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BIOMEDICAL IMAGING AND THERAPY FOR PERSONALIZED HEALTHCARE

Publications · Brochures

Radiation Protection and Dose Optimisation

A Technologist's Guide

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Foreword

Pedro Fragoso Costa

Since its inception, more than 20 years ago, the EANM Technologist Committee (EANM-TC) has contributed greatly in encouraging professional development and scientific exchange amongst nuclear medicine technologists (NMTs). The Technologist's Guide series is one of the most successful EANM-TC endeavours, with an ongoing yearly release since 2004. These brochures have become not only a valuable tool in the clinical workplace but also a reference for educational purposes.

After a long series of clinical guides, it was decided to shift to a more technical, but equally important field: Radiation Protection and Dose Reduction. The major rationale for this choice was the fact that NMTs, radiographers and all medical radiation professionals will have radiation protection concerns, independently of the specific set-up (i.e. nuclear cardiology, PET/CT, conventional NM or therapeutic NM). Furthermore, the newly defined EU Euratom Directive [1] is to take effect in 2018; therefore investing in education and training in the field of radioprotection at this moment is timely and purposeful. Finally, this publication presents an excellent opportunity to become acquainted with the most modern internal and external dosimetry calculation methods and radiological risk assessment and to gain an insight into the European legal requirements in respect of protection against ionising radiation.

This brochure is the product of a multidisciplinary team of health radiation experts, to whom I am extremely grateful. I would like to thank the EANM Physics Committee, SNMMI-TS (Society of Nuclear Medicine and Molecular Imaging Technologist Section) and ANZSNM (Australian and New Zealand Society of Nuclear Medicine) for helping to ensure the outstanding quality of this book. I am very much indebted to Andrea Santos, Sebastijan Rep and Giorgio Testanera for their dedication in reviewing and editing this guide in record time. Finally, thanks are due to Rick Mills and Sonja Niederkofler for their support in language editing and logistics, the EANM Board, the EANM Technologist Committee and all of those involved in the Technologist Guide project.

Pedro Fragoso Costa
Chair, EANM Technologist Committee

Reference

1. European Council Directive 2013/59/Euratom on 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. Official Journal of the European Union; 2014;L13:1-17.

Introduction

Andrea Santos

Since the beginning of the 20th century, ionising radiation has been employed in medicine for both diagnostic and therapeutic purposes. The belief that radioactive sources could heal many different diseases led to a rapid increase in the usage of radioactive material; in conjunction with the lack of knowledge of the biological effects of radiation, this resulted in many accidents and numerous pathologies in both patients and operators.

Ionising radiation procedures for medical purposes have been invaluable in improving patient care. Accordingly, the use of radiation in medicine has continued to increase over the years, accompanied by improvements in safety standards. Nuclear medicine (NM) has been deeply involved in this process. Both applications – diagnostic and therapeutic – showed great initial potential and important advances have repeatedly been achieved over the intervening decades.

The development of NM has been accompanied by great responsibility, since the safety of both the professional and the patient depends on the correct use of radiation. The professional should not be harmed by the radiation needed to perform each procedure and the patient should only be exposed to radiation after the benefit/risk ratio has been considered.

This year's Technologist's Guide aims to give an overview on the principles of radiation protection and to provide the professional with the knowledge required in order to act in accordance with these principles. A further intention is to set out the principles of dose optimisation. There is a consensus that all NM procedures must be justified; furthermore, the radiation used in each procedure must be carefully calculated and based on rigorous quality standards.

This book starts with overviews on the interaction of radiation with matter and the fundamentals of dosimetry. It continues by covering the international basic safety standards and radiobiology principles. The basic concepts of dose optimisation for diagnostic and therapeutic procedures involving the use of radionuclides are explained, and an individual chapter focuses specifically on dose optimisation in the paediatric population. After this, aspects of occupational radiation protection are covered, and finally the design of an NM department is discussed, keeping in mind the particularities that need to be considered in order to ensure compliance with radiation protection standards. Each chapter includes a description of the specific role of NMTs as main actors in procedures who also bear responsibility for the application of radiation protection in daily practice.

In closing, I would like to express my gratitude to all the authors, co-editors and professionals who have contributed their time and expertise to help ensure the realisation of this project: *Radiation Protection and Dose Optimisation – A Technologist's Guide*.

Andrea Santos

Chapter 1: Interaction of Radiation with Matter

Aron Krisztian Krizsan

This chapter provides information on the electromagnetic radiation interactions of significance for medical imaging, especially for nuclear medicine applications, and also offers a glimpse into the practical knowledge required by technologists working in this field. When describing interactions of radiation (electromagnetic and acoustic) with matter, it is necessary to consider whether the wavelength will cause any interaction with the target object (e.g. human tissue) or even result in total absorption of the radiation. There are three radiation wavelength ranges where the absorption characteristics can be used for the purpose of medical imaging: the X-ray window (used in CT, planar X-ray, PET, gamma cameras and SPECT), the radiofrequency window (used in MRI) and the ultrasound window (used in ultrasonography) (Fig. 1).

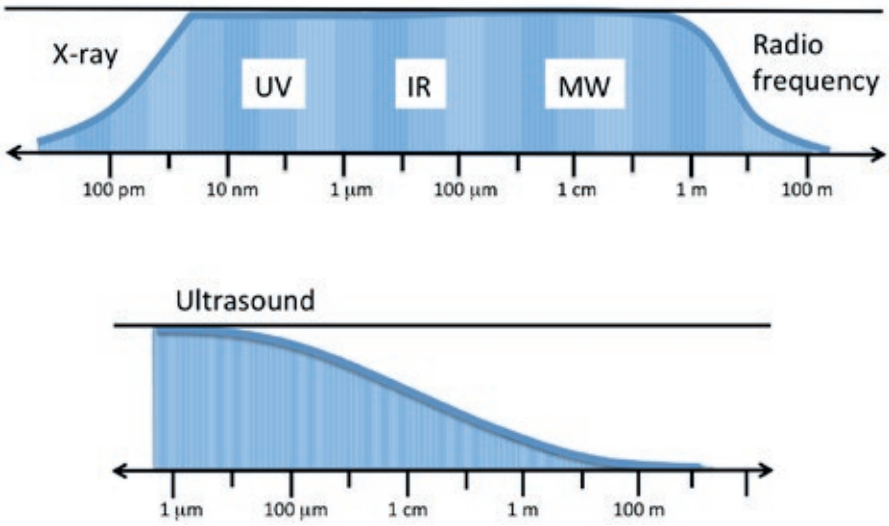

Figure 1: Attenuation of electromagnetic radiation by human tissue for a wide spectrum of wavelengths. The X-ray window is used in CT, planar X-ray, PET, gamma cameras and SPECT while the radiofrequency window is used in MRI. Acoustic radiation is strongly absorbed for wavelengths below 1 mm and therefore is only useful for medical imaging purposes in the ultrasound window [1]. UV, Ultraviolet; IR, infrared; MW, microwave

Ionisation, excitation and bremsstrahlung

Let us consider a radiation interaction as a single system. The comparison of the system before and after the interaction reveals that some quantities remain the same following the interaction. These quantities are often referred to as being ***conserved*** in the interaction. Such conserved quantities include total energy, momentum and electric charge. With respect to ionisation, a distinction is drawn between ***directly ionising particles*** (charged particles) and ***indirectly ionising*** particles (uncharged particles). Directly ionising particles comprise the alpha particles (helium nuclei), beta particles (electrons), protons and any other nuclei. Indirectly ionising particles are the photons (in the adequate energy range) and neutrons. While there is a definite difference between the classical and quantum electrodynamic explanations of interactions between particles, within this chapter the classical model is applicable since the focus is on which particles will survive, where they go and what happens to their energy. On the atomic scale it is practical to use the energy units of ***electron volt (eV)***, which is by definition the amount of energy that an electron gains when it travels through a potential difference of 1 volt (numerically 1 eV = 1.6×10^{-19} J).

An atom becomes ***ionised*** when it ejects at least one electron. Below an energy limit of 13.6 eV, radiation is not able to induce ionisation; therefore, radiation with an energy higher than 13.6 eV is called ***ionising*** while radiation with an energy lower than 13.6 eV is called ***non-ionising***. This (i.e. 13.6 eV) is the least energy required to eject the K-shell electron of the element with the smallest atomic number (hydrogen). When an electron is not ejected from the atom by the radiation but is raised to a higher energy level, the atom enters an "excited" state, a process referred to as excitation. There is then a probability that an incident electron will cause ejection of the K-shell electron in the case of higher atomic number elements, and the vacancy is filled with an outer shell electron (Fig. 2).

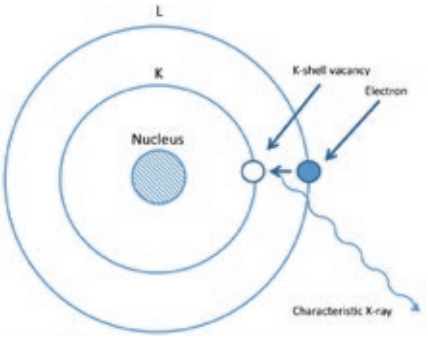

Figure 2: When an outer shell electron moves to fill the inner shell vacancy, characteristic X-rays are emitted in accordance with the energy difference between the electron shells

During this process the energy difference of the two shells is emitted in the form of electromagnetic radiation that is referred to as ***characteristic X-ray*** since the energy is characteristic for the element, X-ray photons

of different energy being emitted according to the characteristics of the electron shells of the atom. The incident electrons may only be repelled by the nucleus, and while they are continuously accelerated in the electric field of the nucleus, electromagnetic radiation is emitted in the X-ray spectrum. This is the so-called bremsstrahlung process. The classical electromagnetic explanation derives from the fact that an electric charge moving with constant velocity would not emit electromagnetic radiation, whereas in the event of acceleration, it would. Two typical X-ray emission spectra with 80 kV and 120 kV applied on the X-ray tube are displayed in Fig. 3.

The integral of the functions displayed in Fig. 3 (and therefore the total X-ray photon number) is proportional to the electric current and to the square of the voltage applied on the X-ray tube. The number of X-ray photons correlates strongly with the image quality in the case of CT imaging.

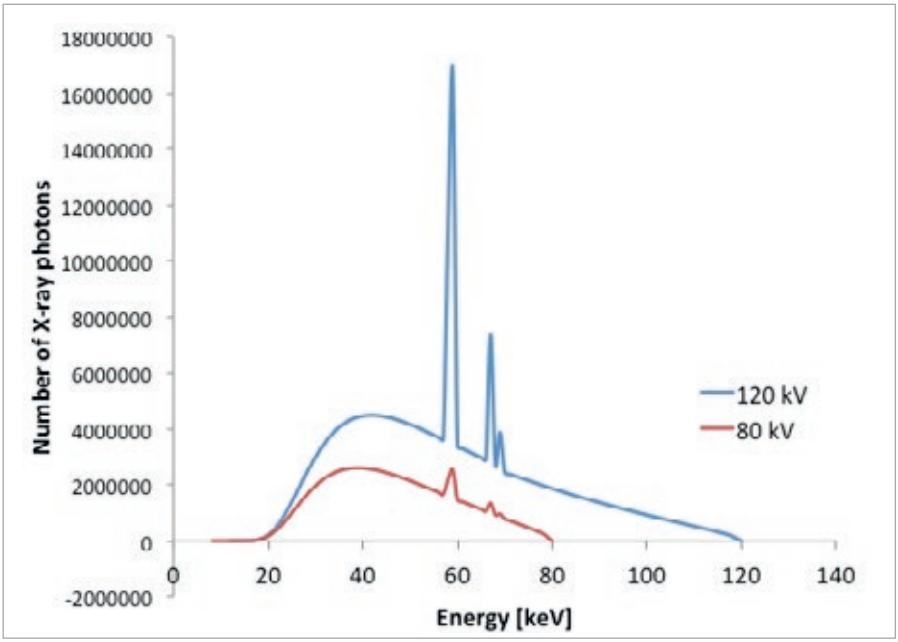

Figure 3: X-ray spectra with different voltages applied on the X-ray tube (120 kV and 80 kV). Peaks in the spectrum represent X-ray photons originating from the characteristic X-ray process, while the wide spectrum is the result of the bremsstrahlung effect. (By courtesy of Dr. Laszlo Balkay)

Radioactive decay and characteristics of radiation

The nuclide of an atom can be unstable in the presence of a certain ratio of protons and neutrons, leading to an emission process called radioactive decay. Radioactive decay has three major forms: alpha (α), beta (β) and gamma (γ). In the case of α-emission, expulsion of a helium nucleus from the atom occurs, that consists of two neutrons and two protons. Alpha decay occurs primarily among heavy elements that are of little interest in nuclear medicine. Beta decay can occur in two forms: β^- and β^+. During β^- decay a neutron in the nucleus is converted into a proton and an electron, followed by ejection of the electron together with a neutrino (ν). The electron in this case is referred to as a β^- particle while the neutrino is a "particle" that has no mass or electric charge. In the case of β^+ decay, a proton in the nucleus is transformed into a neutron and the so-called positron, which is the anti-particle of the electron. This process is followed by emission of the positron together with a neutrino. We sometimes refer to α- and β-particles as charged particles because they carry an electric charge. Gamma emission can occur in several ways. The atom may have three different states: the most stable arrangement of the nucleons, called the ***ground state***; a very unstable state with only a transient existence, which is termed the ***excited state***; and a further unstable state that, however, has a life-time longer than 10^{-12} s and is called the ***metastable state*** [2]. The nuclear transitions between different nucleon arrangements involve discrete and exact amounts of energy and therefore can result (in the direction of the ground state) in emission of particles or γ-rays. The energy difference between the states determines the γ-ray energy. Even a β^- emission with a metastable daughter nucleus can result in a final γ-ray emission [2]. Another route for γ-photon emission is through a β^+ decay, when the ejected positron loses kinetic energy by inelastic interactions with atomic electrons. Then, a temporary particle called the positronium is formed with a final electron. This is followed by the annihilation process, while the mass of the positron and the electron are converted into two 511-keV γ-photons, which are emitted simultaneously at about 180° with respect to each other [3].

Interaction of γ-rays and X-rays with matter

As described in the preceding sections, the difference between X-rays and γ-rays derive from their origin and are not necessarily observable in their energy. Both are forms of electromagnetic radiation and have a certain probability of passing through different processes based on their energy. The energy of X-rays and γ-rays in nuclear medicine applications regularly causes three kinds of interactions: ***photoelectric absorption***, ***Compton scatter*** and ***pair production***. The last-mentioned occurs when a photon interacts with the electric field of a charged particle and the photon disappears while its energy is used to create a positive–negative electron pair (an electron and a

positron). Because both the positron and the electron have a rest mass equivalent to 0.511 MeV, the minimum photon energy necessary for pair production is 1.022 MeV. In nuclear medicine applications this photon energy is rarely used, and therefore we focus below on the other two interactions.

During the photoelectric effect or photoelectric absorption (PEA), the target atom absorbs the total energy of the incident photon. While the photon disappears, this energy is used to eject one of the orbital electrons, which is therefore called a ***photoelectron.*** The kinetic energy of the photoelectron is equal to the difference between the incident photon energy and the binding energy of the electron shell from which it was ejected [2]. The kinetic energy of the photoelectron is deposited in the near site of the interaction during excitation and ionisation processes. Photoelectron ejection from the innermost electron shell is most probable if sufficient incident photon energy is available. A schematic representation of PEA is shown in Fig. 4.

During Compton scattering (CS) the incident photon interacts with a loosely bound outer shell orbital electron. In this case the energy of the incident photon greatly exceeds the binding energy; the photon will not disappear, but after it has been deflected with a scattering angle (θ) some of its energy is transferred to a recoil electron. This interaction looks somewhat like a collision between a photon and a "free" electron. The scattering angle distribution depends largely on the incident photon energy [2]. The process of CS is depicted schematically in Fig. 5.

These interactions (PEA and CS) do not cause ionisation directly as do the charged-particle interactions, but the ejection of orbital electrons and the creation of positive–negative electrons will cause ionisation and, therefore, result in radiobiological effects.

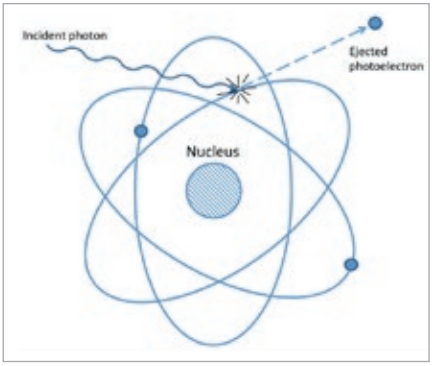

Figure 4: Schematic representation of photoelectric absorption (PEA)

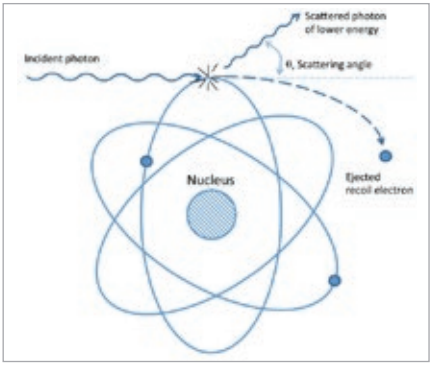

Figure 5: Schematic representation of Compton scattering (CS)

Attenuation in tissues

Both PEA and CS lead to missing or misplaced information when using nuclear medicine imaging techniques. The true signal is therefore attenuated and the final image data need to be corrected for this attenuation. In general, the absorption of any radiation can be described as follows:

$$I_0 \sim I_x e^{\mu x}$$

Eq. 1

where I_0 is the intensity of the radiation impinging on the tissue, x is the length of tissue through which the radiation has to penetrate, I_x is the intensity of radiation after attenuation by the tissue, and μ is the attenuation coefficient. The formula in Eq. 1 applies for both X-ray and γ-ray photon energies. Therefore, the $e^{\mu x}$ factor gives the probability that an attenuating interaction will occur throughout the tissue length x. The thickness of an absorber (e.g. body tissue) that decreases the original intensity of radiation (I_0) by one-half is called the ***half-value layer*** (HVL). In some radiation protection applications (such as shielding) it is useful to calculate the ***tenth-value layer*** (TVL), i.e. the thickness of the absorber that decreases the radiation intensity by the factor of 10 [2]. The total attenuation of a certain tissue is the sum of the PEA and CS attenuation coefficients and varies based on the photon energy. This effect is displayed in Fig. 6 for bone and muscle

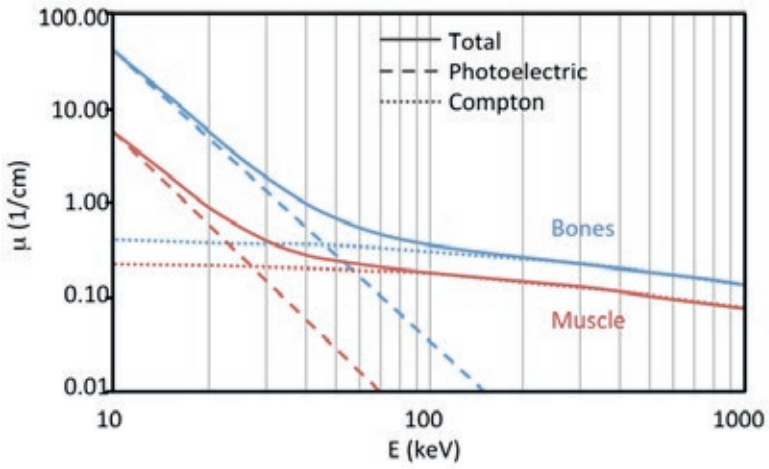

Figure 6: Dependence of total, photoelectric and Compton scatter attenuation coefficient on photon energy for bone and muscle tissues (courtesy of Dr. Nicola Belcari)

density tissues. It can be observed that PEA becomes less dominant at around 50 keV and that most of the interactions are CS for higher photon energies.

In the CT energy range (20–140 keV) both the CS and the PEA effect are present, but above 30–40 keV CS is dominant. For most single-photon emission computed tomography (SPECT) examinations, too, the photon energy results mainly in CS. During SPECT, collimators are used to eliminate at least a portion of the events scattered in the body; however, the missing signals result in a need for attenuation correction (Fig. 7). In modern hybrid SPECT/CT systems, the CT images of the patient are used for the purpose of attenuation correction. This procedure includes co-registration, energy scaling (from CT energy to SPECT energy) and resolution scaling.

In a PET system the coincidence events registered during data acquisition derive not only from true coincidences; rather, they are also biased by the so-called scattered and random events. The γ-photons (originating from the annihilation process) with 511-keV energy have a very low probability for PEA but a significant probability of undergoing CS (over 95%) (Fig. 8). This scatter can occur in the body, changing the direction of the γ-photon while the coincidence is assigned to a misleading line of response (LOR). During 3D PET a very large number of single γ-photons reach the detector ring, including from sections of the body outside of the field of view. Because the coincidence time window is not infinitely narrow (usually be-

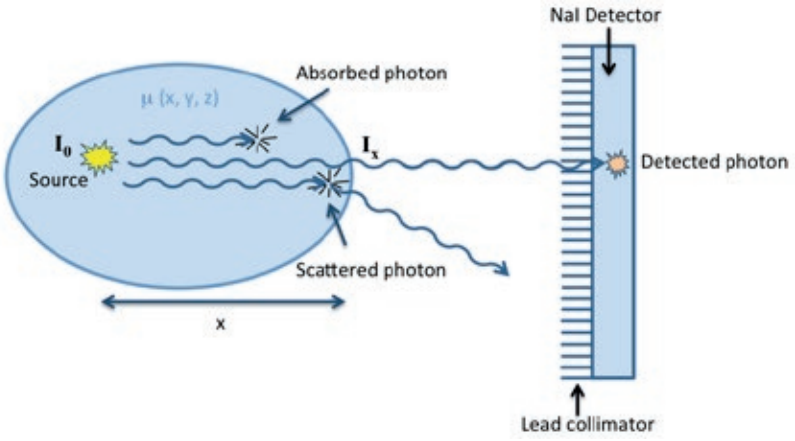

Figure 7: Schematic diagram of single-photon emissions and detection. The detected signal needs to be corrected for PEA and CS

tween 5 and 10 ns), there is a high likelihood that two single photons from two different annihilation events will arrive during the given coincidence time window, resulting in a random coincidence event. These random events then contribute to the noise level of the final images. The final detected count rate will consist of the count rates mentioned above as:

$$M \sim Atten \times T + S + R$$

Eq. 2.

where ***M*** is the measured count rate, ***Atten*** is the attenuation effect, ***T*** is the true count rate, ***S*** is the scatter count rate and ***R*** is the random count rate. Random events, attenuation and CS will result in a distorted PET signal and therefore have a great impact on the image data. Because of the geometry of the patient, these interactions cause severe attenuation that is more prominent in the inner parts of the body and lower at the surface. As discussed above, the results of these interactions are the removal of primary photons from a given LOR and the potential detection of scattered photons in a different LOR. Thus, attenuation and scatter are side effects of the same physical process. Corrections are necessary and include removal of the estimated scatter fraction from the LORs. Moreover, it is necessary subsequently to correct each LOR for the fraction of events missing from that LOR.

The probability that a γ-photon will escape the body depends on the distance between the annihilation site and the surface (***x***) mul-

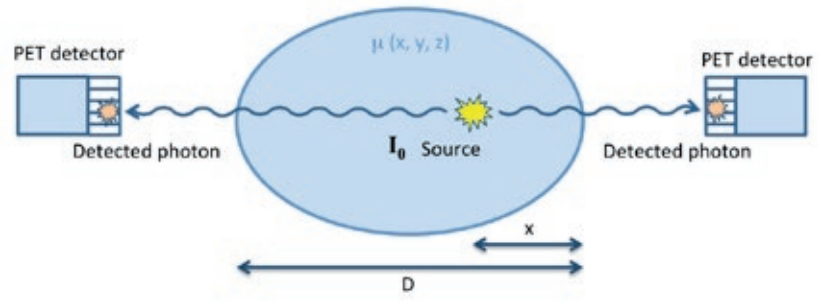

Figure 8: Attenuation probability of a given Line of response (LOR): because of the coincidence detection, the probability of detection of both photons *(p = p1 × p2)* depends on the attenuation coefficient (μ) and the diameter *(D)* along the LOR and is independent of the distance of the annihilation site from the surface (x)

tiplied by the attenuation coefficient of the tissue (μ). The probability of detecting both photons is the product of the individual probabilities that one of the photons will escape the body [4]. Therefore, only the diameter (***D***) of the patient along the LOR contributes to the equation of this probability (Eq. 3), regardless of the distance of the annihilation site from the surface:

$$p = p_2 \times p_1 = e^{-\mu(D-x)} \times e^{-\mu x} = e^{-\mu D}$$

Eq. 3

Attenuation of the signal from a given LOR can be measured with different algorithms from CT or MR images of the same patient. This so-called μ-map is generated using a bilinear scaling method in the case of CT images. For MRI, segmentation algorithms are routinely employed, using a Dixon sequence. Besides attenuation correction, scatter and random corrections are performed on the raw data of PET images. It must be emphasised that all corrections will contribute to the overall noise characteristics of the reconstructed images, while the average image pixel values will be unbiased and will refer more closely to the true signal.

Acknowledgements. The author would like to express his gratitude to Dr. Laszlo Balkay for his advice and thoughtful conversations during the writing process, and to Dr. Nicola Belcari for his help in the figure presentations.

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Different dosimetric approaches for different applications

Dosimetry is the discipline which aims to measure the absorbed dose ***D*** following exposure to ionising radiation. ***D*** in a mass ***M*** is defined as the amount of energy ***E*** deposited in that mass:

$$D\ [\text{gray}] = E\ [\text{joule}] / M\ [\text{kg}]$$

Eq. 1

The importance of ***D*** arises from the fact that biological effects are mainly related to this physical entity. ***D*** is a purely physical quantity [1].

Other quantities were introduced into dosimetry to take into account the observed fact that, for instance, the same absorbed dose ***D*** delivered by neutrons or alpha particles rather than by X-rays or gamma rays results in more pronounced adverse biological effects. In a low-dose regimen (up to 0.1 grays) for radiation protection of workers, members of the public or patients undergoing diagnostic examinations, the dose equivalent ***H*** was defined using a radiation weighting factor W_R:

$$H\ [\text{sievert}] = W_R\ D\ [\text{gray}]$$

Eq. 2

W_R is related to the linear energy transfer (LET) of the radiation, i.e. the density of energy deposited along the particle path. X-rays and gamma rays have a W_R of 1. Heavy particles (hadrons) have a higher W_R. A proton beam has a W_R of 2 and alpha particles, a W_R of 20, while the W_R of neutrons is a continuous function of their energy, with a range between 2.5 and 20 (see ICRP publication 103 for details [2]). Note that, unlike the absorbed dose, the dose equivalent is not a purely physical quantity, as it requires knowledge of the biological effects of irradiation.

In a high-dose regimen (grays), for patient radiation protection in radiotherapy, i.e. in treatment planning, the concept of relative biological efficacy (RBE) is used; RBE has a role similar to W_R in converting the physical gray into the biological effect. For proton therapy, RBE is 1.1, while for alpha particles RBE equals 5 or can be evaluated more precisely if its dependence on incident α-particle energy is taken into account [3]. The value of RBE for alpha particles varies in radiation protection versus therapeutic applications.

It is also to be noted that the degree of accuracy required in dosimetry differs according to the application. In low-dose regimens, estimates of absorbed dose are calculated with a relatively large uncertainty interval, and an inaccuracy of 30% is quite an optimistic figure. By contrast, in the context of external beam radiotherapy, i.e. during treatment planning and verification, inaccuracy should be below 5%.

In low-dose regimens, in order to compare the risk deriving from different practices, a third dosimetric variable was introduced, named effective dose (ED). ED depends on the dose equivalent of each tissue (H_T). For an exposed individual, the risk of radio-induced cancer or hereditary effects is the sum of the risks to each organ, given by the product of the tissue weighting factor W_T and the dose equivalent H_T. W_T is a risk weighting factor defined in ICRP 60 and updated in ICRP 103 [3]. It accounts for the fact that the same dose equivalent to different tissues entails a different risk of deterministic effects. Misleadingly, ED is expressed in the same unit as the dose equivalent, i.e. sieverts, but ED is a completely different concept. ED is a measure of the biological risk of inducing mutations in cells of an exposed body; it is not a physical quantity. ED was conceived in order to permit comparison of risks. It should not be used to compute an absolute number of deaths from a practice, since it is based on the linear, no-threshold risk curve, which could be too conservative [3]. ED focusses on the probability of an effect, i.e. on stochastic effects (cancer induction or gene mutation in gonad cells). For these reasons, ED is applied in a dose range at which deterministic effects are not observable, i.e. in the low-dose regimen. In radiotherapy, ***H*** and ED should not be used. Here the absorbed dose ***D***, potentially weighted with RBE, is the quantity to be adopted.

Dosimetry for radiation therapy

A completely different range of doses is delivered when we enter the field of radiation therapy, where absorbed doses are of the order of tens of grays. Deterministic effects in this field include all kinds of radio-induced toxicity, as well as lesion responses. Dosimetry in radiotherapy aims to predict or to prevent such deterministic effects.

In internal dosimetry for radionuclide therapy a distinction can be drawn between safety-oriented dosimetry and efficacy-oriented dosimetry. The former aims to prevent adverse events in relation to healthy organs. Historically, the most common kind of toxicity is acute and reversible haematological toxicity, or myelodepression, consisting in a reduction in white blood cell and platelet counts. In radiopeptide therapy with yttrium-90 labelled DOTATOC (^{90}Y-DOTATOC), irreversible kidney impairment has been observed, while in radioembolisation, liver decompensation leading to death has been reported [4, 5]. Efficacy-oriented dosimetry attempts to plan the treatment in order to achieve a treatment response.

Dosimetry for therapeutic applications: legal requirements

The legal requirements with regard to dosimetry in any radiotherapeutic exposure derive from Council Directive 97/43, as translated into national legislation. Council Directive 2013/59 [6] repeals the previous Directive and must be converted into national laws by 6 February 2018. It contains three items strictly relating to nuclear medicine therapy:

1. Definition 81: ***"radiotherapeutic" means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes.***

2. Article 56 (the ***Optimisation principle*** applied to radiotherapy): ***For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.***

3. Article 57: Responsibilities:

1. Member States shall ensure that:
(a) any medical exposure takes place under the clinical responsibility of a practitioner;
(b) the practitioner, the medical physics expert and those entitled to carry out practical aspects of medical radiological procedures are involved, as specified by Member States, in the optimisation process.

It is therefore clearly stated that nuclear medicine treatments:
- cannot be considered different from external beam radiation therapy (EBRT);
- should be planned (and verified) individually, through dosimetry of target and non-target volumes;
- should be optimised, i.e. delivered with reasonably low dosage, but not so low as to negate the therapeutic effect of the treatment.

Article 57, a real novelty, remarks on the legal responsibility for ensuring compliance with the optimisation principle.

For a number of historical and practical reasons, the activity to be administered in radionuclide therapy is at present chosen using empirical or raw dosimetric methods. Pre-treatment dosimetry (treatment planning) is only seldom applied. The same can be said for peri-treatment dosimetry (verification).

Note that radionuclide therapy is often delivered in a series of administrations. This is the case in treatments of thyroid cancer with radioiodine and of neuroendocrine tumours with radiolabelled somatostatin analogues (radiopeptides) or iodine-131 metaiodobenzylguanidine (^{131}I-mIBG). Verification dosimetry performed during the first administration can be used as treatment planning for the subsequent administrations, with the limitation that a variation in tumour uptake following one administration (therapeutic response) will also alter the normal organ uptake.

Dosimetry methods

Although "dosimetry" literally means "measurement of the dose", internal dosimetry is always a rather indirect dose calculation. For this purpose, three main methods have been developed:

1. The Medical Internal Radiation Dose (MIRD) schema [7–10]
2. Convolution methods (MIRD pamphlet 17 [8])
3. Patient-specific Monte Carlo-based methods

These methods are characterised by increasing levels of accuracy and complexity. However, their basic needs are the same: quantitative evaluations of the activity content in metabolically active tissues or perfused volumes and of the variations in this activity over time. This represents a profound difference from EBRT dosimetry. The dose distribution from an accelerator beam or from a sealed source (brachytherapy) can be simulated, using as input data a CT scan of the patient and the beam or the source characteristic. In radionuclide therapy, the activity biodistribution and its physiological variation over time must be studied by sequential patient data collection. This may include thyroid uptake measurements, images, blood sampling, whole body counts, and collection of urine samples, depending on the injected radiopharmaceutical and the aim of dosimetry. The frequency and time framework of data collection depend on the nature of the treated disease and on the clearance of the used agent. The consequence may be a non-negligible workload for both the patient and the division. This argument, often used in the past against internal dosimetry, is weak when one considers that a complete EBRT treatment requires daily irradiation for weeks.

The Medical Internal Radiation Dose (MIRD) schema for organ dosimetry

The simplest dosimetry method was proposed by the MIRD Committee [7–10]. Despite its apparently complicated formalism, we try here to develop its main concepts in a non-rigorous but didactic way, following a paper by Mike Stabin [11]. We also use the most popular and historical nomenclature (MIRD Primer 1991) [7], though a new, official, but still unused nomenclature was published in MIRD pamphlet 21 (2009) [8].

The schema was originally conceived to evaluate mean absorbed dose at organ level and was based on the classification of an organ as source or target. A source organ is perfused or displays uptake of the radioactive agent, while target organs passively receive irradiation from source organs. Within this framework, it is important to distinguish between two kinds of radiation:

- Non-penetrating radiation, which is incapable of going beyond the borders of the source organ to reach other organs. Such radiation is typically charged particles (beta particles, positrons, alpha particles).
- Penetrating radiation, capable of transferring energy from a source to a target organ. Such radiation is typically gamma rays or X-rays.

Two important points should be noted. First, the MIRD schema has been extended from the organ level down to the cellular

level, where the source region may be the cell membrane, and the target region, the nucleus. In this case, the classification of charged particles as "non-penetrating radiation" should be revised, since any of these particles can reach the cell nucleus from the membrane. Second, remaining at the organ level, consider, for instance, ^{131}I thyroid uptake. Here, 94% of the absorbed dose is attributable to beta rays and only 6% to 364-keV photons. For liver uptake of the same isotope, the contribution of gamma rays increases to 25%. The relative amount of absorbed dose from gamma rays reaches a maximum of 42% if we consider the largest source for the standard 73-kg male, i.e. its whole body, uniformly filled by radioiodine. If, on the other hand, ^{177}Lu is considered, the low photon abundance means that 96% of the liver dose is due to beta rays, and only 4% to gamma rays. Therefore, for beta-gamma emitters in clinical use, the highest absorbed dose is delivered to source organs by beta particles. This fact is highly relevant in understanding the implications of the MIRD schema in the following different situations of increasing complexity.

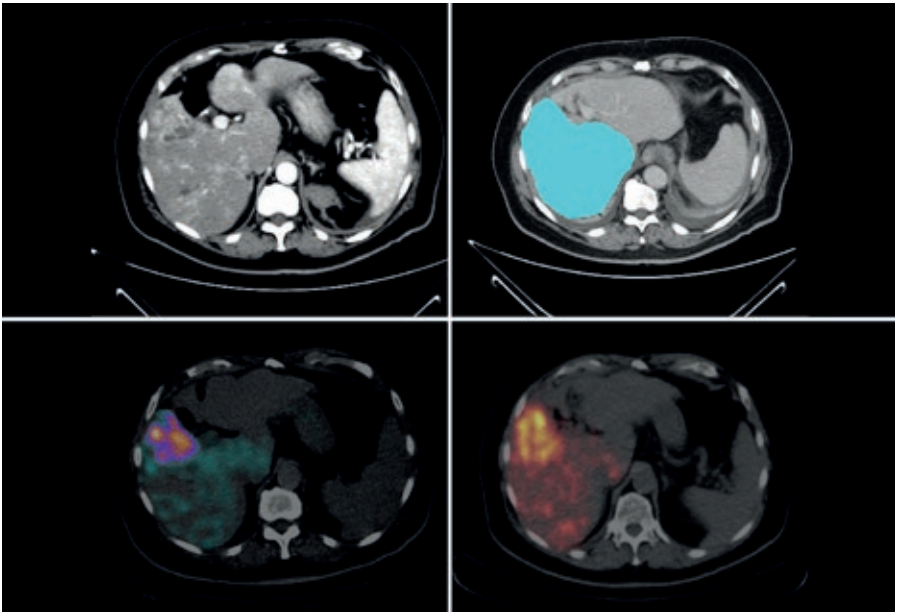

Figure 1: images of hepatocarcinoma treated with 90Y microspheres
Upper left: diagnostic CT arterial phase; Upper right: lobe volumetry on portal phase
Lower left: 99mTc SPECT-CT slice; Lower right: microsphere 90Y PET

Consider as an example an organ subject to self-irradiation only from non-penetrating radiation: a liver lobe injected with ^{90}Y microspheres (Fig. 1). Such devices are permanently trapped in capillaries and release their beta energy in tissue until complete decay has occurred. At each time instant, the lobe dose rate dD/dt (Gy/min) is proportional to the activity burden. Let us introduce the proportionality constant, called S:

$$dD/dt = S\,A(t)$$

Eq. 3

The differential absorbed dose to the organ during a small interval of time dt, during which the activity can be considered constant, is given by the dose rate times dt:

$$dD = S\,A(t)\,dt$$

Eq. 4

The total absorbed dose is given by the sum of all the time intervals, from the zero time (administration) to infinite time. A sum of differential terms is mathematically performed by an integral:

$$D = S \int A(t)\,dt$$

Eq. 5

Since ^{90}Y microspheres are permanently trapped, the time-activity curve (TACT curve) in the lobe is given by the mono-exponential decay curve of the administered activity A_0 of ^{90}Y, with a half-life $T_{1/2}$ = 64.2 h and a decay constant $\lambda = \ln 2 / T_{1/2}$:

$$A(t) = A_0 \exp(-\lambda t)$$

Eq. 6

The integral in eq. (5) can be easily solved:

$$\int A(t)\,dt = \int A_0 \exp(-\lambda t) = A_0 \int \exp(-\lambda t) = A_0 / \lambda$$

Eq. 7

Finally the absorbed dose is given by:

$$D = S\,A_0 / \lambda$$

Eq. 8

The integral in eq. (7) has a simple physical meaning. The activity $A(t)$ is by definition the number of decays per second. $A(t)$ multiplied by the time dt in eq. (4) gives the number of decays during the interval dt. The integral [eq. (7)] is therefore the total number of decays (NDs) of ^{90}Y nuclides in the liver lobe, from the administration to infinite time:

$$\int A(t)\,dt = NDs$$

Eq. 9

Then

$$D = S \times NDs$$

Eq. 10

It is no surprise that the absorbed dose is proportional to the number of decays in the organ.

The problem now is the value of the parameter S. This, too, can be easily calculated (in this first easy case). Solving eq. (10) for S, we have:

$$S = D / NDs$$

Eq. 11

S is the absorbed dose per one decay. From the definition of absorbed dose, it can be inferred that this quantity is given by the mean beta energy (933 keV) emitted by ^{90}Y divided by the perfused region mass ***M***:

$$S = 933\ keV / M$$

Eq. 12

We now have all the parameters needed to compute the absorbed dose to the injected portion of liver with mass ***M*** liver from ^{90}Y microspheres:

$$D = 933\ keV / M \times A_0 / \lambda$$

Eq. 13

This can be approximated, compacting the physical constant into a formula:

$$D\ [Gy] = 50 / M\ [kg] \times A_0\ [GBq]$$

Eq. 14

The multiplication symbol "×" was intentionally inserted. It refers to the basic splitting of the MIRD dose calculation into two factors (eq. 10). The absorbed dose in eq. (13) is the product of two independent terms: the first one (50/***M***), i.e. the S term, accounts for the isotope emitted energy and organ geometry (mass), while the second in this case is simply the injected activity.

Note that for an accurate dosimetric estimation, the organ or the perfused portion mass ***M*** should be carefully evaluated (Fig. 1 upper left, Fig. 2). This is usually done by contouring the organ under study or its portions on CT slices. This necessary step is performed by technologists in a number of centres. For a more accurate determination, a first raw vol-

ume of interest (VOI) is created around the organ. Then the true organ volume is defined by applying a Hounsfield acceptance window; for example, for the kidney in the arterial phase, this can be chosen as [0, 400]. For liver lobe contouring, the technologist usually asks for advice and supervision from the radiologist who performed the injection under angiographic guidance. Knowledge of the angiographic study together with the simulation with technetium-99m macroaggregated albumin (^{99m}Tc-MAA) SPECT is useful in defining the actually perfused portion. The CT portal phase is used since the medial suprahepatic vein defines the border between the right and the left lobe. The mass of the organ is given by its CT volume times the soft tissue density (1.03 g/cc).

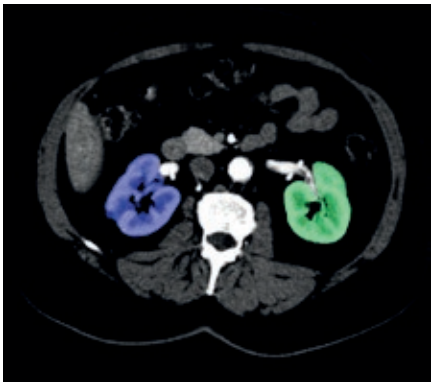

Figure 2: Mass determination on CT slices of kidney in radiopeptide therapy

Absorbed dose to an organ from non-penetrating radiation in the presence of biological clearance

A slight complication arises if the agent displays both physical decay and biological clearance, which is the case for almost all radiopharmaceuticals used in nuclear medicine diagnosis and therapy. We keep as an example the liver after administration of ^{90}Y-DOTATOC. Eq. (7) cannot be solved as easily as for the mono-exponential TACT, but there are several mathematical methods to obtain the value of the integral. The value of the integral represents the area under the curve (AUC). Absorbed dose is therefore always directly proportional to the NDs, corresponding to the AUC. This quantity is defined as cumulated activity $\tilde{A}$:

$$\tilde{A} = \int A(t)\, dt = NDs$$

Eq. 15

$\tilde{A}$ is usually expressed in MBq h, but this is simply a strange way of saying that $\tilde{A}$ is the number of decays occurring in the organ. In order to have a variable which is independent of the administered activity A_0, we divide the cumulated activity (MBq h) by A_0 (MBq), obtaining a time (h). This variable is named residence time τ. This name is misleading. Do not think that once the residence time has elapsed, the organ is free from radioactivity. τ is just the cumulated activity divided by the injected activity. τ allows comparison of the

absorbed dose per unit activity. For any given isotope, the higher is τ, the higher will be the absorbed dose per unit activity.

$$\tau = \tilde{A} / A_0$$

Eq. 16

The basic MIRD equation is:

$$D = S \times \tilde{A}$$

Eq. 17

The simplicity of the MIRD methodology is evident in this product. For ^{90}Y only, S is given by eq. (12). The second term depends on the liver clearance, i.e. on organ biokinetics, which is an individual characteristic. Other, probably more familiar examples of biokinetics in diagnostics are the kidney TACT curves in a dynamic study.

Here we confront the key point concerning the need for individualised dosimetry: ***Every individual shows his or her own clearance curve (TACT) in his or her organs and for each injected radiopharmaceutical.*** This implies that in order to achieve complete dosimetry, i.e. optimised radionuclide therapy, the TACT of each source organ has to be determined in each individual patient. This is usually done with a sequence of scans. Biokinetics may change even for the same patient after a therapeutic administration, since tumour mass and uptake may be reduced owing to therapy. For the pure beta emitter ^{90}Y, the TACT in organs is derived from a sequence of scintigrams taken after the administration of the same molecule labelled with a gamma emitter, in radiopeptide therapy the ^{177}Lu isotope (Fig. 3). TACT can be derived by drawing ROIs on the liver. Examples of such curves for the livers of different patients are shown in Fig. 4.

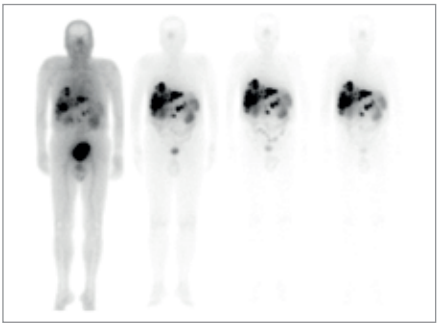

Figure 3: the sequence of ^{177}Lu-DOTATOC whole body anterior images obtained at 1, 18, 40 and 65 h post injection.

Absorbed dose from non-penetrating and penetrating radiations

As long as non-penetrating radiations are considered, the dosimetric calculation is relatively simple, since for each source organ eq. (17) can be applied. The use of penetrating radiations (gamma emitters) introduces two complications. Consider the liver with an uptake of ^{177}Lu-DOTATOC. First, only a fraction of the gamma energy emitted in the liver is depos-

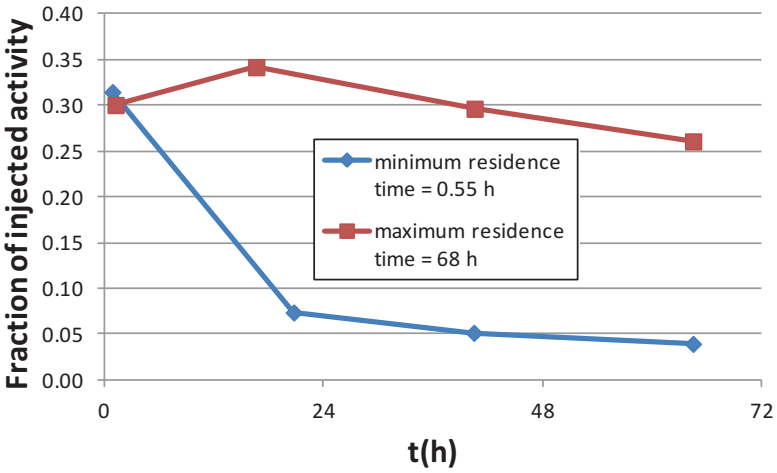

Figure 4: TACT curve in liver after ^{177}Lu-DOTATATE administration. The two patients with minimum and maximum residence time studied in National Cancer Institue of Milan were chosen, corresponding to a non metastatic versus a heavily metastatic liver. The huge difference in AUC between these two patients is evident.

ited in the liver itself. The S value computation becomes non-trivial. Second, another fraction of gamma energy is deposited out of the liver, irradiating all the other target organs. The notation $S_{s \leftarrow s}$ (S "from source to source") is introduced for the self-irradiation, and we have a large set of $S_{t \leftarrow s}$ values (S "from source ***s*** to target ***t***") for cross-irradiation. An additional operational complexity arises from the fact that after a ^{177}Lu-DOTATOC administration, there are several source organs, primarily liver, spleen, kidney and circulating activity. We need the set of $S_{t \leftarrow s}$ for any possible cross-irradiation.

The often mentioned simplicity of the MIRD schema is apparently lost. This is false, since all these S values (Snyder's factors) were calculated by the MIRD committee using Monte Carlo simulations. These values are now available in tables for many isotopes. They are also available online [12]. Therefore, considering again eq. (17), the main advantage of the MIRD method is that S values are available. Clinical dosimetrists have to measure the biokinetics only, and to determine $\tilde{A}$ for all source organs, i.e. only the second term in eq. (17). The basic data required for calculation of the S value, used to determine the absorbed fraction for self- and cross-irradiation, are the total energy emission for each isotope (physical isotope properties) and the organ geometry.

This simplicity has a price. S factors were not determined in real patients. A virtual phantom was drawn, and S factors were derived for that geometric object (Fig. 5). Actually, several phantoms of different size were used. This allowed the above-mentioned simplicity to be achieved, but at the expense of accuracy. When we perform organ MIRD dosimetry, we evaluate absorbed doses to a phantom, not our real patient.

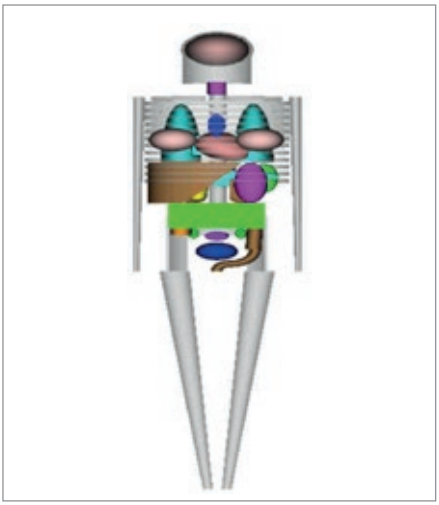

Figure 5: the phantom used to determine the S factors of the MIRD schema

A demanding task still remains. For each considered target organ, for instance lungs, we need to sum all the contributions deriving from source organs (liver, spleen, kidneys, circulating activity). This step has to be repeated for all target organs. In order to avoid manual summing, ad hoc calculation codes have been developed, of which OLINDA/EXM version 1.1 is the most popular [13]. This code needs as input data first, the choice of the phantom among those available, then, the choice of the injected isotope among 814 available, and, finally, the patient-specific biokinetics data, i.e. the residence times of the source organs (Fig. 6). It then proceeds by making $\tau \times S$ multiplications and sums. It needs to be mentioned here that individualised organ masses may be used instead of the standard phantom organ masses.

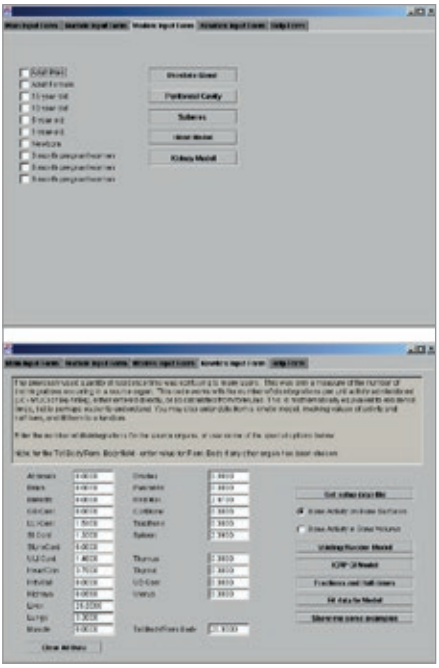

Figure 6: The OLINDA input panels (choice of the phantom, biokinetic data)

The main limitation of present MIRD dosimetry at the organ level is the use of a phantom geometry instead of a real patient geometry. To improve this point, the new S value calculations are based on an anthropomorphic CT-based virtual phantom. Another approximation is the evaluation of only mean organ and tumour doses, since the uptake in organs or lesions is non-homogeneous. The voxel dosimetry approach was introduced to account for non-homogeneous uptake.

In the particular case of OLINDA 1.1, the tumour is modelled only as an ideal sphere. Moreover, differently from normal organs, the tumour is not considered for the cross-irradiation: the tumour dose is calculated for self-irradiation only. Nevertheless, all these approximations have only a minor impact since, as we have seen, the higher dose contribution derives from non-penetrating particles, which are exactly accounted for in source organs in OLINDA calculations.

Easy cases of MIRD dosimetry, feasible without imaging

In many situations dosimetry can provide sufficient information to plan a treatment even without imaging. The main fields of application of this methodology are the treatment of Graves' disease, the treatment of metastatic thyroid cancer and ^{131}I-mIBG treatments. While the first of these cases involves a benign pathology, in the others we are dealing with safety-oriented dosimetry. Therapy can be designed to deliver the maximum tolerable activity (MTA) on an individualised basis. If we were adequately organised to routinely accomplish planning of this nature in all three of these patient classes in Europe, most of the oncological nuclear medicine treatments in Europe would partially fulfil the optimisation principle. The term "partially" is used here because the MTA approach is a maximisation: rigorous optimisation would require also lesion dosimetry, for which imaging would be necessary.

Thyroid Graves' disease

In the case of Graves' disease, efficacy-oriented thyroid dosimetry can be performed without the need for scintigraphic imaging, provided that the mass of the organ is measured on scintigrams or with ultrasound images. The detector is a scintillation probe with a fixed probe–thyroid distance. This allows one to obtain the uptake and the TACT of the organ. The number and the time interval for thyroid counting can be chosen according to the desired accuracy [14, 15].

Blood and red marrow dosimetry for agents without specific marrow uptake

Bone marrow is the organ at risk in most nuclear medicine systemic therapies, including treatment of thyroid cancer with radioiodine, ^{131}I-mIBG therapy, treatment with monoclonal antibodies and the use of bone-seeking agents for bone pain palliation (as employed prior to the introduction of ^{223}Ra chloride). If the injected radioactivity binds to neither

bone nor red marrow nor blood particles, an easy method of dosimetry for blood or red marrow is possible provided that the TACT of the activity concentration in blood samples and the whole-body activity burden are measured [16, 17]. The necessary instrumentation is a gamma counter to count blood samples and a spectroscopic probe or Geiger counter to count the patient body, with a reproducible patient–detector distance. Data collection should last several days, and ideally up to the 6th day for blood sampling in radioiodine therapy.

^{131}I-mIBG whole-body dosimetry

This method was developed as a simplification of red marrow dosimetry to treat neuroblastoma in children, in whom repeated blood withdrawal is inappropriate. In ^{131}I-mIBG therapy of paediatric patients, the whole-body dose has been demonstrated to correlate with haematological toxicity [18]. A limit of 2 Gy whole-body absorbed dose is generally accepted. Since this kind of therapy is based on repeated administrations, peri-therapeutic dosimetry after the first administration can be used to plan the subsequent administrations. The dosimetric method is based on a sequence of whole-body counts (minimum two per day) taken during the hospitalisation for therapy using a Geiger counter fixed on the ceiling above the patient's bed or a portable counter at a fixed distance from the patient. Usually the geometric mean $G = \sqrt{A\,P}$ of anterior A and posterior P counts is considered. The TACT of the whole body is obtained, and a whole-body dose is calculated as:

$$D_{\text{whole body}} = S_{\text{whole body} \leftarrow \text{whole body}} \times \tilde{A}$$

Eq. 18

SPECT imaging for internal dosimetry

Kidneys are another example of an organ at risk. Renal impairment has seldom been observed in treatments with radiopeptides labelled with ^{90}Y. Prevention of such damage requires imaging-based dosimetry. The mean dose MIRD approach presented above has an additional limitation if the adopted imaging methodology is planar (2D). Overlapping of activity from different organs can be only partially corrected by background subtraction. This problem arises, for example, in radiopeptide treatment, where intestinal activity overlaps with kidney activity, or in radioimmunotherapy using labelled antibodies, which circulate for days with negligible excretion (Fig. 7).

In these situations, the organ or lesion mean dose can be more accurately determined if a sequence of SPECT scans is performed (Fig. 8). Dosimetry requires attenuation correction, which can be done in SPECT with a co-registered CT. The increase in the number of SPECT-CT systems in recent years represents a step in this direction.

Attenuation correction is less demanding in planar imaging. A planar transmission scan

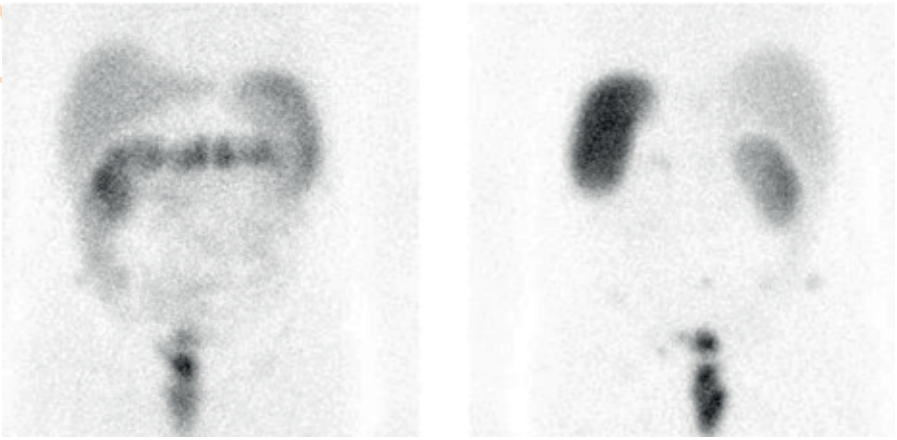

Figure 7: the problem of overlapping sources in planar dosimetry. Anterior and posterior WB images after 177Lu-DOTATOC administration. In radiopeptides treatment, the critical organ activity (kidney) is often overlapped to intestinal activity.

for the purpose of attenuation correction can be easily done by placing a flood source (^{57}Co or ^{99m}Tc) on the lower gamma camera head, below the patient couch (Fig. 9). The most accurate attenuation correction is obtained if the radial distance of the lower gamma camera head from the couch is maximal. A blank scan without the patient is acquired; then, with an identical setting, a transmission scan is performed on the non-injected patient. ROIs are drawn on images recorded by the upper gamma camera head. The ratio between ROI counts in the transmission scan and counts in the blank scan gives a number, whose square root is the attenuation correction factor at the energy of the isotope used for transmission scan. This should then be converted to the energy of the injected isotope (MIRD dose estimate report no. 20 [8]).

In 3D dosimetry, an additional problem still under study is the mutual co-registration of the SPECT image sequence needed to produce the TACT in each studied region. A possible approximated simplification of the method is so-called 2.5 D dosimetry, or hybrid dosimetry [19]. One SPECT examination and a sequence of planar images are acquired, with one planar scan at the same time as the SPECT. Quantification is derived on the 3D image, while the TACT is derived from the sequence of planar images.

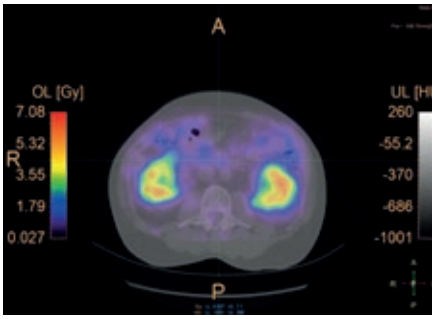

Figure 8: SPECT-CT dosimetry after ^{177}Lu-DOTATOC administration.critical organ activity (kidney) is often overlapped to intestinal activity.

PET imaging for internal dosimetry

PET imaging is now a routine in dosimetry [20], especially after ^{90}Y radioembolisation (Fig. 1, lower right). Here the problem is the infinitesimal positron emission from ^{90}Y (32 per million decays), which requires acquisition times of 15 min per bed position with two bed positions to cover the liver and results in unavoidably noisy images despite the long acquisition time. The huge advantage in radioembolization dosimetry derives from the permanent trapping of microspheres: just one scan is sufficient since TACT is given by the physical decay of ^{90}Y.

The enhanced image quality in comparison with SPECT is outstanding in iodine imaging. Iodine-124 PET should be used for accurate staging after thyroidectomy, given the low diagnostic sensitivity of ^{131}I whole-body scan, and not only for dosimetric purposes [21].

Convolution and direct Monte Carlo methods

Convolution methods go beyond the evaluation of organ mean dose. They aim to compute the absorbed dose point by point, at any location in the studied object. Voxel dosimetry and dose point kernel dosimetry are similar in that the dose from a point or voxel source to the surroundings is calculated. This calculation is repeated for all source voxels, adding the contribution of each source voxel to all target voxels. This process is termed convolution. It overcomes the phantom geometry limits of the MIRD approach. Snyder (S) factors from voxel to voxel are also available. Commercial software can be employed for dosimetry using convolution methods.

Convolution methods can be successfully applied to homogeneous tissues, while in inhomogeneous tissues or at organ–organ interfaces (e.g. bone–tissue or liver–lung), direct Monte Carlo simulation is the most reliable, though also the most demanding calculation. It is based on the simulation of each single radionuclide decay, following the history of the emitted beta and gamma rays, with their probabilistic interactions. The deposited energy from each interaction is recorded. The process is repeated with a different random fate for some ten millions of decays, obtaining a 3D inhomogeneous absorbed dose distribution.

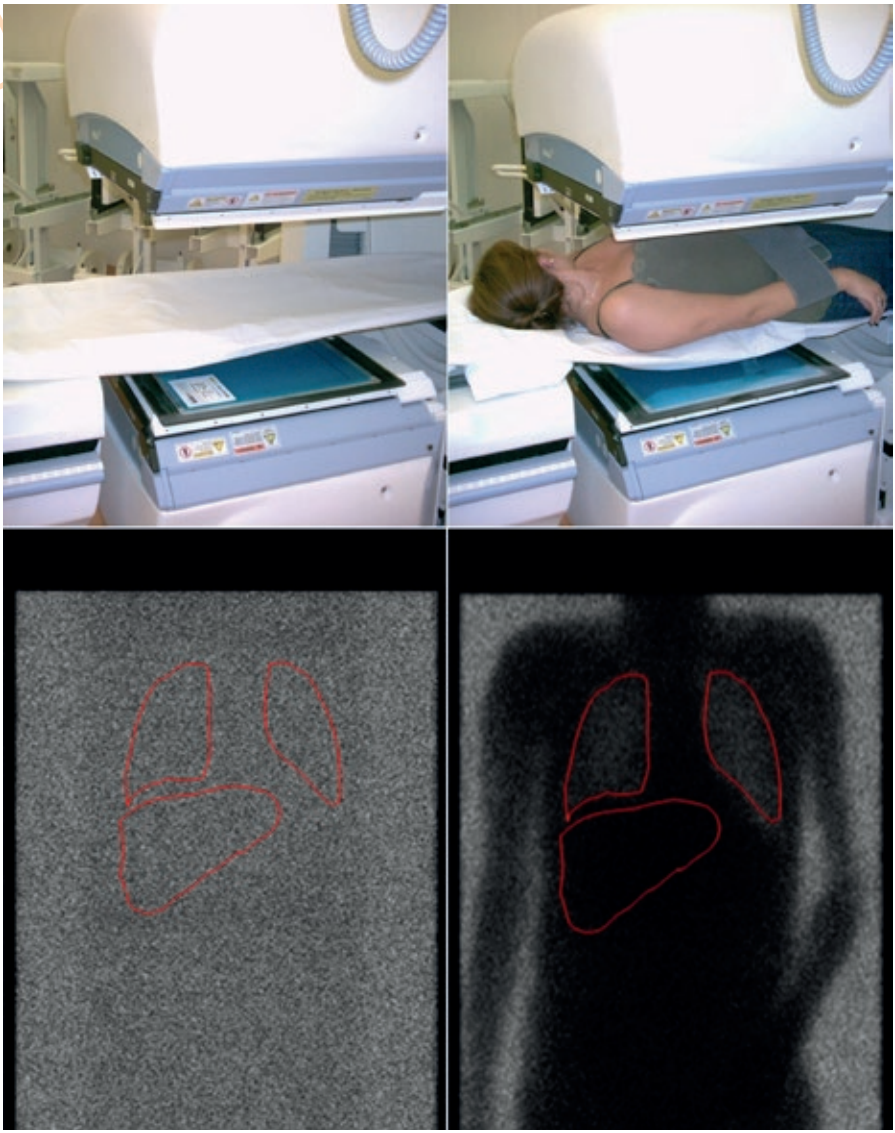

Figure 9: Attenuation correction in planar imaging: operational setting

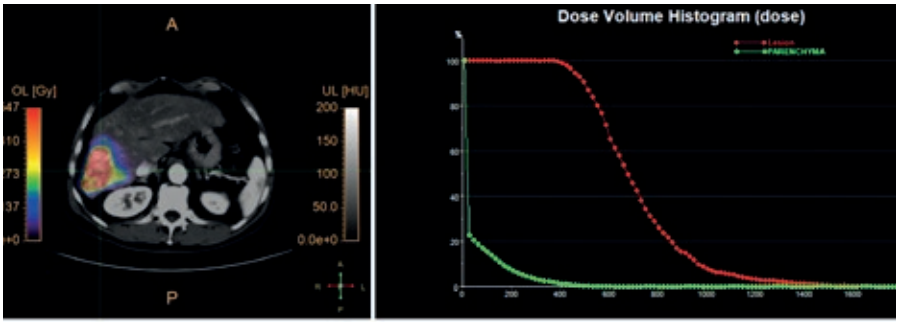

Figure 10: Pre therapy SPECT-CT dosimetry in radioembolization of hepatocarcinoma. Voxel dosimetry map (left) and corresponding integral Dose Volume Histogram (DVH) (right).

From a practical point of view, for dosimetry in a real patient, both convolution and Monte Carlo methods need as input a 3D nuclear imaging sequence of images (SPECT or PET), accompanied by and co-registered with the morphological patient data (CT scan). The problem of mutual co-registration of the 3D image sequence of a non-rigid body requires elastic deformation co-registration. In addition, when we go down to the voxel level, the problem of image noise arises. Voxel counts (and then voxel absorbed dose) have an intrinsic indetermination due to noise, which is given by the Poisson noise, with additional noise introduced by the reconstruction algorithm. Absorbed dose and activity in each voxel are therefore subject to an intrinsic uncertainty. For this problem and for the partial volume effect problem, typical of nuclear medicine imaging, dosimetry at the voxel level and the use of dose volume histograms are still under investigation in radionuclide therapy (Fig. 10), while in external beam radiotherapy, voxel dosimetry is routinely applied.

Segmentation

Segmentation is the process of contouring organs or lesions to define regions of interest (ROIs) or volumes of interest (VOIs). This procedure is necessary to obtain counts in VOIs, which are related to the activity in VOIs. It is also necessary to determine the object volume, i.e. its mass. Segmentation is not a trivial step in the dosimetric calculation, and it can introduce a non-negligible uncertainty. Difficulties may especially arise during liver volume determination in patients with abnormal liver anatomy following hepatic resection. Another problematic situation is the presence of infiltrative liver tumours, whose borders cannot be defined even on CT. Ow-

ing to the need for segmentation, dosimetry is dependent on the skills of the operator. The optimal threshold for segmenting an object in order to obtain quantitatively accurate information is a general problem in nuclear medicine, an example being segmentation for FDG PET target volume delineation for radiotherapy treatment planning [22].

Segmentation requires knowledge of basic anatomy. For this reason, technologists can be usefully employed in this activity. During this work they are usually supervised by an experienced radiologist.

Quantification

Regardless of the kind of dosimetry, the amount of activity in source regions (organs or voxels) needs to be determined. The first requirement is an accurate dose calibrator to measure the administered activity and its residue. In whole-body dosimetry, quantification is immediate since the first body count is taken immediately after the administration, before urinary bladder voiding. Setting the correspondence between obtained initial whole body counts and the known injected activity allows one to proportionally calculate the activity burden in subsequent counts. This is called "patient relative calibration". Calibration of the gamma counter is required to convert the blood sample count rate in a tube into activity, with a correction for non-linearity effects.

The quantification on images is more complex. In contrast to PET scanners, gamma cameras were not conceived to be quantitative. Only the last model of a producer was developed ad hoc, with new hardware and software, in order to provide quantitative SPECT, and then only for ^{99m}Tc. PET scanners are usually considered quantitative, but issues arise when non-conventional isotopes are employed, such as ^{90}Y [23] or ^{124}I.

Quantitative imaging requires the implementation of all the possible corrections for physical effects (attenuation, scatter, dead time, partial volume effect, resolution recovery and, for PET, random correction and time of flight). A system calibration is then necessary, to convert the count rate in a VOI to activity. This requires a phantom containing a known activity: such a phantom can be a point source or an extended phantom, or a hot insert in a water phantom. If a phantom is used, an absolute system calibration is performed. In some particular situations, each patient can be the "calibration phantom" for him- or herself. In the case of liver radioembolisation, the known activity can be imaged on one SPECT or PET scan and can be set in correspondence with the obtained counts (patient relative calibration method, cf. above). Technologists can play a useful role in the calibration process owing to their technical competence on scanners and their authorisation to handle radioactivity.

The necessity of the technologist in clinical dosimetry

The Dosimetry Committee of the EANM has been actively promoting the implementation of dosimetric optimisation of radionuclide therapy for more than a decade. It is not predictable when and to what extent such optimisation will be accomplished. What is beyond doubt is that such an advance on a large scale cannot happen without the employment of technologists. By law, physicists have the responsibility for dose calculations, but several preliminary operations can and should be done by technologists.

In the Nuclear Medicine Division of the National Cancer Institute of Milan, several theses on dosimetry have been written by technologists, including two that addressed in particular the role of the technologist in clinical dosimetry. In such institutions, not only data acquisition (patient handling and scanning, whole body counting, blood sample counting) but also segmentation is ordinarily performed by technologists. Technologists therefore have an essential role in the implementation of clinical dosimetry in radionuclide treatments.

Guidelines of the EANM Dosimetry Committee

The EANM website, under the section "publication" [24], offers a list of published dosimetry guidelines that are freely downloadable.

Disclosure

Carlo Chiesa received honoraria during the past two years from BTG Biocompatibles for lectures, consultancy and one symposium during the 2015 EANM Congress. He was supported by BTG Biocompatibles at the last two EANM Congresses. In 2015 he was also a consultant for MedPace core lab.

The other authors have nothing to disclose.

Ethical policy

This work has an educational goal. All clinical images contained herein were acquired for diagnostic or therapeutic purposes for patient care, after procurement of signed informed consent, before this chapter was compiled. Images were copied here for educational purposes.

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Chapter 3: International Basic Safety Standards

Pedro Fragoso Costa

Introduction

Shortly after the discovery of X-rays (by Röntgen in 1895), radiation damage was already being studied and documented. As early as 1896, an American engineer, Wolfram Fuchs, published an article [1] in which the three fundamental principles of radiation protection were presented:

1. Exposure should be restricted to a minimum.
2. The X-ray tube should be placed at a secure distance.
3. Protective plates should be used for the non-exposed body parts.

The increasing interest in the use of X-rays or radionuclides in medical, industrial and even commercial applications subsequently paved the way for numerous accidents for which the source was the biological hazard caused by ionising radiation [2]. However, the idea that this new radiation could be used to destroy malignant tissues laid the foundations for radiotherapy, and the first treatment of a cancer by this means was reported in 1899 [3]. In the diagnostic field, ionising radiation was used for medical purposes as early as 1897 in military field hospitals [4].

It was not until 1928 that the first international organisation was created for the protection of workers, patients and public against ionising radiation, namely the organisation known today as the International Commission on Radiological Protection (ICRP) [5]. Since then, the ICRP has created, maintained and developed the international system of radiological protection used worldwide as the common basis for radiological protection standards, legislation, guidelines, programmes and practice. The ICRP has published more than 120 publications on all aspects of radiological protection, including fundamental recommendations taking into consideration not only the current understanding of the science of radiation exposure and effects but also societal expectations, ethics and experience gained in application of the system [6].

The International Commission on Radiation Units and Measurement (ICRU) was founded simultaneously with the ICRP, the former having a more fundamental focus on radiation-related quantities and units, terminology and measurement procedures [7].

Nowadays, the ICRP plays a central role in a rather complex set-up of interdependent organisations that work together with the purpose of achieving the goals set by the system of radiological protection, from inception to regional implementation.

Global players

At the international scale, various institutions and personalities have historically played a fundamental role in the peaceful use of atomic energy. The speech by U.S. President Eisenhower in 1953, entitled: "Atoms for Peace" [8], was a milestone in stopping the

"nuclear race" with the former Soviet Union and in delivering a sense of security that the nuclear disasters from Hiroshima and Nagasaki would not be repeated. This speech also laid down the ideological background for the creation of the International Atomic Energy Agency (IAEA) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). The latter, created in 1955, became the official international authority responsible for controlling the levels and effects of ionising radiation from all possible sources, whether peaceful, military, man-made or natural [9]. In 1957 the IAEA was created and empowered to take actions on the development of nuclear energy for peaceful purposes, to provide materials and assistance for practical applications of atomic energy (e.g. energy, industry and health) relevant to the needs of underdeveloped areas of the world, to foster the exchange of scientific and technical knowledge and, finally, to establish or adopt nuclear safety standards [10].

While UNSCEAR presents the field data related to a number of exposure situations (e.g. the atomic bomb in Japan, the Chernobyl accident or epidemiological studies on radon exposure), ICRP and other international bodies use this information in order to make recommendations that will suit the regional specifications and be integrated into the law, as shown by Figure 1.

Figure 1: Radiation protection chain, showing actions and roles of international bodies (adapted from ICRP Publication 109) [11]

International System of Radiological Protection

Since its foundation, the International System of Radiological Protection has been subject to many updates and fundamental changes. Over the years, not only have dose quantities and their units been redefined, but weighting factors and body-related dose quantities have been revised and dose limitations for occupational and public exposures, redefined. Despite the continual implementation of this self-optimisation process, the fundamental principles of radiation protection were in fact defined in the first ICRP recommendations in 1958 [12]: "The objectives of radiation protection are to prevent or minimise somatic injuries and to minimise the deterioration of the genetic constitution of the population". Nowadays, this principle has been reformulated as the prevention of deterministic effects caused by high doses (mainly of an acute nature and appearing after a known dose threshold) and the reduction of stochastic effects caused by both high and low doses and that can be detected a long time after exposure [13].

The concept of dose has been introduced as the quantity of interest relating physical measurements with biological effects of radiation. The term "dose" has been medically appropriated in analogy to the pharmacological dose, as used in the prescription of a medicine [14]. However, there are situations in which exposure to radiation is not related to a medical act. Differentiation of exposure situations is, therefore, a fundamental topic in radiation protection. There are three categories of exposure:

- ***Occupational exposures:*** those exposures that occur in a range of industries, medical institutions, educational and research establishments and nuclear fuel cycle facilities [15]
- ***Public exposures:*** exposures to natural radiation sources and man-made sources [16]
- ***Medical exposures:*** exposures of patients and comforters, carers or volunteers in research and in diagnostic, interventional and therapeutic procedures [17]

Three exposure situations have been defined, which are considered to encompass the entire range of possible situations involving exposure [18]:

- ***Planned exposure situations:*** those situations in which a radioactive source is introduced or operated in a set-up designed for that purpose
- ***Emergency exposure situations:*** unexpected situations that arise from planned exposures and require urgent attention
- ***Existing exposure situations:*** situations that exist regardless of any protective act or decision, mainly regarded as natural background radiation

The use of radiation in Nuclear Medicine is a planned exposure situation. All workers and facilities need to be under regulatory

control, with appropriate authorisation from the competent authority in order to operate. There are situations in which incidents, accidents or errors (e.g. radiopharmaceutical misadministration, spills or contamination) result in a potential exposure [19]. A potential exposure may result from an accident involving a source or an event or sequence of events of a probabilistic nature, including equipment failures and operating errors.

The most important part in a system of radiological protection is the ruling principles that apply to all situations and persons involved. Again, there are three fundamental principles of radiation protection [13]:

1. The principle of ***justification***: Any change to an exposure situation (e.g. a decision to perform a PET/CT scan, changing from an existing exposure to a planned exposure situation) should result in a net benefit to the individual.

2. The principle of ***optimisation of protection***: The likelihood of incurring exposures, the number of people exposed and the magnitude of their individual doses should all be kept as low as reasonably achievable (this is commonly known as the ALARA principle), taking into account economic and societal factors.

3. The principle of ***limitation of doses***: The total dose to any individual from planned exposures, with the exception of medical exposures of patients, should not exceed the established limits (only applies to the occupational and public exposure categories).

IAEA International Basic Safety Standards (IBSS)

As mentioned previously, the development and application support of safety standards is a statutory function of the IAEA. To achieve this mission, IAEA periodically publishes Safety Standard Series, which cover nuclear safety, radiation safety, transport safety and waste safety. The IBSS are a part of the safety requirements category within the IAEA scheme. The latest IBSS [20] is a joint effort of the European Commission (EC), the Food and Agriculture Organization of the United Nations (FAO), the IAEA, the International Labour Organization (ILO), the OECD Nuclear Energy Agency (OECD/NEA), the Pan American Health Organization (PAHO), the United Nations Environment Programme (UNEP) and the World Health Organization (WHO) and uses the latest recommendations provided by ICRP [13], in particular with attention to the possible exposure situations.

In general all safety standards follow the fundamental principle of protecting people from the hazardous effects of ionising radiation. In all possible interactions in which a radioactive source could produce damage to an individual, there is a role for protection. There is, however, a difference between these two concepts: while radiation protection is mainly focussed in controlling exposure to a source, to attenuate its effects, radiation safety is about maintaining control

over exposures. Since radioactive sources potentially represent a danger to individuals, there is also a responsibility to secure those sources and prevent unauthorised access to them. The complementary nature of safety and security is one of the fundamental principles of the IBSS [21] (Fig. 2).

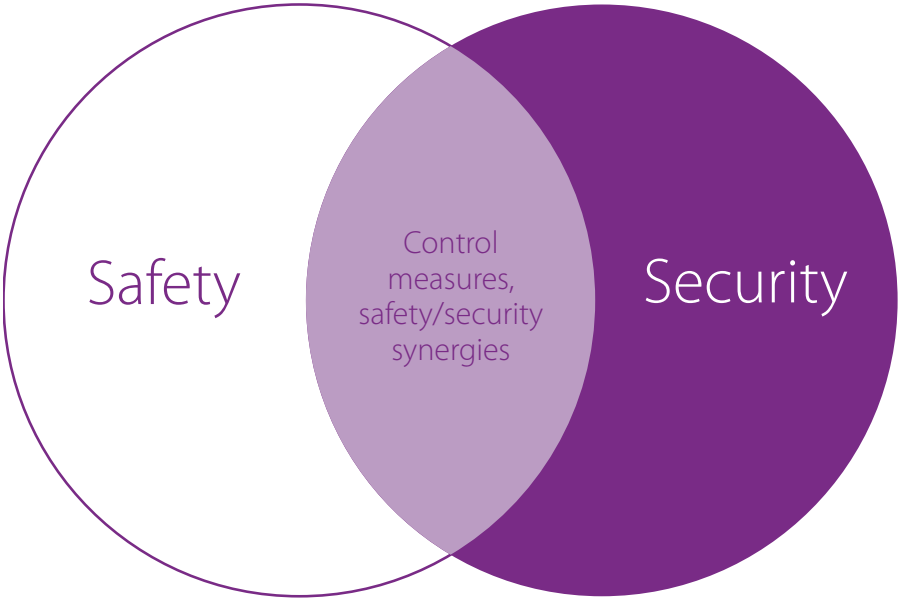

Figure 2: In the health context safety/security synergies can refer to the joint efforts of the chief of a nuclear medicine department and the radiation protection officer in the design of the department, categorisation of radioactive sources, management of radioactive waste and establishment of an emergency response plan (diagram's reproduction with permission by the IAEA) [21]

IBSS provides a series of requirements that must be fulfilled by the government and regulatory bodies. These requirements are divided into requirements that are applied generally (i.e. in all exposure situations) and those that are applied separately for each of the three exposure categories and, for each category, the three possible exposure situations (following ICRP nomenclature). Figure 3 schematises the possible exposure situations and categories to which the IBSS are applicable.

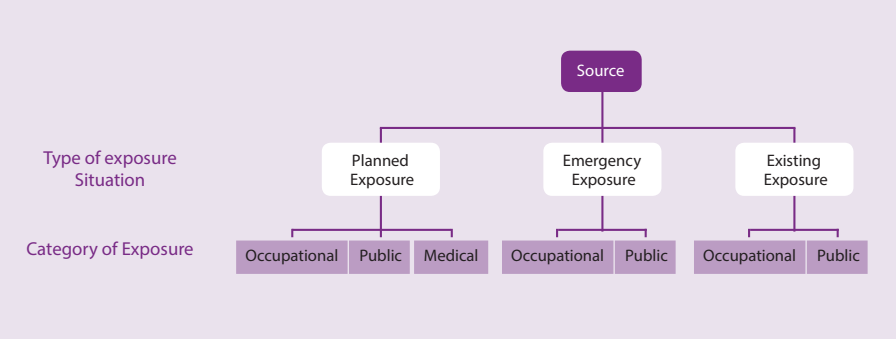

Figure 3: The possible exposure situations and categories according to the ICRP publication 103

With respect to medical exposure in particular, the IBSS [20] presents a series of requirements that have various purposes, including:

- Ensuring that all health professionals working with ionising radiation are specialised in the appropriate area, meet the educational and training requirements in radiological protection and are registered in a database for future assessment
- Ensuring that medical exposures are justified
- Ensuring that protection and safety are optimised for each medical exposure (design considerations, operational considerations, calibration, diagnostic reference levels, quality assurance for medical exposures, dose constraints)
- Ensuring that arrangements are in place for appropriate radiation protection in cases where a female patient is or might be pregnant or is breast-feeding

The IBSS represents a fundamental tool for the establishment of a radiation protection office in any country. While the IBSS is of a non-binding nature, it can be applied and adapted in countries that wish to do so. However, if a country asks the IAEA for IBSS co-sponsorship, then compliance with the security standards is a condition that must be met in order to receive assistance.

European legislation

The recent directive from the European Commission (EC) [22] from December 2013 is the latest legislative act to lay down the IBSS and ICRP recommendations and requirements for EU countries. It is an excellent example of how international standards can be harmonised and applied regionally in different countries.

Type of limit	Occupational	Apprentices and students (aged 16–18 years)	Public	Emergency occupational exposure
Effective dose	20 mSv[a]	6 mSv	1 mSv	<100 mSv[d]
Equivalent doses:				
Lens of the eye	20 mSv[b]	15 mSv	15 mSv	
Skin	500 mSv[c]	150 mSv[c]	150 mSv[c]	
Extremities	500 mSv	150 mSv	150 mSv	

Table 1: Exposure limits according to the EU Directive of December 2013 [22]

[a] In special situations up to 50 mSv/year, as long as the averaged dose in any 5 consecutive years is not above 20 mSv/year
[b] In special situations up to 50 mSv/year, as long as the total dose in any 5 consecutive years is under 100 mSv
[c] Averaged over any area of 1 cm^2
[d] In exceptional situations, in order to save life, prevent severe radiation-induced health effects or prevent the development of catastrophic conditions, a reference level for an effective dose from external radiation of emergency workers may be set above 100 mSv, but not exceeding 500 mSv

The European Basic Safety Standards ensure [23]:

- Protection of workers exposed to ionising radiation, such as workers in the nuclear industry and other industrial applications, medical staff and those working in places with indoor radon or in activities involving naturally occurring radioactive material (NORM)
- Protection of members of the public, for example from radon in buildings
- Protection of medical patients, for example by avoiding accidents in radio-diagnosis and radiotherapy
- Strengthened requirements regarding emergency preparedness and response, incorporating lessons learnt from the Fukushima accident

Especially relevant to the medical field are the requirements in respect of a high level of competence and clear definition of competencies for health professionals in order to ensure the proper radiological protection of patients and workers involved in medical ra-

diation (as set out in the European Directive 2013/59/Euratom [24]). The directive is also an excellent reference document, since it includes modern technical data (e.g. activity concentration values for exemption or clearance of materials that can be applied, radiation weighing factors, tissue weighing factors and effective dose calculation formulas) related mainly to the latest ICRP publication. At the same time it provides new dose limits, in particular with regard to the eye lens. Table 1 summarises the yearly dose limits for workers (covering all authorised practices) and for apprentices and students (aged between 16 and 18 years) who, during the course of their studies, are obliged to work with radioactive sources and the general public. The emergency occupational exposure limit is also shown; it must be ensured that emergency workers liable to incur an effective dose exceeding 100 mSv are informed in advance of the risks and the available protection methods.

All recent publications have placed special emphasis on the use of optimisation tools when managing planned exposures. The annual effective dose limit is a regulatory act that applies to different groups of professionals (e.g. health professionals, reactor operators and researchers). Since this is non-specific to the nature of each individual occupation, it is never to be expected that medical technologists will even approach the effective dose limit within any given year. In these cases, a prospective upper bound of individual doses, known as dose constraint, can be used to define the range of options considered in the process of optimisation for a given radiation source in a planned exposure situation.

Nuclear medicine

The practice of nuclear medicine is regulated by the member states' authorities, whose stance is influenced by the existing recommendations (Fig. 1). The IAEA provides, in addition to the general IBSS, practice-specific regulatory guidance, including with respect to the safe practice of nuclear medicine [25].

All aspects of nuclear medicine are subject to safety requirements, including certification, application of radiation principles (justification of practices, limitation of doses and optimisation of protection), quality assurance of procedures and equipment, facility design and security of sources. In all these areas, health professionals have the responsibility for protection and safety, and the avoidance of accidental exposures resulting from decisions, operation/handling of sources or equipment. Potential accidental exposures may relate to the patient (e.g. radiopharmaceutical misadministration), the health professional (e.g. loss of radioactive shipment, damage to Tc-generator or radioactive spills) or all persons in the department (e.g. fire). In order to avoid or minimise occurrences of these kinds, it is essential for the health professional both to possess knowledge of the factors that may lead to accidental exposures and to provide written operational protocols and materials (i.e. emergency kit) to be used in the event that such exposures occur.

Fact box

Summary of the typical causes of, and factors contributing to, accidental exposures in nuclear medicine (reproduced with permission of the IAEA) [25]

The following types of error can be made:

- Communication errors
- Faulty transmission of information
- Misunderstanding of prescriptions and protocols or use of obsolete protocols
- Errors in identification of the patient
- Use of the wrong source, the wrong radiopharmaceutical or the wrong activity
- Calibration errors
- Maintenance errors

The following factors may influence the frequency and severity of incidents and accidents:

- Insufficient training and expertise of nuclear medicine physicians, medical physicists or nuclear medicine technologists
- No reassessment of staffing requirements after purchase of new equipment, hiring of new technologists or increasing workload
- Inadequate quality assurance and lack of defence in depth
- Lack of a programme for acceptance tests
- Lack of a maintenance programme
- Poor, misunderstood or violated procedures
- Lack of operating documents in a language understandable to users
- Misunderstanding of displays or software messages
- Inattention
- Inconsistent use of different quantities and units

In most accidents there are several contributing factors, which can be summarised as:

- Lack of commitment of the licensee (hospital administrators and department managers)
- Insufficient briefing or training of staff
- Insufficient quality assurance

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Chapter 4: Radiobiological Principles

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*Author responsible for the integrity of the work as a whole

Introduction

A mechanistic understanding of biological effects of ionising radiation is essential for proper evaluation of health risks. Ionising radiation has the potential to disrupt the structure of organic molecules in cells. Thanks to efficient repair mechanisms, damaged molecules can be repaired, but this process is not error free and may cause mutations, cell death or cell transformation, leading to cancer. Quantification of cancer risk, as well as the risk of other stochastic detriments, is possible through epidemiological studies. However, after exposure to low radiation doses, the effects are so limited that epidemiological analyses often lack statistical power. It is here that a mechanistic understanding is of particular importance because it provides reassurance that the risk level extrapolated from the high dose region is not underestimated. This chapter gives a very brief review of the biological radiation effects on cells and organisms.

Physical principles of radiation interaction, LET and RBE

The interaction between incoming radiation and the biological material can be described in terms of ionisation and excitation events. Different types of radiation induce different ionisation patterns. For example, X-ray photons interact sparsely with atoms, while alpha particles create well-localised tracks with dense energy deposition. The energy lost during interaction of radiation with atoms can be measured and is characterised by a variable called linear energy transfer (LET), which is given in units of keV μm^{-1}. The LET is defined as a ratio of the amount of energy, dE, lost by a particle and the length of a track, dl, in a medium where the energy was imparted. The cut-off value of 10 keV μm^{-1} is used by the International Commission on Radiological Protection (ICRP) to discriminate between low LET radiations with LET <10 keV μm^{-1} (e.g. photons, electrons) and high LET radiation >10 keV·μm^{-1} (e.g. alpha particles, heavy ions). LET is an average quantity allowing description of the energy deposition along a certain distance. At the microscopic level, the energy deposition may vary strongly within this distance. The reason for this is that the interaction cross-section (which describes the probability of an interaction) of a charged particle increases as the particle loses its energy along a track. This relation is not linear and the interaction cross-section of an incoming particle is highest at the end of the track, resulting in a large energy deposition in a small volume of matter. This "burst" of energy at the end of a track is called the Bragg peak. It is applied clinically in hadron therapy using protons and heavy ions to deliver a high dose inside the tumour while the tissue ahead of and behind the tumour is spared.

The energy deposited in a mass unit of living matter gives the absorbed dose, expressed in Gy, with 1 Gy corresponding to 1 J kg^{-1}. The absorbed dose is a physical quantity that is used to describe the effect of radiation. Although the same value of the absorbed dose

is used for different radiation qualities, their biological effects per unit dose differ. This difference is described by an experimentally derived value of relative biological effectiveness (RBE). RBE is derived from experiments where a tested radiation is compared with standard radiation, which is X-rays of 250 keV or gamma radiation from a caesium-137 or cobalt-60 source. RBE is defined as the ratio between the absorbed dose of the standard radiation and the dose of the tested radiation, both resulting in the same biological effect. RBE strongly depends on the experimental setup used for its assessment, e.g. the energies of particles, the biological material and the analysed biological endpoint. RBE is strictly related to LET, initially increasing until it reaches a peak at about 100 keV μm^{-1}. At higher LET, RBE values decrease due to a so-called overkill effect which results from two related phenomena: (1) an accumulation of damage per hit cell above a level which is sufficient to cause a detriment and (2) a decrease in the number of hit cells [1].

Cellular effects of radiation

Radiation-induced DNA damage

All cell organelles can be damaged by radiation, but the principal target of radiation exposure is the genetic material of the cell, the deoxyribonucleic acid (DNA). Maintaining the stability of genes is essential for cell survival. When the incoming particle directly ionises atoms in macromolecules like DNA it is called a direct effect of radiation (Fig. 1). This is the dominant process after high LET radiation. About 75% of the cell mass is water, which is targeted when radiation causes indirect effects. This is the main result of low LET radiation. In the process of water radiolysis, a water molecule becomes ionised and the highly reactive free radical ion H_2O^+ is formed. The indirect effect occurs when H_2O^+ reacts with water to form hydroxyl radical OH·, which can diffuse short distances and damage the DNA. This effect relies on the oxygen concentration; if the DNA radical reacts rapidly with an oxygen molecule, it forms a reactive oxygen species RO_2·, which via further reactions yields the chemically stable ROOH in the DNA. In the absence of oxygen, however, the DNA radical can be chemically restored to its reduced form by an H^+ ion to produce H_2O, and is therefore assumed to cause a threefold lower level of DNA damage. Consequently, the presence of proton donors reduces the level of damage by scavenging free radicals. Examples of such radioprotectors are sulfhydryl (SH) compounds like amifostine. These indirect effects are also most easily modified by radiosensitisers during cancer therapy.

Three major types of radiation-induced DNA lesion occur in an irradiated cell: base damage (BD), single-strand breaks (SSBs) and double-strand breaks (DSBs). 1 Gy of gamma radiation has been estimated to induce >1000 BD, about 1000 SSBs and 20–40 DSBs per cell. In comparison, the spontaneous frequencies of these three types of damage are >50,000 total lesions per cell per day. The

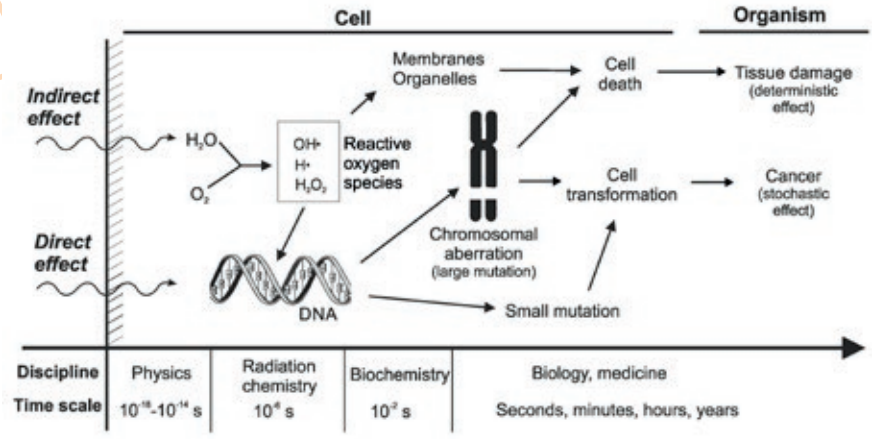

Figure 1: Chain of events in a cell exposed to ionising radiation. Damage pathways that lead to deterministic and stochastic effects are indicated. The bottom line illustrates the time during which various events take place

are repairable in an error-free way. Radiation induces "dirty" DNA DSBs in such a way that pieces of the broken strands must be excised before ligation, with potential loss of genetic material. About half of radiation-induced DSBs are misrejoined, which may lead to changes in the gene sequence of a DNA strand. Moreover, 30%–40% of DSBs induced after gamma radiation are complex and this type of damage creates serious problems for the DNA repair machinery, with an increased probability of misrepair. High LET radiation has higher ionisation density, and hence higher DSB complexity, than low LET radiation. This is the reason for the higher RBE of high versus low LET radiation. SSBs and BD are far less prone to cause cell death than DSBs since they can be easily repaired using the opposite strand as a template, except when two SSBs are located only a few bases from each other, resulting in a DSB [1, 2].

DNA damage repair, chromosomal aberrations and epigenetic effects of radiation

Cells use specialised signalling pathways to sense, respond to and repair DNA damage. Single-base damage is handled by base excision repair, nucleotide excision repair removes bulky DNA adducts induced by ultraviolet light (UV radiation) and mismatch repair corrects mismatches occurring during replication. DNA DSBs can be repaired by either of two processes, non-homologous end

joining (NHEJ) or homologous recombination (HR), where NHEJ is suggested to be the primary repair mechanism for the majority of DSBs. NHEJ occurs in all cell cycle phases and joins DNA ends directly; therefore it is regarded as the more error-prone repair pathway. HR is active during late S/G_2 phase only, where it uses the undamaged homologous strand as a template, and thus is an error-free process. The first attempt to repair damage is made by NHEJ, but if it is unsuccessful there is a switch to HR. For example, HR repairs a larger fraction of high LET-induced damage, where NHEJ is impeded by the complexity of the damage. Another factor that promotes the preferential use of HR is location of the DSB in a region of a more condensed, heterochromatic structure [3].

Despite these repair processes, the probability of damage misrepair increases with damage complexity. Short or long sequences of DNA may be deleted, inverted or translocated to another chromosome. Chromosomal aberrations are changes large enough to be visible at the level of chromosomes, which can be visualised by microscopic staining. Radiation induces chromosome-type aberrations following irradiation in G_1, chromatid-type aberrations after irradiation in G_2 or both after exposure in S phase. Stable aberrations can persist in the progeny of irradiated cells since the chromosomes have exchanged genetic material without changing their overall structure. Unstable aberrations, exemplified by dicentric chromosomes, involve a markedly changed chromosomal morphology and cells carrying them may divide a few times but will eventually die.

Epigenetic changes can also be induced by radiation exposure. These are heritable changes in gene expression that do not alter the DNA sequence per se, such as DNA methylation or acetylation/methylation of residues in histone proteins which wrap up the DNA. There is a global decrease in DNA methylation within one day after radiation exposure of normal cells. Mouse data show that epigenetic alterations could be inherited transgenerationally, but this area of research has not yet been thoroughly investigated [4].

Cell death modes

Cells may survive with mutated DNA but still experience delayed cell death. Alternatively, due to the accumulation of several mutations or genomic rearrangements, neoplastic cell transformation and cancer can arise. Following a high dose of radiation, the DNA damage may exceed a cell type-specific threshold, causing failure to repair damage and promote cell death instead. Death can occur before or after the first post-radiation mitosis; the latter is commonly called mitotic catastrophe and is thought to be a dominant event after radiation, although only as a pre-process. The mechanism of death is the active, programmed death, termed apoptosis, or, in cases of high radiation doses and especially lack of oxygen or energy, necrosis. Cells can also go into permanent cell cycle

arrest, senescence. Since radiation-induced cell death can occur at different time points after exposure, the most commonly used method of measuring cell survival is to assess the ability of cells to form clones, clonogenic cell survival [1].

Normal tissue response to radiation

The effects of ionising radiation at the level of tissues and organisms can be divided into deterministic and stochastic events. Deterministic effects originate from cell death events. If a high number of irradiated cells die, this will lead to necrosis of the tissue. Hence, deterministic effects show a dose threshold that corresponds to the dose which kills a sufficiently high number of cells for the tissue to break down. The threshold dose depends on the tissue type, but also on the irradiated volume. Moreover, lowering the dose rate, or splitting the dose into fractions, has a sparing effect on deterministic effects. Importantly, deterministic effects show a direct correlation between the dose and severity.

Deterministic effects occur in two phases: a prodromal phase and a late, acute phase. Examples of the prodromal phase are skin reddening, vomiting or dizziness. The nature of these reactions is not understood. Following moderate doses of radiation, prodromal effects disappear after a few days and late effects occur after a time delay which may be months or years. Very high doses of radiation induce consequential late effects, meaning an immediate transfer from prodromal effects to late effects. The immune system is always triggered by deterministic effects, so extensive damage of organs and tissues is associated with a massive inflammatory response that by itself can be detrimental and potentiate the radiation effect. Following whole-body exposure this can lead to multi-organ dysfunction syndrome (MODS).

Stochastic effects originate from cells that survive a dose of radiation with mutated DNA, which, in turn, can lead to neoplastic transformation. They are probabilistic in nature in that it is impossible to predict whether a particular cell will carry a mutation or not. Consequently, stochastic effects have no dose threshold. In contrast to deterministic effects, the severity of a radiation-induced neoplasm is independent of the dose. The only relationship between the dose and the effect is the probability of cancer induction. It is important to bear in mind that radiation-induced cancers carry no "fingerprint of exposure". In other words, they cannot be distinguished from cancers induced by other agents. This is the reason why it is generally difficult to estimate the risk of cancer induction by low doses of radiation (below ca. 200 mGy whole-body exposure), where the incidence of spontaneous cancers is much higher than that of radiation-induced cancers [2].

Tumour tissue response to radiation

Radiotherapy and the four Rs

Tumour cells have acquired a number of characteristics that distinguish them from normal

cells. Several of these hallmarks of cancer are relevant for their response to radiation: ability to sustain proliferative signalling, evasion of growth suppressors, resistance of cell death, genome instability and mutations, and tumour-promoting inflammation [5]. Different tumour types also display differences in their inherent radiosensitivity, which provide a basis for the choice of radiotherapy among other treatment modalities such as surgery, chemotherapy, targeted therapy and immunotherapy.

The aim of radiotherapy is to eradicate cancer cells by delivering the prescribed dose of ionising radiation to the tumour with minimal damage to surrounding healthy tissues. This is achieved with the help of various physical techniques. At the same time, efficient tumour control must take into consideration the radiosensitivity of cancer cells, which may vary even within a single tumour. Hence, clinical radiobiology deals with the relationship between a given physical absorbed dose, the resulting biological response and the factors that influence this relationship.

One of these factors is the partial pressure of molecular oxygen inside a cell. Well-oxygenated cells are more sensitive to radiation than hypoxic cells because oxygen participates in the indirect effect of radiation (Fig. 1). Consequently, inactivation of hypoxic cells requires a higher dose than inactivation of normoxic cells. Depending on the localisation inside the body and the density of blood vessels, tumours can have variable levels of oxygen supply. Within a tumour hypoxic cells form populations in areas distant from blood vessels. Hypoxic tumours are generally more difficult to cure. The difference in radiosensitivity between hypoxic and normoxic cells is particularly strong for low-LET radiation like photons, where the indirect effect of radiation dominates. This is one of the reasons why hadron therapy is believed to be most efficient in curing hypoxic tumours. The ratio of doses required to give the same killing effect in normoxic and hypoxic cells is called the oxygen enhancement ratio (OER) [1].

The time schedule of irradiation has a big impact on the final consequence of patient treatment during radiotherapy. In curative external beam radiotherapy the total dose prescribed to the tumour (usually 50–80 Gy) is divided into multiple smaller fractions of 2 Gy per day. That this form of therapy yields the best curative results with minimal side effects has been established empirically. Biologically, the fractionation method is based on four elementary principles called the 4 Rs of radiotherapy: (1) repair, (2) redistribution, (3) reoxygenation and (4) repopulation. 1: Tumour cells generally proliferate faster than normal cells and thus have less time to repair the DNA damage before they enter mitosis and suffer from mitotic catastrophe. Hence, they are more sensitive to fractionated irradiation than normal cells. 2: Radiation induces a cell cycle arrest in the relatively radiosensitive G_2 phase of the cell cycle. This leads to

a redistribution of the cells in the cell cycle so that each next fraction of radiation hits cells that are blocked in G_2, leading to a high level of cell death. 3: As cells become normoxic they begin to proliferate and become radiosensitive. 4: In the first line, radiation kills normoxic, proliferating tumour cells. As these die, hypoxic cells move towards blood vessels and become normoxic. This process of reoxygenation needs some time; hence irradiations should not be carried out during weekends [1].

Radioresistance and cancer stem cells

Another level of complexity is added when consideration is given to tumour heterogeneity, which is not directly related to the oxygen status. Not all tumour cells respond equally to radiation, and accumulating evidence supports the concept of cancer stem cells (or tumour-initiating cells), which are resistant to radio- and chemotherapy. This subpopulation of cells is believed to be responsible for tumour regrowth as well as metastasis. Suggested mechanisms of cancer stem cell radioresistance include both intrinsic factors, such as altered DNA damage repair capacity, enhanced reactive oxygen species defence and activated cell survival pathways, and extrinsic factors, e.g. maintenance of a hypoxic niche. Radiation could also induce microenvironmental changes through release of growth factors and cytokines from cancer-associated fibroblasts and macrophages, which might confer cellular plasticity [6].

Low and high dose rate in brachytherapy

Brachytherapy can be performed at a low dose rate, for example as done in treatment of thyroid cancer with iodine-131. Here, the high affinity of the thyroid gland for iodine is exploited. Another form of low dose rate brachytherapy is applied in prostate cancer patients treated with iodine-125 seeds (called permanent brachytherapy). Seeds are left permanently in the body and irradiation ends when iodine-125 has decayed. As an alternative to seeds, high-activity radioactive sources (iridium-192) can be used in an afterloading setup that yields a high dose rate. In prostate cancer treatment, the choice between low and high dose rate brachytherapy is based on tumour stage but also on economic and practical factors [5].

Irradiation in utero – developmental and teratogenic effects and cancer

The embryo and foetus represent the most radiosensitive stages during the lifetime of a human. Various stages of pregnancy demonstrate different specificities with respect to radiation effects. Gametes and the embryo during the preimplantation stage are characterised by extreme sensitivity to the lethal effects of radiation. This is described as an "all or nothing effect": gametes and embryos either die or survive as normal, with a negligible level of detrimental effects. The lack of genetic transgenerational effects among the children of Hiroshima and Nagasaki survivors can be explained by this mechanism.

Radiation exposure of the embryo after it has implanted in the uterus can lead to three types of effects: growth and mental retardation, malformations and cancer. There is little indication for a threshold of dose. Among Hiroshima and Nagasaki survivors, growth retardation was evident only when the embryo was exposed before week 16 of pregnancy. Mental retardation occurred predominantly following exposure during weeks 8–15, with a four times lower level of effect between weeks 15 and 25. Congenital malformations are uncommon among the atomic bomb survivors, but based on animal studies and women exposed to radiation for medical purposes it is understood that they are induced only when the embryo is exposed during organogenesis (weeks 3–8 of pregnancy) [1].

In their famous "Oxford study" from 1954, Alice Stewart and co-workers showed for the first time that diagnostic irradiation in utero leads to an increased risk of leukaemia during early childhood [7]. The result expanded data from atomic bomb survivors, among whom a large relative risk of childhood leukaemia (10 cases instead of the expected 1.6) was observed among teenagers exposed at the age of 0–9 years [8]. The interest in estimating the risk of childhood cancers has increased in recent years because of modern methods of medical radiography such as paediatric computed tomography (CT). Also, questions have been posed as to whether there is a threshold of dose and whether chronic irradiation is equally as effective as acute irradiation. In this context, it is of interest that two large epidemiological studies, published recently, have shown that natural background radiation is a risk factor in childhood leukaemia, with the lowest effect detectable after an accumulated dose to the bone marrow of 5 mGy [9, 10]. Thus, there is ample evidence that exposure to low doses of radiation, both acutely (as in CT scanning) and chronically (as in areas of high natural background radiation), increases the risk of childhood leukaemia. It is important to note that the level of risk estimated in these studies is consistent with predictions of models based upon data from studies of moderate to high doses received after birth at a high dose rate [8].

Practical application of radiobiology principles

The principles of radiological protection are based on biological and medical evidence of radiation effects. The principles are developed by the ICRP based on scientific data that are regularly summarised by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the Biological Effects of Ionizing Radiation (BEIR) group of the National Research Council (NRC) of the USA. ICRP publishes recommendations which are generally implemented into legal systems of all countries. The latest recommendation was published in 2007 [11].

The ICRP assumes that no deterministic effects occur in any tissue in the absorbed dose range up to around 100 mGy (low LET or high

LET). In the case of stochastic effects, notably cancer, epidemiological and experimental studies provide evidence of radiation risk at doses below 100 mSv (effective dose, see below). At the same time, results of biological experiments on cells and animals support the hypothesis that cancer can arise from a DNA mutation in a single cell. Consequently, no dose threshold exists for stochastic effects and the ICRP assumes that even at doses below about 100 mSv a given increment in dose will produce a directly proportionate increment in the probability of incurring cancer. This dose-response model is generally known as "linear non-threshold" or LNT. The ICRP emphasises that whilst the LNT model remains a scientifically plausible element in its practical system of radiological protection, its adoption is to a large extent guided by the requirement to follow the precautionary principle which is generally applied in health protection.

An important dose concept in radiological protection is the effective dose, which is used for optimising planned radiation exposures. It is calculated based on radiation and tissue weighing factors. The latter are derived from epidemiological results describing the risk of organ-specific cancers following exposure to radiation. The major source of information is the Life Span Study (LSS) on atomic bomb survivors in Hiroshima and Nagasaki. The early evidence was based on cancer mortality data. Thanks to an improved cancer registry system in Japan, current risk estimate can be based on cancer incidence, providing more reliable estimates of risk principally because cancer incidence can allow for more accurate diagnosis.

The atomic bomb survivors were exposed to an acute dose of radiation and statistically significant results on cancer induction are seen only after doses in excess of 200 mSv. However, the nominal risk coefficients for stochastic effects derived from the LSS study are used to predict cancer incidence following occupational or environmental exposure, which is generally low and chronic. For deterministic effects it is known that reducing the dose rate of radiation is associated with a sparing effect. The question arises as to whether the risk coefficients derived from the LSS study should be lowered when they are being applied to low, chronic exposure scenarios. Based on the results of biological experiments, the ICRP decided to introduce a dose and dose rate effectiveness factor (DDREF) of 2, which reduces by half the nominal risk coefficients when applied to low and chronic exposure scenarios. Due to lack of statistical power, current results from epidemiological studies on cohorts environmentally or occupationally exposed to low dose rate radiation do not permit a precise estimate of DDREF. Currently, the value of 2 for DDREF is being debated and a task group of the ICRP is critically evaluating all available evidence in an attempt to come up with a more reliable value [12].

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Chapter 5:
Dose Optimisation for Diagnostic Procedures

Frederic H. Fahey, Alison B. Goodkind and David Gilmore

Introduction

The fields of nuclear medicine and molecular imaging continue to grow due to the ability of the employed procedures to provide physicians with unique information. Specifically, these procedures provide insights into patients' physiology and metabolic processes rather than information on anatomy and structure, as delivered by other imaging modalities. Because disease functional changes typically are visible before anatomical changes, nuclear medicine can allow for early detection and evaluation of the extent of disease; it can also establish whether or not disease is progressing and assist in evaluating the effectiveness of a given treatment. Nuclear medicine methodologies reveal information about nearly all human systems, including the heart and the brain as well as the musculoskeletal, gastrointestinal and urological systems. Nuclear medicine can also be essential for imaging various types of cancer. In addition, these modalities are minimally invasive and safe as they utilise only trace amounts of radiopharmaceuticals and, thus, are non-toxic and non-allergenic [1]. Not only is nuclear medicine often essential for diagnosis, but it can also play an important role in the treatment of many diseases, an example being the administration of ^{131}I for the treatment of thyroid disease. More recently, targeted radionuclide therapy has been shown to be useful in the treatment of bone metastases from prostate cancer and neuroendocrine tumours.

According to the National Council on Radiation Protection and Measurements (NCRP) Report 160, nuclear medicine procedures have increased from 6.3 million in 1984 to 18 million in 2006 [2]. This increase has led to a rise in per capita annual radiation dose to the US population from nuclear medicine procedures. In 2006, the per capita annual dose to the US population from nuclear medicine was estimated to be 0.8 mSv compared to 0.14 mSv in 1982, with a large fraction of this dose attributed to nuclear cardiology.

This increase in the utilisation of nuclear medicine procedures has led to an increase in ionising radiation exposure and thus the possible risk of adverse health effects. Bearing in mind that concerns regarding these risks have been expressed by the media and the general public, the nuclear medicine professional needs to have a solid understanding of their nature and magnitude, as well as of the factors that can affect the radiation dose to our patients and ourselves. Having this understanding will allow us to better communicate with patients regarding the potential benefits and risks associated with nuclear medicine procedures. This can be essential for the patient's health. If a procedure providing important clinical information is not performed due to fear of radiation, it can be detrimental to the patient. This chapter will discuss dose optimisation, which considers the potential risk from undergoing a nuclear medicine procedure, as well as the many benefits that these imaging modalities have to offer patients. Ultimately, performing

the right test with the right dose on the right patient and at the right time is the key to dose optimisation [3].

Radiation dosimetry

Internal dosimetry for nuclear medicine

The Medical International Radiation Dosimetry Committee (MIRD) of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) has developed an equation to calculate radiation dose for internal emitters. The equation describes the radiation dose to a particular target organ (r_T) due to radiation emanating from a source organ (r_S) where the radiopharmaceutical has localised (Fig. 1). Note that an organ can be both a source and a target organ; this is also known as self-dose.

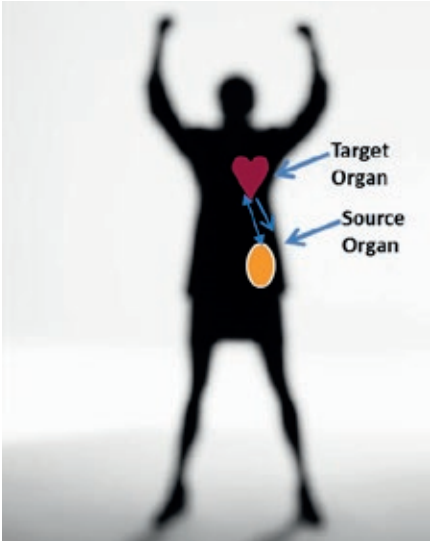

Figure 1: MIRD equation: source organ, target organ and self-dose

The MIRD formula as described in MIRD Report 21 is given by

$$D(r_T) = \Sigma_S \tilde{A}(r_S)\, S(r_T \leftarrow r_S)$$

where $D(r_T)$ is the radiation dose to a particular target organ (r_T), $\tilde{A}(r_S)$ is the time-integrated activity in a selected source organ (r_S) and $S(r_T \leftarrow r_S)$ is the radionuclide-specific quantity representing the mean dose to the target organ per unit activity present in the source organ [4]. Σ_S indicates summing over all source organs where the radiopharmaceutical distributes. For example, with fluorine-18 fluorodeoxyglucose (^{18}F-FDG), the brain, heart, liver, kidneys, bladder and remaining body may be considered source organs. $\tilde{A}(r_S)$ can often be estimated with the simple equation

$$\tilde{A}(r_S) = A_0\, F\, T_{eff}$$

where A_0 is the amount of administered activity, F is the fraction of that activity that went to the source organ and T_{eff} is the effective mean life that describes how long it stayed there. If one assumes exponential clearance, T_{eff} depends on both the physical and the biological half-life

$$T_{eff} = 1.44\, \frac{(T_P\, T_B)}{(T_P + T_B)}$$

where T_P and T_B are the physical and biological half-lives for the particular radiopharmaceutical and source organ. $S(r_T \leftarrow r_S)$ is given by

$$S(r_T \leftarrow r_S) = \Sigma_i \Delta_i \varphi_i / M_T$$

where Δ_i is the mean energy per nuclear transformation for the i^{th} radiation emitted by the radiopharmaceutical, φ_i is the fraction of energy emitted by the i^{th} radiation from the source organ that is absorbed by the target organ and M_T is the mass of the target organ. Σ_i indicates summing over all radiations, i, emitted from the radiopharmaceutical.

As one can see from the above formulas, the estimated dose depends on many factors. Most notably, it depends directly on the amount of administered activity. With respect to internal dosimetry, this is the primary dose index. Radiation dose also depends on the type and energy of the radiation [penetrating (gamma rays) versus non-penetrating (alphas/betas/positrons)] emitted by the associated radionuclide, the size, shape and composition of the source and target organ(s), the spacing between the source and target organ(s) and the type of material separating them, as well as on the energy absorbed from ionising radiation per unit time within the source and target organ(s). Models of patients of different sizes, from newborns to adults as well as pregnant women, have been developed and adopted by a number of organisations such as the European Association of Nuclear Medicine (EANM), the SNMMI and the International Commission on Radiation Protection (ICRP). Thus, if one knows the amount of administered activity, the size of the patient and the biokinetics and physical properties of the radiopharmaceutical in question, one can make a reasonable estimate of the radiation dose to all of the potential target organs. However, it has been estimated that the uncertainty in these estimates could be as much as a factor of 2 [5].

The concept of effective dose (ED) was proposed by the ICRP to provide a risk-based parameter to allow different radiological practices to be compared. Effective dose was developed to be equivalent to the absorbed dose given to the whole body of the patient that would result in the same biological effect. It is the weighted sum of the absorbed dose delivered to each target organ with each organ weighted by its radiation sensitivity. The formula is

$$ED = \Sigma H_T \times W_T$$

where H_T is dose to organ, T, and W_T is the radiosensitivity weight assigned to that organ. Effective dose is based on a population-based estimate of radiation risk and does not apply to a specific patient (Table 1). It should be noted that the risk-based organ

weights are based on population averages across all ages and both genders and thus are not directly applicable to any individual patient. In particular, they do not reflect the higher risks associated with young children, as discussed in the next section.

Tissue or Organ	ICRP 103
Gonads	0.08
Red bone marrow	0.12
Lung	0.12
Colon	0.12
Stomach	0.12
Breast	0.12
Bladder	0.04
Liver	0.04
Oesophagus	0.04
Thyroid	0.04
Skin	0.01
Bone surface	0.01
Brain	0.01
Salivary glands	0.01
Remainder	0.12
Total	1.00

Table 1: List of weights for effective dose (adapted from ICRP Report 103)

The ICRP has published standardised dose estimates for many radiopharmaceuticals. This extensive set of dose estimates represents the best available understanding of the biokinetics of the compounds [6]. Although the tabulated calculations from the ICRP calculations include absorbed and effective doses to children, the biokinetic models used in these calculations are typically derived from adult data. Thus, the applicability of these models to children has not yet been ascertained. The UF phantom sets from the University of Florida provide anthropomorphic models of patients of a variety of sizes and shapes [7]. Another resource for dose estimation is the RADAR website, which also has data on standardised dose methods, models and results. It is important to note that the effective dose is based on a population-based estimate of radiation risk and does not apply to a specific patient.

The primary factor affecting the radiation dose to the nuclear medicine patient is administered activity, as discussed above. However, there are many issues that can be considered when determining the optimal level of administered activity, including the patient size, the imaging time and the type of instrumentation used. The standardisation of administered activities in children will be described in a subsequent section. For planar nuclear medicine and SPECT, factors regarding instrumentation may include the thickness and composition of the detector material, as well as the number of detectors. Another factor that contributes to dose is the choice of collimator (i.e. whether to use pinhole, ultra-high-resolution, high-resolution, general purpose or high-sensitivity

collimation). With respect to PET, the design, composition and configuration of the detector material comes into play. The diameter and axial extent of the detectors also affect the scanner sensitivity. One may also consider the effect that new approaches to image processing and tomographic reconstruction may have on image quality and their potential impact on dose reduction. Recent reports have indicated that the application of adaptive filtering or iterative reconstruction with resolution recovery may allow for a dose reduction of a factor of 2 or more while maintaining or perhaps even improving image quality [8–11].

There is limited information regarding the actual practice of nuclear medicine procedures. Based on surveys of practice, diagnostic reference levels may be developed to serve as guidelines to the clinical practitioner. In some instances, these levels may be regulated to represent acceptable practice. At this point, very little survey data regarding nuclear medicine practice is available in the literature. The SNMMI Dose Opt Task Force and the Intersociety Accreditation Commission (IAC) partnered to look at nuclear medicine practice data within the United States. The IAC provided data that had been submitted to them as part of the accreditation process. For technetium-99m methylene diphosphonate (MDP) bone scans, data from 225 sites and 522 total patient studies were analysed. For ^{18}F-FDG PET, 95 sites and 424 total patients were analysed. The mean administered activity was 930±118 (range 710–1315) MBq for ^{99m}Tc-MDP and 508±117 (range 108–875) MBq for ^{18}F-FDG. There was no difference in administered activity according to the type of site (hospital, private, free-standing and multispecialty, mobile); although mobile units appeared to be associated with a higher activity, information was available for only a limited number of sites in both cases (n=1 and n=3 for ^{99m}Tc-MDP and ^{18}F-FDG, respectively). These data show that although a large percentage of the sites are reasonably consistent with regard to their administered activities, a wide variation still remains (Fig. 2) [12].

Hybrid imaging

PET/CT imaging using a single, hybrid device was introduced commercially around the turn of the century and its clinical impact was recognised immediately. Within 5 years of its introduction, PET-only devices were no longer being marketed. The combination of the functional/molecular information provided by PET and with the anatomical information provide by CT were deemed invaluable by the clinician. A few years later, SPECT/CT was introduced. Although SPECT/CT has been shown to be valuable for a number of specific clinical applications, its application has not been as widespread as that of PET/CT. The CT component of both PET and SPECT involves the use of X-rays that also expose the patient to ionising radiation, which is discussed in this book. However, the total radiation dose to the patient is the sum of that

received from both the administration of the radiopharmaceutical and the CT.

PET/MRI, a new form of hybrid imaging, has recently emerged. This technology has many similarities to PET/CT in that it is able to provide important information regarding patient physiology and anatomy/structure; however, it does not involve CT, and MRI does not expose the patient to radiation. Additionally, MRI may provide unique anatomical information with better soft tissue contrast resolution as compared to CT, as well as other functional information. For example, MRI can provide images related to flow, diffusion and perfusion. In addition, PET/MRI may provide methods to correct for patient motion occurring during the exam. Nevertheless, there are several issues with PET/MRI that need to be resolved in order for it to become the preferred hybrid imaging technique. Most notably, the PET and MRI systems can interfere with one another and technologies need to be developed in order to ameliorate this issue. Moreover, the accuracy of attenuation correction may be limited in some cases as compared to that for PET/CT [13].

PET/MRI has the potential to offer a substantial reduction in the patient dose as compared

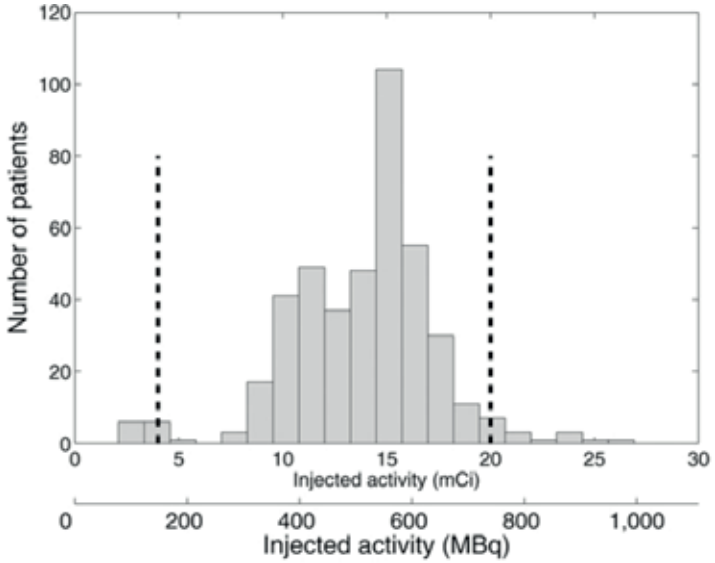

Figure 2: Reference levels in nuclear medicine for 18F-FDG [12] (used with permission of the Journal of Nuclear Medicine)

to PET/CT beyond the elimination of the CT component. Utilising the SIGNA PET/MR, a time-of-flight (TOF) PET/MRI scanner, Queiroz et al. examined both phantom and clinical data. By increasing the PET axial FOV (25 vs 15 cm) and decreasing the PET ring diameter (622 vs 810 cm), the authors determined that PET/MRI could be performed with half of the administered activity [14]. It has also been shown that adopting the longer acquisition time associated with MRI for the PET scan can improve dose optimisation. Oehmigen et al. imaged a standardised phantom to compare the dose from PET/MRI under various time constraints (2, 4, 8 and 16 min) [15]. Ultimately, they discovered that they could reduce radiotracer activity by compensating for longer imaging times. These findings could lead to a large decrease in dose amongst patients, while maintaining imaging quality. Specifically, the effective dose for an FDG PET/CT scan is approximately 12–22 mSv; however, using PET/MRI, the effective dose could be as low as 1.8 mSv. These quantities illustrate a potential for dose reduction of administered activity by a factor of 4–8.

Radiation risk

Estimation of the risk of adverse health effects from exposure to ionising radiation in the dose range commonly encountered in clinical nuclear medicine involves the application of models based on the most current knowledge of pertinent epidemiological and biological data. However, these scientific data were acquired in a situation quite dissimilar to clinical nuclear medicine, and one therefore needs to extrapolate to the condition of interest. This may involve the extrapolation of high-dose data in humans or low-dose data in animals to low-dose (below 100 mSv) effects in humans. Our basic understanding of the effects of exposure to ionising radiation on human health derives from the Life Span Study of the survivors of the bombings of Hiroshima and Nagasaki, as reported by the Radiation Effects Research Foundation. In 2011, Ozasa et al published a review of these data. In this study, 86,600 subjects had been followed from 1950 to 2003, and it was estimated that there had been 527 excess deaths from solid tumours in that population [16]. Other epidemiological studies have evaluated the risk of ionising radiation in humans, and, in general, their results corroborate the findings of the Life Span Study. Data from the Life Span Study clearly indicate a relationship between induction of solid cancer and radiation dose at levels >0.5 Gy. However, uncertainties in the data make it difficult to estimate the risk at the dose range associated with clinical nuclear medicine (i.e. 0.05–0.1 Gy). Differences in dose rate or the fractionation of dose between the epidemiological subjects and nuclear medicine patients can also affect the accuracy of the estimation. For these reasons, the evaluation of findings from investigations in radiobiology can often provide valuable insights.

The National Academy of Sciences Committee on the Biological Effects of Ionizing

Radiation (BEIR) issued a report in 2006 that reviewed the state of knowledge in radiation epidemiology and biology at that time and developed models of radiation risk as a function of dose, sex and age at the time of exposure. This review was published in what is referred to as the BEIR VII Phase 2 report [17]. This report recommended a linear no-threshold model for cancer induction by ionising radiation in solid tumours and a linear quadratic model for leukaemia. Although some controversies exist regarding the scientific validity of the linear no-threshold model for estimating radiation risk at low doses, it may be considered a conservative and thereby prudent model for radiation safety purposes. According to the models provided by the BEIR VII Phase 2 report, those exposed at an earlier age are in general at higher risk for cancer induction from ionising radiation than adults.

Cardiovascular nuclear medicine

The utilisation of myocardial perfusion imaging (MPI) using radiopharmaceuticals has increased substantially over the past 30 years, such that it has become an essential component of the armamentarium available to assess patients for the risk of a significant myocardial event [18, 19]. In 2006, it was estimated that nuclear cardiology accounted for 57% of the nuclear medicine procedures performed in the United States [2]. These studies are typically performed as a rest study followed by a stress study, resulting in an effective dose when using ^{99m}Tc-sestamibi of between 10 and 13 mSv, depending on the actual administered activities. Therefore, nuclear cardiology accounts for about 85% of the total collective radiation dose from nuclear medicine in the United States. On the other hand, more than half of the patients receiving radionuclide myocardial perfusion studies are over the age of 65 years and at lower risk of adverse effects from radiation than younger individuals.

Since nuclear cardiology is the most common nuclear medicine procedure and accounts for the largest contribution to the nuclear medicine collective dose, there have been a number of discussions regarding dose optimisation in this arena [20–22]. In 2011, the Cardiovascular Council of the SNMMI issued a position paper [23] stating that "…radionuclide MPI can provide scientifically validated, accurate, and in certain cases unique information for management of patients with known or suspected coronary artery disease at risk for major cardiovascular events. The radiation exposure risk associated with radionuclide MPI, albeit small and long term as opposed to the higher and more immediate risk for major cardiovascular events, mandates careful adherence to appropriateness criteria and guidelines developed or endorsed by the Society of Nuclear Medicine, the American Society of Nuclear Cardiology, the American College of Cardiology and the American Heart Association. With recent developments in technology, there are many opportunities to further reduce radiation exposure and fur-

ther enhance the benefit-to-risk ratio of this well-established, safe imaging modality."

One approach to dose optimisation in MPI is to perform the stress portion of the study first, with a low administered activity. The rest study is then performed only if the stress study is positive. This approach can yield a substantial reduction in the patient's radiation dose in a number of cases, but requires a 2-day rather than a one-day protocol, which can be inconvenient for the patient. MPI can also be performed with PET using ^{82}Rb or ^{13}N ammonia (NH_3). The radiation dose from either ^{82}Rb or $^{13}NH_3$ can be quite low due to the short half-lives of these two radionuclides (1.3 and 10 min, respectively). However, availability of the PET scanner as compared to a SPECT scanner for MPI may be an issue.

MPI SPECT is most commonly performed on a dual-detector gamma camera configured in a 90° orientation and typically takes about 15–20 min to complete. Over the past decade, SPECT devices dedicated to myocardial SPECT have been developed that not only have a smaller footprint than conventional SPECT systems, but also have higher sensitivity by perhaps a factor of 5–8 relative to a conventional dual-detector SPECT system. This increased sensitivity can be used to reduce either the imaging time or the amount of administered activity (and thereby the patient radiation dose) or a combination of the two. Duvall et al. evaluated the use of the GE 530c camera in conjunction with a stress-only protocol (high dose or low dose) as compared to a standard rest-stress protocol [24]. They showed that similar image quality could be obtained with a low-dose stress-only protocol using this device when compared to the standard technique and instrumentation, but at a fraction of the radiation dose (estimated effective doses of 4.2 and 11.8 mSv, respectively).

The combination of proper patient selection, consideration of a stress-only protocol, new high-sensitivity instrumentation and advanced reconstruction techniques can lead to substantial reductions in the amount of activity administered to the patient, and subsequently in the radiation dose. It is expected that many of these advances will soon become standard practice in nuclear cardiology and that these reductions in radiation dose will thus be routinely realised in the clinic.

Communication of risk

As nuclear medicine professionals, it is important to be able to properly communicate the risk of a given scan to patients and/or their family members. It is also important to be able to discuss these issues with the referring physicians, who clearly understand the clinical reasoning behind the study, but may have little understanding of radiation risk or perceive nuclear medicine procedures as "high dose". Reports have shown that informing patients regarding radiation risk does not adversely affect their willingness to have an appropriately ordered scan [25]. First, the

technologist should explain to the patient that nuclear medicine procedures involve the use of a small administration of ionising radiation. They may also discuss that this may lead to a slight increase in the likelihood of cancer developing within the patient's lifetime. It is important to emphasise the benefits of the scan and that any potential risk is very small. For example, a person who receives an FDG PET scan has approximately a 1 in 2500 probability of developing a fatal cancer as a result of the scan. It has been found that pictorial approaches to communicating risk are more beneficial than verbal explanation of the risk (Fig. 3).

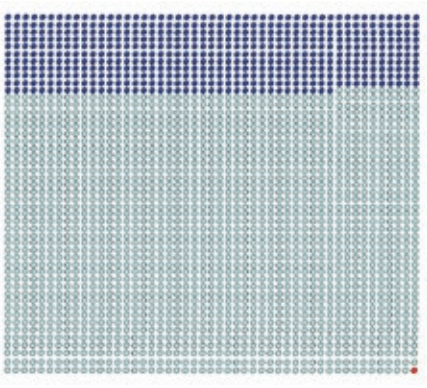

Figure 3: Communicating the risk of FDG PET scan. This pictorial approach may help patients understand the small risk of developing a fatal cancer as a result of this procedure. The red star indicates the risk of developing a fatal cancer (1/2500) [25]. (Used with permission of the Journal of Nuclear Medicine)

While providing cost-benefit analyses to the patient, it may also be helpful to compare the risk to the lifetime risk of death from everyday activities. For example, the likelihood of developing a fatal cancer as a result of undergoing an FDG PET scan is similar to the chance of falling down the stairs and dying (Fig. 4). Another approach to explaining risk is to highlight that individuals receive a similar dose from this procedure as they would receive from background radiation in 1–3 years. A parent who chooses to stay with his or her child while the child undergoes a nuclear medicine procedure would receive a dose on the order of radiation received from a transcontinental flight. Ultimately, it is important to address the patient's concerns in a caring and knowledgeable manner and to clearly elucidate that the benefits of the procedure far outweigh the potential risk.

Programmes for dose optimisation

Paediatric nuclear medicine

In 1990 the European Association of Nuclear Medicine (EANM) published a weight-based guide for calculating the amount of radiopharmaceutical to be administered in children [26]. In 2007, this was replaced by the first version of the EANM Paediatric Dosage card, with guidance for 39 radiopharmaceuticals [27]. The dosage card was amended to include ^{18}F-FDG in 2008 [28]. Most of the radiopharmaceuticals commonly used in paediatric nuclear medicine were represented on this dosage card.

Figure 4: Putting risk into context. The lifetime risk associated with various every day activities as compared to nuclear medicine procedures.

In North America, a survey was performed that demonstrated wide variation in the administered activities of radiopharmaceuticals in children [29]. This survey showed that administered activities per body weight (MBq/kg) and maximum total doses for larger patients varied on average by a factor of 3, and by as much as a factor of 10. For the smallest patients, the minimum dose range factor varied on average by a factor of 10 and by as much as a factor of 20. The Alliance for Radiation Safety in Pediatric Imaging, which had launched the Image Gently program at the time, engaged several practitioners in paediatric nuclear medicine to address this issue. A number of professional societies in North America, including the SNMMI, the American College of Radiology, the Society of Pediatric Radiology and Image Gently, convened as an expert working group to evaluate the possibility of developing consensus guidelines aimed at reducing the wide variability in paediatric radiopharmaceutical administered activities. In addition, it was hoped that this would lead to an overall reduction in radiation exposures from nuclear medicine procedures performed in children. The initiative led to the development, publication and dissemination of the North American consensus guidelines for administered activities in children [30]. A follow-up survey of the initial paediatric hospitals surveyed revealed that

there has been a reduction in administered activities as well as a reduction in the variability [31]. In a recently reported survey of general hospitals in the United States, 82.4% of general hospitals indicated that they were familiar with Image Gently, 57.1% were familiar with the 2010 North American Guidelines for children and 54.9% altered their protocols because of the Guidelines [32].

In 2012, members of both the EANM and the SNMMI met to discuss the possibility of harmonising the guidelines of the two societies. Most of the radiopharmaceuticals covered by the North American consensus guidelines noted that the EANM dosage card could also be used. This discussion identified areas of agreement and discrepancy between the two guidelines. A working group consisting of members of both organisations met over the next few years to study the possibility of harmonising the two sets of guidelines. This resulted in the "Paediatric radiopharmaceutical administration: harmonization of the 2007 EANM paediatric dosage card" (version 1.5.2008) and the 2010 North American consensus guidelines document published in 2014 [33]. Twelve radiopharmaceuticals were included in the new guidelines, with the promise that others will soon be incorporated.

Adult nuclear medicine

In order to address concerns about ionising radiation in medical imaging in adults, in 2010 the American Association of Physicists in Medicine (AAPM), the American Society of Radiologic Technologists (ASRT) and the Radiological Society of North America (RSNA) collaborated to form the Image Wisely campaign. To date, over 19,000 health professionals, 30 medical organisations and 300 medical facilities have taken the Image Wisely pledge to optimise the use of radiation in imaging patients. The Image Wisely campaign launched a website (www.imagewisely.org), which contains a wealth of information on dose optimisation for referring physicians and patients. The initial emphasis of the groups was on CT, but the effort soon grew to encompass other radiological modalities.

Image Wisely collaborated with organisations such as the American Society of Nuclear Cardiology (ASNC), the SNMMI and SNMMI Technologist Section (SNMMI-TS) to address dose optimisation in the fields of general nuclear medicine, nuclear cardiology, PET/CT and nuclear physics. In 2012, a nuclear medicine page on the Image Wisely site was developed to inform patients and referring physicians (http://imagewisely.org/Imaging-Modalities/Nuclear-Medicine).

Conclusion

Nuclear medicine plays an important role in the diagnosis and treatment of many diseases. Considering that they provide such valuable information, the amount of nuclear medicine procedures has soared tremendously in the past several years. This increased utilisation corresponds to an increase in effective

dose amongst the world population. As a nuclear medicine technologist it is important to understand the risk of such procedures and how to communicate the benefits as well as the potential harm from these procedures to patients, family members and attending physicians. Having an understanding of internal dosimetry for PET, SPECT, PET/CT, SPECT/CT and PET/MRI, as well as a comprehension of how the appropriate dose is determined, will help to minimise risk and maximise the many benefits of nuclear medicine.

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Chapter 6:
Dose Optimisation of CT in Hybrid Imaging

Frederic H. Fahey, Elizabeth Romero and Adam Alessio

Introduction

For the past 15 years, hybrid imaging using CT has been an essential aspect of nuclear medicine imaging. Hybrid PET/CT scanners became commercially available around the turn of the century and by 2005, only 5 years later, PET-only scanners were no longer being marketed by any of the major manufacturers (Fig. 1A). The combination of the functional and molecular imaging capabilities of PET with the superior anatomical correlation of CT was deemed invaluable by clinicians, particularly in the field of oncology. In addition, the ability to utilise the rapidly acquired and relatively low-noise CT for attenuation correction in lieu of the much slower transmission scan reduced the time required to perform a whole-body PET scan by close to 50%. More recently, SPECT/CT has been clinically established, particularly for certain medical indications (Fig. 1B). However, the use of CT exposes the patient to ionising radiation in addition to that from the administration of the radiopharmaceutical inherent to nuclear medicine. As will be discussed, depending on how it is used and thereby how it is acquired, the CT can comprise a small or a considerable fraction of the radiation absorbed dose received by the patient. In this chapter, we will review the way CT is typically used in the context of hybrid imaging, how it is acquired, the range of associated radiation doses and approaches to optimise the acquisition in order to obtain the image information necessary to address the clinical question at hand while delivering the lowest possible radiation dose.

Uses of CT in hybrid imaging

In the practice of hybrid imaging, either PET/CT or SPECT/CT, the CT can be acquired and subsequently used for three distinct purposes or a combination thereof. In the first case, the CT portion can be used for attenuation correction of the emission scan (i.e. PET or SPECT) since it provides the photon transmission information necessary for this purpose. If the CT is only used for attenuation correction, the CT acquisition parameters can

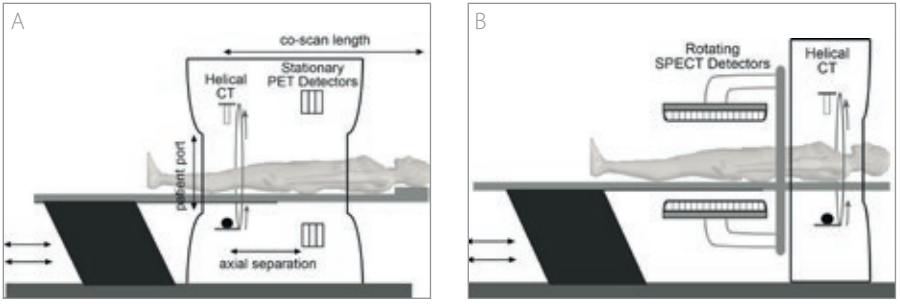

Figure 1: PET/CT and SPECT/CT. Illustration of the major PET/CT (A) and SPECT/CT (B) scanner components for conventional designs

be substantially reduced without impairing the ability of the CT to provide adequate attenuation correction [1]. Secondly, it can be used for anatomical correlation of the PET or SPECT data. In this instance, the CT need not be of diagnostic image quality, but it must be of a sufficient standard to permit correlation with the emission scan based on adequate depiction of the anatomical features of interest. Lastly, the CT may be acquired in a manner appropriate for a diagnostic CT study of the region of interest. If the patient requires a CT and an emission scan for diagnosis, the ability to acquire both in a single imaging session is not only convenient and efficient for the patient, but also allows dose reduction by potentially eliminating the need for an additional CT scan. In many instances, the CT portion of hybrid imaging may be used for more than one of the above-mentioned purposes. For example, a CT of diagnostic quality may also be used for anatomical correlation and attenuation correction or a CT for anatomical correlation may also be used for attenuation correction. These three uses of CT have considerably different requirements with respect to both the complexity of the image data acquisition and the radiation dose delivered to the patient.

The probability of detecting a photon emitted from the centre of the patient is lower than that of detecting a photon emitted from the patient's periphery. In regions of the body where the tissue has similar attenuating properties, a single value for the linear attenuation coefficient, μ, can be assumed and the correction can be substantially simplified. For example, in SPECT of the abdomen, all of the soft tissue can be assumed to have a μ value similar to water (i.e. 0.15 cm^{-1} for the 140-keV gamma ray emitted by ^{99m}Tc) and a first-order Chang correction can be applied. However, this single tissue approach cannot be applied in the thorax, where the lungs have considerably different attenuating properties compared to soft tissue. Thus, to adequately perform attenuation correction for emission tomography in the thorax, one must incorporate transmission data into the reconstruction process, and CT has been shown to be very useful in this regard. In fact, this was one of the early motivations for the development of hybrid imaging. For CT-based attenuation correction to be applied, certain adjustments need to be made since the nature of CT does vary from that of emission tomography.

The first adjustment is that the energy at which these studies are acquired is different. In CT, the tube voltage is typically between 80 and 140 kVp, and, thereby, the effective photon energy is probably between 40 and 80 keV whereas the photon energy associated with SPECT (assuming ^{99m}Tc) and PET is routinely 140 or 511 keV, respectively [2]. In general, this necessitates a reasonably simple adjustment through application of a multilinear transformation between the reconstructed CT (or Hounsfield) unit and the corresponding linear attenuation coefficient

(or μ), as shown in Fig. 2. For example, a CT value of 0 corresponds to water and thus can be assigned the μ-value of 0.15 cm^{-1} or 0.093 cm^{-1} for ^{99m}Tc SPECT and PET, respectively. For CT values below 0, the material can be considered a mixture of soft tissue and air, and for CT values greater than 0, a mixture of soft tissue and bone. A third region may be applied to compensate for CT contrast material. Due to the change in materials in these three regions, the slope also changes (Fig. 2). In general, this transformation has been shown to work quite well [2].

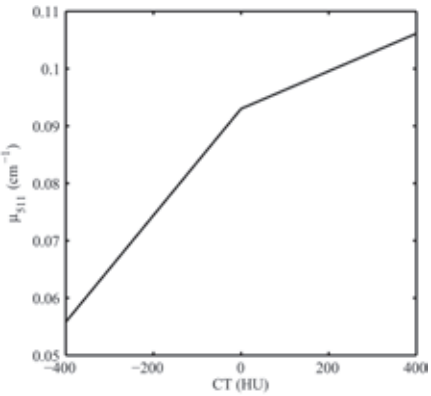

Figure 2: Bi-linear scaling method used to convert CT pixel values to linear attenuation coefficients for PET at 511 keV. Similar conversions are used to convert for different SPECT energies (figure used with permission [1])

The second required adjustment is due to the variation in spatial resolution between the modalities. The spatial resolution associated with CT is on the order of a millimetre whereas it is typically 5–10 mm for PET and 10–15 mm for SPECT. This difference in spatial resolution between transmission and emission tomography would lead to an edge artefact. Thus, the CT data are typically blurred to the resolution of SPECT or PET prior to applying the correction. As a result the typical method for CT-based attenuation correction is as follows: acquire the CT scan and reconstruct it, apply the energy transformation from CT energies to that for SPECT or PET, re-project the transformed data to generate a correction matrix, smooth the correction matrix to the resolution of PET/SPECT and, lastly, apply these modifications during reconstruction.

If the CT scan is truly only to be used for attenuation correction, the acquisition parameters, both kVp and mAs, can be reduced almost as far as the device will allow (e.g. 80 kVp and around 10 mAs) and an acceptable attenuation correction can still be applied [1, 3]. For example, this may be reasonable for brain PET, where MRI is the anatomical modality of choice and CT is not used clinically. However, in many cases, the low-dose CT is used for anatomical correlation of the PET data. This can be particularly useful when the pertinent PET or SPECT scan finding is merely an amorphous feature in space with few anatomical landmarks for localisation. In these cases, the CT image quality may only need to be sufficient for localisation and less than that necessary for diagnosis. Thus, the

mAs can often be drastically reduced by a factor of possibly 3–5, depending on the task at hand and the size of the patient, leading to a considerable reduction in radiation dose to the patient compared to that for a diagnostic CT scan. The scan may also be easier to acquire, not requiring a breath hold or positioning of the patient's arms above the head for the entire scan.

Lastly, there may be instances where acquiring a diagnostic CT scan in conjunction with the PET scan makes the most sense. For example, it may be reasonable to acquire an abdominal/pelvic CT in conjunction with the PET scan, leading to a more efficient imaging approach as well as being more convenient for the patient. This approach may be particularly helpful in children or other challenging patients, when the ability to perform both scans simultaneously may reduce the need for sedation or other approaches to immobilisation. On the other hand, diagnostic CT requires the highest radiation dose to be delivered to the patient. One should keep in mind that diagnostic CT is often applied to specific regions of the body such as the head/neck, the chest, the abdomen or the pelvis whereas the typical ^{18}F-fluorodeoxyglucose PET field of view encompasses all of these. Therefore, approaches that limit the diagnostic quality CT to the area of interest (e.g. to the abdomen and pelvis in the above example) while delivering a low dose to the rest of the field of view may be most appropriate.

CT acquisition and dosimetry

CT measures the differential absorption of X-rays passing through the patient and thus provides a 3D map of tissue density. The CT signal is more specifically related to electron density, which in many cases is well correlated with mass density. X-rays are generated when electrons from the cathode of the x-ray tube are liberated via thermionic emission and accelerated towards the anode through an applied voltage. When the electrons strike the anode, they de-accelerate, leading to the production of bremsstrahlung and characteristic X-rays. The number of electrons striking the anode per second is characterised by the tube current in milliamperes (mA). Thus the total number of electrons striking the anode is directly related to the product of the tube current and the duration of the exposure (in seconds) reported in mAs. Therefore, the total number of X-rays generated and subsequently the X-ray dose to the patient is directly proportional to mAs. The voltage across the tube, reported as the kilovoltage peak (kVp), determines the energy of the electrons striking the anode (in keV) by definition and thereby the maximum energy of the resultant X-rays. In addition, higher energy electrons are more efficient at generating X-rays and higher energy X-rays are more likely to exit the tube and its filtration prior to reaching the patient. As a result, the X-ray exposure or air kerma rate varies roughly as the square of the kVp.

The emitted X-rays, after passing through the patient, are detected by a two-dimensional

array of detectors. The X-ray tube and the detector array are fixed relative to each other and rotate constantly about the patient, typically at a speed of about one to three revolutions per second. This provides full sets of transmission projection data for subsequent reconstruction. In addition, the image bed moves during the acquisition, allowing a volume of the patient to be imaged in a helical fashion. The table speed is generally reported relative to the beam width as a parameter known as the pitch, given by

$$Pitch = \frac{\text{Table distance travelled in a single gantry rotation}}{\text{Width of the beam collimation}}$$

A pitch of unity (1:1) indicates that the table travels a distance equivalent to the width of the beam collimation during a single gantry rotation. Faster table speeds lead to pitch values greater than 1:1 (e.g. 1.5:1), yielding slightly under-sampled data. However, in most cases, interpolation between the acquired axial data can yield an adequate reconstruction.

The CT signal is quantified in CT or Hounsfield units, which estimate the mean linear attenuation coefficient within a voxel relative to that for water:

$$\text{CT number (or Hounsfield units)} = 1000 \times \frac{\mu_V - \mu_{water}}{\mu_{water}}$$

where μ_V represents the measured mean linear attenuation coefficient within the voxel of interest and μ_{water} is the linear attenuation coefficient for water at the effective keV for the X-ray spectrum of the CT acquisition.

Modern CT scanners, including those incorporated into hybrid systems, typically provide some level of automatic exposure control (AEC). In many cases, the low-dose topogram or "scout" acquisition used to determine the CT field of view also serves to provide information for the AEC. For example, less radiation may be necessary for imaging the lungs as compared to the abdomen since there is less attenuation, and less is needed when acquiring data in the anterior–posterior direction rather than the lateral direction as the body is thinner in this direction. Subsequently, the mA can be modified accordingly during the acquisition. Typically, the user can define some criteria such as a maximum mA level or a noise index that sets the acquisition at a given exposure level that is then modified. AEC can lead to a 25–40% reduction in radiation dose depending on the nature of the acquisition and the size of the patient.

The radiation dose delivered by CT is typically characterised by the CT dose index (CTDI), defined as the dose delivered to a standard acrylic, cylindrical phantom (16- or 32-cm diameter for the head or whole-body acquisition, respectively). When CTDI is averaged over several locations within the phantom (central and

peripheral) and normalised by the pitch, it is referred to as $CTDI_{vol}$. The dose–length product (DLP in units of mGy-cm) is the product of $CTDI_{vol}$ and the axial length of the CT acquisition in cm. DLP may be more closely linked to radiation risk as it also takes into account the extent of the scan. $CTDI_{vol}$ and DLP are routinely displayed on the CT operator's console during an acquisition and recorded in the structured dose report or in the DICOM header. It should be noted that these dose indices do not represent the radiation dose to a particular patient, but that measured in standard phantoms. If the size of the patient is known, the $CTDI_{vol}$ can be modified and reported as the size-specific dose estimate (SSDE) [4]. Therefore, CT acquisition parameters should be reduced for smaller patients.

In order to investigate the range of exposures associated with the CT component of PET/CT, data for whole-body PET/CT from the American College of Radiology CT dose index registry were reviewed for over 28,000 PET/CT acquisitions from 35 facilities in the United States. The median values (and inter-quartile scores) for the $CTDI_{vol}$ and DLP reported for these scans were 6.3 (4.0, 9.0) mGy and 541 (364, 831) mGy-cm, respectively. From these values, the estimates of the median (and inter-quartile scores) of the effective dose are 8.9 (6.0, 13.4) mSv [5].

Best practice in patient positioning in CT acquisition for hybrid imaging

Positioning of the patient during CT scanning is important as it will affect the image quality as well as the dose of radiation that is delivered to the patient. The patient should be positioned so that the radiation from the X-ray beam is not applied to sensitive areas that do not need to be imaged. Using laser lights for positioning is helpful to ensure that the patient is in the isocentre of the gantry. If the patient is not in the isocentre then the dose delivered from the CT could be too low or too high. If the dose is too low, the image quality suffers and the scan may need to be repeated; too high and the patient receives unnecessary radiation dose. This, along with the use of a scout or topogram scan, can help in ensuring that the field of view is consistent with the exam that was ordered. For example, if a chest CT is ordered, the scout scan will show whether the entire chest cavity is in the field of view.

If motion is detected in a scan, it may need to be repeated; therefore it is essential that the patient is instructed to remain as still as possible during scanning and is positioned comfortably. If needed, soft positioning devices can be used to help the patient to hold still. In some paediatric patients or patients who are experiencing high amounts of anxiety, a sedative can be administered to help with compliance during the scan.

Guidelines and national regulations for acquiring CT within hybrid imaging

CT scans are routinely performed in the United States and account for a large proportion

of diagnostic radiology exams. The clinical information that is gained from CT exams is incredibly beneficial to patient outcomes and outweighs the risk that comes with the radiation exposure. However, in 2009 and 2010 reports were released regarding 400 patients who received radiation overdoses from a CT exam [6]. Similar reports regarding the risk of radiation have led to a growing concern regarding the safety of CT.

In the United States, the American College of Radiology (ACR) has published a practice parameter for performing diagnostic CT scans [7]. This is not a set of rules but rather an educational tool designed to advise on how to provide care for patients undergoing CT scans. The audience for the ACR document is physicians. For technologists, the American Society of Radiologic Technologists (ASRT) has also published Computed Tomography Practice Standards in their Practice Standards for Medical Imaging and Radiation Therapy [8]. Again, this is not a rule book, but a guide to appropriate practice in the performance of diagnostic CT.

National and local authorities may regulate what training and credentialling is required to perform CT in the context of hybrid imaging. This varies greatly depending on the jurisdiction and may depend on whether the CT portion of the study is being used for diagnostic purposes.

The field of radiology and CT continues to grow and evolve, with ongoing changes in technology. Accordingly, all professionals working in the field need to ensure that they are fully acquainted with the latest developments. Technologists need to be aware of published practice standards and the changes in regulations in order to perform scans that provide the best image quality and ensure optimal patient care.

Conclusion

The addition of CT to both PET and SPECT has had a substantial impact on clinical practice. However, CT exposes the patient to ionising radiation in addition to that associated with the administration of the radiopharmaceutical. Therefore, basic knowledge of the physical aspects of CT and the factors that affect dose is essential for the nuclear medicine professional involved in hybrid imaging. Care must also be taken to optimise the dose associated with CT. For example, the CT acquisition parameters should be adjusted depending on how the CT is to be used (i.e. for attenuation correction, anatomical correlation or diagnosis) and the size of the patient. Since PET/CT scans typically extend over a substantial portion of the patient's body, it may be prudent to restrict the diagnostic study, when necessary, to the body region of clinical concern.

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Chapter 7:
Dose Optimisation for Radionuclide Therapy

Marga Ouwens

Radionuclide therapy can be used in various ways. The most common form of radionuclide therapy is with radioiodine (iodine-131, ^{131}I). During the 1940s, ^{131}I became the first radiopharmaceutical to be used in humans for the treatment of benign conditions of the thyroid gland. Nowadays, a number of different radionuclides useful for therapy are readily available.

The most important issue in therapy is dose optimisation. The aim is to achieve the best possible result with therapy whilst taking care of the patient by avoiding excessive therapy, in the knowledge that the end result will be the same.

Iodine-131 therapy for benign thyroid disease

Dose optimisation for benign thyroid diseases is usually based on a calculation involving estimation of the size of the thyroid and the ^{131}I uptake after 24 h [1].

It is of utmost importance that the diagnostic acquisitions, and also therapy, occur under favourable conditions. A suppressed (<0.1) thyroid stimulating hormone (TSH) level is important for preservation of healthy thyroid tissue. In addition, anti-thyroid drugs must be stopped for at least 2 days (methimazole and carbimazole) or at least 2–3 weeks (propylthiouracil) before radioiodine administration because they may lower the uptake and the effective half-life of ^{131}I, thereby reducing the effectiveness of treatment [1–3].

The size of the thyroid can be evaluated by ultrasound (size in millilitres) [2] or by static acquisition (size in grams) with a high-energy collimator. For high-energy acquisition, one may use, for example, a timeframe of 10 min, a 256×256 matrix and a zoom factor of 2.29. To determine the thyroid size with a nuclear acquisition, a software program is used whereby the technologist creates automatic or manually drawn regions of interest (ROIs) around the thyroid (Fig. 1). The software is able to convert the number of pixels in the ROI into the approximate weight of the thyroid.

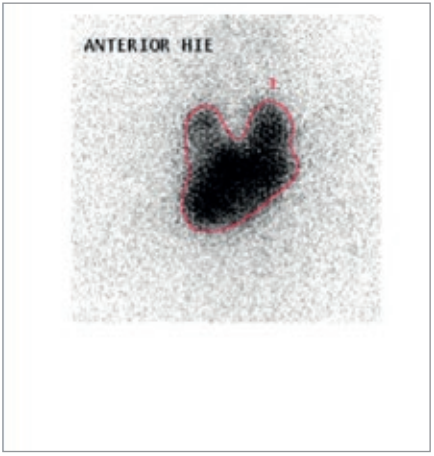

Figure 1: An ROI around the thyroid gives an approximation of the thyroid weight

A static acquisition obtained with a pinhole collimator can be useful in describing the benign disease present (Figs. 2–4). Parameters of a 256×256 matrix and a zoom factor of 1.45 can be used.

Figure 2: An example of Graves' disease (autoimmune hyperthyroidism) [1, 2]

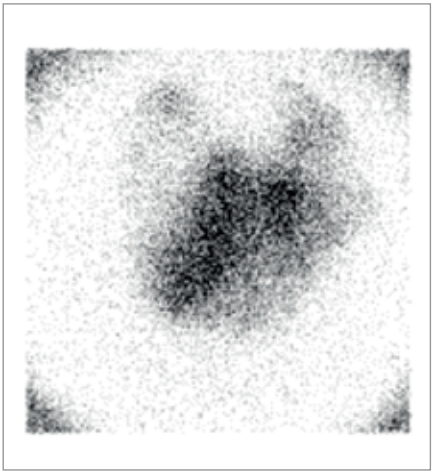

Figure 3: An example of Plummer's disease (toxic multinodular goitre) [1, 2]

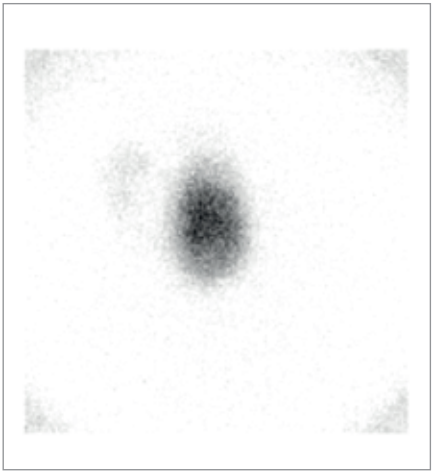

Figure 4: An example of solitary hyperfunctioning thyroid nodule [1 ,2]

There is a possibility that a 'cold spot' on the static acquisition is seen, and further examinations such as a biopsy will then be required.

Some patients suffer from tracheal deviation, e.g. patients with toxic multinodular goitre or non-toxic goitre [2]. In these cases, a SPECT/CT is usually performed to check whether the thyroid is causing the deviation. SPECT complements the morphological information provided by CT by demonstrating radioiodine uptake in the thyroid. If a 'cold' part of the thyroid is found to be the cause of the deviation (Fig. 5), therapy with ^{131}I will not solve the problem, and the patient must be referred to the surgical department [3].

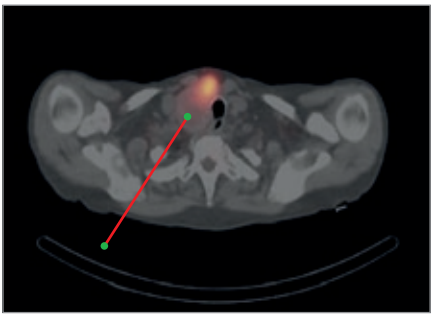

Figure 5: The arrow shows the 'cold' part of the thyroid, causing the tracheal deviation. In this case, treatment with 131I is excluded

Calculation of dose

The aim is to restore euthyroidism, with the exception of 'definitive' treatment of Graves' disease [2] or when a patient is allergic to antithyroid drugs.

There is ongoing discussion regarding the optimal method for determination of the activity that can be recommended for clinical practice: estimation (the so-called fixed dose) versus calculation (based on radioiodine uptake measurements).

The calculated dose method may be used in the selection of a more accurate dose of radioiodine for treatment. There are multiple methods for dose calculation, but the simplest formula is as follows [1]:

$$MBq = (V \times 25 \times Gy) \div [RAIU\ (24\ h) \times T_{eff}]$$

where MBq = the calculated activity in MBq, V = the gland volume in ml or g, Gy = the estimated dose at the thyroid level, RAIU (24 h) = % of thyroid uptake at 24 h, T_{eff} = effective half-time and 25 is a constant.

In either toxic or non-toxic multinodular goitre, radioiodine doses have been empirically established. Currently, an absorbed radiation dose of 100–150 Gy is recommended. In patients with autonomous nodules, the recommended dose is 300–400 Gy. In patients with Graves' disease, the dose applied with the aim of restoring a euthyroid status is approximately 150 Gy, whereas the dose to achieve complete ablation is in the range of 200–300 Gy [2].

Hypothyroidism is a possibility in the longer term, certainly when a complete ablation has been planned. Some of the reasons for choosing a higher dose (ablation) are the presence of Graves' disease and allergies to antithyroid drugs [3].

Patient preparation

At the initial consultation, patients should be advised of what the treatment will entail.

In addition to the likely effectiveness of the treatment, the patient's attention should especially be drawn to:

- the slow onset of action of radioiodine
- the effect of radiation on the thyroid and the body
- the possibility of persistent or recurrent hyperthyroidism and what may be done about it
- the possibility of hypothyroidism and its symptoms, implications and treatment
- the need for regular follow-up to detect hypothyroidism [3].

The nuclear medicine physician should inform the patient of the common side effects of treatment:

- Nausea and vomiting are acute side effects. At lower doses there is a lower incidental risk.
- Patients with a large goitre may notice transient swelling of the goitre and dyspnoea. The swelling lasts for approximately 1 week following therapy and some discomfort or dyspnoea may be associated with it [1, 2].
- Slight discomfort of the salivary glands may be present, but injury is uncommon [2].
- Hypothyroidism is the main late side effect of radioiodine treatment. Its rate varies and its incidence continues to increase over time, so that life-long follow-up is essential [1, 2].
- Administration of prednisone helps to prevent exacerbation of ophthalmopathy. The status of thyroid eye disease activity can be established by an experienced ophthalmologist [1–3].
- A hypersensitivity reaction following the administration is very unlikely [2, 3].

Absolute contra-indications [1–3] to therapy are pregnancy and breastfeeding:

- In female patients of childbearing potential, a routine pregnancy test should be performed within 72 h before the administration of ^{131}I [1–3].
- Breastfeeding should be stopped before administration of ^{131}I.

Special recommendations and radiation protection information, applicable with or without hospitalisation, must be orally discussed and, in addition, presented on paper [1, 2] prior to commencement of therapy:

- Depending upon national regulations, recommendations relating to conception may have to be provided. Generally, it is suggested that after ^{131}I therapy, contraception should be used for 4–6 months by both men and women [1–3].
- Breastfeeding may not be started after therapy.
- The patient should be encouraged to drink a large volume of fluid for a 24-h period following radioiodine therapy to lower the radiation dose to the bladder [2].
- Contamination may occur at home. The most common cause of such contamination is radioactive urine. Sitting while urinating and washing of hands are important to prevent contamination.

Another possibility is contamination with radioactive saliva. Tableware must not be shared before being cleaned (extra care must be taken when feeding children) and no kissing is permissible for a few days.

- The patient may need to take time off work/school for a period in accordance with the activity of radioiodine received and the nature of his or her work [2, 3].
- The patient should avoid prolonged close contact with (small) children and pregnant women for a period in accordance with the activity of radioiodine received [2, 3].
- Usually the patient is advised to keep a distance between themselves and (other) adults, and to keep contact times as short as possible for a limited amount of time, depending on the activity of radioiodine received. [2].
- There may be restrictions on travel depending on the activity of radioiodine received [3].

Iodine-131 therapy for thyroid carcinoma

There are multiple choices for establishing the necessary dose for radioiodine therapy, but administration of a 'fixed dose' of ^{131}I is the simplest and most widely used method.

The indications for radioiodine are as follows:

- ***Remnant ablation***: The dose may be 1.11, 1.85, 2.59 or 3.7 GBq, according to the volume of the tissue, the uptake and the level of thyroglobulin (Tg) [4, 5] (Fig. 6).
- ***Lymph node metastases*** may be treated with 3.7–6.5 GBq. Cancers that extend through the thyroid capsule and have been incompletely resected are treated with 3.7–7.4 GBq [4, 5].
- Patients with ***distant metastases*** are usually treated with 7.4 GBq [4, 5]

The main goal is to ablate the thyroid tissue with one therapeutic dose. The thyroid tissue can be ablated successfully when it is small enough and there are no metastases. Metastases can also be treated, but with a palliative response. Therefore a patient with metastases could return for further treatments [4].

When the thyroid tissue is too large for ablation with only one therapeutic dose, or there are metastases in lymph nodes, an experienced surgeon is consulted to clarify whether a second or third surgical intervention is possible before giving ^{131}I therapy.

It is of utmost importance that the TSH value exceeds 30 mIU/L [4]. This value may be obtained:

- At least 3–6 weeks after surgery in the absence of thyroid hormone replacement therapy [4, 5].
- After 4–5 weeks of levothyroxine (LT_4) withdrawal [4] or after 2–3 weeks of triiodothyronine withdrawal (LT_3) [5].
- After administration of recombinant TSH in two intramuscular injections on two consecutive days, if the patient is under hormonal treatment [4, 5].

Patient preparation

The nuclear medicine physician should inform the patient of the most common side effects of treatment:

- An acute side effect is nausea and vomiting.
- Salivary dysfunction is the most common side effect associated with high-dose radioiodine. Prevention of salivary damage is an important issue.
- Salivation-inducing snacks, such as lemon candy, have proved helpful in preventing salivary side effects of ^{131}I therapy. The sour ingredient stimulates the salivary glands to produce saliva, and the increase in salivary flow reduces radiation exposure. Lemon candy should not be used until at least 24 h following ^{131}I therapy, because before that time it will just increase damage owing to a higher blood flow [4, 6].
- Hypothyroidism will already be present owing to the thyroidectomy. The radioiodine therapy may exacerbate the hypothyroidism a little. Levothyroxine should be initiated a few days after radioiodine administration.

Absolute contra-indications [4] to therapy are pregnancy and breastfeeding.

- In female patients of childbearing potential, a routine pregnancy test should be performed within 72 h before each administration of ^{131}I [4, 5].
- Breastfeeding should be stopped 6–8 weeks before administration of ^{131}I [4].

Special recommendations and radiation protection information must be orally discussed and, in addition, presented on paper prior to commencement of therapy [5]:

- Depending upon national regulations, recommendations relating to conception may have to be provided. Generally, it is suggested that after ^{131}I therapy, contraception should be used for 4–6 months by both men and women [4].
- Breastfeeding may not be started after therapy.
- Patients should be encouraged to drink a large volume of fluid for a 24-h period following radioiodine therapy to lower the radiation dose to the bladder [2].
- Contamination may occur at home. The most common cause of such contamination is radioactive urine. Sitting while urinating and washing of hands are important to prevent contamination. Another possibility is contamination with radioactive saliva. Tableware must not be shared before being cleaned (extra care must be taken when feeding children) and no kissing is permissible for a few days.
- The patient may need to take time off work/school for a period of a duration in accordance with the activity of radioiodine received and the nature of his or her work [2, 3].
- The patient should avoid prolonged close contact with (small) children and pregnant women for a period in accordance with the activity of radioiodine received [2, 3].

- Usually the patient is advised to keep a distance between themselves and (other) adults, and to keep contact times as short as possible for a limited amount of time, depending on the activity of radioiodine received [2].
- There may be restrictions on travel in accordance with the activity of radioiodine received [3].

Post-therapy whole-body scintigraphy is usually performed because of its high sensitivity in localising and characterising the extent of thyroid remnant and tumour and in detecting previously occult lesions. Scintigraphy should not be performed sooner than 72 h or later than 7 days after radioiodine administration. Whenever available, SPECT or, preferably, SPECT/CT should be performed at the same time [4]. By providing a three-dimensional image of involved lymph nodes, the SPECT study is an excellent way of visualising lymph node lesions, whilst the CT component adds morphological information to the functional data furnished by SPECT alone [4, 5].

Samarium-153 therapy

Samarium-153 (^{153}Sm) EDTMP is a radiopharmaceutical that is effective in the treatment of painful metastatic disease of the skeletal system. The highest prevalence of such bone metastases occurs in prostate and breast carcinoma patients, in whom pain relief is the most important criterion for improvement in quality of life. Patients considered for ^{153}Sm-EDTMP will have pain that limits normal activities and/or is not easily controlled by regular analgesics. [7].

Samarium-153 EDTMP concentrates in osteoblastic lesions, with high tumour-to-normal bone tissue and tumour-to-soft tissue uptake ratios. While the benefits of ^{153}Sm-EDTMP are evident after a single injection, treatment over a longer duration (weeks to months) is possible. The treatment can be repeated at an interval of at least 8 weeks, depending on the recovery of adequate bone marrow function.

The skeleton-seeking nature of this radiopharmaceutical results in immediate delivery of beta radiation to disease localisations. Because of the relatively long range of the beta particles emitted by ^{153}Sm, the main dose-limiting factor in this treatment method is the toxicity to bone marrow cells. This toxicity restricts the maximum dose that can be used for the palliative treatment of painful skeletal metastases and precludes more extensive use of ^{153}Sm-EDTMP in clinical settings.

Calculation of dose

Patients are given a standard "fixed" dose: 37 MBq/kilogram body weight [7, 8].

Patient preparation

Before the therapy is administered, some precautions need to be taken. It must be ensured that kidney function is normal (owing to the excretion in urine). Adequacy of bone mar-

Figure 6: Dose of 3700 MBq

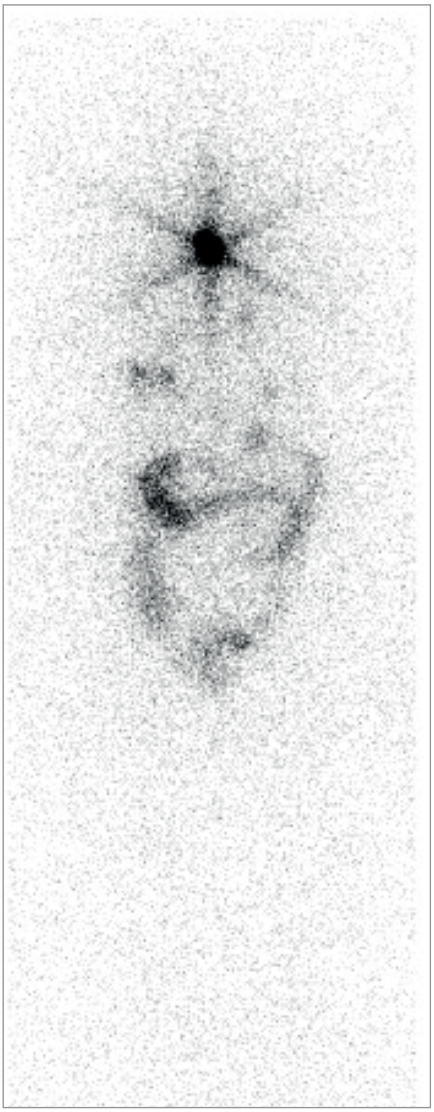

Figure 7: Dose of 7400 MBq

row reserve must be checked within 7 days prior to the proposed treatment, and positive bone scintigraphy must be obtained no more than 4 weeks before initiation of treatment [7]. There are conflicting data as to whether bisphosphonates inhibit the uptake of radiolabelled phosphonates in bone metastases [7].

Patients to be treated with ^{153}Sm are informed of the radioactivity to be administered, the type of radiation involved and the effect of the radiation (beta-radiation) on the bone marrow. Retreatment is possible [7].

The nuclear medicine physician must speak to the patient about the common side effects of treatment and provide other relevant information.

- Bone marrow suppression can be caused by this therapy. It is important that the patient's blood count is monitored for 6 weeks following the injection.
- Between 60% and 80% of patients benefit from ^{153}Sm-EDTNP therapy [7].
- Patients should be warned of the risk of a temporary increase in bone pain (pain flair), usually within 72 h [7].
- Pain reduction is unlikely within the first week; it is more probable in the second week and may occur as late as 4 weeks after injection. Patients should continue to take prescribed analgesics until bone pain decreases and should receive advice regarding subsequent analgesic dose reduction where appropriate [7].
- Patients should be informed of the duration of the analgesic effect, generally 2–6 months, and that retreatment is possible [7].
- It should be checked that the patient understands that ^{153}Sm-EDTMP is a palliative treatment especially designed for treating bone pain and that it is unlikely to cure metastatic cancer [7].

The contra-indications are bone marrow suppression (low blood cell count) (relative), pregnancy and breastfeeding (both absolute) [7].

Special recommendations and radiation protection information must be discussed orally and, in addition, presented on paper prior to commencement of therapy [7].

Keeping the principles of beta and gamma radiation in mind, the following measures are necessary:

- Patients must be advised to reduce unnecessary radiation exposure to family members and the public [7]. They must be told:
  - To avoid prolonged close contact with (small) children and pregnant women for a period in accordance with the activity received.
  - To keep a distance between themselves and (other) adults for a period in accordance with the activity received.

- Patients must be informed that radioactive urine is the most common source of contamination and that rigorous hygiene must be observed in order to avoid contaminating groups at risk using the same toilet facility. Sitting while urinating and washing of hands are urgent matters. Patients should be warned to avoid soiling underclothing or areas around toilet bowls for 1 week post-injection and that significantly soiled clothing should be washed separately. A double flush is recommended after urination. If their hands are contaminated with urine, patients should wash them abundantly with cold water, without scrubbing. Special precautions (catheterisation before and until 24 h after treatment [7]) have to be taken when a patient has unmanageable urinary incontinence.
- Patients must be advised, when necessary, that pregnancy should be avoided for at least 6 months after therapy [7].
- Patients should be appropriately hydrated before and after therapy [7].
- Patients must be told that there may be restrictions on travel, depending on the activity of radioiodine received.

Radium-223

Radium-223 (^{223}Ra) is used for radionuclide therapy primarily in patients with prostate or breast cancer and painful bone metastases [9].

The skeleton-seeking property of ^{223}Ra is similar to that of other radionuclides, like ^{153}Sm. The difference is that ^{223}Ra is an alpha-emitting nuclide [9], while ^{153}Sm is a beta-emitting nuclide. The radiation characteristics of alpha particle-emitting radionuclides seems more favourable than those of beta-particle emitters. The former are able to irradiate in a smaller target volume (such as skeletal metastases) (Fig. 8) and there is less exposure of surrounding normal tissues, i.e. less bone marrow toxicity is to be expected [9].

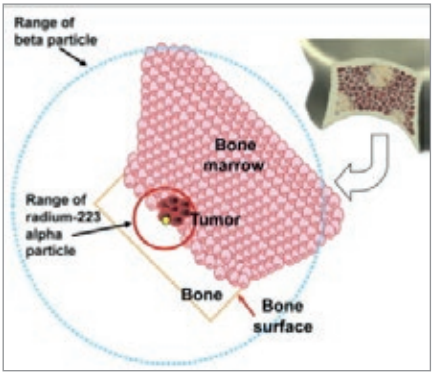

Figure 8: Mechanism of action of ^{223}Ra [9]

In a phase 3 trial of Alpharadin in symptomatic prostate cancer patients (ALSYMPCA), there was a 30% reduction in the risk of death among patients receiving ^{223}Ra treatment compared with those receiving placebo. Median overall survival was 14.9 months with ^{223}Ra and 11.3 months with placebo [9]. In that study a treatment cycle comprised one injection every 4 weeks, and a completed course consisted of six cycles [9]. Control of blood samples is always necessary before the

next treatment to confirm absence of bone marrow toxicity.

The skeleton-seeking nature of this pharmaceutical results in immediate delivery of alpha radiation to the disease localisations. Because of the relatively short gestation of the alpha particles of these radionuclides, bone marrow toxicity is less likely.

In the aforementioned study, ^{223}Ra had a beneficial effect in delaying pain and preserving health-related quality of life [9].

Calculation of dose

The dose is calculated in a standard way: 50 kBq/kilogram body weight.

Patient preparation

Before the therapy is administered some precautions are taken. It is checked that haematological, liver and kidney functions are normal/adequate and a positive bone scintigraphy is obtained, revealing at least two visible metastases.

When a patient is treated with ^{223}Ra, the patient is informed of the radioactivity to be administered, the type of radiation involved and the effect of the radiation (alpha radiation) on the bone marrow.

The nuclear medicine physician must speak to the patient about the common side effects of treatment:

- Bone marrow suppression can be caused by this therapy. It is important that the patient's blood count is monitored following the injection.

Bone marrow suppression is an absolute contra-indication.

Special recommendations and radiation protection information, applicable with or without hospitalisation, must be orally discussed and, in addition, presented on paper prior to commencement of therapy.

Keeping the principles of alpha and gamma radiation treatment in mind, the patient is advised:

- Because alpha radiation travels only a short distance, there are no restrictions on contact with children, pregnant women or other adults.
- The most common route of contamination is via radioactive faeces or urine. Sitting while urinating and washing of hands are urgent matters.

Special precautions must be taken when a patient has unmanageable urinary incontinence.

The facility and personnel

The facility requirements will depend on national legislation on the therapeutic use of radioactive agents [2, 7]. They may vary by country and by radionuclide, also depending on the dose.

When inpatient therapy is required, this should take place in an approved environment with appropriately shielded rooms. The rooms must have separate washing and toilet facilities and the patient must be under continuous surveillance by the staff [5, 7].

The administration of ^{131}I for the treatment of thyroid carcinoma is typically performed under hospitalisation (inpatient) and patients are discharged in accordance with national radioprotection regulations [5].

The administration of all radionuclide therapies should be undertaken by appropriately trained medical staff with supporting nursing staff, when inpatient therapy is required, and an available medical physics expert. All of the clinical staff must know and respect the radiation protection measures relating to staff protection, handling of radiopharmaceuticals and patient safety. Lead shielding, lead disposal bins and lead transport holders are provided to weaken the strength of the radiation. Staff must be aware of procedures for waste handling and disposal, handling of incidental contamination, and monitoring of personnel for accidental contamination and control or limitation of its spread. Physicians responsible for treating patients should have a general knowledge of the pathophysiology and natural history of relevant diseases, should be familiar with alternative forms of therapy and should be able to liaise closely with other physicians involved in patient management. Clinicians involved in unsealed source therapy must also be knowledgeable about and comply with all applicable national and local legislation and regulations.

External and, more importantly, internal contaminations need to be prevented; avoidance of internal contamination is especially important with ^{131}I. Internal contamination, usually caused by accidental ingestion of a radionuclide, results in a higher dose to the personnel involved and is more difficult to eliminate than external contamination. The use of gloves when handling radioactivity is very important.

It is recommended to check personnel who have contact with patients treated with ^{131}I (physicians, technologists, nursing staff), for the possibility of internal contamination. The check can be performed periodically or at random. A check 24 hours after assisting therapy may result in a bigger chance of detection of an internal contamination. It is the responsibility of the health care professional to perform the appropriate checks, but national regulations regularly demand checks twice a year, with supporting documentation.

In many countries, therapies with ^{223}Ra, ^{153}Sm and low-dose radioiodine are performed in an outpatient setting.

In patients presenting with unmanageable urinary incontinence, inpatient treatment (if

not regular standard of care) may be considered, in accordance with the national legislations. This should be discussed before commencement of treatment. An indwelling catheter is recommended before therapy is given.

Radioiodine is preferentially administered orally (capsule), but can be administered in liquid form or intravenously in patients in whom vomiting is a problem. The liquid form has the advantages that it is less expensive and can be stored and easily dispensed as needed, but the risk of spoiling and contamination is higher [2].

Samarium-153 and ^{223}Ra are administered intravenously [7, 8]. Approval for the clinical use of radiopharmaceuticals may vary between countries. The choice of the radiopharmaceutical is based on the physical characteristics of the radionuclide in relation to the extent of metastatic disease, the bone marrow reserve and the availability of the radiopharmaceutical in individual countries [7].

Conclusion

It is very important to administer the recommended dose for both diagnostic and therapeutic purposes. Thyroid disease is highly treatable with ^{131}I, provided that precautions are maintained and radiation protection of the personnel involved is clearly understood. The patient needs to be informed of the need for prevention of contamination to other family members. The nuclear medicine technologist plays a major role in the diagnostic imaging and treatment of a patient with thyroid disease; in particular, the technologist is responsible for performance of scintigraphy and dose calculations, thereby enabling the nuclear medicine physician to make optimal treatment decisions. With ^{153}Sm and ^{223}Ra therapies, a "fixed dose" is used, and the patient also needs to be informed of the need for prevention of contamination. Certainly in the case of ^{223}Ra therapy, the technologist plays an important role in patient care given that patients attend regularly for their treatment.

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Chapter 8: Paediatric Dose Optimisation

Ana Isabel Santos and Diego De Palma

Paediatric population and the importance of dose optimisation

The paediatric population is a very inhomogeneous patient group broadly encompassing those aged 0–18 years, the precise definition varying between countries in accordance with legal differences with respect to the upper age limit. The distinction in medicine between this group and adults is justified, given that the human body grows and matures up until roughly the age of 18 years. Growing or renewing tissues are more sensitive to the mutagenic effect of ionising radiation (which is why in adults the tissues more susceptible to radiation damage are the bone marrow and the gastrointestinal tract epithelium). The younger the child, the larger the number of growing cells; this implies that children are much more sensitive to radiation damage than adolescents and that the latter are more sensitive than adults. Using the current system of risk assessment, the risk of developing a solid tumour after radiation exposure is about 3 times higher for a 1-year-old child and 1.8 times higher for a 10-year-old child compared with an adult [1, 2]. Gender also influences the risk: compared with males, females are exposed to a further 50% increase in relative risk owing to the higher radiosensitivity of breast tissue and the associated incidence of breast cancer [ICRP 103]. An additional fact that contributes in explaining the higher radiosensitivity of children is their longer life expectancy.

It is also to be borne in mind that a risk estimate is a statistical entity derived from the data available for much larger exposed populations such as the Japanese atomic bomb survivors [1, 3] or people living in Belarus and Ukraine at the time of the Chernobyl fallout [4]. Although, for example, no epidemiological study has to date found a definite association between the diagnostic use of iodine-131 and increased risk of thyroid cancer [5, 6], the utmost attention and care are required in children when balancing the potential impact of exposure associated with a diagnostic procedure against the expected benefit.

Radiation burden and ways to minimise it

In nuclear medicine, the radiation burden associated with a procedure, measured as the effective dose (ED), is generally expressed as mSv/MBq of administered activity of the radiopharmaceutical. The given value is modified according to the age of the child (for practical reasons, rounded at fixed reference ages), but the calculation admits as the only variable the amount of activity administered. All other factors influencing the residence time of the radiopharmaceutical in the body, e.g. frequency of voiding, bowel status, hydration, and renal function, are considered as constant or roughly divided into two categories (e.g. normal/abnormal renal function). Radiopharmaceuticals primarily undergo renal excretion; this means that the bladder is the critical organ for calculating the ED. Teaching a toilet-trained child to drink generously

and to void the bladder at fixed intervals is a safe and simple way to reduce the radiation burden. Similarly, administration of small amounts of furosemide in a toddler helps, as does frequent changing of diapers.

With the increased use of hybrid cameras, concern over the additive radiation burden and risks of CT [7, 8] is increasing. When performing hybrid procedures involving CT, such as SPECT/CT and PET/CT, the importance of dose optimisation must not be neglected, and it has to be obtained mainly with the use of standardisation of low-dose protocols [2, 9, 10].

The EANM dosage card

Considering that in nuclear medicine, the ED received after the administration of a radiopharmaceutical depends on the administered activity, there is a definite need to standardise and minimise the latter. The first version of the EANM dosage card was prepared and published in 1990 by members of the EANM Paediatric Committee [11]. At that time, the main purpose was to help in harmonising administered activities across Europe; this card, substantially an "expert consensus paper", used the child's weight as the reference for scaling down activities. It has to be noted that the value was calculated using body surface; the authors thereafter gave weight as the reference because it is easier to obtain and, in children, displays a direct relationship with body surface. A minimum was also set for each radiopharmaceutical, in order to avoid an excessively long scan time. Another problem encountered at that time was the variability in adult reference activities, which was later partially overcome by the publication as law in many EC countries of the Diagnostic Reference Levels. In 2005 an important paper [12] was published, aimed at defining a scaling system based on keeping the ED stable across the different ages. The authors found that radiopharmaceuticals can be grouped into three classes, each with a different set of scaling factors. This led to the publication of a new version of the EANM dosage card [13], and for the first time an online dosage calculator was made available via the EANM website.

This version of the EANM dosage card received some criticism, mainly focussed on the "minimum activity to be administered" concept [14–17]. A footnote was then added admitting that experienced teams can use activities lower than those recommended, but asserting that the overall value of the card as a general reference remained intact [18]. After this publication, a joint EANM–SNMMI group started a process aimed at harmonising recommendations between the two societies [19, 20]. The last update in this respect was published in 2014 [21, 22] and a further new version of the EANM paediatric dosage card is now available, both as an online calculator and as an App for Android/IOS devices [http://www.eanm.org/publications/dosage_calculator.php?navId=285].

Image quality and dose optimisation

The desire to keep administered activities as low as possible (the ALARA principle) will probably find new allies in improvements in hardware and software, since a better sensitivity and an improved signal-to-noise ratio have to be pursued. The availability of PET scanners with a larger axial field of view and a smaller ring diameter will be of benefit, and simultaneous acquisition PET/MR hybrid systems will allow longer PET acquisition times [23]. Considering conventional nuclear medicine, the advances in instrumentation for cardiac imaging, such as cameras with cadmium-zinc-telluride (CZT) solid-state detectors [24, 25], may also impact positively on paediatric nuclear medicine, allowing better image quality with lower administered activities. Among software improvements, the most important include enhanced planar processing [26, 27] and iterative reconstruction with resolution recovery [28, 29]. Simple measures such as acquisition of renal studies with technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) in dynamic mode, for further movement correction and reframing into a single image, can also help in obtaining diagnostic quality images with low administered activities [30].

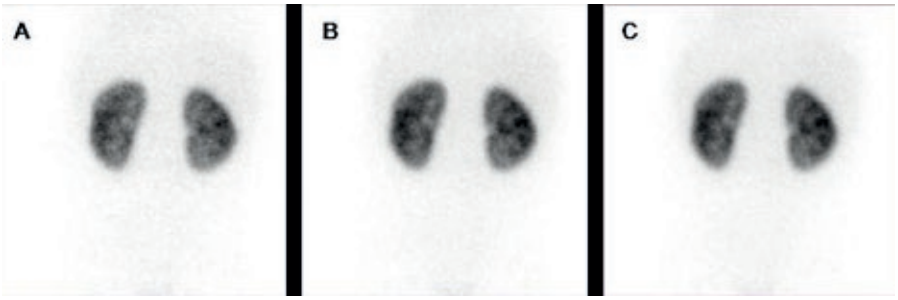

Figure 1A–C: A set of three 99mTc-DMSA images, obtained from a dynamic scan of 40 images, 15 s each. A) Image obtained from the sum of the first 20 images, for a total acquisition time of 300 s. B) Image obtained from the sum of the first 30 images (450 s). C) Image obtained from the sum of all 40 images (600 s). The images show no difference in quality after both qualitative and semi-quantitative (cortex/medullary ratio and noise index, i.e. the ratio between the standard deviation and the mean counts per pixel in the kidney region of interest) assessment

Best practice principles

While the need to estimate risk related to the radiation burden must always be kept in mind, this risk must not be allowed to overshadow those risks associated with ionising radiation-free procedures when, like MRI, they require sedation, general anaesthesia or the use of contrast media.

Another clinical risk that must be weighed against the risk associated with radiation exposure is the danger of missing some clinically relevant information because of either (a) poor quality radionuclide imaging on account of a low count density or movement artefacts due to an excessively long acquisition time or (b) failure to perform what would have been a useful scan.

Take-home messages

The process of dose optimisation and reduction in paediatric nuclear medicine is a comprehensive one, with different and concurrent approaches [10, 23].

A practical approach to dose reduction entails:

- Compliance with the justification process: only studies capable of yielding results that may change the clinical management of the child should be performed, especially when dealing with benign diseases;
- Use of (basically) the activities calculated according the EANM paediatric dosage card;
- Use of rational systems to expedite elimination of the radiopharmaceutical via urine or stools;
- Careful evaluation of the impact of modern or new hardware/software technologies. For example, compared with PET/CT, PET/MRI requires a longer acquisition time per bed position, due to the MRI sequences. As PET image quality represents a product of acquisition time and radiotracer activity, the implication is that radiation exposure may be reduced by lowering the injected radiotracer activity.

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Chapter 9: Occupational Radiation Protection

Sebastijan Rep

Introduction

The main task of radiation protection is to ensure that the received radiation exposure is restricted to a minimum, thereby protecting everybody in the department. An important aspect of this process is knowledge and understanding of radiation sources and of the methods that can be used to limit exposure to these sources. This knowledge can be deployed to minimise external exposure as well as to prevent internal and external contamination.

The three basic methods used to reduce the external radiation hazard are (a) restriction of the time of exposure, (b) maximisation of the distance from the source and (c) shielding [1–4]. Good radiation protection practices require optimisation of these fundamental techniques.

Internal radiation exposure occurs when the body is contaminated internally with a radionuclide. Thus, internal radiation protection is concerned with preventing or minimising the deposition of radioactive substances in personnel.

Another important aspect in the radiation protection process is knowledge of the type of radiation emitted from the isotopes (sources), which is required for selection of the best available protection method [1, 2].

Protection of workers against external radiation exposure

Time

The less time one spends standing in the field of radiation, the lower is the dose received. Working at high speed, proper preparation and practice outside the range of radiation ensure that the actual exposure time is indeed the minimum time needed to perform the tasks while simultaneously restricting the likelihood of error that would necessitate repeated performance of the same tasks. Examples of good practice that shorten the exposure time are:

- Precise planning and organisation of work
- Work rate
- Restrictions to ensure that personnel remain within the radiation field only for the actual duration of work
- Distribution of work among more staff
- Preparation of equipment in a clean environment

There is a direct linear relationship between radiation dose and time (dose = dose rate × time). The radiation dose increases in linear fashion as the duration of exposure increases [5].

Distance

Radiation dose rate decreases with increasing distance from the source. The decrease in the dose rate with distance is not linear: dose rate from a point radiation source decreases by the square of the distance. A radiation source can be regarded as a point source when one is within three times the largest dimension of the source. For this reason, almost all sources in nuclear medicine can be assumed to be

point sources. It is also important to note that for point sources in air the radiation spreads uniformly to all sides [6].

When extrapolating from measurements at longer distances, assuming a point-source distribution can lead to significant overestimation of dose rates closer to the patient. A linear-source model with attenuation correction can be used to more accurately reflect the activity distribution for some procedures. In a line-source model, the fall-off of the dose with distance depends on both the distance and the length of the source [1, 7]. In practice, this implies that doubling the distance in any direction will reduce to one-quarter the value of the exposure.

Bearing in mind the above, maximisation of distance from the radiation source is a simple and very effective method for reducing radiation exposure to workers. The distance between workers and the radioactive source can be maximised by using long-handled tools to keep radioactive materials well away from the body and by storing radioactive materials as far from workers as possible [8].

The distance from the source of radiation is increased if:

- Pliers, tweezers and other adapted tools are used.
- Remotely operated tools are used.
- Television surveillance is used.
- One communicates at distance.

It is important to know how to derive the dose rate at a certain distance from a known dose rate at a different distance. In this case, a slightly modified equation is used for the dependence of dose rate on distance [1–4]:

$$I_1 * D_1^2 = I_2 * D_2^2$$

where I_1 is the intensity at the original distance (D_1) and I_2 is the intensity at a new distance (D_2) [5].

Shielding

Although maximisation of distance from the source and limitation of the time of exposure are important measures for protection against external radiation, the shielding factor is also very important for reduction of the dose rate in a nuclear medicine department. In practice the shielding depends on the type of work, the type of radiation, the total activity and the practice and workload of each area in the department. In fact, all departments are designed and built to incorporate barriers that take these factors into account.

All sources used in nuclear medicine arrive in their own container (shield) and best practice warrants that all prepared activities and sources are manipulated or transported within this container, with additional protection. The shielding normally varies between 3 and 6 mm of lead equivalent, according to the energy and type of radiation. However,

protection can in fact be provided by any material with a sufficient thickness.

Due to the scattering of gamma rays and the bremsstrahlung, the radiation shield is difficult to calculate. For this reason, it is advisable to consult a radiation protection officer [1–4]. The method of shielding depends on the type of radiation. Gamma radiation decreases exponentially with the thickness of the shield and can be written as:

$$D = D_x * \frac{1}{2^n}$$

where n is the number of half-value layers (HVL): $n = d/d_{1/2}$. D_x indicates the dose rate without a shield and D, the dose rate with a shield (at the same distance from the source) [5].

Values of HVL for photons with different energies (keV) are shown in Table 1.

The same equation can be written using the tenth-value layer (TVL):

$$D = D_x * \frac{1}{10^n}$$

where n is the number of tenth-value layers: n = d/d1/10 [5].

These formulas include only photons that pass through the shield and do not entail any interaction. It turns out that the contribution of stray radiation from the thick shielding is substantially higher than the attenuated radiation that comes directly from the source. Therefore, the equations shown are only estimates [10].

A 0.25-mm lead apron will provide a dose reduction of 59% for $^{99m}TcO_4$ (140 keV) while a 0.5-mm lead apron, weighing about 8.5 kg, will provide a dose reduction of about 76% [11, 12]. A lead apron is of little use at higher energies, examples being ^{131}I (360 keV) and ^{18}F (511 keV). Thus a 0.25-mm lead apron will provide a calculated dose reduction of about 3% for ^{18}F and 6% for ^{131}I while a 0.5-mm lead apron will provide a calculated dose reduction of about 6% for ^{18}F and 11% for ^{131}I [13].

Beta radiation contributes to external exposure in two ways: via the beta rays themselves, i.e. fast electrons (or positrons), and via scattered radiation (bremsstrahlung) that is the result of interaction of the electrons or positrons with matter. Beta particles are relatively easy to stop, and therefore bremsstrahlung is the major contributor to external exposure. The proportion of bremsstrahlung radiation can be reduced by using a material with a low atomic number Z (polyethylene, acrylic glass) instead of a high Z material. Therefore, the internal shield is intended only to stop beta particles and is enclosed by an outer sheath made of material with a high Z (lead), which reduces the bremsstrahlung [1, 14].

Specific gamma-ray dose constant (Γ)

For every isotope it is possible to use the specific gamma-ray dose constant (Γ) to estimate an absorbed dose. The constants of the isotopes more commonly used in nuclear medicine are published in the literature. The absorbed dose is directly proportional to the time of exposure and the activity at the point of origin and inversely proportional to the square of the distance from the same point. It can be seen from Table 2 that for 1 MBq of ^{18}F at 1 m and for an exposure of 1 h, an absorbed dose of 0.143 mSv is obtained.

Protection of workers against internal radiation exposure

Internal contamination is the presence of radioactive material inside the human body and results from the ingestion or inhalation of radioactive material (radionuclides). The more common ways for radionuclides to enter the body are:

- With food and drink (ingestion)
- By breathing (inhalation)
- Through the skin (absorption)
- Through open wounds (absorption)

The received dose can depend on the mode of entry into the body. In contrast to external exposure, alpha and beta emitters are the most dangerous sources of internal exposure [1, 10].

The concentration of radionuclides in the body decreases over time, in the absence of new entry, because of natural radioactive decay and because of biological elimination from the body via the digestive tract, urinary tract and exhalation. Options for artificially accelerated washout of radionuclides in the body are very limited, so the main protective measure against internal exposure is prevention of entry of these materials into the body. Accordingly, protection begins with the prevention of contamination of the environment in which people live and work.

Unlike in external exposure, in an internal exposure the doses received cannot be directly measured, but only calculated or estimated [15].

Protection against internal exposure is based on the following principles:

- Limitation of open sources: radiation sources and processes that can cause radioactive contamination of surface or air should be limited to a reasonably small number of specific areas.

- Monitoring of areas with radiation sources: Premises on which there is radiation activity should be appropriately designed architecturally. Surfaces should be made of materials that allow efficient decontamination, and special care must be taken to ensure controlled drainage and good ventilation with air filtration. Work with open sources involving a possibility of contamination is carried

out within a controlled area to which access is physically restricted. Only workers who meet certain conditions (regarding personal protective equipment, training, etc.) are allowed to work in this area, and at the exit there must be suitable equipment for measurement of personal contamination and, if needed, decontamination.

- Protection of workers: Eating, drinking and smoking must be strictly forbidden in areas where open sources are present.
- Protection of workers: Workers must always wear personal protective equipment when manipulating sources. This is intended to prevent contamination of the skin (through the wearing of protective clothing) and to limit the intake of radioactive substances by inhalation (through use of respiratory equipment) [10, 15].

Effective half-life

Different tissues and organs in the human body display differing susceptibility to a variety of radioactive isotopes. It is known that iodine accumulates in the thyroid, calcium in the bones, etc. Some other elements are evenly distributed throughout the body.

Also, radioactive isotopes of each element accumulate in specific target organs after entering the body. Thus, 90Sr and 223Ra accumulate in the bones and 131I in the thyroid while 60Co and 137Cs are distributed throughout the body. No substance, radioactive or not, remains in the body indefinitely. Normal biological processes remove all substances from the organism; their concentration decreases approximately exponentially. On the basis of the biological and radioactive half-time, the effective half-time can be calculated. The equation for calculating the effective half-life is:

$$T_{EF} = \frac{T_F * T_B}{T_F + T_B}$$

where T_{EF} is the effective half-life; T_F is the half-time of the isotope and T_B is the biological half-life [1, 5].

Personnel monitoring for external and internal radiation exposure

The best way to estimate the total dose to which a person has been exposed is by means of personal dosimetry. In the case of nuclear medicine both whole-body dosimetry and extremity dosimetry are advised. External radiation exposure is measured by personnel monitoring devices.

Three main types of monitoring device are in use today: film badges, thermoluminescent dosimeters (TLD) and optically stimulated luminescent (OSL) dosimeters. If the body is exposed more or less equally, the dosimeter should be worn on the trunk of the body. This will allow the dose to internal organs to be estimated.

When wearing a protective lead apron, the dosimeter should be worn inside the lead apron. Ring badges or wrist badges must be worn when amounts of radioactive material on the hands may be high. Ring badges must be worn on the inside of gloves to avoid contamination. Internal contamination may also be controlled by using a whole-body counter [1].

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Photon energy (keV)	HVL d½ cm	
	Lead	H_2O
25	0.002	1.5
50	0.008	3.2
100	0.01	4.1
250	0.08	5.5
500	0.40	7.1

Table 1: Values of HVL for photons of different energies (keV) and two materials (as examples) [9]

Radionuclide	Physical half-life	mSv m²/MBq h
^{64}Cu	0.529 days	0.0324
^{67}Cu	2.578 days	0.0157
^{18}F	109.8 min	0.143
^{67}Ga	3.261 days	0.0204
^{68}Ga	68.3 min	0.134
^{123}I	0.55 days	0.0435
^{124}I	4.2 days	0.185
^{125}I	14 days	0.0384
^{131}I	8.04 days	0.0595
^{111}In	2.83 days	0.0868
^{13}N	9.96 min	0.148
^{15}O	2.04 min	0.148
^{82}Rb	76 s	0.159
^{99m}Tc	0.251 days	0.0204
^{201}Tl	3.044 days	0.0121

Table 2: Physical half-lives and gamma constants for various radionuclides [5, 6]

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Chapter 10: Nuclear Medicine Department Design

Elizabeth Bailey

Introduction

Designing a new department is time consuming and complex; however, getting the design and layout correct will create an environment that is safe and efficient for both staff and patients. Outlining the operations of the department and the types of service offered is the first step in developing a design plan, which can be modified throughout the project. The design process must ensure engagement with all the relevant stakeholders, both internal and external. External stakeholders, including referrers, should be consulted to better define the types of service to be offered (nuclear medicine and/or PET); this will enable you to estimate the expected number of patients and bookings, remembering to allow for future growth and development. Engaging the staff in reviewing the current workflows and protocols will assist with compliance if changes in process are required. Compliance with regulations is mandatory, with advice needed from the medical physicist and radiation safety expert on minimum room size, shielding and other services, with a particular focus on radiation shielding and occupancy rates. This chapter summarises the issues that need to be addressed when designing a new department, provides a step-by-step guide to department design and outlines the role of the technologist in the design process.

Requirements of a nuclear medicine department

The requirements of a new department will depend on the functionality and services being offered. The design and floorplan will vary significantly according to whether the department will have a single gamma camera, a SPECT/CT, a PET/CT or a PET/MRI, whether it will have cardiac exercise stress testing facilities and whether it will offer radionuclide therapy. Therefore one of the first steps in the process is to engage your invested stakeholders, including the institution (hospital) executive, referrers, other departments and clinical areas within the hospital and the patients who will use the service. This process offers an ideal opportunity to review your current practice (if updating an existing department) or to define the goals of the new department, which should help to identify the services to be provided and therefore the equipment needs. For example, if you are setting up a small single gamma camera practice in a small rural (non-metropolitan) hospital adjacent to a small radiology department, then it is likely that you will be required to provide routine non-urgent studies and an occasional urgent acute procedure and to operate Monday to Friday business hours (8 a.m. to 5 p.m.). Therefore, a single SPECT/CT, a small hot lab, one office, a small reception with a waiting room to house up to five or six people, a shared reporting area with radiology and other standard features would be considered adequate. However, a large university hospital providing acute services, surgical and interventional procedures, cancer care services, extensive outpatient clinics covering all specialties and a 24-hour emer-

gency department will likely have three or more SPECT/CT systems, at least one or two PET/CT scanners, cardiac stress testing facilities, lead-lined inpatient rooms for radionuclide therapies and all the standard features needed to provide a comprehensive service. Knowing this information prior to designing the layout and workflow of the department will ensure that the new nuclear medicine department will meet the expectations and needs of patients and referrers.

Regulations and minimum standards at a local, state and national level can vary between countries. During the design process, consideration must also be given to international standards regulating radiation protection, shielding and waste storage, hot laboratory minimum specifications, gamma camera/SPECT/PET room layout and size and mandatory facility services based on department size and occupancy rate [1–5]. It is important to consult infection control and occupational safety guidelines as these will provide information on the number and location of patient/staff toilets and hand-wash basins, dirty utility rooms, waiting rooms, medical services including oxygen, suction, nurse call buttons, cardiac arrest/emergency alarm and closed circuit television (CCTV) monitoring. These must be taken into consideration when defining the layout and will impact on the space available for hot laboratories, uptake rooms for PET, changing rooms, cardiac stress testing facilities and consultation rooms, possibly affecting the number of services that can be performed.

Issues to consider when designing a nuclear medicine department

When designing a nuclear medicine department, there are several factors and issues that should be considered. The project plan and development working group should include representation from each of the professional groups within the department, including nuclear medicine physicians, radiologists, nuclear medicine technologists, medical physicists, radiopharmacists and nursing and administrative staff. This will ensure that the department meets the needs of the patients, referrers and other important stakeholders while creating an efficient and safe work environment for the employees.

Be aware of the other departments and clinical areas surrounding the new floorplan, especially paediatrics, ultrasound waiting rooms and maternity clinics, as this will impact on shielding requirements. Areas to be considered include not only those that are immediately adjacent to the department but also those above and below it. All attempts should be made to ensure that hot areas are not adjacent to high-risk areas; for example, the PET hot lab should not share a common wall with the maternity clinic.

It is common practice in most nuclear medicine departments to install lead-lined glass in gamma camera control rooms so as to be able to observe the patient during the nuclear medicine test. This is still recommended for the nuclear medicine gamma camera

area; however, CCTV monitoring is preferred for the PET unit as the thickness of lead glass needed to provide adequate shielding has a high refractory index, making it very difficult to clearly and safely observe the patient. It is also very costly to install. Consideration should also be given to the use of CCTV monitoring in the hot patient waiting areas, uptake rooms and radionuclide therapy rooms throughout the nuclear medicine department. This will reduce staff radiation dose and allow the nursing and technologist staff to safely monitor the patients in a 'cold' non-radiation area.

In PET departments, the thickness of lead required to provide adequate shielding for staff can make doors very heavy and can represent a manual handling risk for staff. Therefore the designs should be reviewed in consultation with a medical physicist expert in order to ensure compliance with radiation safety regulations while minimising the occupational manual handling risks. A maze design may be an option that minimises the number of heavy doors required yet still provides adequate radiation shielding.

The design should include clearly defined 'hot' and 'cold' areas throughout the department plan with restricted access to patients. The nuclear medicine department staff should have areas within the department such as the control room, staff recreation room and toilet that are non-radiation areas. These should be clearly identified in the design and workflow.

Consideration should also be given to the location of radiation-sensitive equipment such as gamma counters, dose calibrators and area monitors. If the background radiation level is too high, the measurements will be erroneous and therefore impact on clinical results. If this is unavoidable, then the rooms containing this type of equipment will need to be appropriately shielded. Given the higher risk of surface contamination and radiation spills in areas such as the hot laboratories, radiopharmacies and gamma and PET camera rooms, it is preferable that the flooring is continuous with no joins, non-absorbent and easy to clean. The bench surfaces ideally should be stainless steel with a lip at the front to prevent spillage from bench to floor and continuous to the back surface or wall. The IAEA provide guidelines on radiation safety standards that incorporate radiopharmacy and hot laboratory design [6].

The relevant clinical staff, including the technologist, will need to develop a concise list of the types of study and the radionuclides to be used in the department. If the department is to offer a full suite of diagnostic procedures, PET tracers (with short and long half-lives), radioiodine therapies and other radionuclide therapies, then this will significantly affect the equipment needs, shielding, waste storage in the hot laboratories and quality control minimum standards. These must be defined before designing the layout and workflow of the new department.

Many PET departments commonly use auto-dispensing and injectors for fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) and the equipment is large and difficult to manoeuvre between patients, especially between uptake rooms when they are not located adjacent to each other. It is important to take this into consideration as part of the design phase. Departments are now being designed with a small area or corridor between the uptake rooms to locate the injector, with the walls having a small hole where the extension tubing from the auto-dispenser to the IV site can be connected to reduce the radiation and manual handling needs for the staff, as illustrated in Fig. 1.

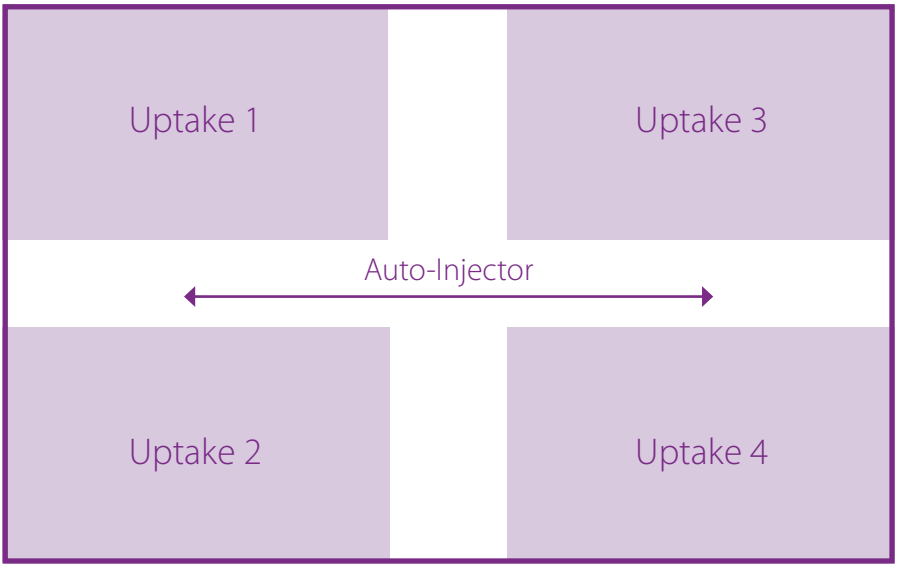

Figure 1: An example of the layout and functionality of the PET uptake rooms if an auto-dispenser and injector are to be used to administer [^{18}F]FDG

The equipment list, both medical and non-medical, must be finalised early in the design process as it impacts on many other items within the department, including the location and number of power and data outlets, lighting (including dimmable), temperature control, medical/emergency services and the location and number of CCTV monitors. This is particularly important for the PET area uptake rooms, which need to be kept at a constant temperature and to have dimmable lighting to desensitise the patient during

the uptake period. The ambient temperature in the gamma camera rooms will be critical to avoid damage to the sensitive NaI detector crystals, especially if equipment is to be installed and not used for a significant time prior to department operation.

As part of the planning and development process, new workflows for patients and staff must be identified, especially with respect to the transit of patients into and out of the department. It is preferable to avoid transiting through or past 'cold' staff areas when entering and exiting the department, specifically the control rooms, reporting rooms and staff recreation rooms.

Layout and design considerations

Defining the types of study to be performed in the new department will determine the equipment needs and therefore the design and layout of the facility. There are, however, many common features that will be mandatory in order to comply with local and national regulations irrespective of the equipment to be installed. These include emergency services, radiation shielding, room sizes, infection control for location and number of hand-washing facilities, size of reception areas and office space and the minimum standards for patient holding bays. Organisations such as the American Association of Physicists in Medicine (AAPM), the International Council on Radiological Protection (ICRP) and the International Atomic Energy Agency (IAEA) provide guidelines on radiation shielding calculations, room layout and method for determining occupancy rates [1, 4, 7]. Local and national health regulators often provide health facility guidelines that cover minimum room sizes, infection control standards, safe workplace recommendations and non-medical equipment needs [7, 8].

The design plan and layout will vary depending on whether you are renovating or building within an existing floorspace as compared to being given a 'blank canvas' with the ability to design the space as required, which is often easier. Current design guidelines and regulations specific to the country and the area that you are building must be taken into consideration, as must the radiation safety regulations. There are many examples of effective department designs, especially for new PET departments, that have been successfully implemented [9]. The design layout examples given below list the potential medical and non-medical equipment necessary for a nuclear medicine department ranging in size from a small single gamma camera department to a larger department with multiple gamma cameras and PET/CT.

Example 1 – a single gamma camera, either SPECT or SPECT/CT (Fig. 2)

- Waiting room to house up to six patients;
- Reception and administrative staff area with enough space for a single receptionist and an office for a practice manager;
- SPECT or SPECT/CT camera room with the radiation shielding determined as per the

regulations, dependent on the isotopes to be used. It is important to remember that a larger floorspace will be needed for SPECT/CT, usually up to 46–48 m^2 (495–517 ft^2), compared with 40–42 m^2 (430–455 ft^2) for SPECT only;

- Gamma camera control room with space for up to two nuclear medicine technologists and located in a low patient occupancy section of the department, considered a 'cold' or non-radiation area for the staff;
- Patient toilet and a separate staff toilet, not necessarily in the department but within close proximity for the staff;
- Hot laboratory that includes a small radioactive waste storage area, with the size and radiation shielding determined by the radionuclides to be used and the procedures to be undertaken;
- Cardiac stress laboratory with a treadmill or

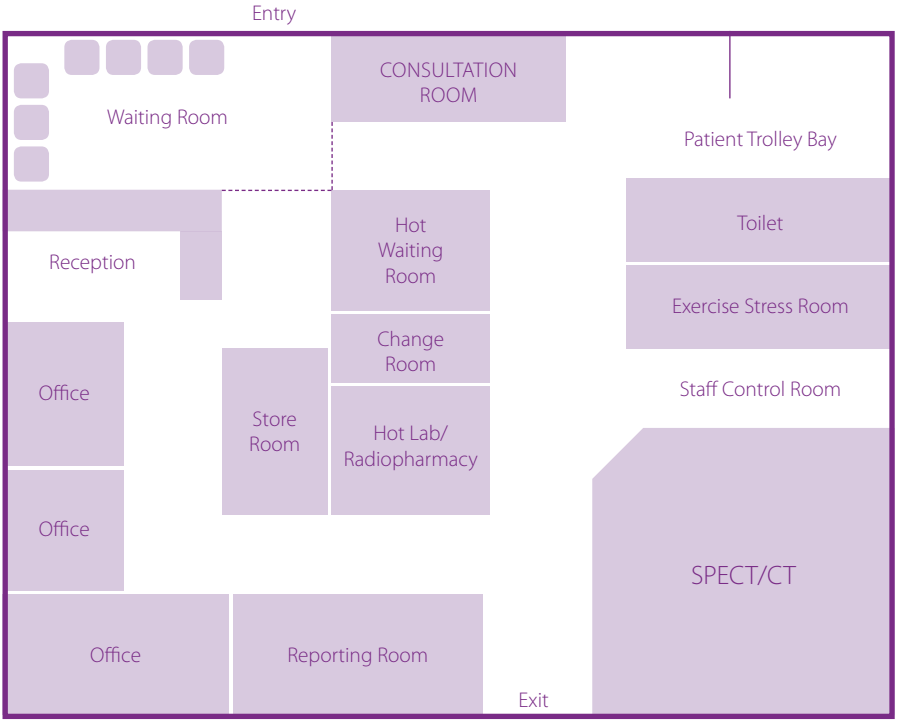

Figure 2: A sample floorplan for a small single gamma camera (either SPECT or SPECT/CT) that accommodates trolley bed patients and cardiac exercise stress testing

bicycle to be used for myocardial perfusion studies. The room will need to be fitted with a full emergency services panel and cardiac arrest response trolley with a defibrillator. A separate changing room may be needed, depending on the number of studies to be performed per day;
- Consultation/injection room equipped with the materials needed for injection of the radiopharmaceuticals;
- Reporting room with one reporting workstation;
- A small storage room for general stock items and non-medical stores;
- A small staff room with a beverage bay and sitting area that is located in a 'cold' or non-radiation area of the department.

Example 2 – two gamma cameras, with 1 × SPECT and 1 × SPECT/CT (Fig. 3)
- Waiting room to house up to ten patients;
- Reception and administrative staff area with enough space for two receptionist staff and an office for an office/data manager;
- SPECT camera room with the radiation shielding determined as per the regulations dependent on the isotopes to be used, size 40–42 m^2 (430–455 ft^2);
- SPECT/CT camera room with the radiation shielding determined as per the regulations dependent on the isotopes to be used. It is important to remember that a larger floorspace will be needed for SPECT/CT, usually up to 46–48 m^2 (495–517 ft^2);
- Gamma camera control room with space for up to three nuclear medicine technologists and located in a low patient occupancy section of the department, considered a 'cold' or non-radiation area for the staff;
- Patient toilet and a separate staff toilet;
- Hot laboratory and/or radiopharmacy for manufacture that includes a radioactive waste storage area. The size and equipment needs of the hot laboratory and waste storage will vary depending on the radionuclides used and the diagnostic or therapeutic services performed;
- Cardiac stress laboratory with a treadmill or bicycle to be used for myocardial perfusion studies. The room will need to be fitted with a full emergency services panel and cardiac arrest response trolley with a defibrillator;
- A pass-through hatch may be useful in certain areas within the department, for example between the hot laboratory and the cardiac exercise laboratory or the radionuclide therapy room. This will avoid staff transporting patient doses in heavy shielded canisters between rooms;
- A separate change room for the cardiac patients located either adjacent to or opposite the cardiac exercise stress room;
- A consultation or interview room with a patient trolley bed that can be used for brain perfusion and activation studies;
- An injection room equipped with the materials needed for administration of the radiopharmaceuticals to patients;

- Reporting room with two reporting workstations. The room will need to be adequately temperature controlled as there will be several high-end computers that generate heat, increasing the ambient room temperature;
- A small storage room for general stock items and non-medical stores;
- A separate staff room with a beverage bay and sitting area that is in a 'cold' or non-radiation area of the department;
- Patient holding bays to accommodate a patient transferred on a trolley or wheelchair. This is optional and may not be needed for departments that only accommodate outpatient procedures;
- A nursing staff station adjacent to the patient holding bays (optional, as above);
- Office area with up to two separate rooms to be used by the nuclear medicine physician/radiologist and a medical physicist,

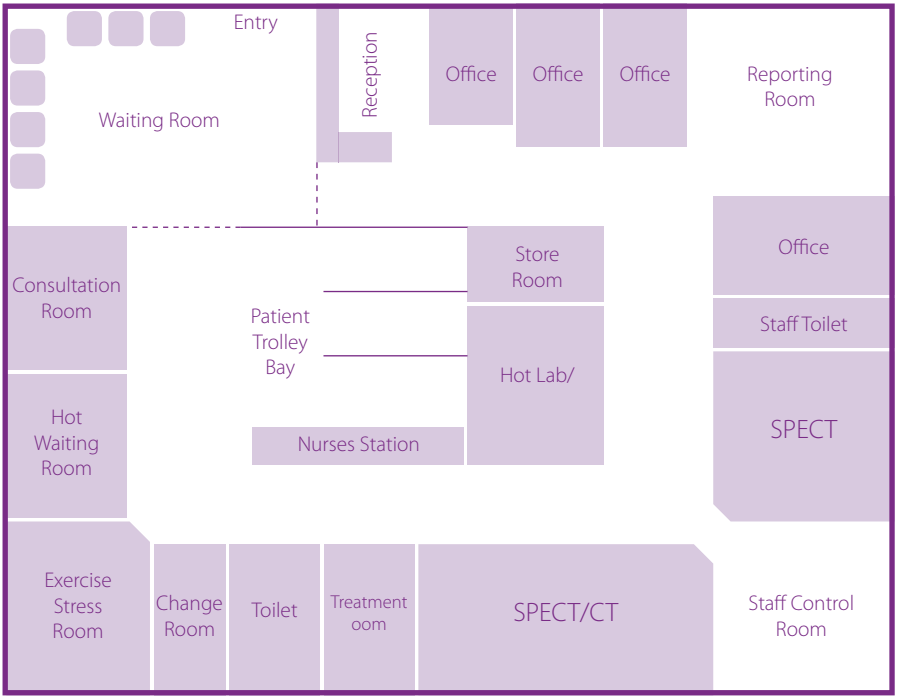

Figure 3: A sample floorplan for a two-gamma camera department with both a SPECT and a SPECT/CT that includes a separate change room, multiple holding bays for patient trolleys, a nursing staff station and a 'hot' radioactive patient waiting room

radiopharmacist or chief nuclear medicine technologist;
- A separate shielded waiting room to be used by patients following administration of the radiopharmaceutical, especially for tests that require patients to wait between imaging time points or to be monitored, e.g. cardiac patients. It is important to remember that there is a requirement that all attempts be made to keep the exposure to members of the general public, especially pregnant women and small children, as low as reasonably achievable (ALARA) [10, 11].

Example 3 – 1 × SPECT, 1 × SPECT/CT and 1 × PET/CT (Fig. 4)
- The nuclear medicine department should include the areas outlined in example 2; however, the waiting area will need space for up to 12 patients. The items listed below are specific to the PET/CT area.
- PET/CT camera room with a minimum size of 48–50 m^2 (516–538 ft^2) and the option to include radiation therapy lasers and treatment planning imaging palettes ('flatbed' palettes);
- A PET/CT equipment room that is temperature controlled, either in the camera room itself or located in a separate area in close proximity to the machine;
- A PET control room for up to three nuclear medicine technologists and a nurse;
- A separate PET patient toilet, which should be able to accommodate a patient in a wheelchair;
- A PET hot laboratory, which may include a small waste storage area if the facility will be using longer half-life tracers such as iodine-124 or copper-64;
- A consultation or interview room to be used for non-radioactive patients prior to injection;
- A common report room for both nuclear medicine and PET is preferable, with at least two reporting workstations, and it may be desirable to have a concertina door to separate the two reporting zones if needed;
- A separate change room located in the PET area close to the department exit so that patients can easily find the exit when finished, thereby minimising the PET staff radiation dose;
- Uptake rooms, with the number needed dependent on the type of PET system installed, the number and type of studies to be performed per day and the space available;
- If the facility will be performing studies on patients who require a higher level of care during the uptake period or plans to do complex procedures such as brain activation studies, catheterisation or anaesthetics, a larger uptake room (12–13 m^2 or 125-139 ft^2) will be required, fitted with full medical services including anaesthetics;
- A separate radiopharmacy specifically for manufacture, dispensing and tracer development. If a hot cell is required, remember to check the floor weighting and access to compressed air and

nitrogen. A hot cell can weigh up to 8 tonnes and require a large amount of space;

- A meeting room or combined meeting room/library is a good addition to larger departments to allow for internal as well as external meetings and to provide continuing education opportunities for the staff.

When defining the layout, functionality and workflow of the department, it is important to include clearly designated 'cold' or non-radiation areas for the staff at a reasonable distance from any radioactive sources, including the patients, X-ray sources such as CT and the hot laboratories. A separate 'hot' waiting area located within the department with appropriate shielding is suggested to minimise

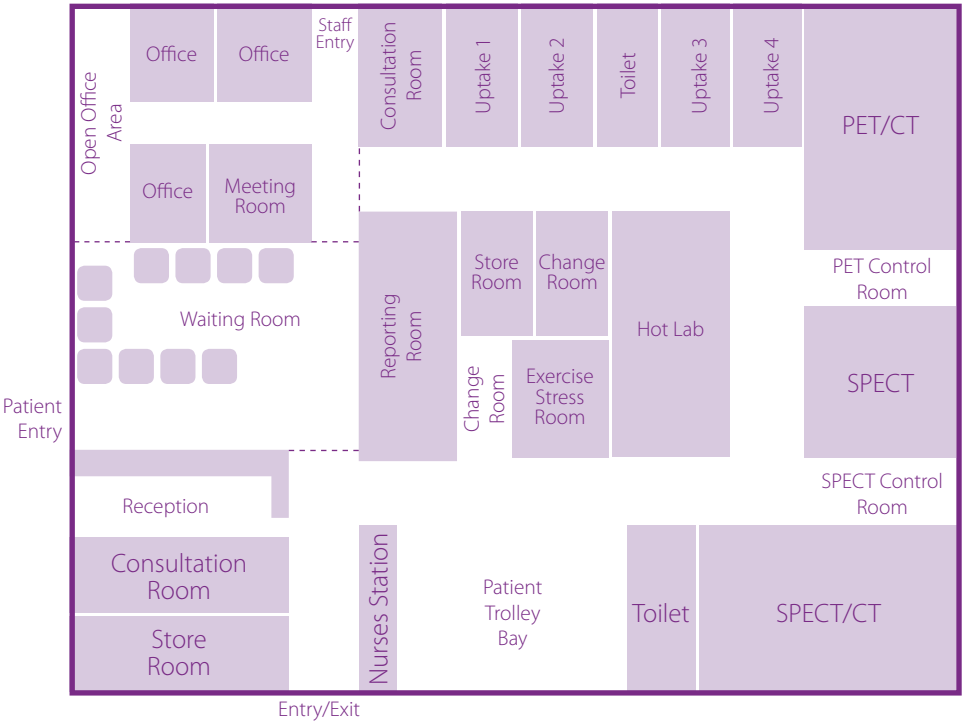

Figure 4: A sample floorplan for a larger department that includes two gamma cameras, both a SPECT and SPECT/CT, and a PET/CT. The addition of a meeting room/library can be used for continuing education of the staff and allows additional space for both internal and external clinical and non-clinical meetings

the radiation exposure to reception and administrative staff as well as members of the general public. The use of mobile lead shields may be helpful, especially in the radionuclide therapy areas, where nursing and other non-medical imaging staff may be monitoring the patient for medical complications.

Radionuclide therapy facilities

The equipment, floorspace, shielding, room layout and waste storage requirements will vary depending on the radionuclide therapies being provided and the radiation protection legislation specific to each country. The radiation exposure rate for a patient at the time of discharge following radionuclide therapy and the waste storage and disposal guidelines, e.g. with regard to the need for sewerage holding tanks, vary significantly between countries [3, 4, 11]. The mandatory shielding based on the radionuclides to be used, the minimum room size and the sewerage and waste requirements must be incorporated during the design phase.

Newer radionuclide therapies using lutetium-177 are commonly performed as a day procedure in most countries due to the low gamma emission (<15%) and the medium-energy beta emission. It is common practice to treat four to six patients in a single room, with each patient being administered 7–8 GBq and the treatment taking 4–6 h to perform. As part of the design process, consideration must be given to the total activity in the room at a given time as well as the occupancy rate of the room for staff, patients and visitors. The radiation shielding requirements with respect to infrastructure such as walls, flooring and ceiling, internal protection devices including mobile or fixed personal protective equipment, the minimum room size to safely accommodate six patients and the need for a separate toilet impact significantly on the room layout; it must be ensured that a 'cold' zone is provided for the staff involved in administering the therapy and monitoring the patient [12].

The use of radioactive iodine, specifically iodine-131, for treatment of thyroid cancer or for labelling of mIBG or Lipiodol in the treatment of metastatic phaeochromocytoma, neuroblastoma or liver cancer, will require a fully equipped isolation room or ward. The room size, radiation shielding, waste storage facilities (including holding tanks for biological radioactive waste) and discharge exposure rates should be determined on the basis of the radiation regulations and guidelines for the individual country. Patients treated with iodine-131 must be admitted and isolated from the general public for a period of time that will vary between countries. The determination of the isolation period is based on a number of factors including the administered activity, the allowable exposure rate at the time of discharge and personal factors specific to the patient including living arrangements, cognitive ability and independence status as measured using, for example, ECOG performance status scoring [13].

Radiation safety and regulatory considerations

The radionuclides to be used in the department and the number of X-ray imaging equipment items, such as CT, to be installed will impact dramatically on the level of shielding required. The AAPM, ICRP and IAEA provide detailed guidelines on shielding requirements that are recognised internationally [10, 14]. These guidelines should be used under the guidance of a medical physics expert and consideration must be given to the routine doses administered for each procedure and the number of studies to be performed per day as these factors will impact on the amount of any particular radioisotope that will be stored and used in the hot lab, and the radiation level of the unsealed ('hot' patient) sources moving throughout the department.

The IAEA and local authorities from many other countries provide comprehensive state-based, national and international guidelines on radiation protection and waste storage. Area monitoring of the background radiation and contamination in staff areas may be a regulatory requirement. This may include the checking and recording of contamination on the skin or clothing for staff working in the hot laboratories, mandating the need for wall or bench mounted surveillance meters at the exit of the laboratory. Waste storage needs will be determined by the tracers and isotopes used, if they are gamma, beta or alpha emitters, the energy and half-life of the products manufactured and the activities. This is less of an issue in PET due to the short half-life of most PET tracers; however, if iodine-124 or copper-64 are to be used, then a heavily shielded long-life waste storage should be located near the PET laboratory [15]. These guidelines often include information on security of sources and each country will have specific regulations with which you will need to comply. It is therefore important to identify during the design phase a secure delivery access point for the daily radiopharmaceutical deliveries that uses a path with a low general public occupancy rate.

Nuclear medicine department design: A step-by-step guide

The process for designing a new department or remodelling an existing layout will vary between departments and even countries due to differences in the role of the various stakeholders and staff members and the mandated regulations. This is a step-by-step guide to designing a nuclear medicine department from the perspective of a nuclear medicine technologist that can be used as a guide.

I. Identify the size, shape and location of the proposed floorspace.
II. List the equipment needs and the types of equipment that will be installed in the new department.
III. Review the guidelines and regulations specifically relating to minimum room size, room fit-out specifications such

as medical services, power, and air conditioning as well as the fire safety and radiation safety regulations for shielding and occupancy. This should be done in consultation with a medical physicist or a radiation safety expert.

IV. Determine the department workflow for patients, staff and visitors. This will assist in defining the restricted and limited access areas, the 'hot and 'cold' areas within the department and the location of staff amenities such as staff recreation room, lockers and toilet.

V. Draft a layout for the department to include all equipment and services.

VI. In consultation with the other relevant stakeholders, create a room data sheet for each area or room within the department that concisely defines the room specifications, both medical and non-medical.

VII. Review the room data sheets with a focus on lighting, temperature control (especially in the PET area), medical service needs for each space, power (including high voltage for rooms in which CT equipment is to be installed) and the type of flooring and bench surfaces in the radiation area, including camera rooms and hot laboratories. Review the number and location of data outlets for computing equipment and the location of CCTV monitors.

VIII. Modify the draft plan after reviewing the room data sheets and confirm that the layout will meet the needs of the department and other invested stakeholders such as patients and referrers.

Technologist's role in the design process

The technologist is an integral part of the design team and is the best person to advise on workflows, clinical procedures and patient needs. There are certainly particular tasks for which the technologist should have ownership and these have been identified as:

a. Determine the patient, staff and general public workflow. This will include identifying how patients will move through the department when undergoing procedures. This may differ between outpatients and inpatients, between walking patients and patients who are in a wheelchair or bed bound, and between PET and other nuclear medicine procedures.

b. Provide details on the number of staff employed and their role within the department. This will help to identify staff who will require a separate office and to assess the need for any shared office space, separate physics laboratories, radiopharmacy facilities for manufacture and dispensing and meeting rooms or library facilities for ongoing education and professional development. It can also identify training needs and discrepancies in the skills of the existing staff.

c. Review the current types and number of studies performed daily, weekly and monthly and evaluate whether this will change in the new or updated facility. This information will be used to determine the equipment needs and the expected occupancy rates of the rooms and to identify any future staff education or training needs. The medical physics expert can then use this information to determine the shielding requirements for each space.

d. Accurately determine future storage needs. Storage of both clinical and non-clinical equipment can often be problematic in new facilities, so this assessment is important. It is common for a new department to increase its workload in the first 12 months of operation so the design must take into consideration future development and growth to include room for expansion.

e. Carefully review the room data sheets, which will list all services, equipment, furnishings and flooring for each area. Specifically look at:

   ix. Lighting
   x. Air conditioning or temperature control, especially in a PET facility
   xi. Data and power outlets
   xii. The height and depth of the benches, desks and workstations
   xiii. The location of any CCTV monitoring to comply with the safety regulations for patient monitoring during a procedure
   xiv. The optimal location of handwashing facilities to comply with infection control legislation
   xv. What you will need in each of the rooms if you will be doing paediatric studies: perhaps a TV and/or DVD player in the camera room, a separate children's area in the waiting room or extra storage for immobilisation devices

a. Review the manual handling policies and ensure compliance with these, especially in areas such as the hot laboratory and radiopharmacy where staff may be required to lift heavy equipment, e.g. molybdenum-99 generators. Similarly, review infection control standards to ensure that the design will comply with these and consider the number and location of hand-washing facilities, the need for a dirty utility or pan room, the types of flooring used in clinical areas and the benchtop surface materials for the hot laboratory.

b. If new equipment is to be installed, assess the staff education and training needs and develop a training programme in consultation with the manufacture. This will also include identifying changes in workflow and writing or updating any new protocols and procedures.

The technologist can also play an important part in reviewing the future direction of the

department and consult with the other nuclear medicine professionals to outline a plan for implementing any potential new services. This could be the testing of new tracers, the addition of new technologies such as PET/MRI and increasing staff participation in research.

Conclusion

As a technologist, being involved in the development and design of a new department or modifications to an existing department can be very rewarding and challenging. It will assist in developing your understanding of the importance of a well-designed department that has good workflow for patients and staff, creating a safe environment for everyone. The most important step is to pre-plan the functionality and services to be offered and to understand the needs of the patients, referrers and institution that will be using your services. Allowing for future development and the introduction of new procedures in the design plan will ensure that your department can be progressive, provide a high level of service and be a rewarding place to work.

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