmentation describes the automatic selection of voxels, generally within a bounding region encompassing the area of interest based upon the voxel values from the functional image. This method is commonly used for SUV measurements in PET, where voxels can either be just the maximum voxel value (in the case of SUV_{max}) or a group of voxels above a particular percentage threshold of the maximum voxel value, such as $SUV_{50,}$ i.e. all voxels above 50% of the maximum [10]. This technique is more susceptible to image noise, reconstruction parameters and partial volume effects as it is determined from the functional voxel values. Figure 4 shows how the maximum voxel value and the mean of all voxels within a 37 mm spherical region change as the acquired counts are reduced.

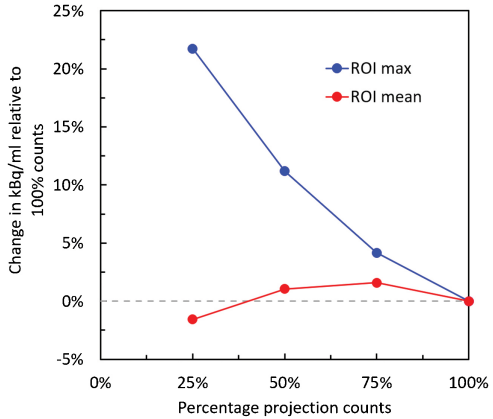


Figure 4. Percentage change in measured activity concentration as the acquired counts are reduced, relative to the 100% count image. The measurements are performed on the 37 mm sphere of a NEMA IEC image phantom acquired on a SPECT/CT system (images shown in Figure 1). The activity concentration was measured using a 37 mm diameter spherical region of interest (ROI). The mean of all voxels within the ROI is shown as "ROI mean" while the maximum voxel in the region is shown as "ROI max". The former reflects of the anatomical segmentation techniques, while the latter reflects functional segmentation techniques.

CHAPTER 4

QUANTITATIVE IMAGING

REFERENCES

1. Armstrong IS and Hoffmann SA. Activity concentration measurements using a conjugate gradient (Siemens xSPECT) reconstruction algorithm in SPECT/CT. Nucl Med Commun 2016; 37 1212-17. https://doi.org/10.1097/MNM.0000000000000586
2. Marin et al. Accuracy and precision assessment for activity quantification in individualized dosimetry of [^{177}Lu]Lu-DOTATATE therapy. EJNMMI Physics 2017; 4:7. https://doi.org/10.1186/s40658-017-0174-7
3. Gnesin S, Ferreira PL, Malterre J et al. Phantom Validation of Tc-99m Absolute Quantification in a SPECT/CT Commercial Device. Computational and Mathematical Methods in Medicine 2016; 4360371. https://doi.org/10.1155/2016/4360371
4. Boellaard R, Delgado-Bolton R, Oyen WJG et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015; 42:328–354. https://doi.org/10.1007/s00259-014-2961-x
5. Peters SMB, van der Werf NR, Segbers M et al. Towards standardization of absolute SPECT/CT quantification: a multi-center and multivendor phantom study. EJNMMI Physics 2019; 6:29. https://doi.org/10.1186/s40658-019-0268-5
6. Kaalep A, Sera T, Oyen WJG et al. EANM/EARL FDG-PET/CT accreditation - summary results from the first 200 accredited imaging systems. Eur J Nucl Med Mol Imaging 2018; 45:412–422. https://doi.org/10.1007/s00259-017-3853-7
7. Hudson HM and Larkin RS. Accelerated Image Reconstruction Using Ordered Subsets of Projection Data. Trans Med Imaging 1994; 13:601-9. https://doi.org/10.1109/42.363108
8. Price E, Tipping J, Cullen DM et al. Positional dependence of activity determination in single photon emission computed tomography. Nucl Med Commun 2019; 40:865–872. https://dx.doi.org/10.1097/MNM.0000000000001034
9. Armstrong IS. Spatial dependence of activity concentration recovery for a conjugate gradient (Siemens xSPECT) algorithm using manufacturer-defined reconstruction presets. Nucl Med Commun 2019; 40:287–293. https://doi.org/10.1097/MNM.0000000000000960
10. Boellaard R, Krak NC, Hoekstra OS et al. Effects of Noise, Image Resolution, and ROI Definition on the Accuracy of Standard Uptake Values: A Simulation Study. J Nucl Med 2004; 45:1519–1527

5

PRE-AND POST-THERAPY IMAGING

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DISCLAIMER: Medical practice may vary between Europe and North America. The following chapter essentially reflects American practice and does not correspond fully to the EANM guidelines.

INTRODUCTION

Diagnostic nuclear medicine has been instrumental in the diagnosis, staging, and treatment of cancers since the 1940s (1). In the past decade, theranostics has made many advances and has become a prominent part of nuclear medicine. Traditional targeted radionuclide therapy has been effective in treating thyroid cancer, neuroendocrine cancer, neuroblastoma, prostate cancer and liver cancer. Radioligand therapy is a novel approach to treating the disease at a cellular level and will utilise both pre- and post-therapy imaging. For pre-therapy imaging, both PET/CT and SPECT/CT have been utilised by physicians to evaluate which patients are candidates for therapy, evaluate disease extent, and determine potential treatment plans. Post-therapy imaging is used as a diagnostic tool for treatment response assessment, treatment planning, restaging, and other patient management decisions. Post-therapy imaging can provide individualised dosimetry and dose adjustments for subsequent radiotherapy treatments, which can minimise radiation exposure to other organs while still achieving promising therapeutic response. Additionally, it may redefine traditional chemotherapy schemes and treatment durations. Post-therapy imaging may also be used to quantify the biodistribution of the radiotherapeutic analogues in tumours or areas of interest to further refine treatment doses. Post-therapy imaging provides clinical utility and can be easily integrated into a patient's care plan when their disease is treated with radiotherapy to provide continuity of care. This chapter will discuss the importance of post-therapy scanning and how post-therapy imaging protocols can be adopted and deployed at your respective institutions.

THYROID CANCER

Radioiodine therapy to treat thyroid disease is universally common throughout the nuclear medicine community and transcends both adult and paediatric populations. Radioiodine-131 [^{131}I]NaI administered orally can be used to treat hyperthyroidism (i.e. Graves' disease, thyroid autonomy) and shrink large non-toxic goitres. In addition, risk-adapted post-operative [^{131}I]NaI administration is pivotal in differentiated thyroid cancer management. Patient preparation for radioiodine therapy is important. The attending nuclear medicine physician or endocrinologist is responsible for instructing each patient on correct preparation procedures for the radioiodine therapy and its clinical effectiveness. Prior to administering [^{123}I]NaI capsules, ensure that the patient has not received intravenous contrast agents used in CT and radiography studies 1–2 months before activity is administered. The aim of raising TSH levels (to increase iodine uptake) can be achieved by withdrawing medication or by rhTSH injection.

Low-iodine diet

Dietary preparation starts 2 weeks before the patient's appointment. Patients are usually asked to avoid iodised salt and sea salt; seafood, including fish, shellfish, kelp, or seaweed; food containing red food dye, such as red or pink cereals, sweets or vitamins containing iodide; eggs (food products with small amounts of milk and eggs are acceptable); check all ingredient labels and avoid food containing any of the following: iodised salt, sea salts, iodates, iodides, algin, alginates, carrageenan, agar. Patients should reduce their intake of milk and other dairy products, including ice cream, cheese and yoghurt, and avoid breads made with iodide conditioners (most yeasted breads).

TSH stimulation and thyroglobulin measurement

The attending nuclear medicine physician or endocrinologist will instruct each patient to stop taking levothyroxine (thyroid hormone withdrawal (THW)) approximately 14 to 28 days before the [^{123}I]NaI diagnostic capsule is administered. Alternatively, recombinant human TSH (Thyrogen®) is an effective way to increase radioiodine uptake in thyroid tissues and improve disease evaluation for ablation and adjuvant intent, though thyroid hormone withdrawal is still the preferred preparation for treating advanced disease. Intramuscular injections of Thyrogen® are administered on 2 consecutive days. [^{123}I]NaI capsules may be administered to the patient the day after the last Thyrogen® injection was administered. Serum sampling for thyroglobulin is also required before administration of radioiodine, and a thyroid-stimulating hormone (TSH) blood test should be performed to ensure the patient is stimulated.

Diagnostic imaging procedure for thyroid cancer

Oral administration of gamma-emitting radioiodine-123 [^{123}I]NaI is commonly used for neck and/or whole body diagnostic imaging of thyroid cancer. Imaging of [^{123}I]NaI is versatile and can be accomplished with a variety of collimators, such as low-energy high-resolution (LEHR), medium-energy general-purpose (MEGP), or [^{123}I]NaI-specific collimators offered by vendors such as extended low energy general purpose (ELEGP). Many nuclear medicine departments have access to an equivalent collimator for diagnostic imaging. Diagnostic imaging protocols may need to be modified, depending on the collimator used for imaging. The other tracer used for

diagnostic imaging is orally administered low activities of [^{131}I]NaI, also for dosimetric intent. Disadvantages of using [^{131}I]NaI include the risk of stunning, which could reduce the ability of normal thyroid or metastatic tissue to trap and retain radioiodine and thus hinder treatment efficacy. Another disadvantage of using [^{131}I]NaI is that overall image quality is inferior compared to [^{123}I]NaI. (Figures 1 and 2 show the same patient getting [^{123}I]NaI and [^{131}I]NaI for diagnostic work-up.)

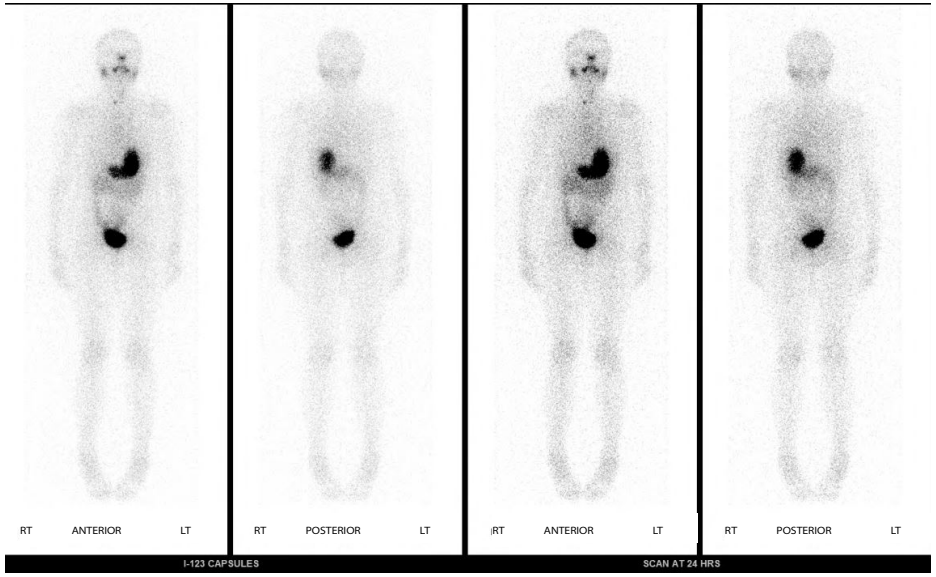


Figure 1. 9-year-old patient diagnosed with left- sided thyroid mass via ultrasound. Neck/chest CT was performed and showed mediastinal adenopathy consistent with metastatic thyroid CA; total thyroidectomy was performed. Referred for thyroid cancer scan 3 months after total thyroidectomy with RAI therapy; patient weight was 42kg, administered activity was 77.7 MBq of [^{123}I]NaI, extended low-energy general-purpose (ELEGP) collimators were used, whole-body scan acquired at 12.0 cm/min.

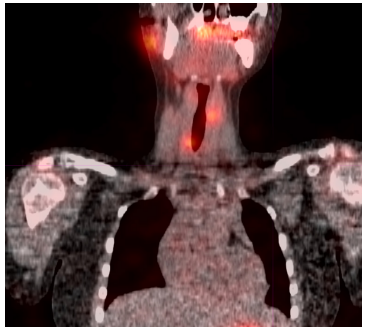


Figure 1b. SPECT/CT of the neck and chest were acquired 24 hours after dosing; patient was treated with 2427.2 MBq of [^{131}I]NaI.

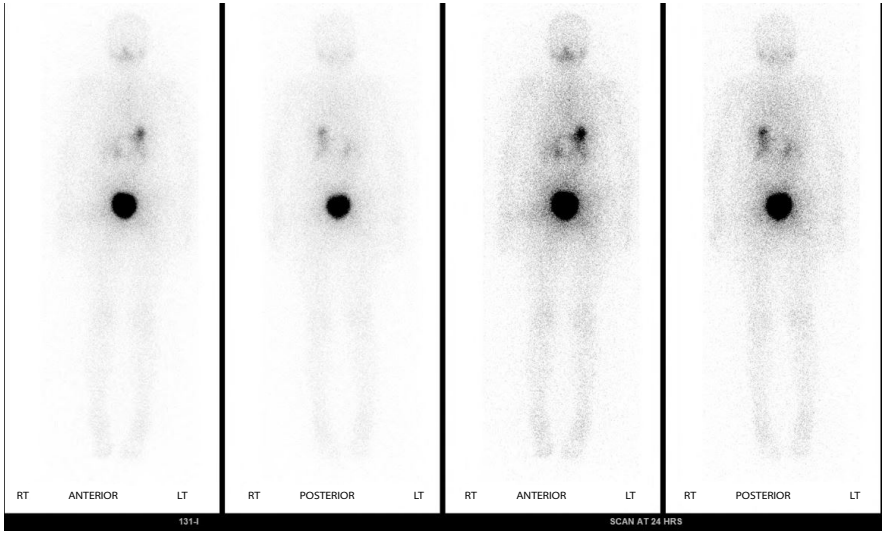


Figure 2. This is the same patient as the [^{123}I]NaI diagnostic whole-body image performed 10 months after the [^{123}I]NaI diagnostic thyroid cancer scan. Patient is now 10 years old, weight at time of activity was 47.9 kg, patient activity was 56.61 MBq of [^{131}I]NaI orally. HEGP collimators were used, whole-body scan acquired at 8.0 cm/min. This figure is included to show a direct comparison of [^{123}I]NaI vs. [^{131}I]NaI for diagnostic scanning.

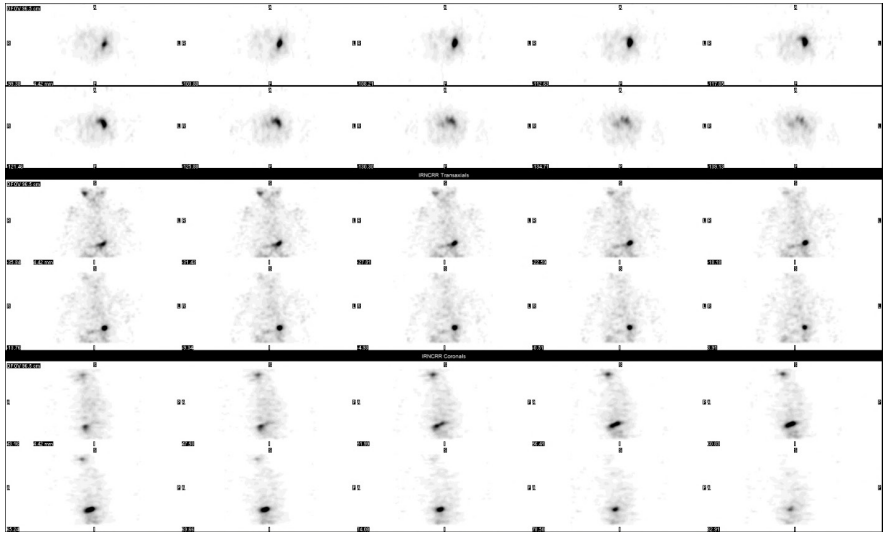


Figure 2b. SPECT of the neck and chest were acquired 24 hours after dosing.

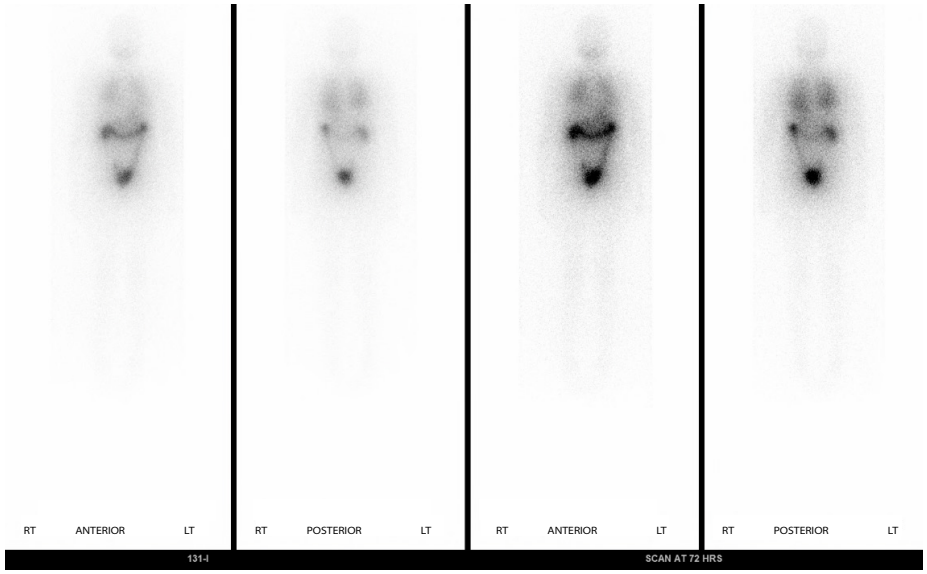
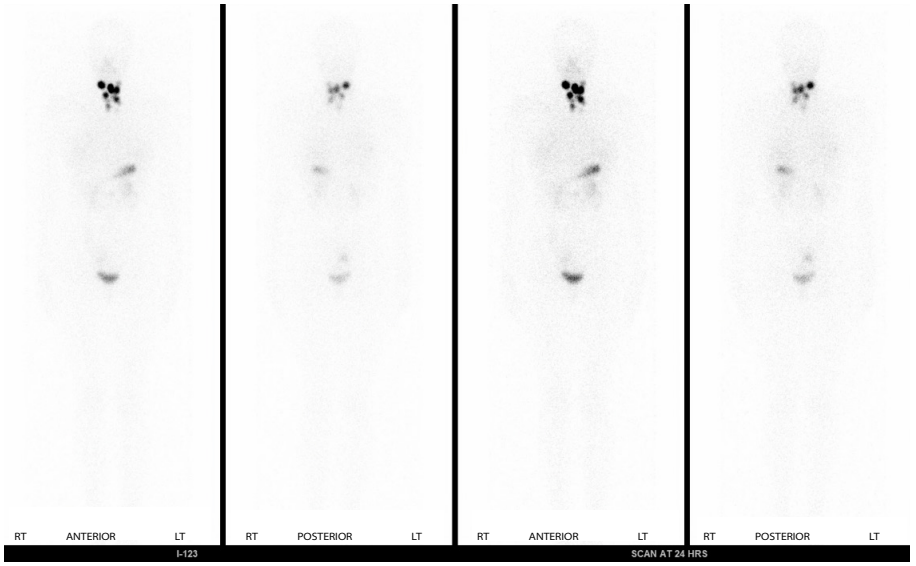


Figure 3. Caption: Post-therapy scan of patient from Figure 2. Patient was treated with 7067 MBq of [^{131}I]NaI administered as a capsule; patient was imaged 3 days post therapy due to convenience for travelling; diffuse radiopharmaceutical uptake is noted in the lungs; this is a good example of why post-therapy imaging is important, as the diagnostic scan did not demonstrate the same level of lung disease.

^{123}I diagnostic imaging procedure for thyroid cancer

The activity used for diagnostic thyroid cancer work-up is typically 74 MBq/70 kg (1.06 MBq/kg). Extended low energy general purpose (ELEGP) collimators specifically designed to image [^{123}I]NaI can be used for imaging of patients who are being worked up for thyroid cancer. Iodine-specific collimators have increased sensitivity and similar spatial resolution compared to medium-energy collimators (2,3). The standard imaging protocol described in this chapter is to use ELEGP collimators, perform a whole-body scan with a scan speed set at 12cm/min, acquire a 10-minute static of the neck and upper chest in a 256x256 matrix, acquire a SPECT/CT neck and upper chest with SPECT parameters set at a 128x128 matrix, 30 sec/stop, view angle = 6 for a total of 60 views, 159 keV primary peak +/- 7.5%, 130 keV scatter window +/- 7.5%; CT settings are set for soft tissue and are weight based.



(Figure 4. Caption: 18-year-old patient with papillary thyroid CA with follicular variant, status post thyroidectomy 3 months prior; administered activity was 80.105 MBq of [^{123}I]NaI for routine thyroid cancer scan. 24-hour uptake was 7.8%; discussion between endocrinologist, nuclear medicine physician and ENT resulted in a decision to defer therapy and return to OR for surgery; dosimetry work-up abandoned after 24-hour scan.)

Patient imaging using low-energy high-resolution (LEHR) or low-energy all-purpose (LEAP) collimators would follow the same acquisition parameters as described above using ELEGP collimators. Low-energy collimators are the most common and widely utilised collimator in nuclear medicine. Many departments do not have the luxury of owning multiple sets of collimators and revert to using low-energy collimators for imaging [^{123}I]NaI. When acquiring [^{123}I]NaI images with low-energy collimators, more noise will be present in the image acquisition due to septal penetration of the 2.5% high-energy photons [^{123}I] NaI when compared to medium-energy collimators (4).

Medium-energy general-purpose (MEGP) collimators may also be used for imaging [^{123}I]NaI. The advantage of using MEGP collimators over low-energy collimators would be to reduce image noise while maintaining resolution. A disadvantage of using MEGP collimators is that the image acquisition parameter speed must be slowed down so that sufficient counts can contribute to the image. Imaging parameters using [^{123}I]NaI with MEGP collimators for thyroid cancer work-up are to perform a whole-body scan with a scan speed set at 8cm/min, acquire a 10-minute static of neck and upper chest in a 256x256 matrix, acquire a SPECT/CT neck and upper chest with SPECT parameters set at a 128x128 matrix, 35 sec/stop, view angle = 6 for a total of 60 views, 159 keV primary peak +/- 7.5%, 130 keV scatter window +/- 7.5%; CT settings are set for soft tissue and are weight based.

^{131}I diagnostic imaging procedure for thyroid cancer

In a similar way to [^{123}I]NaI, [^{131}I]NaI may also be used for diagnostic imaging of patients with thyroid cancer. The decision to use [^{131}I]NaI over [^{123}I]NaI may be physician preference, or the fact that [^{123}I]NaI is unavailable. Patient dose (MBq/kg) is also scaled to an adult equivalent of 74 MBq/70 kg (1.06 MBq/kg). High-energy general-purpose collimators (HEGP) must be used to image the 364 keV photons. Institutions that do not have HEGP collimators should not use [^{131}I]NaI for diagnostic imaging. Imaging acquisition protocols must be adjusted to account for the reduced sensitivity of HEGP collimators. Whole-body scan speeds when imaging [^{131}I]NaI should be set to 6–8 cm/min to account for the reduced sensitivity of HEGP collimators. SPECT acquisition should be set to 40 sec/stop, view angle = 6 for a total of 60 views, 364 keV primary peak +/- 10 %, 297 keV scatter window +/- 10%; CT settings are set for soft tissue and are weight based.

Post-therapy imaging for thyroid cancer

Patients who have received a therapeutic dose of [^{131}I]NaI for thyroid cancer should be imaged after the therapy to assess the remnant thyroid tissue or the patient's overall disease burden. Post-therapy imaging is typically recommended on day 5–8 post [^{131}I]NaI therapy. The main advantage of acquiring a post-therapy image is to ensure that thyroid disease visualised with diagnostic [^{123}I]NaI imaging is visualised with therapeutic [^{131}I]NaI for comparative purposes. SPECT/CT can be utilised for [^{131}I]NaI post-therapy imaging for radiation dosimetry (5). Whole-body scan speeds when imaging [^{131}I]NaI post therapy can be set at faster imaging speeds such as 15 cm/min due to the greater radioactivity administered to the patient. Neck and chest images can be acquired for 3–5 minutes with a 256x256 matrix. SPECT acquisition should be set to 15 sec/stop, view angle = 6 for a total of 60 views, 364 keV primary peak +/- 10 %, 297 keV scatter window +/- 10%; CT settings are set for soft tissue and are weight based.

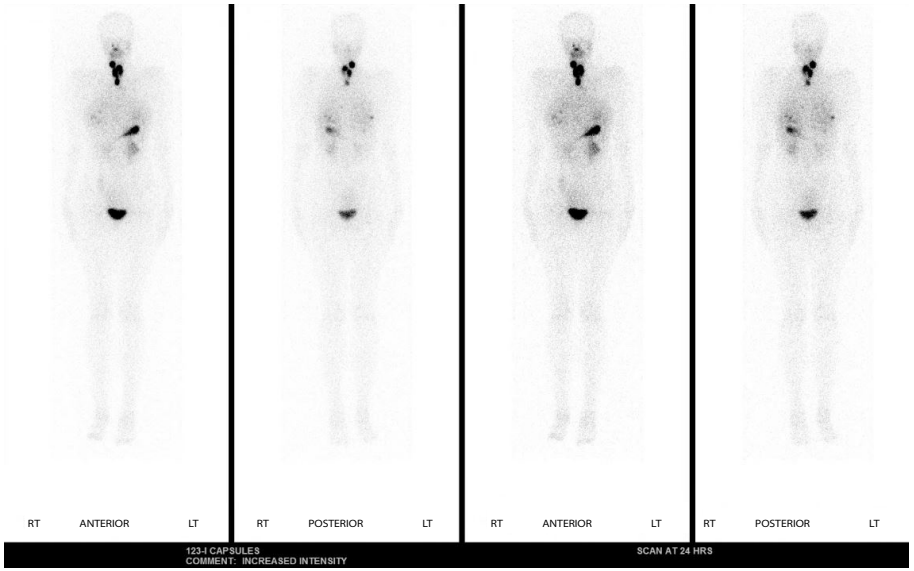


Figure 5a. (Same patient as in Figure 4) Caption: 18-year- old patient returned for repeat thyroid met scan 2 months after neck dissection; 77.478 MBq of [^{123}I]NaI was administered, patient weight at the time of scan was 56.7 kg, 24-hour uptake was 8.3%.

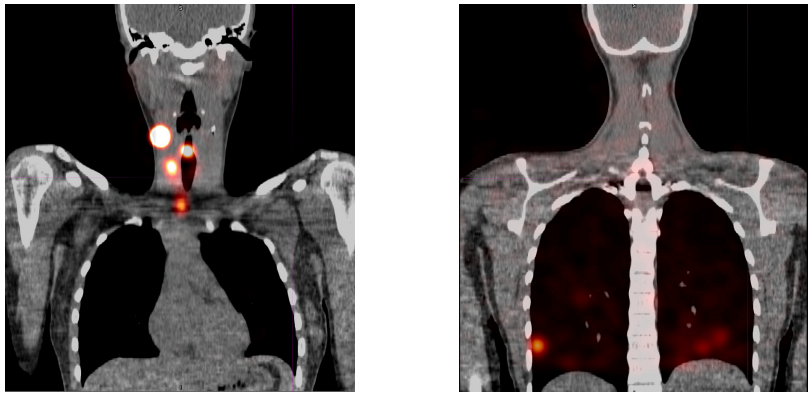


Figure 5b, 5c. SPECT/CT result showed bulk disease present in the neck with new lung disease that was not seen on the scan 3 months prior. Patient underwent dosimetry for [^{131}I]NaI therapy; discussion between endocrinologist and nuclear medicine physician resulted in decision to proceed with treatment given new lung disease.

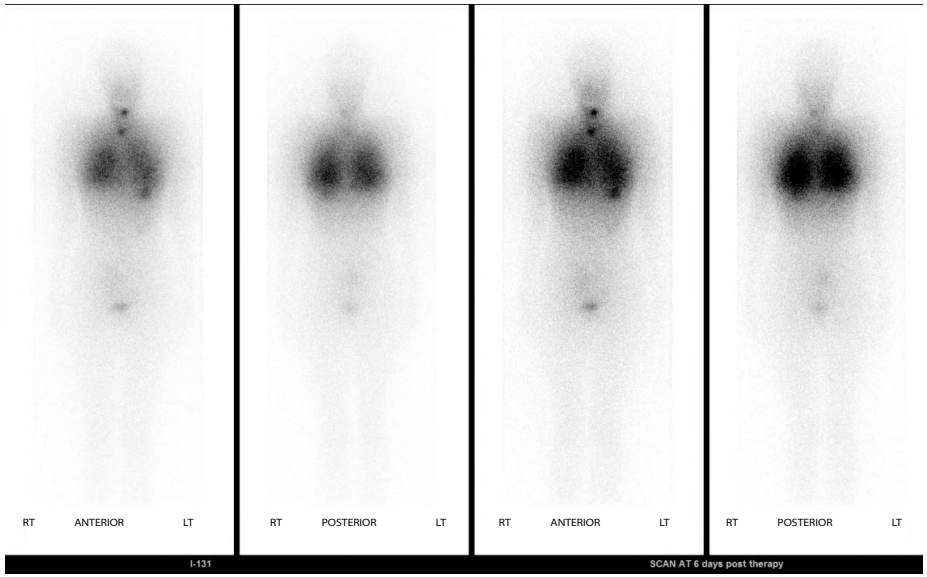


Figure 6. Caption: 18-year-old patient (same patient as in Figures 4 and 5) was given 3910.9 MBq of [^{131}I]NaI in capsule form. Post-therapy scan was acquired 6 days after therapy; HEGP collimators were used, whole-body scan at 15 cm/min; [^{131}I]NaI accumulation in residual disease in the neck as above, extensive diffuse radioiodine uptake within both lungs, consistent with pulmonary metastases.)

NEUROBLASTOMA

[^{123}I]I-mIBG diagnostic imaging

Since 2008, [^{123}I]I-Iobenguane (referred to as [^{123}I]I-mIBG) has been a commercially available product sold under the trademark name AdreView®. [^{123}I]I-mIBG imaging is commonly utilised to diagnose and stage neuroendocrine tumours such as neuroblastoma, paraganglioma, and pheochromocytoma. Intravenous patient dosing is administered slowly over 1 to 2 minutes. Activity for diagnostic imaging is 5.18 MBq/kg with maximum doses typically set at 370 MBq. Although it should be avoided, venous catheters and ports may also be used for injecting [^{123}I]I- mIBG as long as the lines are adequately flushed with normal saline and are heparinised to prevent clotting. Oral administration of potassium iodide or Lugol's solution (equivalent to 100 mg iodide for adults, body weight-adjusted for children) or potassium perchlorate (400 mg for adults, body weight-adjusted for children) to block uptake of unbound ^{123}I by the patient's thyroid should be given 1 hour before, or at least 20 minutes before [^{123}I]I-Iobenguane injection. Patients, particularly children, do not like the salty flavour of Lugol's solution. Adding the prescribed dose of Lugol's solution to a patient's beverage of choice will make administration easier. Enteric tubes may also be used for administration of Lugol's solution. AdreView® also contains benzyl alcohol at a concentration of 10.3 mg/mL. Benzyl alcohol has been associated with a fatal "gasping syndrome" in premature infants and infants of low birth weight. It is not recommended to administer AdreView® to neonates or infants under 1 month of age (6).

The standard imaging protocol described in this chapter, with corresponding figure images, is to use ELEGP collimators to perform a whole-body scan with a scan speed set at 12 cm/min; acquire a lateral skull image for 3 minutes with a 256x256 matrix; SPECT/CT acquisition of the abdomen (or primary tumour location) with SPECT parameters set at a 128x128 matrix, 30 sec/stop, view angle = 6 for a total of 60 views, 159 keV primary peak +/- 7.5%, 130 keV scatter window +/- 7.5%; CT settings are set for soft tissue and are weight based.

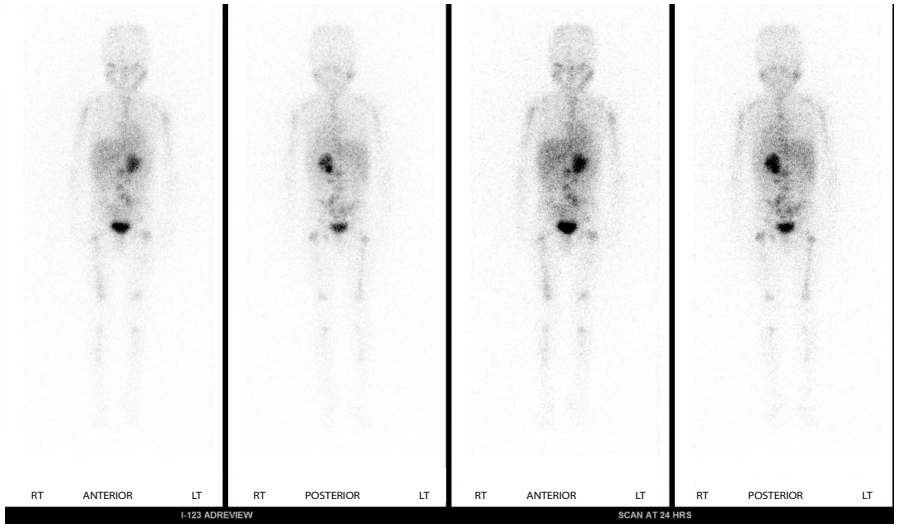


Figure 7. Caption: 4-year-old patient newly diagnosed with neuroblastoma; patient weight at time of imaging was 19.4 kg and patient was dosed with 95.83 MBq of [^{123}I]I- mIBG; standard imaging protocol was followed. On the [^{123}I]I-mIBG whole-body planar images there is persistent diffuse skeletal metastatic disease. An intensely mIBG-avid mass remains in the left upper quadrant with other paraspinal soft tissue foci of mIBG avidity. Curie score based on the planar images = 3, 3, 2, 3, 3, 3, 2, 3, 3, 2 = 27; referred for [^{131}I]I-mIBG therapy.

[^{131}I]I -mIBG post-therapy imaging

Post-therapy [^{131}I]I-mIBG imaging is routinely performed prior to patients being discharged from the hospital. Post-therapy imaging may be performed a variable amount of days after dose administration. Variability of discharge often hinges on government regulations that require a patient to remain in hospital until ambient radiation dose level, measured at 1 meter, drops to or below an approved level. Due to radiation safety precautions, [^{131}I]I-mIBG is administered on an inpatient basis. [^{131}I] I-mIBG therapy patients are placed in lead-lined rooms with appropriate lead integrity for ^{131}I therapy along with en-suite bathroom facilities. Foley catheters are often placed to reduce radiation exposure to the patient's bladder during therapy. Foley bags can be placed in lead-lined containers to minimise exposure to the patient and care providers. Connectors, tubing, and a peristaltic pump can be used to pump urine from the Foley drainage bag into a toilet. After a patient has completed [^{131}I]I-mIBG therapy and before being discharged, it is good practice to have the patient bathe so that any potential skin contamination is removed.

Imaging protocol for [^{131}I]I-mIBG therapy is equivalent to post-therapy imaging for thyroid cancer. Administered radioactivity of [^{131}I]I-mIBG is typically in the thousands of MBq, and on some occasions exceeds the 37 GBq level. Scan speeds can be shortened for younger patients in order to avoid general anaesthesia.

Whole-body scan speeds when imaging ^{131}I should be set to 15 cm/min to account for the reduced sensitivity of HEGP collimators. Lateral skull images can be acquired for 2–3 minutes with a 256x256 matrix. [^{131}I]I-mIBG uptake in the basal ganglia and cerebellum is common (7). SPECT/CT may be acquired. SPECT acquisition should be set to 15 sec/stop, view angle = 6 for a total of 60 views, 364 keV primary peak +/- 10 %, 297 keV scatter window +/- 10%; CT settings are set for soft tissue and are weight based. SPECT/CT could be used for radiation dosimetry, or if lesions are visualised on the whole-body scan that were not visualised with [^{123}I]I-mIBG, diagnostic imaging can be performed prior to [^{131}I]I-mIBG therapy.

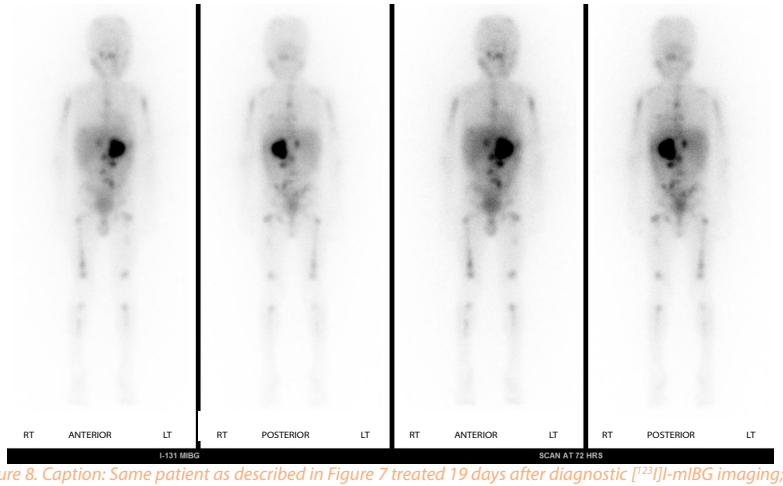


Figure 8. Caption: Same patient as described in Figure 7 treated 19 days after diagnostic [^{123}I]I-mIBG imaging; patient weight at time of therapy was 19.4 kg and patient was dosed at treatment level of 666 MBq/kg, administered dose of [^{131}I]I-mIBG was 13.727 GBq; patient met discharge criteria of <7 mR/hr after 3 days and underwent post-therapy imaging. Abnormal radiotracer uptake is present within the calvarium, axial and appendicular skeleton and in multiple abdominal masses.

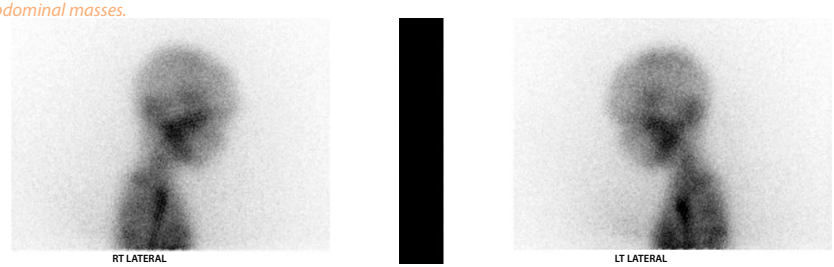


Figure 9. Caption: Same patient as in Figure 8. Post-therapy lateral skull images are acquired as standard post therapy; image demonstrates [131I]I-mIBG uptake in the basal ganglia and cerebellum, considered to be a normal variant.

POST-THERAPY IMAGING IN PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)

PRRT is a targeted systemic molecular therapy for patients with gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs). GEP-NETs are tumours of neuroendocrine cells typically found in the pancreas, stomach, small intestine, rectum, colon or appendix. Although mostly non-functioning, some tumours are associated with a clinical syndrome due to hormone production (functioning NETs). Well-differentiated GEP-NETs express somatostatin receptors that are the target of PRRT. Imaging of somatostatin receptor expression using PET/CT is routinely used for disease staging/restaging and selection of candidate patients to be treated with PRRT. [^{177}Lu]Lu-DOTATATE was the first PRRT radiopharmaceutical approved by the United States Food and Drug Association in 2018: it acts by binding to the somatostatin receptors on the surface of a GEP-NET. [8] [^{177}Lu]Lu-DOTATATE is typically given once every 8 weeks for a total of 4 doses (in association with standard octreotide treatment). ^{177}Lu-Lutathera® is a safe and effective treatment for GEP-NETs that has been shown to increase progression-free survival and overall survival. [9] Imaging is typically done before and after treatment to assess eligibility and treatment response, respectively.

Pre-therapy imaging

Nuclear imaging for NETs was first done using [^{111}In]In-octreotide, a tracer that has been used for decades to diagnose somatostatin receptor-positive GEP-NETs. Many institutions perform imaging at 4 h and 24 h post injection. Both a whole-body scan and at least one SPECT/CT should be acquired. Two sets of images are often done when using this radiopharmaceutical due to bowl radioactivity that can be more prevalent on 24 h imaging. However, 4 h images should not be used alone as there is often high background radioactivity. One option to improve target to non-target radioactivity may be to prescribe a laxative between the 4 h and 24 h scans or to have the patient follow a clear liquid diet. For [^{111}In]In-octreotide, peaks of 172 keV ± 10% and 245 keV ± 10% should be used with medium-energy general-purpose collimators. The patient will first complete a whole-body scan positioned feet first supine, 256 x 256 matrix, continuous with body contour; a scan speed of 5 cm/min should be used for 4 h imaging, while 7 cm/min can be used for 24 h imaging. Following the whole-body scan, a nuclear medicine physician will review the images and determine which region to acquire a SPECT/CT of based on where disease is seen. Depending on disease extent and location, a one-, two- or three-bed SPECT/CT may be performed. The SPECT/CT parameters are 128 x 128 matrix, 30 sec/stop, view angle of 6 for a total of 60 views. Standard CTAC imaging parameters should be used as defined by the imaging institution; for adults this is typically 30–60 mAs and 100–120 kV.

Novel PET/CT tracers were later discovered and showed higher accuracy in well-differentiated NETs and high inter-observer agreement. These tracers are labelled with [^{68}Ga]Ga-DOTATATE or [^{64}Cu]Cu-DOTATATE. [^{68}Ga]Ga-DOTATATE has become the main tracer used for GEP-NET imaging, while [^{64}Cu]Cu-DOTATATE was introduced later on. Both PET/CT agents have proved to have better imaging quality than the previously used nuclear imaging tracer [^{111}In]In-octreotide. For PET/CT imaging no patient preparation is required. A standard uptake time of 55–75 minutes should be used. The technologist should verify that the PET/CT scanner is set to [^{68}Ga]Ga-DOTATATE or [^{64}Cu]Cu-DOTATATE and images should be acquired vertex to mid-thigh, 1 to 3 minutes per bed depending on patient body habitus and sensitivity of the PET scanner. For CT imaging a standard breath hold should be used with CTAC imaging parameters defined by the imaging institution; for adults this is typically 30–60 mAs and 100–120 kV. A diagnostic CT of the abdomen and pelvis may also be requested, using intravenous contrast media: it is recommended to perform this scan after the PET/CT in order to avoid attenuation correction artefacts. [10] Figure 10 shows a pre-therapy PET/CT maximum intensity projection image of a patient with metastatic carcinoid tumour.

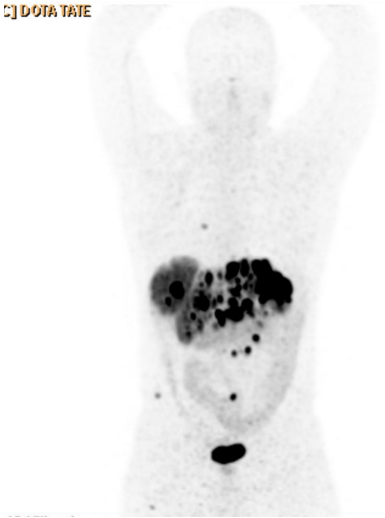


Figure 10. PET/CT maximum intensity projection image. The pre-therapy scan was completed using a dose of 4.1 mCi of [^{68}Ga]Ga-DOTATATE. Imaging began at 61 minutes post injection.

Post-therapy imaging

Post-therapy imaging for [^{177}Lu]Lu-DOTATATE therapy can be performed at variable time points including 1 h, 4 h, 24 h, 72 h or 96 h post therapeutic infusion. Same-day imaging may be complicated by scanner availability and infusion timing; for this reason, 24 h imaging may be a favourable standard for an institution to adopt. Both a whole-body scan and SPECT/CT should be performed. For [^{177}Lu]Lu-DOTATATE, peaks of 113 keV ± 10% and 208 keV ± 10% should be used with medium-energy general-purpose collimators. The patient will first complete a whole-body scan positioned feet first

supine, 256 x 256 matrix, continuous with body contour at a scan speed of 10-13 cm/min. Following the whole-body scan, a nuclear medicine physician will review the images and determine which region to acquire a SPECT/CT of based on where disease is seen or suspected. Depending on disease extent and location, a one- to two-bed SPECT/CT may be performed, to encompass chest, abdomen or pelvis. The SPECT/CT parameters are 128 x 128 matrix, 30 sec/stop, view angle of 6 for a total of 60 views. Standard CTAC imaging parameters should be used as defined by the imaging institution; for adults this is typically 30–60 mAs and 100–120 kV.

Figure 11 shows the planar post-therapy imaging of the patient from Figure 10 after two cycles of [^{177}Lu]Lu-DOTATATE therapy. The image on the left was acquired 24 h post first [^{177}Lu]Lu-DOTATATE therapy using a dose of 198.2 mCi given over 38 minutes. On the right, post-therapy imaging was acquired 24 h post second [^{177}Lu]Lu-DOTATATE therapy using a dose of 199.1 mCi given over 36 minutes. Post-therapy imaging visualises hepatic metastasis as well as one lymph node that was seen on the pre-therapy scan.

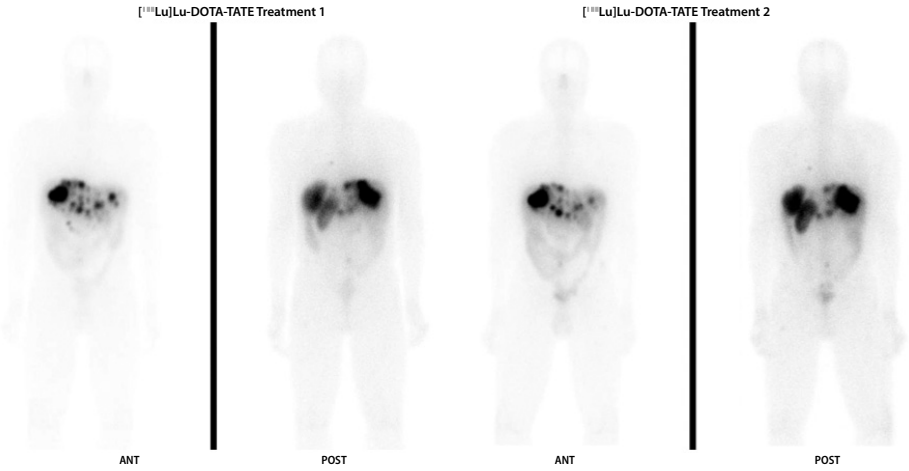


Figure 11- Left: Planar post-therapy imaging acquired 24 h post first therapy using a dose of 198.2 mCi. Right: Planar post-therapy imaging acquired 24 h post second therapy using a dose of 199.1 mCi.

Figure 12 shows post-therapy imaging after two cycles of [^{177}Lu]Lu-DOTATATE therapy. In this image we can see the difference between absorbed doses in the kidneys. Dosimetry can be performed after each therapy to determine absorbed dose to major organs at risk, which include the kidneys. The post-therapy image on the left was acquired 24 h post first [^{177}Lu]Lu-DOTATATE therapy using a dose of 197.7 mCi given over 31 minutes. On the right, post-therapy imaging was acquired 24 h post second [^{177}Lu]Lu-DOTATATE therapy using a dose of 198.3 mCi given over 35 minutes. Post-therapy imaging shows well-visualised extensive metastasis to the bone and several lesions in the liver.

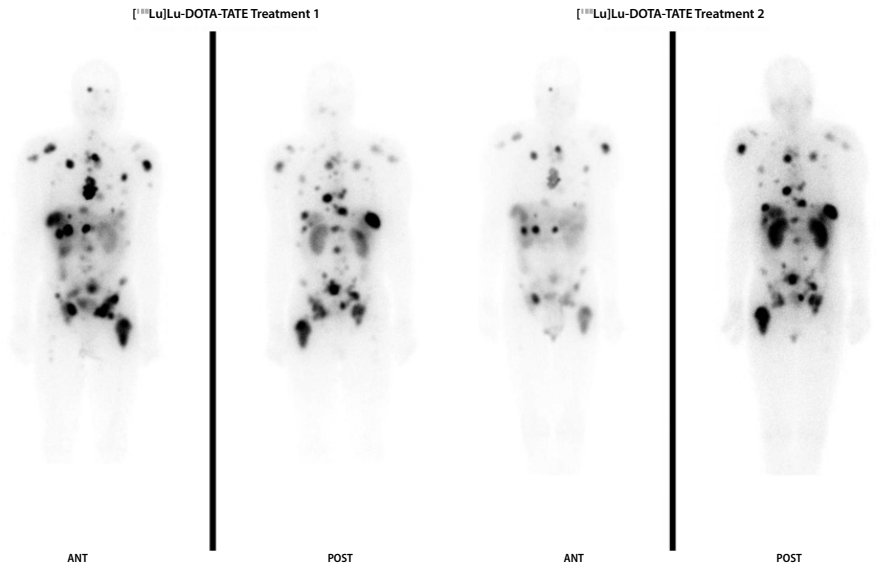


Figure 12-Left: Planar post-therapy imaging acquired 24 h post first therapy using a dose of 197.7 mCi. Right: Planar post-therapy imaging acquired 24 h post second therapy using a dose of 198.3 mCi.

POST-THERAPY IMAGING IN ^{90}Y RADIOEMBOLISATION

Radioembolisation is a palliative treatment used to treat tumours in the liver by depositing glass or resin microspheres filled with radioactive 90-Yttrium (^{90}Y) or ^{166}Ho. ^{90}Y is infused intra-arterially by an interventional radiologist in conjunction with nuclear medicine specialists. This treatment is used to target tumour cells versus healthy liver cells, delivering a radiation dose by way of microspheres. A pre-therapy evaluation for treatment planning must be performed using nuclear imaging to ensure that no significant lung shunting is present and to identify the lesions to verify the dose that will be injected.

Pre-therapy imaging

Pre-therapy imaging for ^{90}Y is done in order to assess lung shunting in the patient. The lung shunting calculation may lead to a dose adjustment, which makes this imaging crucial for treatment planning and patient safety. This imaging is completed in conjunction with the interventional radiology (IR) department. The patient will undergo angiography in the IR suite, which may include coil placements to occlude other arteries or vessels and ensure the microspheres remain in the liver. Once the intra-arterial catheter is in place, the nuclear medicine team will administer 1–5 mCi of [^{99m}Tc]Tc-MAA. [^{99m}Tc]Tc-MAA is used as it is a particulate that is comparable to the size of the tiny resin or glass microspheres. The interventional radiology team will complete the procedure and the patient will then proceed to the nuclear medicine department for imaging. Images should be acquired as soon as possible after administration of [^{99m}Tc]Tc-MAA: this is because the tracer will begin to redistribute and the free pertechnetate will be more prominent in the thyroid, stomach and bladder. [11]

Imaging will consist of planar views for shunt calculation and a SPECT/CT over the liver. A peak of 140 keV ± 10% should be used, with low-energy high-resolution collimators. Two five-minute static images should be acquired over the chest and abdomen. For the chest image the liver should be at the bottom of the field of view for lung visualisation. The abdomen view should place the liver at the top/middle of the field of view to assess for extrahepatic perfusion. ROIs are drawn for both the lungs and the liver, and the shunt is calculated. A one- or two-bed SPECT/CT may be requested. Standard imaging will include a SPECT/CT of the liver; however if lung shunting is present a two-bed SPECT/CT may be requested to encompass all of the lungs and liver. Parameters are 128 x 128 matrix, 30 sec/stop, view angle of 6 for a total of 60 views. Standard CTAC imaging parameters should be used as defined by the imaging institution; for adults this is typically 30–60 mAs and 100–120 kV.

Post-therapy imaging

Post-therapy imaging after intra-arterial infusion of ^{90}Y-microspheres captures bremsstrahlung radiation. Imaging can be done using a gamma camera or a PET/CT scanner. Bremsstrahlung scans can be clinically useful in evaluating intrahepatic and extrahepatic biodistribution. Imaging typically occurs 2–8 hours after microsphere infusion and includes a static image of the liver and SPECT/CT over the liver. For this imaging a medium-energy general-purpose (MEGP) collimator is used with an energy window of 80 keV +- 30%. The static liver image is acquired for 5 minutes over the liver using a 256 x 256 matrix. In this image you will typically be able to see evidence of extrahepatic leak if it is present; based on this static a two-bed SPECT/CT may be needed to cover a larger area of the body. The SPECT/CT parameters are 128 x 128 matrix, 30 sec/stop, view angle of 6 for a total of 60 views. Standard CTAC imaging parameters should be used as defined by the imaging institution; for adults this is typically 30–60 mAs and 100–120 kV.

PET/CT scans may provide better information than a SPECT/CT for ^{90}Y post-therapy imaging. SPECT/CT can be limited by scatter and septal penetration due to the continuous energy. PET/CT images are superior when it comes to spatial resolution [12]. PET/CT should be acquired 2–3 hours post ^{90}Y infusion. A standard PET/CTAC protocol is used, scanning vertex to mid-thigh at two minutes per bed for a scan time of around 15 minutes [13]. Figure 13 shows pre-therapy imaging using [^{99m}Tc]Tc-MAA, visualising any extrahepatic shunting that may be present. In comparison, the image on the right shows the same patient post treatment, indicating where the ^{90}Y-microspheres were distributed.

^{90}Y post-therapy imaging is important to localise where the microspheres have deposited. Microspheres may deposit outside the liver despite the pre-therapy imaging, as this treatment is dependent on angiography catheter placement. If extrahepatic activity is detected on post-therapy imaging, management may change. ^{90}Y post-therapy imaging can be performed using either SPECT/CT or PET/CT. Figure 14 shows the difference between SPECT/CT and PET/CT imaging post ^{90}Y-microsphere therapy. The PET/CT image of the patient demonstrates better spatial resolution than the SPECT/CT image, which can be an advantage of choosing this modality for imaging.

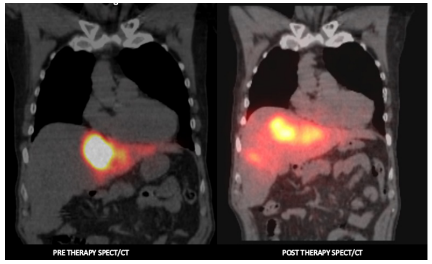


Figure 13Left: Pre-therapy SPECT/CT imaging with [99mTc] Tc-MAA injection. Right: Post- therapy 90Y SPECT/CT.

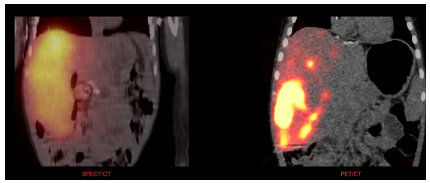


Figure 14Left: SPECT/CT imaging post 90Y-microsphere therapy Right: PET/CT imaging post 90Y-microsphere therapy.

CONCLUSION

Theranostics represents an emerging field of nuclear medicine. Both pre-therapy and post-therapy imaging procedures will be increasingly utilised as new radiopharmaceuticals become available for therapy. Post-therapy imaging allows targeted dosimetry. This imaging will advance the way in which radioactive therapy doses are determined and will most likely become the standard of care in theranostics as the field advances. Moreover, post-therapy imaging can provide clinical information that can aid in subsequent treatment planning without adding significant radiation dose to the patient by simply imaging the therapeutic activity that has been administered to the patient. The field of theranostics will continue to evolve as new radionuclides are developed and the imaging capabilities of PET/CT and SPECT/CT advance. Table 1 describes practice guidelines for implementing pre- and post-therapy imaging. Standardisation of imaging parameters will allow comparison between each subsequent post-therapy and restaging scan. Post-therapy imaging will impact the clinical management of patients by influencing personalised treatment decisions. Radiotherapy can provide target-based dosimetry tailored to disease type and radiotherapeutic analogue. As nuclear medicine evolves, theranostics including post-therapy imaging will become part of common clinical practice.

Radiopharmaceutical	Pre-Therapy Imaging Guidelines		Post Therapy Imaging Guidelines	
[^{131}I]NaI	[^{123}I]NaI Gamma camera: ELEGP, LEHR or MEGP collimators, 159 keV primary peak +/- 7.5%, 130 keV scatter window +/- 7.5% Planar whole body: 12cm/min, 256 x 256 matrix, body contour SPECT/CT: body contour, 128x128 matrix, 30 sec / stop, view angle = 6, 60 total views	[^{131}I]NaI Gamma camera: HEGP collimators, 364 keV primary peak +/- 10 % 297 keV scatter window +/- 10% Planar whole body: 6-8 cm/min, 256 x 256 matrix, body contour SPECT/CT: body contour, 128x128 matrix, 40 sec / stop, view angle = 6, 60 total views	Gamma camera: HEGP collimators, 364 keV primary peak +/- 10 % 297 keV scatter window +/- 10% Planar whole body: 15cm/min, 256 x 256 matrix, body contour SPECT/CT: body contour, 128x128 matrix, 30 sec / stop, view angle = 6, 60 total views	
[^{131}I]I-mIBG	[^{123}I]I-Iobenguane Gamma camera: ELEGP, LEHR or MEGP collimators 159 keV primary peak +/- 7.5%, 130 keV scatter window +/- 7.5% Planar whole body: 12cm/min, 256 x 256 matrix, body contour SPECT/CT: body contour, 128x128 matrix, 30 sec / stop, view angle = 6, 60 total views		Gamma camera: HEGP collimators, 364 keV primary peak +/- 10 % 297 keV scatter window +/- 10% Planar whole body: 15cm/min, 256 x 256 matrix, body contour SPECT/CT: body contour, 128x128 matrix, 30 sec / stop, view angle = 6, 60 total views	
[^{177}Lu]Lu-DO-TATATE	[^{111}In]In-octreotide Gamma camera: MEGP collimators peaks of 172 keV ± 10% and 245 keV ± 10% Planar whole body: 5-7 cm/min, 256 x 256 matrix, body contour SPECT/CT: body contour, 128x128 matrix, 30 sec / stop, view angle = 6, 60 total views	[^{64}Cu]Cu-DOTATATE or [^{68}Ga] Ga-DOTATATE PET/CT: Vertex to mid-thigh, 1-3 minutes per bed based on patient's body habitus and scanner sensitivity	Gamma camera: MEGP Collimators peaks of 113 keV ± 10% and 208 keV ± 10% Planar whole body: 10-13 cm/min, 256 x 256 matrix, body contour SPECT/CT: body contour, 128x128 matrix, 30 sec / stop, view angle = 6, 60 total views	
^{90}Y-microspheres	[^{99m}Tc] Tc-MAA Gamma camera: LEHR collimators, peak of 140 keV ± 10% Statics: Chest and abdomen, 5 minutes each to calculate shunting SPECT/CT: body contour, 128x128 matrix, 30 sec / stop, view angle = 6, 60 total views		Gamma camera: MEGP collimators peak of 80 keV +- 30% SPECT/CT: body contour, 128x128 matrix, 30 sec / stop, view angle = 6, 60 total views	PET/CT: Vertex to Mid Thigh, 2 minutes per bed based on patients body habitus and scanner sensitivity

Table 1: Guidelines for pre- and post-therapy imaging

REFERENCES:

1. HERTZ S, ROBERTS A. RADIOACTIVE IODINE IN THE STUDY OF THYROID PHYSIOLOGY: VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism. JAMA. 1946;131(2):81–86. doi:10.1001/jama.1946.02870190005002
2. Sekikawa, Y., Funada, K., Akamatsu, G. et al. Monte Carlo simulation of the acquisition conditions for 177Lu molecular imaging of hepatic tumors. Ann Nucl Med 35, 823–833 (2021). https://doi.org/10.1007/s12149-021-01620-9
3. Morphis, M., van Staden, J.A., du Raan, H. et al. Evaluation of Iodine-123 and Iodine-131 SPECT activity quantification: a Monte Carlo study. EJNMMI Phys 8, 61 (2021). https://doi.org/10.1186/s40658-021-00407-1
4. Dobbeleir AA, Hambÿe AS, Franken PR. Influence of high-energy photons on the spectrum of iodine-123 with low- and medium-energy collimators: consequences for imaging with 123I-labelled compounds in clinical practice. Eur J Nucl Med. 1999 Jun;26(6):655-8. doi: 10.1007/s002590050434. PMID: 10369952.
5. Ferrari, M., De Marco, P., Origgi, D. et al. SPECT/CT radiation dosimetry. Clin Transl Imaging 2, 557–569 (2014). https://doi.org/10.1007/s40336-014-0093-8
6. AdreView (Iobenguane I 123 Injection) Label (fda.gov)
7. Susan E. Sharp, Andrew T. Trout, Brian D. Weiss, and Michael J. Gelfand RadioGraphics 2016 36:1, 258-278 https://doi.org/10.1148/rg.2016150099
8. Hennrich U, Kopka K. Lutathera®: The First FDA- and EMA-Approved Radiopharmaceutical for Peptide Receptor Radionuclide Therapy. Pharmaceuticals (Basel). 2019;12(3):114. Published 2019 Jul 29. doi:10.3390/ph12030114
9. Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, van Eijck CHJ, Franssen GJH, Krenning EP, Kwekkeboom DJ. Long-Term Efficacy, Survival, and Safety of [177Lu-DOTA0,Tyr3] octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. Clin Cancer Res. 2017 Aug 15;23(16):4617-4624. doi: 10.1158/1078-0432.CCR-16-2743. Epub 2017 Apr 20. PMID: 28428192.
10. Nakamoto Y, Chin BB, Kraitchman DL, Lawler LP, Marshall LT, Wahl RL. Effects of nonionic intravenous contrast agents at PET/CT imaging: phantom and canine studies. Radiology. 2003;227(3):817-824.
11. Giammarile F, Bodei L, Chiesa C, Flux G, Forrer F, Kraeber- Bodere F, et al. EANM procedure guideline for treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur J Nucl Med Mol Imaging. 2011;38:1393-406.
12. Elschot M, Vermolen BJ, Lam MG, de Keizer B, van den Bosch MA, de Jong HW. Quantitative comparison of PET and bremsstrahlung SPECT for imaging the in vivo yttrium-90 microsphere distribution after liver radioem- bolization. PLoS One. 2013;8:e55742.

6

INFORMED CONSENT

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In this chapter, we will provide an overview on why and how we need to obtain informed consent. The first part deals with informed consent during routine clinical practice. The second part focusses on informed consent in theranostic and radionuclide therapy (RNT) research.

CONSENT

Consent is the patient's agreement to participate in specific medical activities, be they diagnostic or therapeutic. Informed consent means that the patient has substantial knowledge of the nature of the specific procedures, this knowledge being essential in order for true consent to be given. The process of obtaining consent is hence mainly about providing information to the patient and allowing time for them to understand the potential risks and benefits of a procedure and ask questions about aspects they do not understand. The process ends with the documentation of the consent provided by the patient. In many European countries this concept has been incorporated in the legislation regulating medical practice, so that the consent process is actually a legal obligation. However, the formal requirements may differ from country to country.

One topic to address during the informed consent process in our field is the fact that we will administer radioactive substances (pharmaceuticals or devices) to patients. The general public's knowledge about radioactivity is very limited, and this can be a source of anxiety. Proper counselling about the nature of radioactivity and its limited risk in the nuclear medicine setting is of paramount importance. The consent process also requires a discussion of alternatives that could be used instead of the chosen procedure. It can be useful and reassuring for the patient to mention that the proposed therapy has been endorsed by a team of disease specialists on a multidisciplinary tumour board. The discussion should focus on the potential benefits and risks that the RNT entails for the patient. Other aspects to mention include logistical aspects (e.g. hospitalisation on the therapy ward; radiation protection measures) and potential financial aspects of the treatment (e.g. in case of partial or non-reimbursement of costs).

Why informed consent in standard clinical care?

The need for informed consent in routine clinical care derives from the concept of individual autonomy of the patient and his/her/they right to self-determination. This is considered a very important aspect of our lives as human beings and can be envisioned as a logical end result of the millennium-long medical tradition which started with the Hippocratic oath sworn by medical practitioners and culminated in the modern-day Physician's Pledge as part of the Declaration of Geneva adopted by the World Medical Association (1). The Pledge contains the following section: "The health and well-being of my patient will be my first consideration. I will respect the *autonomy* and the dignity of my patient." Respecting the autonomy of the patient requires proper information and final agreement.

How is consent given?

Obtaining informed consent from the patient is the task of the physician, who provides the relevant information and has the knowledge to answer questions raised by the patient. The patient's agreement to participate in specific medical activities can be formulated either implicitly or explicitly. Under Belgian law, for instance, consent is deemed to have been given if the patient, by his/her/they actions, accepts and actively participates in the diagnostic steps or therapies that are performed. The form of the given consent can be either oral, electronic or handwritten. It can be provided by the patient him- or herself, the parent or legal guardian in the case of a minor, or the legal representative in the case of a patient who is not able to exercise his/her/they legal rights by him- or herself. The documentation of the provided consent can be done either by the consenter, by signing an informed consent form, or it can be recorded by the medical practitioner in the electronic medical file.

Legal requirements in different countries may make specific types of consent mandatory (e.g. implicit, or written document).

PROGNOSTIC IMPACT

Theranostic and functional imaging

During the work-up for RNT, patients undergo a substantial amount of imaging procedures. In almost all types of RNT, theranostic imaging is performed to establish sufficient uptake of a diagnostic mimic of the therapeutic radiopharmaceutical, a mimic which is given in trace amounts and entails virtually no risk. Examples include PET/CT imaging of the somatostatin receptor ([^{6}8Ga]Ga-DOTA-somatostatin analogues such as octreotide and octreotate) for peptide receptor radionuclide therapy (PRRT; e.g. [^{177}Lu]Lu-DOTATATE), prostate-specific membrane antigen (PSMA) PET/CT for PSMA-based radioligand therapy (PRLT; e.g. [^{177}Lu]Lu-vipivotide tetraxetan, previously known as [^{177}Lu]Lu-PSMA), [^{123}I]I-mIBG scintigraphy to document norepinephrine transporter expression for [^{131}I]I-mIBG therapy, and bone scintigraphy to document enhanced bone remodelling for [^{223}Ra]$RaCl_2$ therapy. Other imaging used in RNT depicts organ function, for instance [^{99m}Tc]Tc-BRIDATEC (a.k.a. [^{99m}Tc]Tc-mebrofinin) scintigraphy to depict hepatic function for the planning of radioembolisation, or [^{99m}Tc]Tc-MAG3

renography that can be used in the planning of PRRT or PSMA PRLT. Other nuclear medicine procedures include functional tests without imaging, e.g. [^{51}Cr]Cr EDTA glomerular filtration (GFR) assays to determine kidney function before PRRT.

Patients undergoing RNT are hence exposed to a number of routine diagnostic tests. It is important to note that these routine diagnostic nuclear medicine tests are associated with low to very low risks. As these diagnostic tests are based on the "tracer principle", only negligible mass amounts are injected without any pharmacological effect. The patient spends a limited time (15 to 60 minutes) on the camera, which is associated with limited discomfort. Venipunctures are performed, which can result in haematoma and peripheral nerve injuries. However, the incidence of the latter is very low, in the order of 1 per 20 000 to 1 per 67 000 injections (2). The vast majority of contemporary nuclear medicine imaging is hybrid imaging, the main hybrid radiological modality being CT. CT examinations in SPECT/CT and PET/CT can make use of contrast agents, which can pose certain risks. Radiological contrast extravasation was reported in 514 out of 502 391 procedures (~0.1% incidence) in one North American study (3). Pseudo-allergic hypersensitivity reaction to contrast agents can also occur. A recent Korean study observed 1 433 reactions in 19 601 (0.73%) administrations, but only 17 of these reactions were severe (~0.01%) (4); hence the total incidence of CT-contrast agent incidents is less than 1%.

There is a radiation burden associated with diagnostic nuclear medicine procedures, which ranges from ~0.05 mSv (e.g. [^{51}Cr]Cr EDTA GFR assay) to 20–50 mSv for PET scans using zirconium-89 monoclonal antibodies. The radiation burden from hybrid CT, which can range from 1 to 10 mSv, needs to be added to obtain the total radiation burden.

The dominant risk to the patient may originate from the CT part of the examination, mainly from the IV-injected contrast agent, but this risk is less than 1% for predominantly non-severe side effects. Given this low incidence, this does not require extensive discussion in a number of countries, including Belgium.

What to communicate?

Oncological patients undergo numerous interventions, and in many of these very little formal informed consent is obtained. When the examination is prescribed by the referring physician, the nuclear medicine physician will review the medical history, the clinical information provided and the specific question to be addressed. He or she will weigh the risks and benefits of the procedure in this specific situation and validate the examination as justified, after which the examination can be booked.

The focus of the provided information is more on explaining the nature of the examination and the logistics involved (time schedule, required dietary restrictions such as fasting, adjustment of medication, etc.). This information is provided by the referring physician when scheduling the examination and supplemented by the nuclear medicine team (physician and technologist) performing the examination.

Consent in this case is mostly implicit and is marked by the patient turning up for the diagnostic procedure and cooperating during the examination. This type of implicit consent is perfectly acceptable within the legal framework of some European countries.

Radionuclide treatment proper

At our centre, informant consent is obtained during the outpatient visit ("status visit") that takes place before every RNT procedure. The patient is often accompanied by a trusted person who will help the patient throughout the treatment, which can be their spouse, partner, child or a friend. The information is provided to the patient orally and in written form. An extensive report is provided to the referring physician (often an oncologist) as well as the family physician, to create a paper and/or digital trail of consent for the other physicians involved in the patient's care.

During these outpatient visits we first discuss the therapy concept, which is based on targeted radioactivity that will destroy cancer cells by internal radiation. These therapies consist of currently used RNT radiopharmaceuticals, i.e. β-emitters or α-emitters. It is important to realise that the lay public is unfamiliar with the concept of radioactivity. The vast majority of patients are unaware of the underlying physical mechanisms that occur during radioactive decay. The effects of radioactivity are largely misrepresented in the popular media, with a strong exaggeration of the detrimental effects of ionising radiation. Patients may also have fears about potential detrimental effects to themselves or the people around them (e.g. family members and co-workers). It is important to alleviate these fears by providing reliable, evidence-based information. We typically do this by focusing on the type of radiation emitted, i.e. a limited range of beta and alpha particles (~1 cm to 1/10th mm, respectively), which strongly limits the amount of radiation which will actually exit the body of the patient. We stress the potential for contamination, which can occur through urine and blood in the majority of RNT performed, via faeces in particular therapies ([^{223}Ra]$RaCl_2$), and via sweat in some therapies with radiopharmaceuticals containing iodine-131.

Therapy concept – targeted radioactivity

The type of emissions that are used, i.e. β- and α-emitters, and the dominant excretion routes of the radiopharmaceutical (or its radionuclide-containing metabolites) have to be explained. Some radiopharmaceuticals can result in excretion of radioactivity in saliva and sweat, particularly molecules containing iodine-131, so the patient needs to be aware that saliva or sweat can be a route of contamination.

The external dose rate can range from very low with α-emitters (e.g. [^{223}Ra]$RaCl_2$ or Xofigo® in prostate cancer patients) up to hundreds of µSv per hour at 1 metre with radiopharmaceuticals containing iodine-131 given in GBq amounts. With high external dose rates, hospitalisation in a dedicated radionuclide therapy ward is warranted and, depending on the country, may indeed be a legal requirement. Such a mandatory stay and its anticipated length is obviously mandatory information to discuss during an informed consent procedure.

Benefits of radionuclide therapies and goal of treatment

The benefits of RNT vary and depend on a large range of variables, including: (i) the target and type of radiopharmaceutical used; (ii) the cancer type; (iii) the disease setting and stage: e.g. solitary tumour treated by ablative liver radiosegmentectomy with a realistic potential for cure vs. polymetastatic disease in a heavily pretreated patient with a large tumour burden and limited functional reserve; (iv) the oncological setting (adjuvant treatment, e.g. [^{131}I]NaI in thyroid cancer vs. neo-adjuvant setting vs. non-curative tumour control treatment; (v) the therapeutic aim (curative, tumour control, symptom control).

The evidence base for clinically performed RNT is heterogeneous: some therapies are supported by robust data from randomised clinical trials (RCTs), some by data from phase II or even case series, while others predate the era of rigorous prospective evaluation of cancer therapies (e.g. [^{131}I]NaI in thyroid cancer). Some therapies are supported by retrospective studies of RNT that is performed in a "last resort" attempt in patients for whom no other validated options are available and that can be treated at the discretion of the treating physician (e.g. based on the German Pharmaceuticals Act §13(2b)). In this particular setting, the patient should be made aware that the proposed treatment is not supported by any clinical scientific evidence. The benefit is reflected by different endpoints: (i) tumour response (objective decrease on imaging); (ii) progression-free survival (PFS) or overall survival (OS); (iii) improvement of quality of life (QoL) or prolongation of time to QoL deterioration; (IV) potential to improve symptoms, e.g. pain or hormonal symptoms in patients with neuroendocrine tumours. Most of the currently used RNT are corroborated by documentation of at least one of these types of benefit, and for some radiopharmaceuticals (e.g. [^{177}Lu]Lu-vipivotide tetraxetan, previously known as [^{177}Lu]Lu-PSMA) there is data that demonstrates objective response, PFS prolongation, amelioration of QoL, symptom improvement and overall survival.

Risks: RNT side effects

The risks or side effects are the most important item to discuss with the patient during the informed consent process. They are heavily dependent on the specific type of therapy and the radiopharmaceutical or device used. They can be linked to the biodistribution of the radiopharmaceutical we use, the residence time in the different healthy organs and the energy of the emitted particles, which will determine the radiation range within the tissue. The temporal emergence of side effects can be roughly subdivided into 3 broad categories: (i) acute side effects that manifest within 24 hours after injection; (ii) subacute side effects, emerging within days to weeks after administration; (iii) late side effects, which for ionising radiation are known to occur up to years after treatment. Another important distinction is the severity of the side effects. Side effects can be light and have little impact on the patient's functioning and QoL, or they can be so severe as to cause loss of organ function or even death. Finally, the evolution of the side effects is important: this can range from total disappearance ("restitutio ad integrum") to permanent side effects, which are typically associated with late side effects of radiation. Late side effects of ionising radiation are typically irreversible, with increasing severity over time. Once these side effects occur, the resulting damage cannot be undone: the damage is the consequence of the treatment given several years ago and, in contrast to many other systemic therapies, there is no ongoing treatment that can be stopped to reverse the side effects. The treatment responsible for the side effect has already been stopped for months to years when the effect occurs. The common side effects that are known from the literature have to be mentioned for each specific therapy. Severe and irreversible side effects, which fortunately are rare, have to be mentioned and their incidence estimated as precisely as possible. The patient needs to be aware of these potential side effects at the time he or she gives consent to the treatment.

Types of RNT side effects

Acute side effects during RNT are typically not due to the ionising radiation, but are caused by other phenomena. During radioembolisation, an embolisation syndrome can occur due to obstruction of the arterial capillary bed by the radioactive microspheres, resulting in transient arterial hypoperfusion with relative hypoxia and the associated symptoms. Non-radioactive carrier molecules in low-activity [^{131}I]I-mIBG can result in pharmacological effects such as tachycardia and hypertension. The potential of nephroprotective amino acids, administered during somatostatin-receptor PRRT, to induce nausea and vomiting are very well documented.

Subacute side effects are more diverse, with myelosuppression being very frequently encountered in many different types of RNT. Other subacute side effects are more related to particular therapy types such as [^{131}I]NaI, which can accumulate not only in the thyroid gland but also in the salivary glands with associated side effects (e.g. sialadenitis).

One example of late side effects is kidney failure, which is associated with [^{90}Y]Y-DOTATOC-based PRRT. The pronounced difference in end-stage renal failure after PRRT observed with [^{90}Y]Y-DOTATOC (9.2%) (5) vs. [^{177}Lu]Lu-DOTATATE (<0.5%) (6) is in all likelihood caused by the higher energy of the β-radiation emitted by ^{90}Y and thus the more profound irradiation reaching into the most sensitive parts of the kidney, which are the glomeruli. Administration of amino acids can reduce the kidney uptake by 25 to almost 50%, with a lower absorbed kidney dose and hence a lower risk of kidney function deterioration. Data from Rotterdam in which 610 patients treated with [^{177}Lu]Lu-DOTATATE PRRT were observed in a safety cohort showed less than 0.5% renal failure. When using a similar therapy regimen (which was also adopted in the Netter-1 trial), the risk of renal failure is small.

Another example of an RNT side effect is xerostomia (dry mouth), a disorder characterised by reduced salivary flow in the oral cavity, which occurred in 38.8% of the patients treated with [^{177}Lu]Lu-PSMA (approved by the American Food and Drug Administration under the name [^{177}Lu]Lu-vipivotide tetraxetan) in the VISION registration trial (7). Grade 3 events according to the Common Terminology Criteria for Adverse Events (CTCAE) were not observed, so all events were grade 1 or 2. Typically only grade 3 events or higher are considered to be major concerns in oncological patients, and grade 1 and 2 effects are considered minor issues that should not interfere with the treatment. It is important to realise that xerostomia is not a classical side effect of chemotherapy and that the development of the CTCAE criteria has been largely based on the experience with chemotherapy development. CTCAE grade 3 xerostomia is the inability to take food orally, hence requiring either nasogastric tube feeding, gastrostomy feeding or total parenteral nutrition. Grade 2 is alteration of oral intake, e.g. copious fluid drinking and diet limited to puree, hence grade 2 xerostomia can already have a significant deleterious impact on quality of life. In many patients, this is a transient effect. Xerostomia induced by alpha-emitting PSMA ligands might be more pronounced. In the setting of a non-curative tumour control treatment, this type of side effect with a potential effect on quality of life is crucial information for the patient to know before starting the treatment, so that he/she can weigh the benefits against the risks.

Logistics – practicalities

RNT is a complex process with many logistical requirements. These include, amongst others, potential hospitalisation in an RNT ward and radioprotection measures that the patient has to apply at home. RNT can be performed in an outpatient or an inpatient setting. The length of the hospital stay is variable, ranging from 1 night to 5–7 days. Inpatients reside in special rooms built for RNT, which are equipped with shielding for high-energy gamma rays and facilities for collection of radioactive excreta. The latter can be done using decay tanks, centralised waste-water treatment plants or freezer toilets. The patient needs to be informed about their stay on the RNT ward, the necessity to stay inside and the need to use special toilets, if applicable. Furthermore, if radioprotective measures are to be applied at home, the patient needs to be informed about these before consenting. Radioprotective measures can also have an impact on the patient's work, precluding them from carrying out their normal employment for a certain time period. Finally, there can also be a moratorium on incineration of the body in the event of premature death closely after treatment, to limit incineration-induced spread of radioactivity.

Financial toxicity is another topic of concern for oncological patients, and one that should be properly discussed. The cost of therapeutic radiopharmaceuticals can range from €100 to €20,000 or even more for recently developed treatments. The cost may be reimbursed by the health insurance system, either in full or partially. Special private insurance arrangements or solidarity funds can cover the remaining costs in part or in full. The patient should have a realistic picture of the out-of-pocket expenses that a standard treatment would entail.

Therapy-specific printed brochures are very useful to provide patients with all relevant information.

Release card

All patients are provided with a so-called release card after therapy. This card gives the contact details of our department, the contact details of the national agency for nuclear control and the type of treatment that has been performed, as well as the injected activity and its calibration date. The patient should carry the card with them at all times until the date specified on the card.

Informed consent in theranostics and radionuclide therapy research

In the setting of clinical research, the informed consent process has an even more stringent dimension. The concept of informed consent is essential for ethically acceptable experiments with human subjects. It is very important to establish that the aim of a clinical trial is different from that of routine clinical care. A clinical trial is a scientific experiment and its goal and purpose is to gather knowledge. This is recognised and regulated by the "Declaration of Helsinki – Ethical Principles

for Medical Research Involving Human Subjects", which also originates from the WMA (9). Even though the primary purpose of medical research is to generate new knowledge and insights, it is evident that this goal can never take precedence over the rights and interests of the individual research subjects, who are patients or sometimes healthy volunteers. Their rights need to be observed and upheld, and informed consent is a key element of doing so. Eight out of 37 items discussed in the Declaration of Helsinki pertain to informed consent. The Declaration of Helsinki is codified in law in most countries, so these principles are also a legal obligation in most European states.

Extracts from the Helsinki Declaration

Article 25 stipulates that participation of an individual must be voluntary and she/he needs to freely consent to the trial. Article 26 states: "In medical research …, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed." A written document is hence necessary to obtain the consent of the patient for a clinical trial.

When seeking informed consent, this needs to be done without duress and without any pressure on the patient. If the physician who is carrying out the process has a potential conflict of interest, he/she needs to delegate it to a completely independent person. The physician must inform the patient of the elements of the trial that are part of standard care, and the aspects of their care that are related to the research. Indeed, many oncological trials incorporate routine care that the patient would receive anyway if he/she were not part of the trial. Refusing to participate or withdrawing from a trial must never adversely affect the physician-patient relationship.

Informed consent brochure & form

The informed consent brochure is provided by the trial sponsor. It contains the necessary information to explain all aspects of the trial. It has to be in the local language and it must be approved by the ethical committee that is overseeing the trial.

This document also contains an informed consent form, which is a document that has to be signed by the patient and the study team member who informed the patient. It carries the version number of the protocol and a date. There are two copies, one for the patient and one for the study team. The signing of the informed consent document, including the version number of the information brochure, the date of the document and the date of signature, needs to be recorded in the patient's health records.

Within the framework of a clinical trial, the consent form is a very important document: it is the only document that is signed by the subject. During trial inspections and audits, the presence of a properly completed consent form is mandatory for all patients and its absence will be considered a major or critical finding.

The information brochures in contemporary trials are very comprehensive and might not be easy for the patient to understand, despite the fact that the text should be in plain language and reviewed by the ethical committee. Some versions have a one- to two-page summary, which can be a good starting point for the patient. The patient is free to show this document to other people and discuss it with them, e.g. the family physician, who can help the patient in understanding the trial procedures and making a decision on trial participation.

Informed consent and diagnostic clinical trials

In clinical trials evaluating novel tracers, the main focus will be on the imaging procedure, including the radiopharmaceutical or tracer that is going be injected, how is it going be injected and how the scans will be performed (number, duration and time after injection). In phase I/II imaging trials, multiple scans are often performed after tracer injection to document the kinetics of tracer biodistribution. Information is provided about the current knowledge relating to the novel tracer. During first-in-man studies, all knowledge is derived from in vitro and animal experiments, so no human data is available. However, the typically low to very low mass amount that is injected limits the potential for pharmacological effects. Determination of the absorbed dose and effective dose caused by the tracer is an important parameter that has to be determined in the early phase of clinical development. The dose in humans will be established in early dosimetric studies and is hence unknown at inception of the trial, but it can often be extrapolated from other tracers, either with a similar target, with a similar radionuclide or a combination of both. For tracer containing e.g. carbon-11, a 4 times lower and less variable effective dose (μSv/MBq) was observed than the effective dose from fluorine-18 containing tracers (10). This has prompted some to call for the abandonment of dosimetric studies for tracers labelled with carbon-11.

Informed consent and absorbed dose from tracers

The absorbed dose from tracers carries a small risk of being teratogenic or carcinogenic. Clinical trials evaluating novel radiopharmaceutical tracers hence avoid recruiting pregnant patients. The limited carcinogenic risk should be properly explained to participating healthy volunteers and patients. "Radiation Protection 99" from the European Commission provides guidance on the risk assessment of low-dose medical exposure in biomedical research (11), based on ICR 62 (12). This framework is a good basis for providing information about radiation effects in the information brochure. The document provides a clear classification of the acceptable level of risk in relation to the level of societal benefit. If the societal benefit of the research is estimated to be minor, the acceptable carcinogenic risk should be trivial and should be $\sim 10^{-6}$ or less, corresponding to an effective dose in adults of <0.1 mSv (category I). If the societal benefit is intermediate to moderate (as is clearly the case for novel tracers), the acceptable risk can be minor to intermediate, defined as $\sim 10^{-5}$ and $\sim 10^{-4}$, respectively, and the corresponding effective dose range is 0.1 to 1.0 mSv and 1.0 to 10 mSv, respectively (category IIa and IIb, respectively). Doses higher than 10 mSv (up to a maximum of deterministic thresholds for diagnostic agents) are considered to be of moderate risk, and require a substantial societal benefit in order to be justified (which can still be the case for novel tracers). Of note is the fact that these dose thresholds can be increased by a factor of 5–10 for subjects over 50 years old. Conversely, a 2 to 3 times lower dose threshold is advised for children.

Standardised templates have been developed to explain the stochastic radiation effects in informed consent brochures for diagnostic trials, e.g. the template collaboratively developed by the Belgian nuclear medicine society (Belnuc) and the Belgian regulator (Federal Agency for Nuclear Control; FANC). This document provides an approximation of the effective dose caused by the experimental radiopharmaceutical, comparing it to the dose caused by a CT scan of the abdomen, which is a procedure familiar to many oncological patients. Furthermore, the dose is compared to the annual natural radiation exposure. The safety risk is stated according to "Radiation Protection 99", and if it is less than 10 mSv, it is described as minor to intermediate. The document stresses that the health effects are so small that we cannot actually observe them, and that the additional risk of developing cancer is estimated to be 1 in 2 000 at maximum. Finally, it is mentioned that the 10 mSv threshold can be increased by a factor of 5 to 10 in patients over 50.

Informed consent & RNT trials

All aforementioned aspects of informed consent for diagnostic trials are also valid for RNT trials. The major exception is the dose thresholds, since there are no upper dose limits for therapeutic applications of ionising radiation. However, the treatment should be kept safe for the patient and severe and irreversible side effects should be avoided as far as possible. As the safety of the patient is a primary concern in phase I and II trials, there is often an emphasis on dosimetry in these trials. This is based on the knowledge of dose thresholds for normal organs and so-called normal-tissue complication probability curves. Keeping the absorbed dose below the toxicity thresholds will prevent toxicity from developing. These curves are well known for external beam radiotherapy (EBRT), but they might be different for therapeutic radiopharmaceuticals as the microscopic dose deposition can be more heterogeneous than in EBRT. The usefulness of this guidance has therefore been questioned. In the specific setting of phase I trials, the aim is to find the maximal tolerable injected activity (or absorbed dose by an organ at risk) and these trials plan a stepwise increase in administered activity.

Randomised controlled trials (RCTs)

In phase 3 trials, which seek to demonstrate superiority of the experimental treatment over current standard therapy, randomisation is a key element to generate scientific evidence of the highest level (without bias). During the informed consent process it is important to explain why the patient will get one treatment or another one, based on a random event ("a virtual roll of the dice"). The control arm in a phase III randomised controlled trial (RCT) studying a novel therapeutic radiopharmaceutical will often be a non-radioactive treatment.

RCTs are the gold standard for definitive clinical scientific proof of efficacy, and they require clinical equipoise (= assumption that both options proposed are of similar efficacy; there is not one option that is definitely better or worse than the other). In most trials, there is a hypothesis that one of the arms in the trial is better, but until this is proven by an RCT this is a mere hypothesis and one can still assume there is equipoise. During the informed consent process, the patient should therefore be made aware of the fact that both treatment arms are judged to be acceptable based on the current scientific evidence, and that it is intentional that the patient is allocated by chance (in a "random" manner) to one of the arms

In an RCT, a patient population with similar characteristics, defined by the in- and exclusion criteria of the trial, is allocated to a number of arms (minimum 2, no formal maximum but very often only 2), with each arm receiving a different treatment. The odds of an individual patient being allocated to a particular arm are not necessarily equal for all arms. In a two-arm trial, the odds can be 1:1 (even odds for both arms), but they can also be 1:2 (one arm twice as likely as the other). The latter is often used to get more patients in the experimental arm, which is more attractive to patients who have no remaining standard treatment options and desire to be treated with a novel drug that has promising phase II results.

CONCLUSION

Informed consent is a standard practice in medicine and has its origin in the concept of patient autonomy. It is based on 2 pillars: the information provided to the patient and his/her/they act of actively consenting. A range of information and types of consent can be used, and the type chosen is typically based on the risks incurred by the patient. The type of consent ranges from oral to written and from tacit to explicit. The higher the risks, the more formal the documentation should be. The type of information to be provided to the patient varies, but in the field of theranostics and RNT it should include an explanation about the physical aspects of radioactivity, the potential benefits of the procedure, the potential risks (often rare, but with RNT potentially severe and irreversible side effects can occur), details of radioprotection procedures and the potential for financial toxicity. Within the scope of clinical trials it is very important (and also a legal obligation) that the informed consent procedure is recorded in a written document. Clinical trials may entail greater uncertainty for the patient (e.g. unknown dosimetry, limited data about efficacy, randomisation), as the very aim of the trial is to gather the data that are still unknown at its inception.

DISCLOSURES

Christophe M. Deroose is / has been a consultant for Sirtex, Advanced Accelerator Applications, Novartis, Ipsen, Terumo and PSI CRO.

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REFERENCES

1. https://www.wma.net/policies-post/wma-declaration-of-geneva.
2. Kim IJ, Cho H, Yi MS, Park YH, Kim S, Kim DK, et al. Diagnosis and treatment of nerve injury following venipuncture - A report of two cases. Anesthesia and Pain Medicine. 2021 Jul;16(3):299-304. PubMed PMID: 34289298. Pubmed Central PMCID: 8342828.
3. Shaqdan K, Aran S, Thrall J, Abujudeh H. Incidence of contrast medium extravasation for CT and MRI in a large academic medical centre: a report on 502,391 injections. Clinical Radiology. 2014 Dec;69(12):1264-72. PubMed PMID: 25248291.
4. Cha MJ, Kang DY, Lee W, Yoon SH, Choi YH, Byun JS, et al. Hypersensitivity Reactions to Iodinated Contrast Media: A Multicenter Study of 196 081 Patients. Radiology. 2019 Oct;293(1):117-24. PubMed PMID: 31478801.
5. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology. 2011 Jun 10;29(17):2416-23. PubMed PMID: 21555692.
6. Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, et al. Long-Term Efficacy, Survival, and Safety of [(177)Lu-DOTA(0),Tyr(3)]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. Clinical Cancer Research: an official journal of the American Association for Cancer Research. 2017 Aug 15;23(16):4617-24. PubMed PMID: 28428192.
7. 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. The New England Journal of Medicine. 2021 Sep 16;385(12):1091-103. PubMed PMID: 34161051. Pubmed Central PMCID: 8446332.8. Kratochwil C BF, Giesel FL, Weis M, Verburg FA, Mottaghy F, Kopka K, Apostolidis C, Haberkorn U, Morgenstern A. 225Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer. J Nucl Med. 2016 57(12):1941-4. Pubmed Central PMCID: 27390158.
9. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.
10. Zanotti-Fregonara P LA, Innis RB. 11C Dosimetry Scans Should Be Abandoned. J Nucl Med.62(2):158-9. Pubmed Central PMCID: 33310737.
11. https://ec.europa.eu/energy/sites/ener/files/documents/099_en.pdf.
12. Radiological Protection in Biomedical Research. ICRP Publication 62 Annals of ICRP. Oxford: Pergamon Press 1992.

7

HOSPITALISATION

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In radiation therapy, cancer is treated to preserve life and to maintain highest quality of life (1). When the patient is kept as an inpatient following radionuclide treatment, those who are directly or indirectly involved in the use of radiation, which could be clinical scientists, clinical nurse specialists (CNS), technologists or other health personnel, are at risk of radiation exposure (2).

The use of appropriate facilities by well-trained staff can help to minimise radiation exposure. The training should include radiation protection and specific local rules, particularly in situations where there's a risk of significant contamination, for example from urine, faeces and vomiting.

THERAPY FACILITIES

Room design

A designated radionuclide therapy room with its own en-suite bathroom and toilet is specifically designed for such therapies. It is usually on the ward, but isolated from the rest of the patients on that ward. The radionuclide rooms should be controlled areas, safe and comfortable. Emergency conditions such as power failure should be considered in the design.

The room design should have healing environment attributes and be peaceful and quiet, with aesthetically pleasing pictures and exposure to daylight. Studies show that these attributes promote a subjective sense of well-being and encourage a sense of hope and a positive attitude in patients (3). Good lighting provides a calming and comforting environment to the patient and also helps to minimise stress (4).

As patients are in isolation, the room should have all the necessary amenities that they may need during their stay. These include a microwave, refrigerator, toaster and kettle. However, not all patients will use the amenities mentioned, as the hospital provides hot meals for them which are left at the entrance to the room. The room should have its own telephone line and a functioning call bell. It should also be sufficiently heated, with easy-to-regulate temperature controls and good ventilation. For those patients who prefer to bring their own food, it is advised that only disposable cups and plates and cutlery be used due to the risk of radioactive contamination of these items.

The floors and other surfaces should be made of smooth, continuous and non-absorbent material that can easily be cleaned and decontaminated. Absorbent pads can be taped in places or areas most likely to be contaminated, such as around the toilet and sink (2).

A radiation caution sign should be posted on the door, and should be visible to all healthcare personnel and the patient's visitors. The caution sign on the door should remain in place and can only be removed by trained nuclear medicine staff once the patient has been discharged and the room has been thoroughly monitored. It will then be ready for cleaning by domestic staff (Figure 1).

Figure 1. Caution sign.

Work procedures for radionuclide therapies should be formulated in order to minimise exposure to external radiation and contamination and to prevent spillage from occurring. Should there be spillage, care should be taken to ensure the spread of contamination is significantly minimised.

Ventilation

Maintaining good ventilation systems in radionuclide rooms is paramount. Inadequate ventilation could lead to the build-up of radionuclides in the atmosphere, presenting an inhalation hazard to patients and staff.

Shielding

Shielding is needed to reduce alpha, beta or gamma radiation to a safe level for staff and other patients. The shielding should be such that external doses are maintained as low as reasonably practicable (ALARP).

When designing shields, consideration should be given to the type of radionuclide, the intended activity and the principles of optimisation of protection.

Lead is commonly used for radiation shielding as it is highly effective in providing protection from sources of radiation. The radionuclide therapy room should have proper shields, particularly movable lead shields, to allow staff to operate more safely by protecting most of their body.

Toilets

A separate drainage system should be available. A caution sign should be put on the toilet door to help remind the patient to flush twice to ensure that all radioactive urine is washed from the toilet bowl and to wash their hands with copious water. To prevent urine splatter, both male and female patients should be advised to sit when using the toilet.

Preparing the room before hospitalisation

Prior to the patient's hospitalisation, the following should be in place: bins should be provided for temporary storage of linen and clinical waste that might be contaminated with radioactive substances; objects and parts of the room that tend to become contaminated (patient stretchers, chairs, TV remote, telephone and lower walls) should be covered with protective material such as plastic sheets.

There should be a recording chart at the door to record hands / feet monitoring measurements of staff and patient's visitors who enter the room.

Protective clothing such as gowns, gloves and overshoes should always be available in the room before therapy is commenced. This helps to prevent the transfer of contamination to other areas and also protect the body of the wearer. Protective clothing should be removed before leaving the therapy room. A spills kit for radioactive spillages should be available in the room.

Obtaining the patient's consent for therapy

The clinical nurse specialist or technologist should ensure that the patient understands the nature of the radionuclide therapy. They should ensure that specific written instructions for each procedure are in place and that they are reviewed prior to treatment. However, different institutions may do this in different ways.

Before therapy, the patient should be identified through the routine hospital procedure which includes various diagnostic tests such as diagnostic imaging and a blood test. The multidisciplinary team (MDT) discuss each case and refer them accordingly to nuclear medicine for the radionuclide therapy. The patient will be given an appointment date to talk through the treatment in more detail with the consenting healthcare professional. The patient has to consent by signing for the therapy before it can be given.

Preparatory steps prior to the patient's hospitalisation

An important step upon the patient's hospitalisation is the completion of a standard medical admission clerking proforma. The healthcare professional in charge of this process gathers all relevant information about the patient's condition and lifestyle risk factors and documents it comprehensively in the patient record (7,8). In addition to history taking, a physical assessment should also be performed (9). Any concerns are then discussed with the treating team ahead of radiopharmaceutical administration. Besides, this process provides a good opportunity for the patient to familiarise themself with the facilities, thereby potentially reducing the anxiety associated with the upcoming treatment.

While the relationship with the Lead Clinician is paramount for a positive patient experience, it is recommended that the patient is also introduced to a key worker or Therapy Lead (for example, a CNS or a specialist therapeutic radiographer/ technologist), who is identified for each patient to ensure clarity and consistency of communication throughout the treatment pathway (10). This person retains an overview of the whole process and acts as the link to the rest of the multidisciplinary team.

The Therapy Lead often coordinates the following processes:

» Ensures that the patient's medication list and its posology are up to date and will notify the consultant of any possible drug interactions. History of drug allergy or sensitivity is annotated in the patient's individual prescription chart, as part of the patient's notes;

» Confirms availability from night staff and agrees meal times and menus, after checking food allergies/intolerances/ special diets. This includes sour sweets as a protective measure for patients who need to stimulate excretion from the salivary glands.

» **For patients referred for thyroid ablation treatment:** Guides the patient through the post-thyroidectomy recovery process, particularly liaising with the consultant about the thyroxine and calcium levels, as unbalanced levels may cause significant discomfort to the patient. Considering that the radioactive ablation treatment takes place shortly after surgery, this is a matter to address in a timely manner to avoid discomfort during inpatient admission;

» Enquires about the recent use of iodinated contrast agents for imaging purposes (computerised tomography (CT), magnetic resonance imaging (MRI)), antiseptics, eye drops and amiodarone, as well as over-the-counter multivitamin/ herbal supplements, and advises the patient to suspend these for a sufficient period of time (11,12);

» Advises on low-iodine diet for 2 weeks prior to admission (11,12);

» Along with the consultant and the patient, decides on the best option for attaining thyroid-stimulating hormone (TSH) elevation, either by completing thyroid hormone withdrawal or taking recombinant human TSH (rhTSH) once a day for 2 days (11). This aims to stimulate radioactive iodine uptake by any remaining thyroid cells. In addition to the aforementioned, certain blood tests will be required on the morning before therapy to check if any residual thyroid tissue is adequately stimulated.

» **For patients referred for ^{131}I-meta-iodobenzylguanidine (mIBG):** Before therapy the patient is usually commenced on potassium iodate tablets, which help to stop the thyroid from taking up any radioactive MIBG. The tablets should be taken 1–2 days before therapy and the patient should continue taking them during their stay and after discharge (13).

» **For patients referred for ^{131}I and ^{177}Lu therapies:** Explains to the patient the available facilities and provides advice related to the necessarily limited amount of belongings that the patient should bring to the isolation room. These should include toiletries such as a disposable toothbrush, socks and slippers, and comfortable clothes. They should also advise against wearing jewellery and contact lenses (encouraging the use of glasses instead);

» Manages the patient's expectations in relation to the level of support during their stay, so that they are aware that they are being taken care of even if staff do not engage in long conversations after the patient has had the radiopharmaceutical administration;

» Introduces the team members to the patient and respective relatives. The team involved in the care of these patients is vast (oncologist, nuclear medicine consultant, clinical nurse specialist, technologists/radiographers, scientists, healthcare workers, amongst others) and it is important to discuss the healthcare professionals' roles in a manner that is not overwhelming to the patient. Additionally, expert provision of radiation protection information should be consistently and unambiguously offered by all suitably trained members of the team (14);

» Conducts a pre-assessment to establish whether the patient suffers from gastro-intestinal symptoms or conditions, namely vomiting, nausea and reflux. Checks how the patient is feeling on the day of the treatment and assesses the need for administration of an antiemetic. Vomit bowls should be available in the room, in an easily accessible location. While the patient is monitored during treatment, due to radiation protection concerns there may not be a member of staff in the room for the entirety of the process. The Therapy Lead will explain to the patient what to do if they feel sick and how to get assistance (more detailed information on this is provided in Chapter 8).

» Devises contingency plans to ensure the least possible disruption to patient care and/or adequate action in case of emergency. This includes evacuation in case of fire, activation of action plan if there is a flood (e.g. blockage and flooding of the drainage system used in the radioactive toilet) or provision of urgent care due to unexpected clinical deterioration (e.g. heart attack, stroke, anaphylactic reaction) – care must not be compromised regardless of the scenario (15), and it is the team's responsibility to prepare for these kind of incidents. It is essential that the patient is aware of emergency plans, including routes, that all staff know the location of the nearest emergency trolley and are trained in life support procedures, that patients know the location of nursing alarms (which must be checked periodically and prior to any patient treatment) and that a designated radiation protection supervisor/officer is contactable. Contingency plans should be formulated as part of a joint approach with all relevant service managers (nursing wards, nuclear medicine, transport, the emergency department, estates and facilities teams). Specific pitfall and emergency scenarios are discussed in Chapter 8

» **For patients referred for peptide receptor radionuclide therapy (PRRT):** Patients diagnosed with neuroendocrine tumours, especially those with functioning syndromes, often require routine intake of somatostatin analogues (SSA). [^{177}Lu] Lu-DOTATATE is essentially a radioactive version of standard SSA. Therefore, the administration of SSA may interfere with the radiopharmaceutical by competing and saturating the somatostatin binding receptors on the tumour cells, potentially significantly reducing the efficacy of the treatment (16). Patients may either avoid concurrent long-acting SSA intake on the 30 days prior to therapy (administering short-acting analogues instead) or the Therapy Lead may carefully and optimally coordinate appointments so that the long-acting SSA administration is due on the days following PRRT. The latter requires great communication and scheduling skills with management of many interventions (from pharmacy, community care support, nursing, patients), as well as the radiation protection considerations of those administering the SSA injections to the radioactive patient (which may be done by the Therapy Lead).

» **For any intravenous therapies:** Assesses intravenous access prior to the therapy day. Should the patient have difficult venous access, the Therapy Lead will then be able to explore the available options in advance in order to secure appropriate access without multiple painful attempts at cannulation (this may include considering different vascular devices, the use of technological aids such as ultrasound, advising patient on good hydration and how to maintain a body temperature conducive to good circulation (17));

» During the consent process, the patient will have been advised of the need to cease breastfeeding and given an explanation about excretion of therapeutic pharmaceuticals in breast milk (18,19). Nevertheless, the treating team must still check that this advice has been followed. In cases when the patient wishes to discuss this contraindication in more detail, a conversation between the patient, the referring consultant and a lactation consultant is recommended (18). Similarly, pregnancy is a universal contraindication (20), hence the requirement to rule out pregnancy in all fertile-age individuals (by means of a written declaration and a urine or human chorionic gonadotropin (hCG) blood test) (18,19);

» Checks blood test results – this includes results from the last few months to identify biochemical and haematological trends and establish whether the latest values match the treatment eligibility criteria

(9,16,20). Nonconformities should be discussed with the consultant at the earliest opportunity and before proceeding with any procedures. Imaging requirements should also be met as per local protocol. If there are pending scans, these should be diligently organised in order to avoid further treatment delay;

» Continuous improvement through patient feedback is encouraged. However, in order to avoid unnecessary radioactive exposure to staff, alternative ways of seeking feedback should be considered. While a post-therapy phone call is a valid option, capturing the patient experience in real time is known to be more effective than doing this retrospectively (21). Thus, the use of a feedback booklet located in the room allows patients to express their feelings and opinions on the way they are treated as well as on the actual procedure (21). The Therapy Lead informs the patients about this feedback tool and has the responsibility for auditing this booklet periodically and acting on the points raised;

» Billing arrangements – clarifies any charges related to the treatment, including insurance paperwork and car parking costs;

» Books the post-therapy imaging appointments with the nuclear medicine team and checks that the patient is aware of the dates/times. If the Therapy Lead is a technologist, it may be the same person performing the scans.

PATIENT DISCHARGE

In general healthcare, the process of discharging a patient is recognised as globally complex, with several potential sources of error (22). In nuclear medicine, an additional element requires consideration (23): the radiation exposure to the public and the risk of contamination from radionuclide body fluids (19). The aim is to deliver a sensible, individualised and safe release from the hospital. For this purpose, each member of the team should be proficient in their role and liaise with each other in a timely manner (24).

Following administration, these patients present an external radiation hazard due to the gamma emissions of lutetium-177 and beta/gamma emissions of Iodine-131 (25). The European Commission Basic Safety Standards, based on recommendations from the International Commission on Radiological Protection, stipulate that the effective dose limit to a member of public should not exceed 1 mSv per year (1,26). This piece of legislation includes the provision that the dose limit may be averaged over 5 years (5 mSv in 5 years) to allow for doses greater than 1 mSv in any single year to friends and relatives who are in close proximity to the patient and act as comforters and carers (27). This makes these patients challenging to treat as outpatients, thus requiring a variable length of stay in specifically designed hospital facilities. Each centre will have defined safety criteria in line with national legislation/applicable legal requirements, in order to restrict the radiation exposure to the public, to the patients' family members and also to the staff treating these patients (28). Regulatory frameworks in different countries take a prescriptive, conservative approach, often using estimates of retained activity as a release criterion (19). In essence, the retained activity tends to decline substantially (19) after a few days in hospital, which is demonstrated by performing sequential measurements during the patient's stay on the ward (29), usually using an external gamma probe. This methodology has been verified to be fast, reliable and practical (29,30). At the planned discharge time, the final dose rate is to be measured and documented individually, providing it has reached a defined threshold deemed acceptable (2).

However, it should be noted that specific situations may call for tailored instructions – e.g. patients who suffer from incontinence or have had an ostomy may need to have their hospitalisation period extended to guarantee safe collection and disposal of radioactively contaminated excreta (2). Alternatively, according to local governance, the treating team may provide advice on how to handle the generated waste when the patient is at home (e.g. mildly soiled clothing, incontinence pads, diaper pants), or even agree a system where the patient returns those items for storage and decay (19).

Relevant parameters to be considered when planning patient discharge in the context of the aforementioned therapies:

Preferably resolved prior to discharge:

In order to reduce staff exposure and stay length, it is strongly advised that certain matters are resolved ahead of discharge, namely:

» Ensure patient has the required medicines (e.g. pain killers, laxatives, hormone replacement medication, antiemetics);

» Identify the means to be used by the patient to get home (avoiding public transport (15); assess ability to drive autonomously; reserve individual patient transport to avoid pregnant drivers or travelling in close proximity for long periods of time, e.g. rush hour).

» As part of the initial risk assessment, the patient's expected pattern and level of contact with other people, their family/home environment and living conditions (19) will have been discussed, therefore informing the restrictions that the patient will have to follow when returning to their home. Depending on their radiation levels at the point of discharge, these original restrictions may be modified slightly.

» Whereas there is overall agreement that radiation protection rules should be rigorously followed in order to protect the public, the treating team should aim for more than mere acquiescence from the patient. The medical community acknowledges that shared decision-

making affects the patient's compliance with the treatment and subsequent recommendations (31). Therefore, rather than dictating radiation protection restrictions, the patient's input should be encouraged as part of an open discussion regarding their wishes and their perception of the feasibility of the anticipated restrictions, with the goal of increasing the likelihood of the patient's understanding and hence compliance (19). Discharge is a multidimensional process, and patients benefit from a multidisciplinary approach (32) where scientists/medical physics specialists communicate the restrictions while the technologists/nurses act as patients' advocates and help them make sense of the overall process and how it impacts on their lives without losing sight of radiation protection concerns.

At the moment of discharge:

» Patient status: upon discharge, the patient should be clinically well and stable. This should be established by means of an holistic welfare check covering their physical well-being (ability to self-care, manage side effects, caring for concomitant comorbidities), psychological resilience (particularly after an isolation period) and social support and infrastructure arrangements (19,24).

» The patient's hospital notes/records are updated by the Therapy Lead, with details about patient's tolerance to treatment and experienced side effects and alerting to any need to update/modify the care plan. The Therapy Lead should then provide feedback to the referring team (8);

» A discharge note is issued for work purposes (e.g. the PRRT patient should remain off work for 5 days post-therapy (25);

» Patient's belongings are checked for contamination. Depending on the local protocols, contaminated items may be stored in the department until the radiation has decayed, at which point they can be collected by the patient, or specific instructions may be given to the patient on how to handle such items;

» By ensuring continuity of care, the Therapy Lead will reassure the patient about the team's availability to provide assistance and advice after discharge. They will explain what will happen next, who will be providing which part of the care and who/how the patient can contact with any questions and doubts (8,21). The patient should also be made aware of emergency contacts in case their condition changes (24) or in the event of illness or accident requiring hospital attendance (19);

» The patient will be handed written, clear information about radiation protection (12,19). Reiterating these arrangements is a key step to ensure compliance (8).

DECONTAMINATION OF THE THERAPY ROOM

Although the patient is encouraged to practise good hand hygiene, double-flush the toilet and urinate sitting down (15,25), excessive perspiration, blood and urine remain the main sources of contamination during and following therapy (20,33). Due to the radionuclides' half-lives, there is a potential for prolonged contamination. Nevertheless, these rooms are usually in high demand and have a high level of occupancy which requires staff to ensure appropriate decontamination and cleaning before the admission of another patient.

The protective polythene sheets must be carefully removed and the bed linen removed by the nuclear medicine team and monitored. Depending on the available facilities, if the items are contaminated, they may be stored or washed on specific premises (dedicated washing machine). If not contaminated, the items can be laundered as per the usual hospital specifications. The technologists/medical physics team will monitor the room and decontaminate as required. They will look for removable contamination utilising appropriate survey equipment (e.g. Geiger–Müller counter or scintillation survey meter (2)), with an increase in count rate above background indicating the presence of radiation (34). A mobile floor monitor is useful to meticulously check the floor for contamination. When attempting to decontaminate an area, it is reasonable to take into consideration the likelihood of contamination removal and staff exposure. If there are small areas of fixed contamination, these could be covered (to prevent radiation contamination from being transferred to other areas), or it may be appropriate to remove the item from the room and let it decay (e.g. pillow, book). Due to the risk of personal contamination, personnel should be given a personal dosimeter and wear appropriate protective clothing such as shoe covers, apron/gown, mask, double gloves (outer gloves should be changed frequently to avoid cross-contamination) and goggles/eye protection if performing bathroom decontamination to prevent ocular contamination from any splashing (34). ALARP recommendations should be taken into account to reduce exposure: these involve minimising the time of exposure; maximising the distance from the source, if possible; using shielding as appropriate; and the removal or containment of contamination. Protective gear should be removed after use and placed in a clearly labelled, sealed plastic container (34).

All remaining waste and contaminated items should be removed and segregated into bags for disposable items and launderable items (2). Handling and disposal of radioactive waste is covered in Chapter 10. However, it should be noted that the collection, sealing, assessment, labelling and storage in a designated location should always be done promptly in order to reduce

unnecessary exposure of those cleaning the room. Staff must fill in the post-discharge room survey form, which should be analysed by a senior member of the medical physics team before the room is authorised for use.

In summary, the success of a patient release programme is critically dependent on the logistics, the quality and specificity of the information provided to the patient and the skill with which it is communicated (19). This is generally achieved by combining an appropriate release criterion with appropriately tailored instructions and information for the patient that will allow them to deal effectively with the identified risks (19). If the technologist takes on a lead role in the discharge process, it is best practice to be conversant with principles of clinical discharge and to hold prior discussions with the physics team, specifically a medical physics expert, to ensure that the discharge advice is tailored to the personal circumstances of that specific patient. If the patient resembles a "typical case", with no worrying features identified in the pre-therapy risk assessment, then standard radiation protection advice predefined by the local therapy team may be issued by a suitably trained staff member (for example, a medical physicist, clinical scientist, technologist or radiographer) and documented in the patient's notes (10). Where the risk assessment shows unusual patterns of contact or increased likelihood of a risk of contamination, the medical physics team ought to be consulted (14).

REFERENCES

1. Annals of the ICRP. Radiological Protection in Therapy with radiopharmaceuticals - ICRP publication 140. 2019.
2. Bailey DL, Humm JL, Todd-Pokropek A, van Aswegen A. Nuclear Medicine Physics: A Handbook for Teachers and Students.
3. Bonett J. Ceiling art in a radiation therapy department: Its effect on patient treatment experience. Journal of Medical Radiation Sciences. 2015 Sep 1;62(3):192–7.
4. Joseph A. The Impact of Light on Outcomes in Healthcare Settings [Internet]. 2006. Available from: www.rwjf.org.
5. Nuclear Medicine Forum. NVF/DG001: An Aid to the Design of Ventilation of Radioactive Areas. 2022. p. 2–4.
6. dler NE, Page AEK. Cancer care for the whole patient: Meeting psychosocial health needs. Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs. National Academies Press; 2008. 1–429.
7. Cousins S. Checklist clerking document improves health promotion among medical admissions. BMJ Quality Improvement Reports. 2013;2(1):u202209.w1218.
8. Waring J, Marshall F, Bishop S, Sahota O, Walker M, Currie G, et al. An ethnographic study of knowledge sharing across the boundaries between care processes, services and organisations: the contributions to 'safe' hospital discharge. Health Services and Delivery Research. 2014 Sep;2(29):1–160.
9. Kratochwil C, Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, et al. EANM procedure guidelines for radionuclide therapy with 177Lu-labelled PSMA-ligands (177Lu-PSMA-RLT). European Journal of Nuclear Medicine and Molecular Imaging. 2019 Nov 1;46(12):2536–44.
10. Intercollegiate Standing Committee on Nuclear Medicine. Molecular radiotherapy: guidance for clinicians [Internet]. 2019 Sep. Available from: www.rcr.ac.uk
11. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJG, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Vol. 35, European Journal of Nuclear Medicine and Molecular Imaging. 2008. p. 1941–59.
12. Colley PP, Boelaert K, Evans C, Rm E, Ge G, Ja G, et al. Guidelines for the management of thyroid cancer. 2014.
13. Giammarile F, Chiti A, Lassmann M, Brans B, Flux G. EANM procedure guidelines for 131I-meta-iodobenzylguanidine ([131I]I-mIBG) therapy. Vol. 35, European Journal of Nuclear Medicine and Molecular Imaging. Springer Verlag; 2008. p. 1039–47.
14. HSE. RR416 Information to accompany patients undergoing nuclear medicine procedures. 2006.
15. Silberstein EB, Alavi A, Balon HR, Clarke SEM, Divgi C, Gelfand MJ, et al. The SNMMI practice guideline for therapy of thyroid disease with 131I 3.0. Vol. 53, Journal of Nuclear Medicine. 2012. p. 1633–51.
16. European Medicines Agency. Lutathera, INN-lutetium (177Lu) oxodotreotide - Summary of Product Characteristics. 2018.
17. Sou V, McManus C, Mifflin N, Frost SA, Ale J, Alexandrou E. A clinical pathway for the management of difficult venous access. BMC Nursing. 2017 Nov 17;16(1).
18. Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources [Internet]. London; 2022 Jan. Available from: www.gov.uk/arsac
19. IAEA. IAEA Safety Reports Series, No.63 - Release of Patients after Radionuclide Therapy [Internet]. Vienna; 2009. Available from: http://www-ns.iaea.org/standards/
20. Hope TA, Abbott A, Colucci K, Bushnell DL, Gardner L, Graham WS, et al. NANETS/SNMMI procedure standard for somatostatin receptor-based peptide receptor radionuclide therapy with [^{177}Lu]Lu-DOTATATE. Journal of Nuclear Medicine. 2019;60(7):937–43.
21. NHS. The Patient Experience Book - A collection of the NHS Institute for Innovation and Improvement's guidance and support. 2013.

22. Wright S, Morecroft CW, Mullen R, Ewing AB. UK hospital patient discharge: The patient perspective. European Journal of Hospital Pharmacy . 2017 Nov 1;24(6):337–42.

23. European Commission. COMMISSION STAFF WORKING DOCUMENT on a Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) [Internet]. Brussels; 2021 Feb. Available from: https://ec.europa.eu/health/non_communicable_diseases/cancer_en

24. Government HM. Hospital Discharge and Community Support: Policy and Operating Model. 2021 Oct.

25. Levart D, Kalogianni E, Corcoran B, Mulholland N, Vivian G. Radiation precautions for inpatient and outpatient [^{177}Lu]Lu-DOTATATE peptide receptor radionuclide therapy of neuroendocrine tumours. EJNMMI Physics. 2019 Dec 1;6(1).

26. Council Directive 2013/59. Official Journal of the European Union [Internet]. 2014 Jan 17; Available from: https://eur-lex.europa.eu/eli/dir/2013/59/oj

27. ICRP. Annals of the ICRP. Published on behalf of the International Commission on Radiological Protection - Publication 103. 2007.

28. Azizmohammadi Z, Tabei F, Shafiei B, Babaei AA, Jukandan SMQ, Naghshine R, et al. A study of the time of hospital discharge of differentiated thyroid cancer patients after receiving iodine-131 for thyroid remnant ablation treatment. Hellenic Journal of Nuclear Medicine. 2013;16(2):103–6.

29. Kurth J, Krause BJ, Schwarzenböck SM, Stegger L, Schäfers M, Rahbar K. External radiation exposure, excretion, and effective half-life in [177Lu]Lu-PSMA-targeted therapies. EJNMMI Research. 2018;8.

30. Hindorf C, Glatting G, Chiesa C, Lindén O, Flux G. EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry. European Journal of Nuclear Medicine and Molecular Imaging [Internet]. 2010;37:1238–50. Available from: https://link.springer.com/article/10.1007/s00259-010-1422-4#citeas

31. Deniz S, Akbolat M, Çimen M, Ünal Ö. The Mediating Role of Shared Decision-Making in the Effect of the Patient–Physician Relationship on Compliance with Treatment. Journal of Patient Experience. 2021;8.

32. Stockwell G, Santoso R, Layton K, Grealish L. Partnering for Discharge Improving hospital discharge processes for older people with complex care requirements Implementation Guidelines. 2019.

33. Seregni E, Maccauro M, Chiesa C, Mariani L, Pascali C, Mazzaferro V, et al. Treatment with tandem [90Y]DOTATATE and [^{177}Lu]Lu-DOTATATE of neuroendocrine tumours refractory to conventional therapy. European Journal of Nuclear Medicine and

8

PATIENT CARE

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For the purpose of this chapter, the following therapies are considered: ^{131}I-NaI for oncological disease, ^{131}I-metaiodobenzylguanidine (mIBG), ^{223}Ra therapy, [^{177}Lu]Lu-DOTATATE and ^{177}Lu-prostate-specific membrane antigen (PSMA), relating to the management of adult patients.

DIFFERENCES IN THERAPEUTIC VS DIAGNOSTIC CARE

Diagnostics and molecular therapies are two simultaneously evolving fields within nuclear medicine which are interconnected and which harbour great potential for the technologist's role. While diagnostics is characterised by a fast-paced environment, time pressures and critical demand, therapies have a more in-depth holistic approach that allows the team to build a relationship with the patient and to optimally? coordinate several stages of their care. The technologist thus has the opportunity to integrate the regular molecular radiotherapy multidisciplinary team (MDT), which brings together the nuclear medicine physicians, physicists, oncologists and referring clinicians (1). Close alignment of diverse services is recommended to facilitate a dynamic approach that will meet the complex needs of the patient (2). Guidance has pointed out that it is helpful if the patient's point of contact is not only the lead clinician but also a designated key worker (for example, a clinical nurse specialist (CNS) or specialist therapeutic technologist/radiographer) who is identified for each patient to ensure clarity and consistency of communication (1). The aim is to act as a service coordinator to oversee the complete treatment pathway. This staff member will liaise with the patient, referring physicians, nuclear medicine physicians and other nuclear medicine centre staff members, representatives from the radiopharmacy department (if present at the hospital), other departments and the pharmaceutical suppliers. A single point-of-contact person ensures queries are addressed in a smooth, timely manner (3). Rather than focussing on the functional aspects of care, this role contributes to the relational facets which matter significantly to patients. Relational aspects of care include feeling listened to or informed, while 'functional' refers to the process of delivering care, such as efficient procedures. Patients care about their experience of care as much as they do about clinical effectiveness and safety; continuity of care and aftercare support play a substantial role in patient satisfaction (4). As a suitably trained, registered healthcare professional, the technologist can assist the consultant in assessing the patient's fitness to proceed with treatment safely, particularly where therapy requires a period of isolation for radiation protection reasons (1), developing robust care pathways and ensuring prompt recognition of significant clinical changes during the course of therapy (e.g. the need for interventions prior to treatment, such as blood transfusion due to low haemoglobin levels during the 6 months of ^{223}Ra therapy for bone metastases from castration-resistant prostate cancer) (2). It is especially productive if the key worker is introduced to the patient at an early stage, such as at the time of the initial consultation. Advanced planning of a structured sequence of topics for discussion ensures that all necessary information is covered during the initial consultation and sufficient time is dedicated to answering the patient's questions (2).

Service continuity is particularly relevant in therapies, as the delivery of the radiopharmaceutical and its administration are time sensitive. In order not to impede the clinical workflow, the introduction of an established system to provide cover for absent team members is recommended (2), as well as the anticipation of potential complications and action plans on how to handle them.

COMPLICATIONS DURING TREATMENT

Patients undergoing radionuclide therapy present with varying degrees of health and performance status. It is important to recognise the intent of the therapy (curative or palliative) and adapt the approach accordingly. Supportive palliative care and symptom relief come under the remit of patient management during radionuclide therapy, since they are not mutually exclusive and, for the most part, are interchangeable (5). Equally fundamental is to understand how the treatment may impact on the patient's life, especially if they suffer from co-morbidities. Depending on their level of health literacy and awareness of the disease stage, they may need additional support and counselling. In order to tackle different types of complications, team members from different healthcare backgrounds act as a network of expertise (6) with the ultimate goal of streamlining care provision without compromising the patient's experience. This approach is intended to maximise patient benefit while minimising the risks and side effects and ensuring the best quality of life achievable for the patient (5).

The following scenarios are all common and advice on how to handle them is provided below. Nevertheless, the observed care and restrictions are patient- and institution-dependent and should be considered in the specific context.

Nausea and vomiting

^{131}I therapies – Gastrointestinal symptoms following administration of ^{131}I compounds (both ^{131}I capsules and intravenous (IV) solutions for oncological thyroid disease or [^{131}I]I-mIBG for neuroendocrine tumours (7)) are known to occur with variable frequency (common and very common respectively for vomiting and nausea) (8,9). Oral administrations are potentially more serious, as vomit will be highly radioactive during the period immediately following administration. Every patient should be urged to inform staff if they fail to swallow the radioiodine or regurgitate (10) within the first 24h after administration. As a precaution, they should be shown where the sickness bowls are located in the room (they should be easily accessible) and instructed, if possible, to vomit into such a container or directly into the toilet. Both actions allow the contamination to be contained, which is preferable to having the furniture or the floor highly contaminated (11). The referring team must be informed straight away, as the effectiveness of the therapy will likely be diminished. Immediate imaging should help to estimate how much was absorbed before being expelled. The Therapy Lead should assess the need for prophylactic antiemetics (12) (e.g. does the patient usually suffer from reflux/nausea/vomiting/migraines or are any of these symptoms induced by stress?).

^{177}Lu therapies – Nausea is common both in [^{177}Lu]Lu-PSMA and in [^{177}Lu]Lu-DOTATATE administration (5,13,14). It can be strongly associated with the concomitant administration of the amino acid solution. This solution, meant for renal protection purposes, should be preceded by the administration of antiemetics (at least 30 minutes prior) in order to maximise the antiemetic efficacy (15). Other strategies may include commencing at a low rate of 100 mL/h for the high concentration amino acid solution and increasing slowly (e.g. by 20–50 mL/h every 15–20 min) (14); a premedication regime consisting of a 5-HT3 antagonist (e.g. granisetron, ondansetron, or palonosetron), an NK1 receptor antagonist (e.g. fosaprepitant) or an H2 receptor antagonist (e.g. famotidine), and benzodiazepines may also be required for anticipatory nausea and vomiting (14). Additionally, traditional methods such as cooling and pressure aids may also be beneficial. As in the aforementioned approach for ^{131}I therapies, patient education is imperative to ensure the patient understands the importance of where and how to contain emesis under these circumstances (14).

^{223}Ra therapy – Nausea and vomiting, as well as diarrhoea, are considered very common on the first days following administration of this therapy. Particular attention must be paid to the increased risk of dehydration (16,17). Due to the excretion route of ^{223}Ra, caution must be taken when prescribing antimotility and antiemetic medicines as they may affect the normal elimination through the faeces and result in retained radioactive faeces (which may consequently mean an increased exposure to the bowel).

Incidents

Spillage of body fluids – A spill of blood (e.g. when removing the cannula), vomit or urine must be dealt with promptly. Staff and patient must avoid the spread of contamination and initiate decontamination procedures (from the periphery of the contaminated area, moving towards the centre, using decontaminating agents as available (18)). Staff should not automatically interrupt the treatment flow for fixed areas of contamination, but could cover, delineate, and mark the area until another member of staff arrives. There is a risk of contamination or incorporation from spills of bodily fluids. In the case of ^{131}I compounds and ^{223}Ra therapy, another relevant path of incorporation is inhalation. Staff contamination or incorporation is strictly to be avoided, and personal protective equipment is to be worn at all times (19). Following the ALARA ("As Low as Reasonably Achievable") principle, it is recommended to minimise the time spent in radiation areas, to maximise the distance from radiation sources, and to use adequate shielding. The treated ^{223}Ra patient should leave the facility without undue delay (20).

If the **patient becomes contaminated**, the first objective is to prevent the spread of radioactive materials, since people who are externally contaminated with radioactive material can contaminate other people or surfaces that they touch. The process begins by carefully removing all contaminated clothing, working from head to toe, and rolling it outward away from the patient's skin, trapping the contaminant material inside. If necessary, clothing should be cut off without tearing it to prevent spread of radioactive materials through contact. Clothing should be placed in a plastic bag labelled "radioactive" and stored appropriately (18,19). The exposed intact skin should be showered or washed with regular warm water, using gentle sponges (not abrasive, as these might break the skin). Hot water must be avoided because it enhances the absorption of the radioactive material due to increased skin blood flow. Cold water should also be avoided since it closes skin pores, consequently trapping contamination inside (18). Eyes should be washed abundantly (19). If contaminated with urine, patients should wash their hands with abundant cold water (without scrubbing).

Renal impairment and incontinence

Renal impairment is often a contraindication for radionuclide therapy. Dialysis may be considered, depending on the centre's set-up. Globally, in patients with reduced renal function the following interventions are used: accurate determination of renal function (by performing glomerular filtration rate test), nephro-urology consultation, and extensive

hydration (e.g. 2–3L of fluid intake, if clinically appropriate). Diuretics (e.g. furosemide) should be considered in the case of dilated renal pelvis and delayed outflow (5).

^{223}Ra therapy: Wherever possible, dialysis should be performed no earlier than approximately 24h after administration, as less than 1% of the administered activity should remain in the blood at this time (20). The radioactive urine must be collected from the dialysis unit: some centres make use of facilities with decaying tanks (20) while others arrange for appropriate storage.

^{131}I therapies: In patients with renal failure, dialysis should be carried out within 24h following radioiodine administration (21).

[^{177}Lu]Lu-DOTATATE therapy: Although not suitable in patients with renal impairment owing to nephrotoxicity, it appears safe for use in patients with end-stage renal failure on renal haemodialysis. Dosimetry can be used to plan the therapy. For radiation protection purposes, the first two sessions of dialysis at least should be performed in an isolated room and the dialysis waste should be stored for decay (22). Wherever possible, the patient should have ^{177}Lu-based treatments instead of ^{90}Y-based therapies (5).

Renal radioprotective action should be applied for patients with compromised renal function. For instance, to counteract and decrease the high kidney retention of radiopeptides, positively charged amino acids such as L-lysine and/or L-arginine are co-infused to competitively inhibit the proximal tubular reabsorption of the radiopeptide (5). Particular attention and care should be given to avoid possible electrolyte imbalance (hyperkalaemia and hypernatraemia) and the associated metabolic acidosis, which can lead to exacerbated nausea and vomiting, as discussed above. These side effects should be managed by hydrating the patient with normal saline and possibly by repeating corticosteroid or antiemetic administrations (5).

Some centres may choose to administer gelofusine, a succinylated bovine gelatine molecule commonly used as a plasma expander, which further minimises kidney-absorbed radiation dose by about 45% through its interaction with the megalin/cubilin receptor-mediated transporter system (5). It is essential to discuss this method with the patient, as some may not wish to use it for cultural/religious reasons.

When it comes to **incontinence**, there is potential for contamination associated with treatment of incontinent patients and a risk assessment should be carried out when considering how a therapy is to be undertaken (9). The following options may apply:

Catheterisation: Directly before the administration of ^{223}Ra therapy for inpatients with urinary incontinence. The catheter should remain in place for 24h after the treatment (20) and 48h after [^{177}Lu]Lu-DOTATATE administration (5). Leakage can occur from around a catheter, from a split urine bag, or from inadvertent opening of the tap on the bag. Care is needed to protect urine bags when patients move or when manual handling is applied to move the patient. Basic biological protection measures normally provide adequate safety, but both staff and carers need to be aware of the precautions to be taken and the potential risks (10). Urine bags should be emptied frequently (5) by competent, trained staff members and disposed of/stored appropriately.

Absorbent pads, rubber sheets, or pants can be used (20) but should be changed frequently. The treating team should advise on storage and disposal. Significantly contaminated clothing should be washed separately.

Others

» Hypertension: Due to its chemical composition, ^{223}Ra may contain up to 54 mg of sodium per dose. This has to be taken into consideration for patients on a sodium-controlled diet (16), for whom it could be beneficial to monitor the blood pressure before and after administration.

» In patients undergoing [^{177}Lu]Lu-DOTATATE therapy who suffer from severe cardiac insufficiency, volume overload might lead to acute cardiac insufficiency and decompensation and should therefore be avoided. Formulations with lower amounts of amino acids and hence lower volumes should be chosen (5). Oral hydration should be moderately increased, under close monitoring.

» Faecal incontinence: For those undergoing ^{223}Ra therapy, hospitalisation is encouraged in cases of unmanageable faecal incontinence resulting in seriously ill patients (16).

» Common acute non-haematological toxicities with [^{131}I]I-mIBG also include anorexia and sialadenitis and usually occur within a few days after administration. Most of them are mild and controllable (7). With regard to sialadenitis and xerostomia, massage of the salivary glands area, increased hydration, use of sialagogues (e.g. lemon juice, lozenges, pastilles or chewing gum) and prescription of anti-inflammatory and analgesic medication have been reported in the literature (7,23).

Hormonal crisis

Side effects of [^{177}Lu]Lu-DOTATATE therapy tend to be mild, providing the necessary precautions are taken. They may be acute, related to the administration of amino acids or to the radiopeptide itself, or chronic (5). It is known that long-acting somatostatin analogues (SSA) possess secretory inhibiting action. Not only are they used as first-line pharmacological treatment for neuroendocrine tumours; they are also approved for preventing and alleviating the symptoms of carcinoid syndrome (nowadays known as "hormonal crisis"), for example flushing and diarrhoea, bronchial obstruction (5), hypotension or extreme

changes in blood pressure, and arrhythmias (24,25). This results from the release of a variety of vasoactive peptides and hormones into the bloodstream, and these clinical manifestations can turn out to be life-threatening (25). While they may happen unpredictably, they typically occur during treatment or within 2 days after the initial treatment (24). Practitioners should avoid lingering near the patient unnecessarily, spend as little time as necessary in close proximity to patients treated with radiopharmaceuticals, and maintain an appropriate distance. However, if the medical condition of a patient deteriorates to such an extent that intensive nursing care becomes necessary, urgent medical care is a priority and should not be delayed or hindered (5,19). Pre-treating patients at high risk of crisis (due to previous occurrences, known high tumour burden or extensive liver metastases) has been suggested, although this is not done at most centres (14,26). Vital signs (at least blood pressure and pulse) should be monitored before and after therapy infusion in symptomatic patients. Therapeutic interventions should be undertaken to treat the functional syndrome effects or exacerbation, with particular care for electrolyte imbalance (5). The team should consider the possibility of carcinoid symptom flare after cessation of long-acting SSA 4–6 weeks before treatment and may opt for short-acting SSTA to control the symptoms (26). Although this chapter will not cover specific posology (as this should be discussed by the treating team and depends on the availability of pharmaceuticals in each country), it is worth noting that some centres have published their protocols on how to handle carcinoid crisis, highlighting the need for every department to develop an action plan (24,26).

Clinical deterioration and death

The Therapy Lead should use their clinical judgment to convey the severity of the patient's health decline to consultants, based on close monitoring of the patient's quality of life, performance, and indicators such as blood count at defined time intervals. All these factors must be considered before proceeding to subsequent cycles. For patients with haematological values lower than the limits indicated for the therapy cycle, adjustments may be needed (e.g. blood transfusion, or the consultant may decide on a lower activity and/or extension of the interval to the following cycle (5)).

For patients who have metastatic bone disease, attention should be paid to **symptomatic skeletal events**. These include pain (including pain flare, defined as a transient increase in bone pain (27)); pathological fracture, which may lead to orthopaedic surgical intervention; or spinal cord compression (16,27,28). These may be addressed by parallel administration of bisphosphonates (providing there are no contraindications such as pre-existing dental disease and kidney disease (29)), prescription of pain analgesia, and monitoring of symptoms in order to spot early signs of complications. In the event of unexpected admission to hospital (e.g. following a fall and suspicion of fracture), mechanisms should be in place to alert the nuclear medicine treating team so that they can plan accordingly in a manner that reduces radiation exposure of accident and emergency staff and supports the patient's management, recovery and healing, including the need for orthopaedic intervention (20). In terms of resuming treatment, six to ten weeks have been mentioned as sufficient for adequate consolidation after orthopaedic intervention, but the actual timing depends on the individual radiographic assessment (16).

Other **unforeseen scenarios** comprise cases of stroke or heart-related conditions. Life-saving efforts shall take precedence over consideration of radiation exposure of medical personnel, who should proceed with emergency care while taking precautions against the spread of contamination and minimising external exposure (19). When such events occur during the patient's stay in hospital, the on-call consultant must be notified without delay. As part of the standard checks prior to initiating treatment, a resuscitation trolley must be available, and a trained emergency team must be contactable (5). Biochemical blood tests are a frequent procedure upon admission. If the patient's blood is still radioactive, instructions for handling of radioactive laboratory specimens must be followed (these should be developed with the biomedical sciences team in advance, as part of a contingency plan). As a rule of thumb, the specimen should be handled by the minimum number of people for the minimum amount of time, and used equipment (including pipettes, pipette tips, test tubes, gauze sponges, absorbent pads) should be disposed of accordingly and marked with a radioactive label. Ideally, a designated area should be set aside, away from other inpatients (with a temporarily designated toilet, if possible) and only non-pregnant staff members should care for that patient. These patients pose a radiation hazard when in accident and emergency departments or intensive care wards, and the nuclear medicine team should assess the usefulness of using portable shielding. Rotation of staff is likewise advisable. Close communication with the treating team and the medical physics department is necessary, particularly regarding the need to issue personal monitors to staff and to manage waste streams.

Therapeutic facilities are discussed in greater detail in the Hospitalisation chapter, but it is worth emphasising that a single location is preferable. Patient management during the therapy itself consists of several stages, but having a designated treatment room and nearby restroom reserved for the treatment day can prove very useful. Patients may be debilitated or feel drowsy (e.g. from

the antiemetics in [^{177}Lu]Lu-DOTATATE therapy (30)) and may need help due to restricted mobility or pain. Consultation schedules should allow sufficient time, so that the patient does not feel rushed – 60 min for initial consultation, with the duration being adapted for follow-up appointments depending on the patient's status (2).

Patients undergoing outpatient treatment should be forewarned of the rare possibility of an overnight hospital stay should a complication occur (e.g. a neuroendocrine hormonal crisis or severe emesis) (14,15).

Lastly, some patients who are referred for nuclear medicine therapies are in the palliative stage of the disease or may experience disease progression despite everyone's best efforts. It is important to identify when it is time to liaise with other services, such as community nursing support or hospice referral (31). As patients approach the end of their life, it is important to initiate discussions about preferences for end-of-life care (31), including cessation of radionuclide therapy if this is not achieving the desirable outcome. On the other hand, if the patient is benefiting from it and prefers to continue with the therapy, coordination of care is paramount (31). Nonetheless, consideration must be given to restrictions after death due to a potentially radioactive body (11) (e.g. autopsy of the corpse; is the patient an organ donor, does the patient intend to be embalmed/buried/cremated or have their body donated to medical science?). The Medical Physics Lead must be notified immediately in such cases, which are expected to increase in line with the growing use of radionuclides in palliative treatment. In cases where death occurs in hospital, access to the room occupied by the deceased should be controlled until the room has been decontaminated and surveyed and the body removed (11).

EXTRAVASATION

Extravasation is defined as the process by which a fluid or medicine unintentionally leaks into the surrounding tissue. In respect of cancer therapies, extravasation refers to the inadvertent infiltration of chemotherapy agents into the subcutaneous or subdermal tissues surrounding the IV or intra-arterial administration site (32). The same concept is applicable to the radionuclide pharmaceuticals used in nuclear medicine therapies (33).

Notwithstanding the fact that not all extravasation incidents result in ulcerative and necrotic tissue damage, patients still experience pain and discomfort in addition to disruption of treatment and prolonged hospitalisation for the management of extravasation (34,35). The occurrence of extravasation is an unwanted and stressful situation that may result in a significant unintended radiation dose to localised tissues (36) and in severe and irreversible local injuries (34) (for instance, an extravasation of ^{223}Ra can potentially cause serious injury such as tissue necrosis (16)).

It is also important to consider the concomitant drugs, particularly amino acid infusions, which are typically used to protect the kidneys against radiation: extravasation of this solution or other infusion drugs can cause cutaneous complications because of the hyperosmolarity effect, and demands attentive follow-up (37).

Prevention

Patient-inherent anatomical or behavioural features and procedural/device characteristics are the two main risk categories associated with extravasation. These aspects are well documented in the literature (32,34,36), and Table 1 summarises the points that are pertinent to the purpose of this chapter.

Specific precautionary methodology to adopt regarding radionuclide therapy administration:

» IV access should be assessed prior to the therapy itself (e.g. by the Therapy Lead, when doing routine blood tests). This will allow the team to plan accordingly, avoiding constraints on the therapy day. Depending on the skillset of the treating team, some centres may consider using ports and/or central lines. Interaction with other medicines which are delivered through these devices must be clarified.

» Staff should be knowledgeable about the latest clinical evidence pertaining to handling of extravasation/side effects, including the supplier's information/Summary of Product Characteristics of each radiopharmaceutical. Chemical phlebitis should not be confused with extravasation (32), and staff should be experienced enough to distinguish symptoms, conduct a high-quality clinical assessment and differential diagnosis, and be able to rule out chemical phlebitis (35).

» The technologist should do a visual assessment of the injection site and carefully observe the IV device once this has been inserted (35). Patency of the peripheral IV site should be monitored continuously throughout administration (14). A three-way stopcock is recommended to manage multiple fluid intake (e.g. saline and radiopharmaceutical). Absorbent or water-impermeable material may be useful to avoid contamination of the patient's skin adjacent to the site of injection (16).

» For cases of multiple infusion (e.g. peptide receptor radionuclide therapy), some departments might find it useful to place cannulas in contralateral arms and to keep both of them in place until the end of the procedure (this way, if the second cannula used for the amino acid infusion is no longer usable but the infusion is not yet concluded, the first one can be used instead of attempting to place another one in close proximity when the patient is already highly radioactive).

Patient-related factors	Procedure-related factors	Good practice preventive measures
Dehydration	Inexperienced staff1	Encourage hydration
Sclerosed veins	Multiple attempts at cannulation1	Cannulation should be avoided over joints, inner wrist, and the lower extremities
Prominent but mobile veins	High flow pressure / spontaneous retraction of catheter	
Coagulation abnormalities resulting in increased vascular permeability		
	Choice of equipment (peripheral catheter of choice, size; winged steel infusion devices ('butterfly' needles) must not be used for infusion of vesicant drugs as the needle can be easily displaced or puncture the venous wall)	Discuss central venous access with the consultant, if needed
Small and fragile veins		Use aids for cannulation (hot water bags, ultrasound)
Obesity		
Impaired circulation (e.g. lymphoedema, advanced diabetes, among others)		After cannulation, check for blood flow
		Flush with 10mL normal saline and check for signs of extravasation
Trypanophobia (needle phobia)		
Hypaesthesia, preventing the patient from immediately alerting the staff member or communicating changes in sensation	Device accessories: inappropriate cannula stabiliser device/poor cannula fixation, inadequate dressing	A blood return (flashback) should always be obtained before drugs are administered; check regularly
Communication difficulties		If there is a cannula in place: check which medications were previously infused. If appropriate, flush 10–20 ml of saline solution between different drug infusions
Prolonged infusion, especially if the patient remains active in the room		

Table 1: Common patient- and procedure-related risk factors and preventive measures to minimise the chances of extravasation. 1 It is not advisable for junior members of staff, or others without sufficient experience, to attempt to cannulate therapy patients. As per best practice, multiple attempts by the same member of staff are not recommended.

Suspicion and course of action

It is very important to build trust between the treating team and the patient and to inform the latter of the need to communicate any adverse symptoms during the procedure (e.g. redness, pain and swelling of the injection site). In this particular context, an open dialogue allows for early identification of extravasation. Other signs which frequently raise suspicion of a possible extravasation (also known as "tissuing") are the absence of blood return, resistance on the plunger of the syringe during delivery of the medicine, or an interruption to the free flow of an infusion (32). Unfortunately, even when extravasation is identified early, progressive extravasation can give rise to ulcerated and necrotic tissue over time (35).

Every department should formulate a standard operating procedure for extravasation, giving consideration to the following steps:

» If there is any sign or suspicion of extravasation, it should be assumed that it has occurred and administration should be interrupted (16,34,36). The consultant should be informed immediately, and advice should be sought from a radiation protection expert.

» The IV device should be left in situ. Aspiration of some of the extravasated fluids should be attempted before the needle is withdrawn (16,34), even though this is generally not productive owing to tissue blockage at the needle terminus (34). There are no known antidotes for radiopharmaceuticals in use at the time of publication; however, if the extravasation occurred with other concomitant infusions for which there are known antidotes, it is usually recommended that administration is attempted through the same IV line, since it is very important to deliver the antidote directly into the extravasated area or in close proximity to this area for maximum efficacy (34).

» If the area presents a different coloration or swelling, the use of a pen to delineate the area (15) can assist in monitoring changes over time. With the consent of the patient, the area should be photographed (34).

» Dose rate measurements should be undertaken and, ideally, images acquired for dosimetry purposes (localised image of the injection site, whole body, and hybrid imaging of the pathological area of interest), including for monitoring and calculation of skin dose (10,33,36). It may prove useful to have images of the affected area in subsequent days to document the evolution of the extravasation. The effect on the uptake quantification of the original area of interest should be noted, particularly if it was meant to be used for assessment of treatment response, as it will be indicative and not sufficiently reliable. Moreover, the ability of the patient to hold the arms above the head should be taken into consideration (e.g. for a SPECT/CT of the abdominal area if carrying out [^{177}Lu] Lu-DOTATATE therapy) since this may be

weakened due to discomfort in the arm. Leaving the arms by the side may affect visualisation of the organ of interest if the two are too close, resulting in less counts to the desired organ (10). The technologist should aim to obtain the most suitable images while preserving patient comfort.

» Resting and elevating the affected site for 48h may aid in the normal absorption and drainage of loculated extravasated fluids (16). Compression stockings have also been suggested (38).

» Gentle massage of the area may be used to promote lymphatic drainage which, if successful, could reduce the local radiation dose (16) (this should only be attempted if tolerated by the patient). The area should be checked every 2–4h, so it may be advisable for the patient to remain an inpatient (34).

» Local cooling or warming (depending on the type of drug and whether vasoconstriction or vasodilation is intended) for at least 15–30 min four times a day for 24–48h. Alternatively, this can be applied immediately for 30–60 min, alternating on and off every 15 min, for 1 day. The warming approach has been suggested for ^{223}Ra (16) as well as for ^{131}I (38), since the hyperthermic effect induces vasodilation and, in principle, should aid radiopharmaceutical clearance. Direct pressure on the site is to be avoided because it can spread the extravasated drug to a much broader area (34).

» Early plastic/reconstructive surgery and/or physical therapy and rehabilitation consultations are usually suggested for non-radioactive extravasations (34,35) and may have a place in this context (33,36,37). However, due to the radioactivity, this would require close collaboration between the nuclear medicine and surgical teams to manage exposure, biological samples, and waste streams.

» Systemic analgesics and/or local pain medication may be prescribed (34).

» Documentation of the steps and timing of each procedure, as well as every member of staff involved. Such data is to be used later to write a formal report of the occurrence.

» A consultation with the patient, the consultant, the nuclear medicine technologist, the clinical nurse specialist and the medical physics team should take place to explain the incident and the consequences to the patient, apologise and decide on the way forward.

Documenting the extravasation incident

Although departments across the world will have their own local risk management systems in place with specific guidance on how to report an incident, some information is mandatory (32,34) for patient safety and follow-up, for legal purposes, and in the interests of shared learning (36), namely:

1. Patient identification (external reports to be anonymised);
2. Incident timeline, including date and time when the occurrence was first suspected and steps taken;
3. Name of the extravasated pharmaceutical and any other medicines administered on the same day;
4. Symptomatology, observed and as described by the patient;
5. Description of the IV access (easiness of device insertion, device specification, number of venepuncture attempts, location, volume of fluid administered to test patency);
6. Estimation of the extravasation area – visible dispersion size, volume of the pharmaceutical;
7. Images acquired/measurements in the following days;
8. Duty of care and candour – an open, honest approach is recommended, with apologies being issued to the patient and subsequent patient interactions, including any complaints that may be filed (39–41).

To conclude, this chapter addressed potential operational and clinical complications and exemplified how service resilience and preparedness are fundamental components to improve standards of care. More than simply administering a capsule or an injection, it is vital to develop a comprehensive and coordinated multidisciplinary strategy to sustain seamless services with optimal patient outcomes, even in the most uncommon circumstances.

The administration of therapeutic radionuclides requires that the technologist recognise unexpected events and reactions and hold the necessary expertise to evaluate the extent and severity of potential complications (38). They should be familiar with local pathways of care beyond nuclear medicine so that they can act promptly and guide the patient's journey in a confident and caring manner. Furthermore, medical physics play an important role in the investigation of radiokinetic dosimetric models for extravasation.

REFERENCES

1. Intercollegiate Standing Committee on Nuclear Medicine. Molecular radiotherapy: guidance for clinicians [Internet]. 2019 Sep. Available from: www.rcr.ac.uk
2. 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. European Journal of Nuclear Medicine and Molecular Imaging. 2017 Sep 1;44(10):1671–8.
3. 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. European Journal of Nuclear Medicine and Molecular Imaging. 2017 Sep 1;44(10):1671–8.
4. NHS. The Patient Experience Book - A collection of the NHS Institute for Innovation and Improvement's guidance and support. 2013.
5. Zaknun JJ, Bodei L, Mueller-Brand J, Pavel ME, Baum RP, Hörsch D, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Vol. 40, European Journal of Nuclear Medicine and Molecular Imaging. Springer Verlag; 2013. p. 800–16.
6. HSE. RR416 Information to accompany patients undergoing nuclear medicine procedures. 2006.
7. Kayano D, Kinuya S. Current Consensus on I-131 MIBG Therapy. Nuclear Medicine and Molecular Imaging. 2018 Aug 3;52(4):254–65.
8. Giammarile F, Chiti A, Lassmann M, Brans B, Flux G. EANM procedure guidelines for 131I-meta-iodobenzylguanidine ([131I]I-mIBG) therapy. Vol. 35, European Journal of Nuclear Medicine and Molecular Imaging. Springer Verlag; 2008. p. 1039–47.
9. Committee for Medicinal Products for Human Use (CHMP). Guideline on core SmPC and Package Leaflet for sodium iodide (131I) for therapeutic use [Internet]. London; 2016 Oct. Available from: www.ema.europa.eu/contact
10. Martin CJ, Marengo M, Vassileva J, Giammarile F, Poli GL, Marks P. Guidance on prevention of unintended and accidental radiation exposures in nuclear medicine. Journal of Radiological Protection. 2019 Apr 16;
11. IAEA. IAEA Safety Reports Series, No.63 - Release of Patients after Radionuclide Therapy [Internet]. Vienna; 2009. Available from: http://www-ns.iaea.org/standards/
12. Colley PP, Boelaert K, Evans C, Rm E, Ge G, Ja G, et al. Guidelines for the management of thyroid cancer. 2014.
13. Kratochwil C, Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, et al. EANM procedure guidelines for radionuclide therapy with 177Lu-labelled PSMA-ligands ([177Lu]Lu-PSMA-RLT). European Journal of Nuclear Medicine and Molecular Imaging. 2019 Nov 1;46(12):2536–44.
14. Hope TA, Abbott A, Colucci K, Bushnell DL, Gardner L, Graham WS, et al. NANETS/SNMMI procedure standard for somatostatin receptor-based peptide receptor radionuclide therapy with [177Lu]Lu-DOTATATE. Journal of Nuclear Medicine. 2019;60(7):937–43.
15. European Medicines Agency. Lutathera, INN-lutetium (177Lu) oxodotreotide - Summary of Product Characteristics. 2018.
16. Poeppel TD, Handkiewicz-Junak D, Andreeff M, Becherer A, Bockisch A, Fricke E, et al. EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2018 May 1;45(5):824–45.
17. Committee for Medicinal Products for Human Use. Radium-223 (Xofigo) Summary of Product Characteristics. 2020 May.
18. Domínguez-Gadea L, Cerezo L. Decontamination of radioisotopes. Vol. 16, Reports of Practical Oncology and Radiotherapy. Urban and Partner; 2011. p. 147–52.
19. Bailey DL, Humm JL, Todd-Pokropek A, van Aswegen A. Nuclear Medicine Physics: A Handbook for Teachers and Students.
20. Poeppel TD, Handkiewicz-Junak D, Andreeff M, Becherer A, Bockisch A, Fricke E, et al. EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2018 May 1;45(5):824–45.
21. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJG, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. Vol. 35, European Journal of Nuclear Medicine and Molecular Imaging. 2008. p. 1941–59.
22. Kalogianni E, Ruiz DL, Corcoran BJ, Devlin LA, Vivian GC, Mulholland NJ. 177 Lu-Dotatate therapy for the treatment of metastatic neuroendocrine tumours in a patient on haemodialysis—dosimetric considerations . BJR|case reports. 2015 Nov;1(3):20150177.
23. Hoffman HT, Chaudhry US, Menda Y, Robinson RA. Current Management of Radioiodine Sialadenitis. Current Otorhinolaryngology Reports. 2014 Jun 15;2(2):70–84.
24. de Keizer B, van Aken MO, Feelders RA, de Herder WW, Kam BLR, van Essen M, et al. Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. European Journal of Nuclear Medicine and Molecular Imaging. 2008 Apr;35(4):749–55.
25. del Olmo-García MI, Muros MA, López-de-la-Torre M, Agudelo M, Bello P, Soriano JM, et al. Prevention and Management of Hormonal Crisis during Theragnosis with LU-DOTA-TATE in Neuroendocrine Tumors. A Systematic Review and Approach Proposal. Journal of Clinical Medicine. 2020 Jul 12;9(7):2203.
26. Tapia Rico G, Li M, Pavlakis N, Cehic G, Price TJ. Prevention and management of carcinoid crises in patients with high-risk neuroendocrine tumours undergoing peptide receptor radionuclide therapy (PRRT): Literature review and case series from two Australian tertiary medical institutions. Vol. 66, Cancer Treatment Reviews. W.B. Saunders Ltd; 2018. p. 1–6.
27. Handkiewicz-Junak D, Poeppel TD, Bodei L, Aktolun C, Ezziddin S, Giammarile F, et al. EANM guidelines for radionuclide therapy of bone metastases with beta-emitting radionuclides. European Journal of Nuclear Medicine and Molecular Imaging. 2018 May 16;45(5):846–59.
28. Parker C, Zhan L, Cislo P, Reuning-Scherer J, Vogelzang NJ, Nilsson S, et al. Effect of radium-223 dichloride (Ra-223) on hospitalisation: An analysis from the phase 3 randomised Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial. European Journal of Cancer. 2017 Jan 1;71:1–6.
29. Ganesan K, Bansal P, Goyal A, Roane D. Bisphosphonate. 2022.
30. Abbott A, Sakellis CG, Andersen E, Kuzuhara Y, Gilbert L, Boyle K, et al. Guidance on 177Lu-DOTATATE Peptide Receptor Radionuclide Therapy from the Experience of a Single Nuclear Medicine Division. Journal of Nuclear Medicine Technology. 2018 Sep;46(3):237–44.
31. End of Life Care Strategy - Promoting high quality care for all adults at the end of life [Internet]. London; 2008 Jul. Available from: www.dh.gov.uk/publications
32. Pérez Fidalgo JA, García Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F. Management of chemotherapy extravasation: ESMO-EONS clinical practice guidelines. Annals of Oncology. 2012;23(SUPPL. 7).
33. Osborne D, Kiser JW, Knowland J, Townsend D, Fisher DR. Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements. Health Physics. 2021 Mar;120(3):339–43.
34. Ener RA, Meglathery SB, Styler M. Extravasation of systemic hemato-oncological therapies. Vol. 15, Annals of Oncology. 2004. p. 858–62.
35. NECN Guidelines for Management of Extravasation Guidelines for the Management of Extravasation "Quality and safety for every patient every time." Newcastle; 2019 Nov.
36. van der Pol J, Vöö S, Bucerius J, Mottaghy FM. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. European Journal of Nuclear Medicine and Molecular Imaging. 2017 Jul 16;44(7):1234–43.
37. Sakulpisuti C, Chamroonrat W, Tepmongkol S. Cutaneous Management after Extravasation of High-Concentrated Amino Acid Solution Administered for Renal Protection in PRRT. 2022; Available from: https://doi.org/10.3390/tomography8010029
38. Bonta D v., Halkar RK, Alazraki N. Extravasation of a therapeutic dose of 131I-metaiodobenzylguanidine: Prevention, dosimetry, and mitigation. Journal of Nuclear Medicine. 2011 Sep 1;52(9):1418–22.
39. Strickland NH, Hons M. Duty of candour: implications for radiologists. 2019.
40. The duty of candour: guidance for providers. 2021.
41. Can professional regulation do more to encourage professionals to be candid when healthcare or social work goes wrong? [Internet]. London; 2013 Sep. Available from: www.professionalstandards.org.uk.http://www.professionalstandards.org.uk/policy-and-research/right-touch-regulation[Accessed

9

WASTE MANAGEMENT

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RADIOACTIVE WASTE MANAGEMENT

Nuclear medicine is an important tool for diagnosis and therapy using medical radioisotopes. With the advent of theranostics, the medical community and industry witnessed a dramatic change in the landscape of therapy radionuclides, transitioning from a ^{131}I-dominated discipline to one predominantly using ^{177}Lu-based radiopharmaceuticals that emerged out of diagnostic tracers. Over 10,000 medical departments around the world use radioisotopes in an array of 100 different nuclear medicine procedures, totalling about 49 million medical procedures each year (1). With the current evidence of [^{177}Lu]Lu-PSMA efficacy in castration-resistant prostate cancer, a considerable growth in the use of novel therapeutic radiopharmaceuticals is expected in the next decade (2). As a consequence of handling these materials, a wide range of radioactive waste is produced. Radionuclides in nuclear medicine are used in unsealed forms and can be classified according to their application for diagnostic, therapeutic or research purposes. With growing public awareness of the consequences of pollution, the need to take account of the social and environment effects of radioactive waste disposal has increased. When setting up a waste management system, each part of the radionuclide pathway must be considered, from consignment, synthesis in radiopharmaceutical form and administration to disposal and release. Radioactive waste can be in liquid, solid or gaseous form, and this will determine the methods available for disposal. It is also important to consider the content of long-lived impurities arising from a specific production process, for example the presence of ^{177m}Lu, or ^{227}Ac and ^{227}Th in ^{177}Lu- or ^{223}Ra-labelled radiopharmaceuticals, respectively. Despite the existence of specific regional legal frameworks pertaining to radioactive waste management in the European space, the latter all fall under the principles set out in EU directives, which focus mostly on minimising radioactive waste production, safe and appropriate waste management, allocation of responsibilities to duly trained personnel, and the principle of transparency and accountability.

WASTE MANAGEMENT SYSTEM

Radioactive waste as a product of human activity, be it in nuclear power generation or for medical, agricultural or industrial purposes, must be processed in a waste management system. The basics of any radioactive waste management system are founded on the principles of radiation protection, i.e. justification, optimisation and limitation. These basic concepts, together with ethical and geopolitical aspects, can be recognised in the nine principles of radioactive waste management defined by the IAEA (Table 1) (3). Radioactive waste management comprises all administrative and operational activities involved in the handling, pre-treatment, treatment, conditioning, transport, storage and disposal of radioactive waste.

A functional and effective radioactive waste management system should observe the above-mentioned principles, guaranteeing the protection of human health and the environment.

Principle	Description
Principle 1: Protection of human health	Radioactive waste shall be managed in such a way as to secure an acceptable level of protection for human health.
Principle 2: Protection of the environment	Radioactive waste shall be managed in such a way as to provide an acceptable level of protection of the environment.
Principle 3: Protection beyond national borders	Radioactive waste shall be managed in such a way as to ensure that possible effects on human health and the environment beyond national borders will be taken into account.
Principle 4: Protection of future generations	Radioactive waste shall be managed in such a way that predicted impacts on the health of future generations will not be greater than relevant levels of impact that are acceptable today.
Principle 5: Burdens on future generations	Radioactive waste shall be managed in such a way that it will not impose undue burdens on future generations.
Principle 6: National legal framework	Radioactive waste shall be managed within an appropriate national legal framework including clear allocation of responsibilities and provision for independent regulatory functions.
Principle 7: Control of radioactive waste generation	Generation of radioactive waste shall be kept to the minimum practicable.
Principle 8: Radioactive waste generation and management interdependencies	Interdependencies among all steps in radioactive waste generation and management shall be appropriately taken into account.
Principle 9: Safety of facilities	The safety of facilities for radioactive waste management shall be appropriately assured during their lifetime.

Table 1. Principles of radioactive waste management defined by the IAEA

Waste disposal can be categorised into two types: 1) disposal sites within areas where people live, monitoring wastes until safety concerns are no longer present (this could be a decay storage room in a nuclear medicine department), or 2) disposal sites isolated from living areas due to the long time period required until substances are below a radioactive level considered harmless (e.g. geological disposal of high-level radioactive wastes) (4).

In general, radioactive waste from the medical sector does not present a significant long-term waste management problem when compared to wastes generated from nuclear fuel cycle operations (5). However, when setting up a nuclear medicine therapy ward, a number of resources must be present to comply with local radiation protection regulations (which are based on the above-mentioned principles). These include delayed patient release after therapy, strict control of aqueous radioactive wastes and separate storage of long-lived contaminants such as ^{177m}Lu.

EXCLUSION, EXEMPTION AND CLEARANCE

The concepts of exclusion, exemption and clearance are fundamental in understanding the scope of regulatory control of radioactive waste.

Exclusion: Some radiation exposures are always present in our lives, and as such there are no realistic steps that can be taken to control either the source or the magnitude of the exposure. These sources are said to be excluded from regulatory control. Examples include ^{40}K in the body and cosmic radiation on the earth's surface (6).

Exemption: Some radiation sources have such a low level of risk that they can be exempted from regulatory control. The conditions for exemption are 1) the effective dose expected to be incurred by any member of the public due to the exempted practice or source is of the order of 10 µSv or less in a year, and 2) either the collective effective dose from one year of performance of the practice is no more than about 1 man Sv or an assessment for the optimisation of protection shows that exemption is the optimum option (6, 7).

Clearance: In some cases, regulatory control over certain radioactive sources or radioactive material is no longer necessary. Clearance is defined as the removal of radioactive materials or radioactive objects within authorised practices from any further regulatory control by the regulatory body (6).

TYPES OF WASTE

For legal and regulatory purposes, radioactive waste is material for which no further use is foreseen that contains, or is contaminated with, radionuclides at activity concentrations greater than clearance levels as established by the regulatory body. Radioactive waste must be managed safely and in such a way as to avoid imposing an undue burden on future generations; that is, the generations that produce radioactive waste have to seek and apply safe, practicable and environmentally acceptable solutions for its long-term management.

In order to classify biomedical radioactive waste generated in the field of nuclear medicine therapy, it is useful to consider various characteristics of this waste. These include origin, hazardousness and radiological, physical, chemical and biological properties, as well as volume and quantity per unit of time (8).

Furthermore, it makes sense to divide these wastes into certain classes according to their radiological properties, half-life and amount of activity. Radioactive waste in the field of nuclear medicine therapy can generally be classified as "very short-lived waste" up to a half-life of about 100 days and activity concentrations of about 10^{8} - 10^{9} Bq/g (5). Exceptions are test emitters for quality control of dose calibrators (e.g. ^{137}Cs), gamma cameras and hybrid devices (e.g. ^{57}Co and ^{68}Ge) as well as long-lived impurities in certain radiopharmaceuticals that arise during manufacture (Figure 1). These can at most be classified as "low-level waste" and "intermediate-level waste" (8).

A closer look at the physical properties leads to a further classification into open or sealed substances in solid, liquid and gaseous form, which are discussed in more detail below (5).

Product	Primary radionuclide	Half-life	Radionuclide impurity	Half-life
Lutathera®	^{177}Lu	6.7 days	^{177m}Lu (0.01 %)	160 days
Xofigo®	^{223}Ra	11.4 days	^{227}Ac (0.004 %) ^{227}Th (0.5 %) (9)	21.8 years 18.7 days
TheraSphere™	^{90}Y	2.7 days	^{88}Y (< 0.01 %) ^{152}Eu (< 0.01 %) ^{154}Eu (< 0.01 %)	107 days 13.5 years 8.6 years

Table 1. Principles of radioactive waste management defined by the IAEA

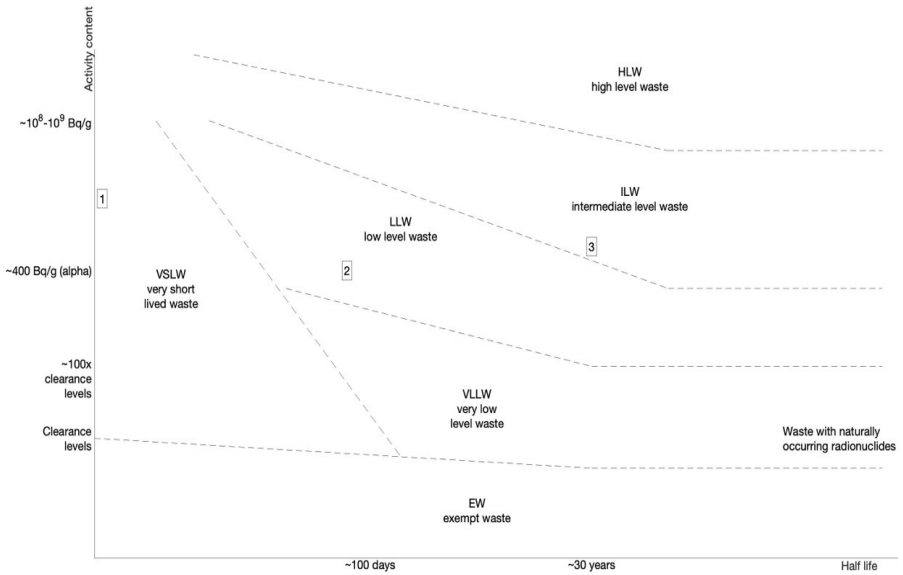

Figure 1b: Classification of radioactive waste (IAEA GSG-01)

Example in Figure	Half-life	Activity	Example
1	< 100 days	GBq	^{177}Lu
2	> 100 days	MBq	^{177m}Lu
3	> 30 years	MBq	^{137}Cs

1. Solid waste: In the case of solid waste, it is useful to distinguish combustible or non-combustible and compactible or non-compactible waste (5). These solid wastes include used protective clothing, air filters, paper towels, containers of used radiopharmaceuticals, animal carcasses, organs and tissues. In addition, solid wastes may be sealed sources, such as test radiators used for equipment quality control or calibration.

2. Liquid waste: Liquid waste is mostly contaminated waste water from the therapy ward consisting of contaminated washing water and excretions and, if applicable, other body fluids. It may also include unused radiopharmaceuticals or reference solutions.

3. Gaseous waste: Gaseous waste includes, on the one hand, gases that are collected and filtered by means of a special, shielded fume bonnet during processing or preparation for the application of radiopharmaceuticals. On the other hand, these can also be gases that are released into the air during radioiodine therapy through the patients' exhalation and are filtered through corresponding air exchange rates of the rooms and filter systems on the building roof (HVAC).

WASTE FLOW DURING NM THERAPY

Before practically implementing a waste management system, a prospective assessment of the processes pertaining to radionuclide handling in the respective context (e.g. biomedical use) must be performed. Such an assessment includes the total radionuclide inventory (including impurities) per year, waste types, waste generation and possible routes of disposal. An example of a diagram detailing the basic steps of radionuclide therapy waste management is given in Figure 2.

Essentially, we identify the pathway of radionuclides beginning in the hot lab, which starts with radiopharmaceutical arrival and dispensing to individual therapeutic activities (Figure 2, A and B). During the administration of therapeutic activities the main fraction of radionuclide content is transferred to the patient, thereby entering the therapy ward. The remaining content is stored temporarily in shielded containers (Figure 2, C), before being transferred to the decay storage room (Figure 2, F). The same happens with any solid waste originating from the therapy ward. Liquid waste is collected and stored in decay tanks (Figure 2, D), while gaseous waste is filtered in HVAC active coal cassettes (Figure 2, G).

All steps referred to in Figure 2 carry additional radiation protection concerns that need to be taken into account in a global radiation protection system that goes beyond waste generation alone. For example, the external radiation exposure due to radiopharmaceutical arrival and dispensing (Figure 2, A and B), or the risk of internal radiation exposure from breathing gaseous radioiodine during and after the administration of ^{131}I (Figure 2, E).

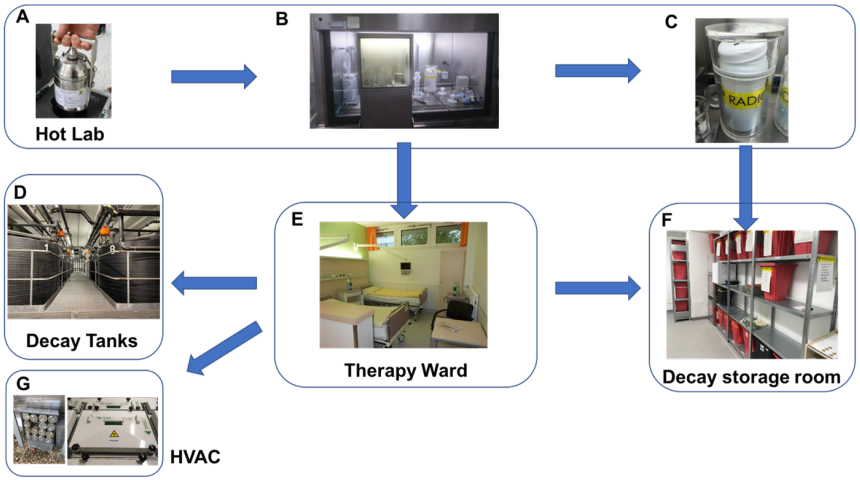

Figure 2: Pathway of Radionuclides

PRACTICAL EXAMPLES

The following gives a brief insight into the practical disposal of solid, liquid and gaseous biomedical waste generated during nuclear medicine therapy.

1. Solid waste: All solid waste is collected as it is generated via appropriately provided containers according to properties such as hazardousness (e.g. biological hazard) and physical properties (e.g. combustible, compactible). Furthermore, sorting by radionuclide takes place at the same time, so that a mixture of radionuclides is avoided. This enables easier determination of activity and release. Otherwise, the radiation protection legislation requires the activity quantities to be determined for all radionuclides present and taken into account in the release calculation via a summation formula.

The containers described are taken to separate decay rooms at the hospital. There, the incoming waste is managed by means of a release counter system (Figure 3). This is a measuring chamber equipped with ten sodium-iodide scintillation detectors. Using a calibration determined for each container geometry and each radionuclide, it is possible to determine the specific activity (activity per mass) of the container from the measured count rates. The container weight is determined by means of an integrated balance. An initial measurement determines the point in time at which these values will fall below the respective release values, i.e. the unrestricted release values issued by the licensing authority within the scope of the handling permit and the legally defined release values. When this point in time is reached, a second measurement is carried out in the release counter system for additional testing. If the values are below the release values specified, the waste can then be fed into the regular, hospital-specific waste cycle as non-radioactive material.

Figure 3: Release counter system

2. Liquid waste: Most of this waste is waste water from the therapy ward. It is fed to the decontamination plant below the therapy ward (Figure 4), collected there in eight collection containers with a total volume of 16 cubic metres each and decontaminated according to the principle of delay and decay. With an average run-in time of 30 days in one of the containers, always keeping one container empty as a reserve in case of a malfunction and adhering to the maximum legally permissible activity concentrations (activity per volume), this results in an average duration of 190 days until a container is pumped out. By treating the wash water and reusing it for toilet flushing, water consumption can be reduced, thus extending the run-in period and decay time of the tanks. Before the tank currently in the intake reaches the maximum fill level, the contents of a filled tank must be discharged into the sewage system to fulfil the above-mentioned condition of keeping an empty tank permanently in reserve. To make this possible, the contents of the corresponding tank are sampled and analysed. Sampling is carried out at a sampling point provided on each tank (Figure 5, left). The analysis is carried out with a high-purity germanium detector (Figure 5, centre). The geometry of the sample and the detector are matched to achieve the highest possible yield. The shape of the vessels used for sampling (Figure 5, right) is the so-called 'Marinelli

Figure 4: Decontamination plant with eight tanks

geometry'. The content corresponds to one litre. The high-purity germanium detector has a corresponding efficiency calibration for this geometry to allow determination of the activity concentration.

3. Gaseous waste: The gaseous waste from the fume bonnets of the hot laboratory and the exhaled substances described above are channelled to filters via the heating, ventilation and air-conditioning systems and filtered out of the air at that point (Figure 6). These filters are then fed into the waste cycle as solid waste

Figure 5: Sampling point (left), sample measuring station with HPGe detector (centre) and Marinelli vessel (right)

Figure 6: HVAC covering (left) and filter (right) on the building roof

FUTURE PERSPECTIVES

In future, the challenges in the area of waste management will probably lie mainly in adapting the stages within the clearance system to handle increasing volumes of waste. In this context, for example, the BioChroma technology (Figure 7) appears to be a promising alternative or supplement to the widely implemented process of delay and decay in the treatment of radioactive waste water from a therapy ward.

Instead of collecting all the waste water from the therapy ward and then waiting until it falls below the exemption values, the BioChroma technology actively filters the radioactive substances from the waste water. In this process, the waste water is first homogenised and then fed into buffer tanks. This preliminary stage of biological treatment is designed to eliminate anaerobic areas and associated odours. The waste water then enters a sedimentation process in which larger particles that could be troublesome in the biological reactor are filtered out. In the subsequent biological treatment plant, any solid matter is separated through further clarification and filtration. This is followed by the adsorption filter process, consisting of activated carbon filters and selective ion exchangers to remove the dissolved radioactive components. In the final step, the remaining clarified water is transferred to storage tanks that are subject to constant metrological monitoring before being discharged into the sewage system.

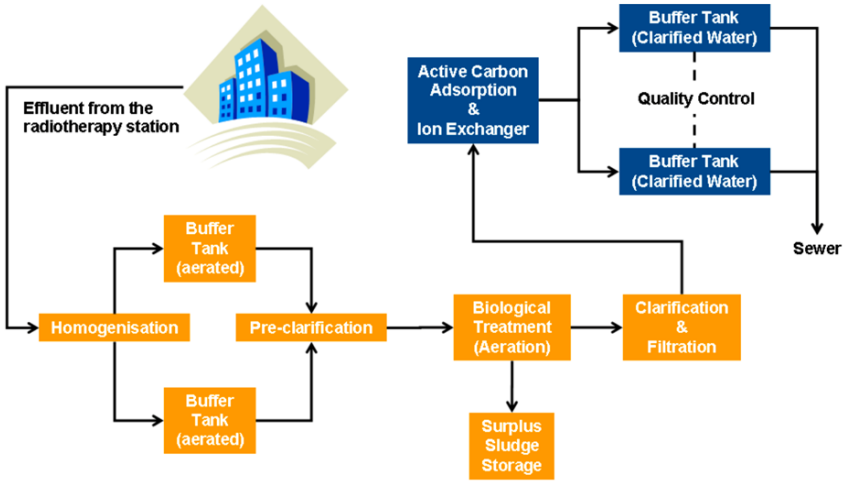

Figure 7: Diagram of the BioChroma process (11)

In this process, about 2000 litres are filtered daily. The daily inflow in a decontamination plant based on the principle of delay and decay in a therapy ward with eight beds and eight decontamination containers with a capacity of 16 cubic metres each is about 450 litres. Thus, a decontamination system using BioChroma technology would enable significant improvements in the area of waste water management, which could, for example, increase the number of patients treated and their water consumption (10, 11).

REFERENCES

1. SMeR study on sustainable and resilient supply of medical radioisotopes in the EU (JRC/BRU/2017/A.7/0001/0C)
2. 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.
3. IAEA. The Principles of Radioactive Waste Management. IAEA, editor: International Atomic Energy Agency Vienna; 1995.
4. Nagasaki S, Nakayama S. Radioactive waste engineering and management: Springer; 2015.
5. IAEA. Management of Radioactive Waste from the Use of Radionuclides in Medicine. Vienna: International Atomic Energy Agency Vienna; 2000.
6. IAEA. Application of the concepts of exclusion, exemption and clearance. International Atomic Energy Agency Vienna; 2004.
7. Lee W, Ojovan M. Fundamentals of radioactive waste (RAW): science, sources, classification and management strategies. Radioactive Waste Management and Contaminated Site Clean-Up: Elsevier; 2013. p. 3-50e.
8. IAEA. Classification of Radioactive Waste. Vienna: International Atomic Energy Agency Vienna; 2009.
9. Bundesamt für die Sicherheit der nuklearen Entsorgung. Vollzug der Strahlenschutzverordnung; hier: Strahlenschutzmaßnahmen bei der Anwendung von Xofigo 2015 [updated 04.03.2016; cited 2022 22.04.]. Available from: https://www.base.bund.de/SharedDocs/Downloads/BASE/DE/rsh/3-bmub/3_106.pdf?__blob=publicationFile&v=1.
10. Banerjee S, Mitra S. Radioactive and hospital waste management: A review. International Journal of Latest Trends in Engineering and Technology (IJLTET). 2013;3(1):275-82.
11. Rodríguez JC. BioChroma–A New and Patented Technology for Processing Radioactive Wastewater from Nuclear Medicine Therapy Facilities in Hospitals and Clinics. World Journal of Nuclear Medicine. 2012;11(1):12.

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