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Radiation Safety and Accidental Radiation Exposures in Nuclear Medicine

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Medical radiation accidents and unintended events may lead to accidental or unintended medical exposure of patients and exposure of staff or the public. Most unintended exposures in nuclear medicine will lead to a small increase in risk; nevertheless, these require investigation and a clinical and dosimetric assessment. Nuclear medicine staff are exposed to radiation emitted directly by radiopharmaceuticals and by patients after administration of radiopharmaceuticals. This is particularly relevant in PET, due to the penetrating 511 keV γ-rays. Dose constraints should be set for planning the exposure of individuals. Staff body doses of 1-25 μSv/GBq are reported for PET imaging, the largest component being from the injection. The preparation and administration of radiopharmaceuticals can lead to high doses to the hands, challenging dose limits for radionuclides such as ^{90}Y and even ^{18}F. The risks of contamination can be minimized by basic precautions, such as carrying out manipulations in purpose-built facilities, wearing protective clothing, especially gloves, and removing contaminated gloves or any skin contamination as quickly as possible. Airborne contamination is a potential problem when handling radioisotopes of iodine or administering radioaerosols. Manipulating radiopharmaceuticals in laminar air flow cabinets, and appropriate premises ventilation are necessary to improve safety levels. Ensuring patient safety and minimizing the risk of incidents require efficient overall quality management. Critical aspects include: the booking process, particularly if qualified medical supervision is not present; administration of radiopharmaceuticals to patients, with the risk of misadministration or extravasation; management of patients' data and images by information technology systems, considering the possibility of misalignment between patient personal data and clinical information. Prevention of possible mistakes in patient identification or in the management of patients with similar names requires particular attention. Appropriate management of pregnant or breast-feeding patients is another important aspect of radiation safety. In radiopharmacy activities, strict quality assurance should be implemented at all operational levels, in addition to adherence to national and international regulations and guidelines. This includes not only administrative aspects, like checking the request/prescription, patient's data and the details of the requested procedure, but also quantitative tests according to national/international pharmacopoeias, and measuring the dispensed activity with a calibrated activity meter prior to administration. In therapy with radionuclides, skin tissue reactions can occur following extravasation, which can result in localized doses of tens of Grays. Other relevant incidents include confusion of products for patients administered at the same time or malfunction of administration devices. Furthermore, errors in internal radiation dosimetry calculations for treatment planning may lead to under or over-treatment. According to literature, proper instructions are fundamental to keep effective dose to caregivers and family members after patient discharge below the Dose constraints. The IAEA Basic Safety Standards require measures to minimize the likelihood of

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any unintended or accidental medical exposures and reporting any radiation incident. The relative complexity of nuclear medicine practice presents many possibilities for errors. It is therefore important that all activities are performed according to well established procedures, and that all actions are supported by regular quality assurance/QC procedures.
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Introduction

Nuclear Medicine services adhere to high safety standards in order to maintain the quality of the service. But safety cannot be guaranteed in a discipline that uses sophisticated technologies and radioactive materials, as part of a complex, multi-step process. However, the growth of clinical applications in Nuclear Medicine (NM) has been accompanied by the development of a culture of an intrinsic multi-disciplinary nature, which has paid close attention to the wide variety of safety aspects involved.

Tools have evolved that are adapted to ensure the safety of patients, staff, the public, and the environment and this review considers things that can go wrong, illustrated with examples, together with the development of measures to prevent them in the future.

Medical radiation accidents and 'unintended events' that might lead to 'accidental or unintended medical exposures' of patients or exposures of staff or the public are included here under the umbrella of the term 'incident'. The term "unintended exposures" in the context of medical procedures is taken as meaning the exposure of a patient to a different radiation level than it was planned for the procedure carried out.

The majority of unintended medical exposures will lead to a small increase in risk of stochastic effects, primarily cancer induction, and result in no obvious effect on the health of the individual subject. These require a clinical assessment of the magnitude of the additional dose and an explanation of the risk, usually in general terms. However, tissue reactions (deterministic effects) in the skin can occur occasionally following extravasation of radiopharmaceuticals used for therapy, which can result in localized doses of tens of Gy.

Incidents Involving Staff Exposure

External Exposure of Staff From Radioactive Materials

NM staff are exposed to radiation emitted directly by radiopharmaceuticals contained within vials and syringes, and sealed sources used for quality control (QC), but will also be irradiated during contact with patients containing radioactivity at some stages during the imaging process or the delivery of therapy. Protection when dealing with patients is in most cases achieved through maintaining distance and limiting the time spent in close contact, but because staff deal directly with patients, there is a potential for individuals to receive high doses from external radiation. Emphasis should be placed during training on the need for technical staff to explain procedures to patients prior to administration of radiopharmaceuticals and the need for nursing staff to maintain a safe distance from patients whenever practicable. Staff members in other departments may also receive unnecessary radiation doses, if exposed to NM patients following injection of radiopharmaceuticals. So, for example, NM departments should not send patients for ultrasound scans during the periods when they are waiting for radiopharmaceutical uptake and bio-distribution to be established before imaging.

The 511 keV γ-rays from PET radionuclides are more penetrating than those from other imaging radionuclides, so require a greater level of shielding. Since patients need to rest for a period of time prior to the scan to allow the radiopharmaceutical to be taken up in affected tissues, both the design of the facility and the workflow require careful planning to ensure that staff members are not exposed unnecessarily during periods when they are not dealing directly with patients. Poor planning of patient workflow and work procedures that do not provide sufficent protection can increase staff member doses considerably. Since there is a risk that doses to staff may be significant, Dose Constraints (DC) well below dose limits should be set for the purpose of planning the exposure of individuals. DC are tools for optimization of protection and safety that are set based on realistic assessments of exposures individuals might be expected to receive. They provide values against which managers can compare results from personal dosimetry, help to identify individuals receiving higher doses so that action can be taken, and so aid in maintaining exposures at levels that are as low as reasonably achievable. Realistic values can be determined based on the anticipated exposure situations and workload within departments. Risk assessments should be undertaken prior to a service being set up to plan the workflow and practices to maintain dose levels within agreed DC, and these should be reviewed periodically thereafter.

Staff body doses reported for PET imaging cover the range 1-25 μSv per GBq activity administered,[1-8] with the largest component being from the injection.[3,9] The wide range in reported values reflects differences in planning and optimizing the protection, the doses can only be used as a rough initial guide to ones that staff at a particular facility might receive. As a starting point, the external dose rates from patients injected with ^{18}F-fluorodeoxyglucose (FDG) are much higher than in conventional NM being typically 45 μSv h^{-1} at 1 m[5,7,9], compared to 10 μSv h^{-1} or less for ^{99m}Tc.[10-13] Published whole body dose values for PET staff are in the range 4-10 μSv per patient, so a workload of

500 patients/year per individual staff member might be expected to give rise to an annual effective dose of 2-5 mSv.

It is important to have comprehensive dose monitoring arrangements in place to establish realistic doses that staff members are receiving. Instruction on wearing and use of dosemeters should be included in staff training and data on dose levels reported to staff members at regular intervals to enable them to review their practices in relation to the doses measured. In certain circumstances where staff work between PET and other radionuclide imaging areas, the constraint may require staff to be rotated between locations, in order to maintain their doses below an agreed DC. This can all be evaluated in the risk assessment, based on which practices are planned.

In order to draw attention to any doses received by staff that might approach the constraint, it is useful to establish investigation levels set below the DC. These provide a tool to highlight doses higher than anticipated. Dose constraints and investigation levels are generally set in terms of the annual dose received during a calendar year. Investigation levels are based on assessments of local practices and should be included in the local rules. If an individual exceeds an investigation level the employer should complete an investigation to determine the cause(s) as soon as possible, so that action can be taken to evaluate what has led to doses being higher than expected, and ensure that adequate controls are put in place to maintain the individual's doses below the constraint in the future. In addition to investigation levels that apply to the annual dose, it can sometimes be helpful to have additional action levels linked to measurements from single dosemeters in order to identify when an unusual exposure has occurred within a shorter time frame.

Staff Members Who are Pregnant

If a female worker has declared that she is pregnant, additional controls may need to be considered to protect the embryo/fetus. Since protection of the fetus should be broadly similar to that applied to members of the public, the working conditions should be such as to ensure that the additional dose to the embryo/fetus would not exceed 1 mGy during the remainder of the pregnancy. This might equate to a dose of 1 mSv to the surface of the abdomen for staff working with ^{18}F, but 1.3 mSv for staff working with ^{99m}Tc. A risk assessment should be carried out to carefully review the exposure conditions of the pregnant woman and assess whether the current work performed is likely to result in the fetal dose approaching the agreed DC. Their working conditions should be changed, if required, to ensure that the dose to the fetus from routine work, and from radionuclide intakes is extremely low, and the probability of any accidental exposures is low.[14,15] Restrictions may or may not be required, but should not mean that the pregnant women need to avoid work with radiation or should not work in designated radiation areas. However, females who have declared that they are pregnant should not be involved in dealing with radiation incidents and emergencies.

Protection of the Hands When Handling Radiopharmaceuticals

Protection of the body when handling radiopharmaceuticals is provided through local shielding of vials and syringes, and bench top shields, but the preparation and administration of radiopharmaceuticals can lead to high doses to the hands. The tips of the fingers receive the highest doses when manipulating syringes and vials during the dispensing of radiopharmaceuticals. Measurements made in 30 nuclear medicine departments from six European countries showed finger doses ranging from about 20-800 μSv per GBq for preparation and administration of ^{99m}Tc.[16] The hands can receive high doses if appropriate protection measures are not in place. The dose is dependent upon both the technique used and more particularly the amount of shielding. Vials should be shielded at all times either by specialized tungsten vial shields, recommended for radiopharmacies, or lead pots. Syringe shields can reduce finger doses by 85% during dispensing and drawing up of injections, and should be used wherever practicable.[17] Tungsten or lead glass can provide good protection for most γ-ray emitters and Poly-methylmethacrylate, possibly with an outer layer of lead to reduce bremsstrahlung radiation, for β-emitters. The fingers are also irradiated when radiopharmaceuticals are injected and doses can again be significant if syringes are not shielded[17] or fingers are placed on the needle during an injection.[18] Placement of a butterfly syringe or cannula in a vein prior to introduction of a radiopharmaceutical can reduce finger exposure where there are potential problems in delivering injections. Where practicable, automated modules for dispensing and drawing up radiopharmaceuticals, especially with PET radionuclides, can reduce doses substantially, although cost may be an issue.[19,20]

Doses from administration of β-emitting radionuclides such as ^{90}Y and ^{32}P and even ^{18}F can reach the level where dose limits are exceeded[21] or even cause tissue reactions.[22] Since radionuclides used for therapy emit particle radiations which are capable of delivering significant doses, consideration of potential finger doses and protection is extremely important. A survey of extremity doses for therapy involving ^{90}Y conducted in the ORAMED project measured finger doses for 54 workers from six European countries.[21] This study recorded finger doses from the preparation of ^{90}Y ibritumomab tiuxetan ranging from 1.2 to 43.9 mSv GBq^{-1} and doses up to 7.4 mSv GBq^{-1} for the administration. The wide range resulted from variations in training and protection facilities in the different institutions. Other workers have published similar values for finger doses during ^{90}Y therapy[22-25], or for ^{177}Lu therapy.[26] The contact dose rate for a vial containing 1 GBq of ^{90}Y can be as high as 700 mSv/min^{-1}[27], so there is a potential for staff to receive doses not only above the dose limit, but ones that would result in tissue reactions if shielding, handling tongs and other appropriate protection measures are not used. In order to check dose levels and identify problems, monitoring using finger stall dosemeters on the tips of the thumb and first three fingers of each hand is recommended for workers handling ^{90}Y

therapy.[18] The dosemeters require thin active layers to enable the true value for $H_p(0.07)$ to be measured.[28]

Contamination With Radiopharmaceuticals

Any handling of unsealed radionuclides will be accompanied by the potential for spread of contamination and intake of radiopharmaceutical into the body. The risks can be minimized by taking basic precautions, such as always carrying out manipulations in purpose-built facilities, wearing appropriate protective clothing, especially gloves, and removing contaminated gloves or any skin contamination as quickly as possible. The potential for a spill is kept to a minimum by using vials with a rubber and metal closure and avoiding vials or any other vessels containing radioactive liquid being left in places where they may be knocked over and broken. In addition, a spill kit should be available where radionuclides are handled to deal with any spillage that does occur.[29]

Most radiopharmaceuticals for imaging and other diagnostic applications are administered by intravenous injection, and a cannula or butterfly is often used to reduce levels of finger exposure. However, this means that there are more connections at which leaks may occur, so it is important for staff to ensure that these are secure and that there is no blockage that could result in radiopharmaceutical being sprayed over the operator or patient. All physicians, technologists, and nurses who may carry out injections should have been thoroughly trained in injection technique, including assessment of the patency of the patient's venous pathway, and precautions such as flushing needles and cannulas with saline before starting an injection, and not exerting excess pressure if the resistance is high. The training should also include practices for needle disposal into a sharps container to reduce the risk of needle stick injuries and use of safe recapping devices if it is necessary to measure the residual activity in the syringe.[30,31]

Aerial contamination is a potential problem when handling radioisotopes of iodine that can readily vaporize[32], and manipulations of significant quantities of radioactive iodine should be carried out in laminar air flow cabinets. Aerial contamination may be produced from apparatus delivering gaseous or aerosol radiopharmaceuticals if it is not used effectively by a patient. Checks need to be made that mask used for lung ventilation studies fit closely to the patient's facial contours and that the patient is able to tolerate wearing the mask for the duration of the procedure. Low levels of personnel contamination resulting from release of radioactive gas to the environment have been reported in cases of inadequate patient collaboration[33,34], and if this occurs, the results of the ventilation study being performed will not be reliable.

Contamination From Patient Fluids

Another source of potential contamination that can be more difficult to deal with is that from body fluids of patients to whom a radiopharmaceutical has been administered. The period over which there is a risk will depend on the physical half-life of the radionuclide and the biological half-life of the radiopharmaceutical involved. The risk from the majority of diagnostic procedures will be relatively small and trivial after the first day, but there are greater potential risks of contamination from treatment of therapy patients and these may persist for several days.

Risk assessments should be carried out to identify the safest approach taking account of the facilities available and the patient cohort. If an ^{131}I therapy patient fails to swallow the radio-iodine or regurgitates it, significant contamination could occur. Any vomit will be highly active in the period following an oral administration of ^{131}I therapy. The use of capsules for oral administration of ^{131}I therapy rather than liquid, where possible, will reduce the scale of spread of radioactivity during and immediately after the administration, as a patient may cough when drinking a liquid. However, a patient may vomit when swallowing a capsule, so the choice of method needs to take the patient's condition into account, as well as the difference in cost, which will be significant for some countries. In order to reduce the risk of a contamination event occurring in a public area, which would be more difficult to contain, iodine therapy patients should remain in the department in an area with a wash-basin and toilet for 15-20 minutes following administrations.

Incontinent Patients

The treatment of incontinent patients will inevitably have the potential for leading to contamination and a risk assessment should always be carried out, to determine how a therapy is to be undertaken. Sanitary pads may be adequate for patients undergoing diagnostic NM tests, but are unlikely to be appropriate for therapy patients. Catheterization may be considered, but there will be associated contamination problems from leakage and disposal of the liquid of which carers will need to be aware, so that they can take any necessary precautions. A split urine bag or inadvertent opening of the tap will lead to a spill of contaminated urine, so there is a need to protect the bags when patients are moved and empty them frequently using basic biologic protection measures to minimize the potential risks.

Methods that can be used for clean-up of spills and decontamination, together with items that should be contained in the spill kit are described in other texts[35,36] and will not be considered here. If the skin becomes contaminated from routine procedures or during any decontamination following a spill, absorbed dose rates at the skin surface can be significant. If this is the case, an evaluation of the skin dose in terms of Hp(0.07) should be undertaken.[37,38]

It is good practice to have a dedicated room for radiopharmaceutical administrations, that has a sealed floor with coving for easy decontamination, wash-basin/sink, drip trays, shields, supplies of absorbent material, and a spill kit.[39] Then if an accident occurs, only this room is contaminated and it can be cleaned and returned to a safe state in a controlled manner, without other activities within the department being affected. Such a room can

be used for both injections and oral administrations, and the room can provide a location where iodine therapy patients can be asked to remain for a period before being discharged.

Quality Management and Fundamentals of Patient Safety

NM has some very special characteristics, compared to other disciplines in diagnostic imaging and to the broad field of radiology. The exposure of patients to ionizing radiation is not from radiation emitted by a medical device, but depends on the administration of a radiopharmaceutical. The exposure may occur at a different time, even hours before a diagnostic procedure; in case of therapy, the irradiation of the patient may continue for days or even weeks after discharge of the patient from hospital.

Furthermore, the desired result does not simply depend on the action of the radioactive pharmaceutical; in most cases, the preparation of the patient, and pre-treatment or medical interventions during the procedure, are instrumental in determining the final result. Examples are the preparation of the patient (fasting, avoiding physical activity, etc.) without which ^{18}F-FDG would not provide any useful information; the absence or introduction of stress testing in myocardial single photon emission computed tomography (SPECT), or the administration of other medicines, like ACE inhibitors in dynamic renal scintigraphy. An example of an intervention affecting the outcome of the use of a therapeutic radiopharmaceutical is the discontinuation of thyroid hormone replacement therapy before administration of ^{131}I.

Therefore, the result of a NM procedure, both in terms of clinical efficacy and safety, is not simply determined by a device or a pharmaceutical, but by the entire process. The whole process needs to be well controlled in order to produce quality results in a safe manner. Only a comprehensive approach can ensure justified and optimized patient exposure and consistent reduction in the risk of incidents.[40-43]

Critical Steps in the Process: Booking

Requests for a NM examination should include all necessary information, and be reviewed and accepted by a qualified NM (or equivalently recognized) practitioner. This is not merely an administrative task, but it is closely related to the justification of a NM procedure. Nowadays, this aspect is taking on new facets as a consequence of the increasing digitalization of the booking process: in an increasing number of situations, it is now possible for the referring phyisician, or directly for a patient with a prescription, to book a procedure online without intermediate filters. This is in general a positive development made available by information technology and internet connectivity, but it is not free from risks.[44-46] If the requests are not reviewed and finally approved by a qualified NM physician, errors may be introduced in the booking process: a wrong procedure or wrong indication picked; the wrong radiopharmaceutical chosen; or an inappropriate time selected for the study.

All of these may cause a non-justified exposure of the patient to radiation, and result not only in an unnecessary radiation dose, but also a failure to carry out the examination and provide the diagnosis at the time it was required.

Misadministration

Many incidents in NM are connected with identification of patients. Misadministration is a typical incident that may occur in NM. Indeed, it should be noted that there is no uniform and generally accepted terminology for defining unwanted events in NM, and this does not favor full awareness of the type of events, their systematic reporting, and the dissemination of information. In this paper, the term misadministration is used to indicate events in which:

- a different radiopharmaceutical is administered instead of the intended one;
- a different activity is given instead of the prescribed one;
- a unit dose prepared for patient A is administered to patient B, even if it is the correct radiopharmaceutical and activity;
- a wrong administration route is used.

In the literature, some authors refer to this type of event as "maladministration".[47] We decided to use "misadminitration", following the UK Radiopharmacy Group.[48]

One of the root causes of this type of incident may be the incorrect identification of the patient; labeling and identification of the radiopharmaceuticals are dealt with in another section.

Even in the case of a diagnostic examination, using limited activity of a short-lived NM radionuclide, a misadministration is considered a serious event, since exposure of the patient in this case is completely unjustified.

Correct patient identification is actually an issue in all hospital activities.[49,50] There are several methods to properly identify patients:

- confirm the patient's name by asking at every step of the process; the question should be "Can you please tell me your name?" and not "Are you Mr. . . . ?", suggesting the name;
- ask the patient to give at least one more element to define their identification, such as their date of birth or address;
- check the patient's ID card, if feasible;
- assign to every patient an identification number and cross-check the number at every step of the process;
- assign to each patient a wristband or equivalent, with an identification bar code.

A color in the background of the wristband, or of the label bearing the patient number, can help to identify specific groups of patients.

It is recommended that at least two independent identifiers are used to confirm patient identity.

Initially introduced in the 1990s, in recent years, wristbands have been adopted in many hospitals, to improve patient identification[51,52], thanks also to the availability and accessible cost of computer connected scanning devices. Identification wristbands are widely used for inpatients, but they are of great use and should be recommended for all cases of outpatients undergoing procedures that pose a risk. However, even wristbands are not error free[53,54], but when available, can grant a consistent reduction of risks of wrong identification. When their introduction is not feasible, for example, for cost reasons, or absence of Hospital infrastructure, labels with a coded patient number can be a satisfactory, less costly option.

Other factors that have been shown to contribute to causing misadministrations are[55] :

- high workload;
- multitasking work of staff members;
- interruptions during the performance of key operations;
- stress;
- need for re-training, for example, after a long leave.

Data Management

The management of patient data and images by means of Hospital Information Systems, specific Radiological Information Systems (RIS) and Picture Archiving and Communication Systems (PACS) has greatly improved quality and safety in diagnostic imaging departments. Nevertheless, on the other side, these new, powerful digital systems have introduced new types of potential errors; furthermore, the distribution of errors along the process is changing.[56] In the past, diagnostic imaging departments used films and the patient name was photo-stamped on each film, using an analog light device; an eventual error, once identified, could be corrected simply using a pen. Nowadays, an error in the patient data should be very carefully managed, since the procedure of for example, entering patient folders, modifying names or codes, or moving an image from one folder to another, involves the potential risk of disrupting data integrity and compounding the error through the introduction of further mistakes while attempting to address the initial problem.[57,58] These activities should form part of a well-defined and carefully monitored process of Patient Information Reconciliation[59], aiming to coordinate all operations of correction/updating of identification data, correction of errors, merging of different image acquisitions etc.[58]

It should be noted that, despite the complexity, sophisticated features, and high cost of RIS / PACS systems, they still do not provide specific functions to manage cases where patients have the same or similar names safely. The booking of patients with similar names on the same working day should be avoided; when this is not feasible, at least a warning should be issued by software platforms, alerting staff when there is a potential risk of confusion; labels/stickers should be printed and placed on patients' forms.

Extravasation of an Injection

As we have already seen in the case of misadministration, for extravasation, a relatively frequent type of incident, there is also not a generally accepted standard term.

Some authors refer to extravasation as the inadvertent administration of a vesicant pharmaceutical into surrounding tissues, which can lead to tissue necrosis, while the inadvertent administration of non-vesicant products into the surrounding tissues is termed infiltration. Even if for some relevant radionuclides, such as ^{99m}Tc, it is unlikely that there will be any noticeable consequence after such an event, since radiopharmaceuticals in general have the potential to produce tissue reactions, use of the term extravasation is preferred in this paper; this is also in agreement with the general definition given in NHS England Guidelines.[60]

Management of extravasation is actually a general problem in the administration of any kind of pharmaceutical. In the radiology field, reports have been published for both CT and MR contrast media[61,62], and general recommendations for the prevention of extravasation are available.[63]

As to NM, a comprehensive review has been published in recent years.[64] This paper included an extensive bibliographic search that identified 37 publications, reporting 3016 cases of extravasation of diagnostic radiopharmaceuticals, of which three cases reported some symptoms. Eight publications reported 10 cases of therapeutic tracer extravasation, indicating skin ulceration as the most severe symptom.

Tracer extravasation has been identified in several reports of scans of the whole body that included the injection site in the acquired images, like ^{99m}Tc-MDP bone scintigraphy or ^{18}F-FDG positron emission tomography (PET).

Although there was no specific clinical follow-up after extravasations described in these publications, no adverse reactions have been reported following events involving the most widely used diagnostic radionuclides, such as ^{99m}Tc, ^{201}Tl, ^{123}I, ^{18}F and ^{68}Ga. Nevertheless, it should be remembered that the possible consequences of an extravasation are not limited to local reactions, but will have a more subtle effect when quantitative or semiquantitative imaging procedures are involved. For example, the standardized uptake values obtained would be influenced by a significant extravasation of ^{18}F-FDG, and this should be taken into account while analyzing images and reporting. Extravasations should not only be avoided wherever possible, but also reported in order to avoid false interpretations of the PET/CT exam.[65] Developing a quality improvement plan and monitoring PET injections can lead to reduced extravasation rates.[66]

A few complications following therapeutic extravasation have been reported, some of which caused severe soft tissue damage. Until recently orally administered ^{131}I has been the therapeutic radionuclide used most widely, but with the increasing focus on intravenously administered beta and alpha emitters, like ^{177}Lu, ^{223}Ra, and ^{225}Ac, increasing

attention will be needed on extravasation of therapeutic radiopharmaceuticals. This is particularly important since the therapeutic options after an extravasation are limited[64,67,68], thus prevention is the most important aspect.

Examples of incidents involving therapeutic extravasation are discussed later in the section on radionuclide therapy.

Suggested preventive measures include the choice of optimal needles and cannulas for intravenous administration and proper training of staff in the injection technique. A check of patency by flushing with saline solution should be made before injecting any therapeutic radiopharmaceutical via an intravenous catheter. It is of utmost importance to stop the administration immediately when a problem is recognized.[64,68]

Some published preventive measures[67] are:

- to recognize the symptoms (erythema, venous discoloration and swelling),
- to know the risk factors (which are related to radiopharmaceutical, patient, site of injection and injection technique),
- to assess severity (from erythema to skin necrosis, depending on the radionuclide) and
- to know how to avoid them (training and awareness of staff, choice of injection site, testing the route of drug administration and using a catheter for administration of therapeutic radiopharmaceuticals).

The management of extravasation should be immediate and a specific emergency kit should always be available. General measures recommended are the immediate cessation of injection, aspiration of fluid extravasation, delineation of the extravasated area with an indelible pen and informing the relevant physicians responsible for the patient.

Specific measures should be implemented, based on the radiotoxicity of the radionuclide and the type of radiopharmaceutical.

A multidisciplinary approach is essential from an early stage to manage the extravasation effectively.[67] The NM Physician should inform the patient about the risks and how they will be managed.

The knowledge of any possible patient-specific risk factors is particularly important in the cases of infants and young children. Recommendations are available on treatment of extravasation injuries in pediatric patients.[69]

Incident Reporting

Incident reporting systems are a tool in health institutions to monitor unexpected events, incidents and close calls, activate corrective actions and provide useful information to the clinicians to prevent repetitions.

In addition to local reporting systems, or reporting systems descending from regulatory requirements, given also the relatively low frequency of incidents in NM, it is useful to have a wider base of data collection. The IAEA introduced SAFRON in 2012, a web-based system for incident reporting in radiotherapy. In 2019 this has been extended also to the reporting of incidents in nuclear medicine therapeutic applications. These include therapies with radiopharmaceuticals and radioactive medical devices such as SIRT.[70,71]

Like other state of the art reporting systems, the SAFRON has an easy, guided data introduction, completely anonymous, guaranteeing the privacy of patients and reporting institutions. It makes possible for professionals in the field to obtain relevant information on incidents, a statistical analysis of their modality, consequences and possibilities for mitigation, and contributing then to diffuse knowledge and learn from previous lessons.

Risks and Incidents in Radiopharmacy

Quality assurance (QA) programs should be implemented in radiopharmacies at all operational levels.[72,73] In addition to national regulations, international guidelines and protocols are available for compounding of radiopharmaceuticals in hospitals.[72,74] Special guidelines for Good Manufacturing Practice provide information on radiopharmaceutical production for wider application, taking limitations due to the radioactive properties into account.[75-77] QA and Good Manufacturing Practice guidelines cover a very wide field, including receipt and basic control of radiopharmaceuticals received ready to use from an external radiopharmacy, up to prevention of microbiological contamination of radiopharmaceuticals.[78] The design of the radiopharmacy, selection, validation, maintenance and calibration of equipment, and staff education and training[79-81] all contribute to safety of staff and patients, but a full discussion of all these factors is beyond the scope of this paper.

As discussed elsewhere in this review, patient identification is of utmost importance. Equally important is the correct identification of the radiopharmaceutical product, beginning with the radionuclide or generator eluate, right through to the individual patient dose, be it in a syringe, capsule, or other form. Identification labels should always indicate the radionuclide and pharmaceutical product[82], dosage form, and calibration date and time. The expiry date and time are crucial, especially for products containing short-lived radionuclides.[83] The International Pharmacopoeia and WHO guidelines on good manufacturing procedures provide complete lists of details that should be given on the primary container of any radiopharmaceutical, as well as those to be provided on the outer container (often the vial or syringe shield).[75,83] Clearly indicating the route of administration is especially important for products that can be used for several types of studies, for example, ^{99m}Tc-DTPA used as an aerosol for lung ventilation imaging, or injected intravenously to evaluate kidney function. Incorrect or incomplete identification of radiopharmaceuticals can lead to several problems, including cross-contamination of products in the radiopharmacy, dispensing of the wrong product, or confusion of patient doses, which could result in the exposure of one or more patients to radiation without any benefit in obtaining

diagnostic information or the desired therapeutic effect. Errors in labelling of radiopharmaceutical vials can lead to a cluster effect, that is, misadministration of products to several patients.[84-86] Color coding of labels on product vials and syringes or syringe shields may assist in distinguishing between different radiopharmaceuticals. Radiopharmacy management software often uses bar codes to identify vials containing generator eluates, radionuclides or radiopharmaceuticals, and doses dispensed for specific patients.[87]

The limited number of incidents relating to diagnostic radiopharmaceuticals found in literature[88-90], all addressed microbiological problems, rather than radiation incidents. Regarding therapeutic radiopharmaceuticals, the SAFRON system[70] collects reports on safety-related events in radiotherapy. Of the 24 reports logged under "radionuclide therapy" until May 27, 2021, 10 reports describe incidents due to misreading or failing to verify the prescribed amount of radioactivity, selecting the wrong dose or exchange of doses for different patients, or not realizing that rescheduling the date of treatment would affect the activity of the ordered dose. In all these cases, the intended organ dose was exceeded. Two of the cases were reported as major, and one as a potentially serious incident. The high number of human errors are ascribed to miscommunication, not following written instructions or protocols, and failure to attend to all the required checking steps. Clearly, radiopharmacy staff should carefully attend to the following points to ensure that the appropriate radiopharmaceutical and dose are dispensed.[91]

- Check details on the request or prescription, including the patient's age and weight and the details of the requested procedure
- Check that the correct kit, injection, or capsule is selected
- Verify the radiopharmaceutical details against patient details
- Verify the dispensed dose against the prescribed and ordered dose
- Measure the dispensed activity with an activity meter prior to administration.

Lack of Quality Control of Products

A wide range of quality tests are prescribed for radiopharmaceutical products. For the current discussion, the focus will remain on the parameters that affect the radiation dose directly, that is, radionuclidic and radiochemical purity, and the measurement of radioactivity.

Both for diagnostic and therapeutic purposes, it is critical that only the relevant radionuclide is administered, without any radionuclidic impurities. Impurities can add to radiation exposure of individual organs or the effective dose due to longer half-lives and unwanted emissions, such as beta emissions in diagnostic imaging products. For most radionuclides, the manufacturer is responsible for ensuring radionuclidic purity. Cyclotrons with accompanying radiochemistry facilities that are located in hospitals, and do not distribute radiopharmaceuticals to other facilities, have to implement the necessary QA and QC procedures to ensure that products meet pharmacopoeial standards, including radionuclidic purity.[92,78] Similarly, facilities which prepare radiopharmaceuticals from generator eluates, often hospital radiopharmacies, are responsible for testing the eluates prior to use. While ^{99}Mo breakthrough can easily be tested using a lead pot which attenuates the 140 keV gamma photons from ^{99m}Tc in an activity meter[93], this is not the case for all radionuclide generators. Procedures for evaluation of ^{68}Ge/^{68}Ga generators have been described.[94-96] Breakthrough of ^{68}Ge exceeding pharmacopoeial limits in ^{68}Ga eluates has been reported, especially in ageing ^{68}Ge/^{68}Ga generators[97,98], but cannot be easily measured prior to use of the eluate. Although the product can be released before completion of the germanium breakthrough test, retention samples of ^{68}Ga eluates or ^{68}Ga-labeled radiopharmaceuticals should be measured after a delay of 24-48 hours to check the trend of ^{68}Ge breakthrough as the generator ages.[99]

An interesting impurity is ^{177m}Lu present in ^{177}Lu produced by neutron activation of ^{176}Lu.[100] As the impurity has a longer half-life than the primary radionuclide (160 days vs 6.7 days), the percentage of the impurity increases as the ^{177}Lu decays. Although the absorbed dose due to ^{177m}Lu is described to be negligible[101], the impurity will affect waste management procedures.

Radionuclidic impurities are closely linked with the production method used to obtain a specific radionuclide. For this reason, the Pharmacopoeia list different radionuclidic impurity limits for ^{99m}Tc obtained from ^{99}Mo produced by neutron activation, by fission, or directly produced by an accelerator.

Radiochemical impurities in radiopharmaceutical products generally have biodistributions that differ from that of the intended radiopharmaceutical.[93] This can affect interpretation of diagnostic images and invalidate quantitative results[102] like measurement of radionuclide excretion or the standard uptake value in PET. In therapeutic radiopharmaceuticals, even low percentages of radiochemical impurities can lead to significant radiation dose to organs other than the target, for instance the bone marrow, which can have serious consequences for the patient's health.[102]

One of the quality parameters for radiopharmaceuticals is that the amount of radioactivity, frequently called "dose" in the pharmaceutical context, should be measured and not deviate more than a specified percentage from the prescribed or intended amount. Note that pharmacopoeial monographs for diagnostic radiopharmaceuticals set content limits at between 90% and 110% of the declared radioactivity at the time and date stated on the label, for example, International Pharmacopoeia monograph for pertechnetate[103], USP monographs for Sodium Pertechnetate ^{99m}Tc Injection and USP ^{18}F-FDG Injection.[195] For therapeutic radiopharmaceuticals, the IAEA recommends stricter tolerance levels, less than 5% deviation from the prescribed administered activity.[29] In fact, this is technically achievable, if the activity meters are properly and accurately calibrated.[104,105,106,107,108,109] It is also important for any radiopharmacy to be aware of the

minimum activity that a measuring instrument can reliably quantify.[110] Diagnostic Reference Levels should be established in terms of administered activity for every specific facility based on national or international guidance[99,111,112], taking into account the available equipment and patient characteristics.[29] Incorrect use of activity meters (often called dose calibrators), for example, selection of an incorrect radionuclide calibration factor, or failure to perform regular testing of the instrument, including stability tests and calibration[68], can lead to administration of too much or too little activity.[113] If the administered activity is too low, the image quality may be sub-optimal, impeding the diagnostic process, and in extreme cases requiring repetition of the entire study, which means that the patient receives unnecessary radiation exposure and diagnosis is delayed. Exceeding acceptable tolerance levels of the recommended dosage should be reported as a misadministration causing excessive radiation exposure. For therapeutic radiopharmaceuticals, errors in both directions have more serious consequences for the patient.

In some cases, doses are scaled for the specific patient. This is especially important for pediatric patients and recommendations for pediatric dosages are available, for example, the European Association of Nuclear Medicine (EANM) dosage card.[114,115] Radiopharmacy staff and NM physicians should be familiar with the calculation methods and minimum recommended doses. Doses may have to be adapted depending on the imaging or study protocol.

The last version of the IAEA Basic Safety Standards[116] introduces a relevant novel adjustment compared to previous editions: calibration and QA/QC of medical equipment are clearly seen as components of patient safety and of optimization of protection. This is a relevant improvement in the perception of QA/QC: while in the past these activities were seen as necessary, due to legal obligation, now their function in the process of ensuring patient safety and optimization of radiation protection is evident. In other words, QA/QC and calibration are not simply to comply with legal requirements, but they are included in legal requirements because they are necessary! In NM this involves all types of scanners, probes and radionuclide activity meters.

Patient Risks and Incidents in Diagnostic Procedures

The justification of a NM examination for a specific patient requires the involvement of both the referring physician and the NM physician: the first knows the patient, his or her clinical history and context, while the second has the advanced knowledge of the procedure to be performed, including the choice of radiopharmaceutical and the optimal acquisition technique. The referral for a NM procedure should be considered more as a request for a professional consultation with the specialist, rather than an order to perform. The joint commitment of both the referring physician and the specialist allows assessment of the appropriateness of a procedure for the specific patient.[116]

In addition to patient-related considerations, any patient exposure should not be considered fully justified if it is not performed using medical devices that are properly installed, maintained, correctly calibrated and regularly subjected to all QA/QC procedures aimed to confirm their optimal working status.

In diagnostic NM procedures, effective doses from the administration of radiopharmaceuticals are typically in the range of 1-10 mSv. A quick assessment of the effective doses and organ doses for most radiopharmaceuticals can be obtained using published factors.[117,118]

The scenario is made more complex by multi-modality procedures. The effective dose due to the CT component of multi-modality studies can vary over approximately two orders of magnitude, depending on the type of NM procedure, the volume of the body irradiated by the transmitted beam and by whether the CT component is simply for attenuation correction or anatomical localization, or a full diagnostic scan is required.[119] As an example, in cardiac SPECT-CT a transmission scan, typically of short duration, is performed for attenuation correction, with an effective dose from the CT component of the order of 0.5 mSv. For a bone SPECT-CT scan in which a diagnostic spot CT acquisition is performed on a single field of view, in addition to attenuation correction, the effective dose from the CT component increases to 6-7 mSv.[120-123]

In PET-CT scans with ^{18}F-FDG, probably the most common practice is to perform a CT for attenuation correction using a tube current just above the minimal level, to obtain images that allow proper navigation in the CT data set, and accurate localization of the emission data. The effective dose due to the CT component used in this way is of the order of 4-5 mSv. If a fully diagnostic CT scan is performed, in an optimized context the effective dose can rise to an order of 7-8 mSv; but if all of the available tools for dose reduction (tube current modulation, beam collimation, iterative reconstruction, etc) are not used properly, the effective dose for the CT component can easily be double and even higher.[120,124,125] Training of CT scan operators in the application of dose saving systems is of utmost importance to ensure that examinations are performed optimally.

Exclusion of Pregnancy/Justification of Use in Pregnancy

While administration of diagnostic radiopharmaceuticals to pregnant females should be avoided, there are instances in which the benefit of a diagnostic procedure can outweigh the low risk of radiation exposure of the embryo or fetus. Such cases must be justified, and the selection of radiopharmaceutical and reduction of the administered dose can assist in keeping the radiation exposure as low as possible.[91] Information about the exposure of an embryo or fetus from different radiopharmaceuticals at different stages of gestation is available.[29,125-128] It should be noted that termination of pregnancy would not be warranted after administration of diagnostic NM procedures as the dose to the embryo/fetus would be substantially less than 100 mGy.[127] Pregnancy in

the use of therapeutic radiopharmaceuticals is discussed elsewhere in this article.

Lactating Patients

Language barriers and literacy can contribute to radiation incidents. A case report describes excretion of 131I in milk which almost led to an incident after a patient received a therapeutic dose of more than 5000 MBq ^{131}I-NaI.[129] The patient came from a rural area, and had brought her baby, whom she was breast feeding, with her to the hospital. Staff in the therapy ward looked after the baby while the patient was in an isolation room. The patient, however, did not understand the main languages used in the hospital very well, and probably also did not understand the need for separation from her baby. During her isolation period, she left her room to find her baby, which she had heard crying. Luckily, ward staff intercepted her and managed to convince her that the baby was well looked after.

A further incident illustrates the need for giving clear instructions to referring clinicians and checking that they are understood by patients. Another example is where a NM department only discovered that a patient was breastfeeding her 9-month-old baby 48 hours after injection of a dose of ^{67}Ga-citrate. The checkbox to indicate breastfeeding had not been crossed on the request form, and as the woman was an in-patient, NM staff did not realize that she had the baby with her in the ward. Breastfeeding was immediately stopped, and the baby was treated with laxatives. The complex estimation of the radiation exposure of the infant is described in a report by Rubow et al.[130]

Administration of radiopharmaceuticals to lactating patients has three radiation safety consequences: 1) the ingestion of radioactive milk would render an unwanted radiation dose to the baby[131], 2) the baby would be exposed to radiation from the mother through close contact during breastfeeding or caring for the baby, and 3) the accumulation of the radionuclide in the milk glands would contribute to exposure of radiation-sensitive breast tissue. Guidelines for interruption or cessation of breastfeeding, including expression of milk prior to and during an interruption, have been published.[29,39,132,133] Briefly, both the excreted radionuclide in the milk and the close contact dose from the mother should be taken into account. Depending on the radionuclide and radiochemical form, breast-feeding can either continue, be interrupted for a period, or should cease entirely before the radiopharmaceutical is administered. For any therapeutic radiopharmaceutical, as well as for diagnostic ^{131}I-NaI, ^{67}Ga-citrate and ^{201}Tl-chloride, timely cessation of breast feeding prior to the NM procedure is recommended.[133-135] The case of radiosynovectomy is not explicitly considered in Appendix III of IAEA Safety Standards SSG-46.[29] A recent study recommended interruption of breastfeeding for a period of at least one month, that substantially means termination, following treatment with ^{90}Y.[136] Allowing sufficient time for weaning will reduce accumulation of milk in the breasts and the associated radiation exposure of radio-sensitive breast tissue.[137,138]

Factors that can Lead to Radiation Incidents

A recent paper by Martin et al[68] discussed the prevention of unintended exposures in NM, taking the cue from the so-called Bonn Call-for-Action[139], of which one specific action was to 'Improve prevention of medical radiation incidents and accidents', as well as from recent IAEA guidance.[29]

Table 1 reports, with some integration and updates, the analysis made by Martin et al on the possible causes of errors leading to sub-optimal imaging procedures or even to incidents.

Errors can be introduced in almost any step of the imaging process.

Nevertheless, incidents do not occur frequently and a study of radiation incidents reported through an internal system over a period of 13 years, found that the frequency at which patient unintended medical exposures occurred was about one in every 3500 procedures and the doses received were relatively low. 80% of the NM patient unintended exposures resulted in effective doses less than 10 mSv and in 33% the effective dose was less than 1 mSv.[38] An exposure giving an effective dose of 10 mSv might have an associated excess lifetime risk of cancer incidence of 1 in 2000 if the risk coefficient is applied for a population of all ages.[140] Risks from exposures between 1 and 10 mSv are described as very low and those for effective doses between 0.1 and 1 mSv are considered minimal.[141,142] Unintended medical exposures from which the risks of stochastic effects are minimal still need to be followed-up, especially if they involve exposure of multiple patients. Incident reporting systems, as previously noticed, are an effective tool in this context, for classifying incidents, investigating causes and learning from previous experiences, in a pro-active, no blame work environment.

The use of effective dose allows the risks to be put into context and compared with exposures from other sources such as natural background radiation or cosmic ray exposure from air travel, but NM staff dealing with specific radionuclides may find the injected activity to be a more meaningful alternative for internal communication. The use of effective dose provides a method for giving an indication of detriment from small exposures, but it applies to a reference person and is derived from risks averaged over a whole population. When the excess effective dose is much greater than 10 mSv a full evaluation of risk for an individual of the same age and sex using doses for individual radiosensitive organs and tissues may be appropriate.[142] Conditions vary throughout the world as to whether an unintended exposure is regarded as clinically significant, as do requirements for reporting of incidents to the competent authority.

Naddaf et al reviewed technical errors in planar bone imaging, showing examples of degradation in image quality due to selection of the wrong collimator, image matrix size or energy peak selection.[143] A variety of papers have dealt with errors and pitfalls in myocardial perfusion imaging. The role of proper QA/QC and accurate calibration of SPECT cameras has been shown to be fundamental in order to avoid artifacts.[144] The increased use of gated SPECT, as a more technically demanding procedure, introduced the possibility of further technical errors in the gating procedure and synchronization[145],

Table 1 Possible Causes of Errors Leading to Sub-Optimal Imaging Procedures or Radiation Incidents, Modified Form the Paper of Martin et al 2019[68]

Component of the Process	Possible Errors
Gamma camera setup	• Wrong collimator / selection of radionuclide / scan duration / matrix size or other acquisition parameters • Omitted or inadequate daily QC tests leading to sub-optimal performance of the system (eg, poor uniformity) or missed detection of faults (eg, a photomultiplier tube not working)
PET scanner setup	• Incorrect daily QC procedure (eg, detector block is not working) • Wrong scan protocol
Multi-modality scans	• Wrong or poorly optimized CT protocol selected • CT study quality unjustifiably too high
In all NM imaging modes	• Sub-optimal balance between acquisition time and administered activity that ultimately determines image noise levels (count statistics)
System calibration	• Omitted or outdated calibrations of a SPECT system (eg, energy, linearity, uniformity, centre of rotation) resulting in poor image quality • Omitted or outdated calibrations of a PET system (eg, uniformity, cross- calibration between the activity meter and the PET scanner) resulting in poor image quality or inaccurate standardized uptake value (SUV) results • Omitted or outdated calibrations of gamma cameras and / or in vivo counting systems, eg, thyroid uptake counters.
Image reconstruction and display	• Wrong reconstruction parameters • Wrong image re-alignment / preparation / display
Mechanical safety	• Patient has not been secured to the imaging bed • Moving components of the scanner have not been checked • Tools, furniture or other objects lie in the trajectory of motion

as well as in the quantitative analysis of data and images.[146] Moody et al reviewed myocardial PET-CT, the precision and accuracy of blood flow measurements, and the precautions to avoid pitfalls and minimize quantification errors.[147]

In a paper reporting some of the results of the IAEA project I-MAP as regards auditing intra-operator variability in reporting myocardial perfusion imaging (MPI) studies, it was confirmed that several factors, in different phases of the procedure, might influence the final results of MPI studies, and require scrutiny. They include pre-examination checks, such as appropriateness of prescription, QA/QC of equipment and radiopharmaceutical preparation, preparatory steps taken during the examination, such as QA/QC of acquisition parameters and of processing, and reporting.[148]

The field of PET-CT imaging is also prone to pitfalls and artifacts that can potentially lead to errors in diagnosis.

Alotaibi et al recently reviewed a cohort of 4099 whole body ^{18}F-FDG scans and found 123 errors (2.2%), but even if relatively infrequent, the number of errors is not negligible.[149] Common pitfalls and causes of image misinterpretation in ^{18}F-FDG PET-CT have been discussed in a variety of papers[150,151], and increasingly with other tracers, for instance in the field of prostate specific agents.[152,153]

Keenan at al. presented a method of periodical technical review, consisting in the re-analysis of all acquired studies by experienced NM technologists, searching for any eventual error in all phases of the process: request/order, organization, prescription, radiopharmacy, administration, and technical errors in imaging. In their review of the studies acquired in one year, they identify a frequency of about 7.5% for failings that can be classified as major, and of about 31% of minors.[154] Such tools are of great relevance and will become a necessary component in the optimization process.

Risks and Incidents in Radionuclide Therapy

Radionuclide therapies involve mostly radionuclides emitting β- or α-particles, which can kill or control proliferation of cancer cells, with limited radiation dose to healthy tissues, and have been successful in the treatment of a variety of benign and malignant diseases.[155] Nevertheless, the risk of damage to normal tissues cannot be completely excluded and incidents have been reported.

Misadministration and extravasation in the case of radionuclide therapy carry the potential for deterministic effects.

Extravasation of Therapy Radionuclides

Chojnowski et al reported four cases of mild radiodermatitis in over 2000 treatments of persistent joint inflammation with ^{188}Re (incidence <0.2%)[156]; while Jacob et al reviewing experience with ^{90}Y synovectomy in the management of

chronic knee arthritis at one centre, observed two cases of skin ulceration and three cases of minor pigmentation at the injection site, in a total of 38 knees treated in 28 patients (incidence 13.2%).[157]

Extravasation during intravenous administration of beta emitters has a high probability of causing deterministic effects in the skin or pain in the patient`s arm; and a number of examples have been reported for therapy using ^{90}Y-ibritumomab tiuxetan[158,159], ^{90}Y-DOTATOC[160], and ^{89}Sr.[161,162] Extravasation incidents involving iodinated molecules have also been reported. Delayed NM images proved to be useful in dosimetric assessment for a therapeutic dose of ^{131}I-metaiodobenzylguanidine and a protocol of controlled catheter placement was adopted to prevent similar occurrences.[163] For the administration of ^{223}Ra dichloride, Wright et al suggested an image acquisition be made immediately after injection to exclude extravasation given the potential risk from an alpha emitter.[164] A report on a skin lesion following administration of this alpha emitter[165] does not clarify whether the event was actually an extravasation or a result of skin contamination, since the patient refused to undergo any verification imaging. The International Commission on Radiological Protection (ICRP) recommends that therapy patients should be monitored for extravasation during infusion and the infusion halted immediately in the event of extravasation.[155]

Although there is no specific treatment for extravasation, ICRP suggest that local hyperthermia, elevation of the extremity, and gentle massage may promote spreading of the radiopharmaceutical and reduce the local absorbed dose.[155] Basic prevention and mitigation actions have been included in updated EANM procedure guidelines for treatment of metastatic prostate cancer with ^{223}Ra[166], as well as in the Society of Nuclear Medicine and Molecular Imaging procedure standard for somatostatin receptor-based peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE[167]; similar recommendations for treatments have not been common in the past, with the exception of ^{90}Y-radiolabelled ibritumomab tiuxetan.[168] It is to be hoped that the future updates of guidelines for both international bodies and major scientific societies, will systematically consider the problem of extravasation of therapeutic radiopharmaceuticals and provide precise indications. Several recent reports on ^{177}Lu extravasation have shown that, when timely actions, such as suction, local heating, massage or exercise were taken, severe consequences and complications could be avoided.[169-172]

Misadministration of Therapy Radionuclides

The incorrect use or malfunction of delivery systems or devices used in the administration of radiopharmaceuticals to patients creates another potential risk. These problems may result in significant differences between the planned activity and the one actually administered, producing either an under-treatment and reduction of clinical efficacy and therapy response, or an unjustified increase in absorbed dose (over-treatment). Additionally, they can lead to radioactive contamination, affecting the radiation protection of patients, of the staff and disturbing or even disrupting operation of a NM department.

Reports on failures of delivery systems are collected in the database of incident reporting of the Nuclear Regulatory Commission of the United States.[173]

Several involve failure to administer the full planned activity in treatments with ^{90}Y micropsheres, and recent examples report under-dosages by 34.5% and 61.5%, due to stasis or adeherence in tubing or catheters (NRC Event Numbers: 54967, 2020 and number 53879, 2019).

In a case of intravenous administration of an investigational drug, ^{131}I-apamistamab (Iomab-B), during a Phase 3 trial, only 53% of the prescribed value was administered, due to leakage from tubing (NRC event number 55142, 2021), while in a treatment with ^{153}Sm-EDTMP the patient received only 4% of the prescribed dose as most of the radiopharmaceutical leaked out through a crack in the locking assembly of the IV tubing connection (NRC Event Number: 53847, 2019).

Leaks in the delivery systems can also result in contamination of the patient's skin, that may not be easy to identify, as in a case of administration of ^{131}I-MIBG for a brain tumor, where the contamination went undetected until the patient developed erythema (NRC Event Number: 53430, 2018).

Some incidents can be caused by unforeseen circumstances: for example, an administered therapeutic dose of ^{131}I was delivered to a patient through a gastrostomy feeding tube (g-tube), but most of the administered ^{131}I activity remained in the wrong portion of the g-tube, resulting in an underdose to the patient's thyroid, and a significant unintended dose to the patient's stomach.[174]

There are also specific risks associated with oral administration of therapeutic radiopharmaceuticals such as ^{131}I capsules or solution. In these cases, a variety of problems that can be generated by the patient him/herself in the ingestion of the product.

There are several reports of errors in cases in which the prescribed activity was given to the patient in two capsules instead of a single one. Examples are a case in which the patient may have assumed that only one was to be taken, and that the second was the result of an error by a second staff member assisting in the administration. In another the patient may inadvertently have swallowed only one of the two capsules, leaving the second stuck on the container (NRC Event Number: 55208, 2019).

Contamination incidents may occur if the patient is unable to swallow a capsule and spits it out, or if he or she coughs or sneezes at the time of ingesting iodine solution[175,176], or if an uncooperative patient does not follow instructions.

One case reported in 2017, that lead to wide-spread contamination, involved an adolescent patient who received a 1.1 GBq capsule of ^{131}I; secretly, taking advantage of going to the bathroom, the patient spat out the capsule and kept it hidden in his hand. During the time needed to understand what had happened, staff moved the patient to several different rooms, to investigate the reason for the abnormal radiation background, with the result that virtually the entire department was contaminated, including the SPECT-CT and

PET-CT diagnostic rooms. This resulted in the department being closed down in order to decontaminate properly, with interruption of the service (NRC Event Number: 52514, 2017).

Radiation Protection of Caregivers, Family Members, and Work Colleagues

People, who share accommodation with a relative who has been treated as a patient with radionuclide therapy, or who work closely with such individuals, may be exposed to risks of both external exposure and contamination from body fluids. They will be less aware of potential risks and unfamiliar with the precautions that need to be taken when dealing with radioactive liquids. Therefore, criteria need to be established for hospitalization and release of therapy patients and these should aim to ensure that the effective doses that members of the public in general might receive are less than the dose limit of 1 mSv/year and preferably below a DC of perhaps 0.3 mSv.

Carers and comforters who may be in close contact with an individual patient can be treated as a special case to whom a source-related dose constraint of a few mSv per episode may be applied, with the consent of the person involved.[116]

The ICRP recommends an effective DC of 5 mSv per episode of treatment for informed caregivers[140], excluding children and pregnant women for whom the constraint remains at the level of the dose limit for the general public of 1 mSv. Recommendations given by the European Union[177] are articulated as a function of age: a DC of 1 mSv applies to the embryo, fetus and children up to 10 years; from 10 to 60 years a constraint of 3 mSv is suggested, while for adults older than 60 years the DC is set at 15 mSv. However, it is not expected that the DC of 3 mSv is applicable when comforting very ill in-patients, such as in the case of mothers taking care of hospitalized children.

Specifying the appropriate length of hospitalization and patient discharge strategy, should take into account the patients' wishes and lifestyle, socioeconomic conditions and their ability to comply with radiation protection instructions.[178,179] In some cases, treatment is possible both on an inpatient and outpatient basis, requiring specific radiation precautions; Levart and colleagues discuss this situation in the case of treatment of neuroendocrine tumors with ^{177}Lu-DOTATATE.[180]

The effective dose to relatives and caregivers of patients treated with ^{131}I for thyroid cancer has been studied by external measurement with TLD dosimeters as well as environmental dosimetry. Typical results are well blow 1 mSv.[181-183] A detailed study with stratification of patients in groups taking into account socio-economical conditions, showed that while the general average of the dose to members of the family was <1 mSv, in the group with the less adequate facilitiess the average value was of the order of 3 mSv.[184]

When children and adolescents are in contact with ^{131}I-therapy patients after release, the role of detailed radiation safety instructions given to the patient prior to discharge can be fundamental in controlling and reducing the exposure of childern to ionizing radiation in the family context.[185]

In the case of pediatric patients treated with ^{131}I-MIBG, most studies published in recent years report effective doses to caregivers in the range 0.2-9 mSv, with an average level below 2 mSv[186,187], but at least one article quotes a wider range of dose values up to about 20 mSv.[188]

Instructions on precautions given to patients on leaving hospital will include recommendations on the delay before the patient returns to work, which should take the patient's work environment and their proximity to others into consideration.

Someone working largely in isolation, for example, an agricultural worker, can return to work earlier than someone working in close proximity to others, for example, in a small office or on a production line.

Pregnancy and Radionuclide Therapy

Therapeutic radiopharmaceuticals should not be administered to pregnant women, and patients should be reminded of the importance of avoiding pregnancy for a period of time after radiopharmaceutical treatment.[29]

Reports of incidents involving the administration of therapeutic radiopharmaceuticals to a pregnant patient can be found in the IAEA SAFRON database[70], in the records of events of the United States Nuclear Regulatory Commission[189,190], as well as in the literature.[191-195] Most relate to administration of ^{131}I, either an ablative dose in treatment of cancer, or for treatment of hyperthyroidism, but a recent report discusses a patient treated with ^{177}Lu.[196,197] In several cases, patient did not follow instructions, and did not discover that they were pregnant until after the therapy had been administered.

Appropriate preventative measures are only possible if the pregnancy is known. Clear signage requesting female patients to report pregnancy to a staff member prior to administration of a radiopharmaceutical should be posted in NM departments. Not all patients may be able to understand such signage, for instance in a multilingual country where a large percentage of the population does not have adequate command of the main language(s) or is illiterate, so an additional illustration can be valuable. Lee et al suggest that serum pregnancy tests should be carried out on all female patients in their reproductive years scheduled for NM procedures that could result in exposures to the uterus exceeding 1 mSv.[198]

If radiation exposure happens in the first three weeks of pregnancy, the risk for the fetus is considered negligible. During organogenesis, there are small risks that whole body fetal doses above a threshold of 100 mGy may result in malformations, growth restriction, and reduction of IQ, although it is unlikely these dose levels will be reached. However, the major risk with ^{131}I is that the radionuclide will accumulate in the fetal thyroid with a risk of ablation.

If the pregnancy is discovered within a few hours of the administration and the fetus is at the stage of having a

functional thyroid, blocking uptake using potassium iodide may be considered, but will only work in the early stages.[155]

Fetal and neonatal hypothyroidism due to *in utero* ^{131}I exposure may require lifelong thyroxine replacement therapy. Furthermore, exposure to radiation in utero may increase the lifelong risk of cancer for the newborn.[29,140]

The Risk of an Error in Dosimetry

An important, even if not always fully considered risk in radionuclide therapy procedures, is related to the potential errors of internal radiation dosimetry calculations, used for planning the treatment.[155]

Currently, accurate dose assessments are included in an increasing number of treatments such as, but not limited to, ^{177}Lu-PSMA, ^{90}Y or ^{166}Ho microspheres, ^{131}I-mIBG for neuroblastoma, and ^{131}I-NaI for benign thyroid diseases[199]; however, wrong therapeutic activity prescriptions resulting from inaccurate dosimetry calculations, may produce a limited response in the tumor or target volume and/or generate unexpected radiotoxicity in normal organs.

Root causes for under- or over absorbed dose estimations have been typically related to a lack of well-established methods for activity quantification and dosimetry assessments, and also to the non-availability of suitable means or tools to perform accurate and reproducible dose estimations.

It was shown that the estimated absorbed radiation dose from ^{90}Y ibritumomab tiuxetan for the treatment of B-cell lymphomas, was underestimated due to methodological problems mainly associated with activity quantification. This resulted in a poor relationship between absorbed dose and response, both in terms of treatment efficacy and toxicity.[168] Other studies have shown the relevance of methodological aspects in avoiding under or over estimation of absorbed doses during the treatment of neuroendocrine tumors with ^{177}Lu DOTA labeled peptides.[200,201]

Errors on dose estimations are also associated with specific technical issues during the different steps of the dosimetry calculations.[155]

In radioembolization of surgically unresectable primary and metastatic liver tumors with ^{90}Y, doses differing from those planned could be delivered due to variations in the catheter position during the baseline angiogram with ^{99m}Tc-Albumin Macroaggregates (MAA), and the second angiogram during microsphere injection.[202] The role of the tumoral volume of interest delineation using the MAA SPECT/CT images versus CT segmentations has been evaluated and described as a key aspect to deliver appropriate treatments and avoid unexpected results.[203]

In general terms volume delineation and tumor or target volume and mass must be accurately defined in calculations to enable appropriate treatment planning during radionuclide therapy. Currently, much research work is devoted to the analysis of sources of uncertainty, and to the techniques necessary to reduce these uncertainties in dosimetric calculations. This is in fact a necessary prerequisite in order to guarantee better safety and efficacy of treatments with radionuclides.[155,204]

Dealing with Incidents When They Occur

Incident Reporting and Investigation

The IAEA Basic Safety Standards require that licensees shall ensure that all practicable measures are taken to minimize the likelihood of unintended or accidental medical exposures arising from flaws in design and operational failures of medical radiological equipment, from failures of and errors in software, or as a result of human error.[116]

The first requirement is that organizations have an established system for reporting any radiation incident throughout an organization.[68,205,206] This may cover all types of events or be devoted simply to radiation incidents, but must be supported by management and supported by all staff, as being an important element in quality improvement. Moreover, it must be operated through a no blame culture to ensure that staff have no fear in acknowledging when events occur. The system should also have appropriate categories to cover the range of incidents that might occur and a method of classifying them in terms of severity, which will often be in terms of a dose quantity such as effective dose. This is likely to determine whether an incident needs to be reported to regulatory authorities.

When an incident is reported local staff should undertake an initial investigation immediately to assess the consequences for the patient(s) affected and provide any additional healthcare necessary, record information about the exposure together with any error codes or unusual signals, and provide a preliminary report on the incident to the service manager. The adoption here of an open “no blame” approach is particularly important for identifying root causes and contributory factors, not to report the culprit.

Any corrective medical actions that are required to minimize the effects should be undertaken immediately and individuals identified who have responsibility for this. When required, counselling of any patient involved in a medical exposure incident should be undertaken by an individual with appropriate experience and clinical knowledge.

The reporting, investigation, and follow-up are crucial in incident management, in building the capacity to prevent incidents, and enabling staff to react appropriately when an incident does occur.[207-209] But in order to gain commitment of everyone, staff should be debriefed following an incident about contributory factors and any changes made to minimize risks in the future.

The wider dissemination of information about radiation incidents and radiation injuries where appropriate can be useful in order to raise awareness and alert others to risks. An example of a system for this is the SAFRON reporting system operated the IAEA which includes radionuclide therapy exposures and allows the sharing of experiences among users.[70,71]

Incident Prevention

Problems that could lead to an accidental exposure can be reduced through the adoption of a strategy that includes the

regular maintenance and calibration of radionuclide imaging and measuring equipment and software. There should be a comprehensive programme of QA, continuing education and training of staff, and the promotion of a safety culture involving awareness and analysis of all the processes involved. The IAEA Safety Guide SSG-46 lists measures to minimize the likelihood of unintended events that might lead to medical exposures.[29]

NM is a complex process that requires specialized facilities and staff with a variety of skills. All staff members require education at the appropriate levels enhanced by comprehensive training in all the tasks that they will need to perform. The training will involve the handling and use of radionuclides, aseptic technique, QA and QC of radiopharmaceuticals, and will also include operation of equipment and understanding the control software. This should be supplemented by programs of continuous professional development and practical training in applications for all staff involved in providing the NM services, including additional training when there are any upgrades to equipment.[116,210]

Since tasks that are carried out regularly need to be performed consistently, the methods should be refined and documented in detailed protocols and procedures for every process. There should be clear definitions of the roles, responsibilities and functions of each staff member, and this should be clearly understood by all staff. A lack of clarity about which individual should undertake a particular task can lead to a vital step in the process or a confirmatory check being omitted, increasing the chance of something going wrong.

All the QA procedures and clinical protocols might be in place, but if staff members simply follow them passively, they will be caught out when there is a change or something different happens. Preventive measures should include checking the robustness of the safety system of the facility against reported incidents (retrospective risk analysis), as well as applying a prospective risk management strategy. A culture of always working with awareness and alertness should be actively encouraged. This can be formalized to some extent by periodically reviewing practices, encouraging staff to think of things that might go wrong, and identifying all the factors that need to be in place to prevent them occurring. Specific QC checks can be put in place at critical points, which staff review quickly to ensure that nothing has been omitted.

Conclusions

The wide variety of aspects to the provision of a NM service mean that there are many things that go wrong. It is therefore important that all stages are performed according to procedures that are understood, agreed, and adhered to by all staff groups involved and that all actions are supported by regular QA/QC procedures. Staff must be familiar with how all aspects of the service operate, be aware of things that can go wrong, and be alert to anything that might disrupt smooth operation. But when an unexpected event does occur, leading to an unintended exposure, staff must recognize their role in dealing with it and reporting through an agreed system at the earliest opportunity. This will provide a route through gradual improvement to ensure a high-quality nuclear medicine service is provided.

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