Radiation Risk

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2.1 Introduction

The practice of nuclear medicine leads to a potential risk of exposure for the patient. The activity of radiopharmaceutical should be administered in order to guarantee the correct balance between risks and benefits. In the last years, the introduction of technological advances, the increased availability of scanning equipment, and new radiopharmaceuticals lead to an intensified use of nuclear medicine examinations. On the one hand, these improvements involved in a remarkable progress in image quality; on the other hand, technological advances do not necessarily imply a decrease in patient exposure to ionizing radiation. The implementation of radiation protection practices aimed to limit radiation exposure in nuclear medicine exams is an utmost need. For pediatric patient, a more attention has to be paid as they have higher tissue radiosensitivity and longer life expectancy.

2.2 Effects of Ionizing Radiations

A type of radiation which has enough energy to eject electrons from atoms or molecules is defined as ionizing radiation. It is well known that the interaction between ionizing radiation and biological tissues or organs may cause changes in cells which may later cause them to become malignant or bring about other detrimental functional changes in irradiated tissues and organs. It is important to note that irrespective of the nature of the primary radiation (which may be composed of particles and/or electromagnetic waves), the energy transfer mechanism always occurs via the secondary electrons which are produced by interaction between the primary radiation beam and the biological targets. At the microscopic level, when incident rays or particles interact with orbital electrons within the atoms, two processes through which radiation interacts with matter can happen: one of these processes is the excitation, the other one is the ionization [14]. Excitation involves raising a bound electron to a higher energy state, leaving the atom in an excited state, while ionization happens when the electron receives sufficient energy to be ejected from its orbit and to leave the host atom. These physical interactions between radiation and specific structures within the cells can cause more or less serious biological damages. These latter are associated to the interaction of radiation with deoxyribonucleic acid (DNA) and can mainly occur through direct and indirect processes.

The direct interaction implies a direct damage of DNA structures after ionization of atoms or molecules, through a sequence of chemical events which can provoke the final biological damage. This is the dominant process for highly ionizing particles, i.e., heavy charged particles, proton and neutrons. On the contrary, the indirect interaction involves secondary electrons which are ejected during the ionization process. These secondary particles, energetic and unbound, are capable of migrating away from the site of their production giving up their energy to the surrounding medium, through a series of interactions with other atoms and molecules. This energy absorption process results in the formation of free radicals and other chemical species, i.e., more reactive molecules which are the true causatives of damages of critical targets in the cells [2].

For example, when the radiation interaction happens with water molecules, the created highly unstable free radicals, such as water ions (H_2O^+) and hydroxyl ($OH^{\cdot}$), can spread through the cell interacting even with distant cellular target. The indirect interaction and its consequently biological detriment are mainly caused by sparsely ionizing radiation, i.e., electrons or x-ray.

In the events timescale, the initial ionization event occurs instantaneously (~10^{-18} s) at the microscopic level, while the chemical changes may appear to operate over a timescale of about 10^{-5} s. Thus, the period during which the chemical damage is caused is relatively long on the microscopic scale.

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These events are the precursors to a chain of subsequent events which may eventually lead to the clinical (macroscopic) manifestation of radiation damage. The clinically observable radiation effects, whose timescale may extend to years, are expressed as the results of the functional impairment after lethal damage inflicted to large numbers of cells or critical substructures [3].

Dealing with these macroscopic effects, an important distinction has to be made between low and high dose effects, whose consequences on biological tissues are really different. This concept is highlighted by the NCRP Report No. 136 [15] and by the BEIR VII Report [10] where a fundamental distinction is made: low to moderate doses encompass the values between 0 and 100 mSv, while high doses include values greater than 100 mSv.

Moreover, a distinction of the effects of ionizing radiation on biological tissues is often made according the required time for the effects to manifest. If an effect occurs within several hours or days after the exposure of the individual to extremely high doses, it is considered as an acute effect. Conversely, delayed or latent effects manifest several weeks or years after the exposure.

In some cases, the damaged component of the genetic material is essential for cell survival, and the cell may die or not be able to undergo proper mitosis. The removal of these cells will not contribute to late radiation effects such as carcinogenesis. Instead, late effects occur when the cell survives the initial genetic damage. The consequences of this damage manifest later, perhaps decades after the initial exposure; such late effects may result from genomic instability due to the initial radiation damage. In particular, cells that are growing rapidly and undergoing mitosis at a higher rate may be more susceptible to late radiation effects than those that are growing more slowly [9].

On the basis of these considerations, the radiation effects can also result in a radiation detriment, which is defined as the harm that would eventually be experienced by an exposed group and its descendants as a result of the group's exposure to a radiation source [11].

The radiation damage may be classified as being either deterministic or stochastic.

Deterministic effects are characterized by a threshold dose level. These effects manifest themselves in the form of harmful tissue reactions, i.e., cataract induction, general radiation syndromes, bone marrow ablation, which could manifest after an exposure to high radiation doses. Above the threshold dose level, the severity of the effect is linearly dependent with dose: if the amount of radiation dose is increased, the lesion severity also grows depending on the number of damaged cells [11].

Stochastic effects, which include both carcinogenic and hereditary effects, are those for which the likelihood of occurring is dose related, but the severity of the resultant condition is not related to the dose received. They may occur without a threshold dose, and for them, an increase on radiation dose will result in a growth of the probability of occurring [11].

In the field of Nuclear Medicine (NM) diagnostic uses, stochastic effects have to be predominantly considered as potential side effects while, for radionuclide therapy applications, the concerns relate to both stochastic and deterministic effects [12].

In addition, there are other parameters that influence the radiation effects and that need to be discussed. In fact, it is well established that the risk of ionizing radiation varies with both age and sex. In particular, for pediatric patients, the risk of radiation effect is higher than in adults. This behavior can be attributed to a twofold cause: on one hand, the tissues of younger subjects are more radiosensitive as they are actively growing and, on the other hand, life expectancy in young people is higher than in adults allowing a longer time for the risk to be realized. Moreover, girls demonstrated a higher risk for cancer induction than boys, which is, in large part, attributable to the excess risk of breast cancer in this population [9].

2.2.1 Evaluation of Radiation Exposure in Nuclear Medicine

Nuclear medicine procedures involve the use of radiopharmaceuticals that emit radiations such as γ-rays, α-particles, β-particles, and positron. These emissions expose the patient to ionizing radiation that might lead to detrimental health effects [11]. Nuclear Medicine offers the possibility to detect early stages diseases, and its non-invasive nature allows to use it as a powerful diagnostic tool in examinations involving children. The administered activities in nuclear medicine procedures are well established in many specialties including oncology, urology, cardiology, gastroenterology, and orthopedics. For pediatric patients, it is highly recommended that practitioners of pediatric nuclear medicine have to develop a knowledge in understanding radiation risk and dosimetry and how this risk may vary in children relative to adults. Using nuclear medicine procedures, expected clinical results can be guaranteed using the lowest possible administered activities and, thus, the minimum necessary risk for patients. To this purpose, as recommended by the Society of Nuclear Medicine and Molecular Imaging, the key to

dose optimization is to perform the right test with the right dose on the right patient at the right time [8]. In order to estimate the dose received by organs and tissues during nuclear medicine procedures, the knowledge of bio-kinetic models about the incorporated radionuclides is needed.

The methodologies developed to assess dosimetric evaluations in nuclear medicine are mainly two: one of these models was developed by the International Commission on Radiological Protection (ICRP) [12], and the other one by the Medical Internal Radiation Dose (MIRD) Committee of the United States Society of Nuclear Medicine [16]. Based on the same theoretical considerations, MIRD model is focused on biological endpoints for which the knowledge of intake is necessary, while ICRP also gives an estimation of the radiation detriment.

The theoretical approach of both methods will be discussed in the following paying particular attention to how risk varies with age. Moreover, the radiation risk and dose calculation will be discussed later for pediatric nuclear medicine.

The calculation of the absorbed doses by the different organs or tissues is based on the definitions of sources and target organs. The target organs or tissues are those for whom the absorbed doses may arise as a result of radioactive decays occurring in other organs, the so-called source regions.

Thus, the absorbed dose in a particular organ or tissue is calculated as the sum of contributions from various sources, including the target organ or tissue itself.

In order to take into account the different radiosensitivity of organs or tissues, ICRP introduced a dosimetric quantity named effective dose. This definition allowed an overall cancer risk computation for a situation in which different organs receive different doses, with or without external irradiation of the whole body.

According to ICRP model, the mean absorbed dose $D(T \leftarrow S)$ to a target organ or tissue T is the sum of the contributions arising from nuclear transformations of the radionuclide in various source organs S and it is given by:

$$D(T \leftarrow S) = \tilde{A} \times \frac{1}{M_T} \sum_i E_i Y_i \varphi_i = \tilde{A} \times S(T \leftarrow S)$$

where $\tilde{A}$ is the time-integrated or cumulated activity, equal to the total number of nuclear transformations in S, and $S(T \leftarrow S)$ is the absorbed dose in T per unit of cumulated activity in S.

The other symbols have the following meaning: M_T is the mass of the target organ or tissue, E_i is the mean energy of radiation type i, Y_i is the yield of radiation type i per transformation, φ_i is the absorbed fraction of energy of radiation type i.

$\tilde{A}$ is the bio-kinetic component, $S(T \leftarrow S)$ represents the physical-geometrical component, as it depends on the radiation type, on the energy emitted per transformation, on the mass of the target organ, and on the geometry of the mathematical phantoms representing the adult and children of various ages.

This model is essential to estimate the dose absorbed by the different target organs or tissues. However, if we wish to compare different procedures and the resulting patient doses for assessment of risk versus benefit, the more appropriate parameter to be consider is the effective dose, as it takes into account the different organs sensitivities. ICRP 106 also reports, for each radionuclide, the bio-kinetic model, the bio-kinetic data, the absorbed dose, and the correspondent effective dose per unit of activity administered for different ages (Adult and 15, 10, 5, 1 years old) [12].

The MIRD Committee follows the same theoretical dosimetric approach described above for ICRP. For each source organ, the radiation dose is calculated and summed to determine the total dose to the target organ.

For pediatric patients, the radiopharmaceutical dose varies from that to an adult as organ masses of children differ from those of adults because they are smaller and closer together. S values for patients of different ages can be used to estimate the radiation dose to children. However, both ICRP and MIRD methods do not take into account individual differences in anatomy and physiology from the standard models. The patient's body may vary from the standard with respect to size, weight, shape, organ orientation, and distances from other organs. These models also make assumptions with respect to the amount of source organ radioactivity, including rates for uptake and clearance of the radiopharmaceutical from that organ. These methods were developed for estimating the average dose to a population and should not be used to estimate the dose to a specific patient [11].

Even though models have traditionally used simple shapes representing the organs, more realistic voxel-based models have been developed with the aim to provide more accurate dose estimations [4]. Using these methods, the radiation dose to organs of patients of different sizes and ages can be estimated.

The software code Organ Level INternal Dose Assessment/EXponential Model (OLINDA/EXM) [17] has been developed to facilitate automated and standardized internal dose calculations for nuclear medicine applications. The OLINDA/EXM code uses the same technical basis (phantoms, organ masses, equations, relationships assumed, and other details) reported by MIRD [16].

2.2.2 Radiation Protection Principles and Considerations on Diagnostic Reference Levels

The ionizing properties of radiation and the correspondent biological effects have to be taken into account in order to implement some radiation protection measures. The ICRP on its 2007 Publication [11] states that practices involving the use of ionizing radiation are regulated by three fundamental principles of radiological protection: justification, optimization, and limitation of doses.

According to the first principle, any medical practice involving patient exposures must be justified: any decision that alters the radiation exposure situation should do more good than harm [11]. It should be in the right balance between risk and benefit, taking into account social, economic, and technical factors involving the realization of the procedure itself.

The second principle states that once the exposure to ionizing radiation is justified, each examination must be performed so that individual doses should all be kept as low as reasonably achievable (ALARA), taking into account economic and societal factors [11].

Dose limits are established to ensure that no individual is exposed to radiation risk level exceeding the appropriate limits recommended by the ICRP. Medical exposure is not subjected to the third principle but to the first two only [5].

In 1997, the European Council of Ministers, following the recommendation of the ICRP in its Publication 73 [13], issued the Medical Exposure Directive (MED) [5] which introduced the Diagnostic Reference Levels (DRLs) for diagnostic exams.

DRLs are part of the quality assurance program and are defined as the dose levels in medical diagnostic practices or, in case of radiopharmaceuticals, levels of activity, for typical examinations for groups of standard-sized patients or standard phantoms for broadly defined types of equipment [5]. DRLs are primarily intended to offer benchmark values as a rough guideline for appropriate practice and can be considered as a useful tool to help physicians in realizing best practices [1]. These levels are expected not to be exceed for standard procedures when good and normal practice regarding diagnostic and technical performance is applied.

In diagnostic nuclear medicine, DRLs are expressed in terms of administered activity. This latter is based on the administered activity necessary for a good image during a standard procedure. DRLs can be used for diagnostic examinations in clinical practice to different aims: set standards to identify average doses, compare local practice with peer institutions and national levels, provide required protocol settings for local practices, and provide legal justification in event of malpractice law suit. However, as administered activity is not expected to be exceeded in standard procedures, it should be approached as closely as possible to produce optimized images [6]. This is the reason because in nuclear medicine an "optimum" value for DRL is used. On the basis of the experience of the professional groups, it is recommended to nationally set reference levels for administered activities of radionuclides with the aim to obtain information for standard groups of patients (adults and children).

In therapeutic nuclear medicine, where all exposure of target tissues should be specially planned for each patient, so that the doses are as low as possible in nontarget tissues, a system of reference levels is not applicable.

The administered activities are highly dependent on the procedures used. Poorly functioning gamma camera or other chain imaging equipment, the calibration of the activity-meter, the nuclear medicine staff expertise can influence DRL values. Therefore, not only it is highly difficult to compare administered activities without knowing precisely the protocol used, but also there is a large variation between DRLs given by different countries. Not all European Member States have still recommended DRLs for nuclear medicine [7].

Only the 64 % of the European countries set DRLs for NM exams, while the 33 % have no DRLs and the data of the remaining 3 % are unknown (Fig. 2.1).

Most European countries provided optimal values for almost all types of examinations produced by the professional groups and approved by the competent authorities, giving national DRLs for NM procedures [7]. The existence of specific guidance showed that some countries had included references for the DRLs such as published guidance, reports or results of national surveys.

It should be noted that DRLs are based on administered activities used for normal size patients (70 kg). If the adult patients are of a nonstandard size, the injected activities need to be correspondently adjusted. A pro-rata adjustment by patient weight is the simplest method to allow for patient size variation [6].

Regarding pediatric patients, it is highly important to give guidance for a dosage and the following effective dose.

For children the administered activity has to be a fraction of that for adults: this can be assessed on the basis of child weight or by age. Basing the evaluation simply on weight, the resulted activity uptake is comparable to that for adults of less weight, but for children aged under 10, it could not be the right strategy due to children smaller organ masses or to a shorter retention times. The European Association of Nuclear Medicine's Task Group on Pediatrics has produced a list of fractions of adult activity (Table 2.1) which gives an acceptable image quality using nomograms for surface area [6].

These fractions are suitable for most nuclear medicine examinations. Both methods require a minimum activity of 1/10th of the adult value and should be used to ensure that imaging times are acceptable in young children (see Table 2.2) [6].

The employment of DRLs in nuclear medicine clinical practice can ensure the right balance between image quality for a specific diagnostic task and the administered activity, especially for pediatric patients.

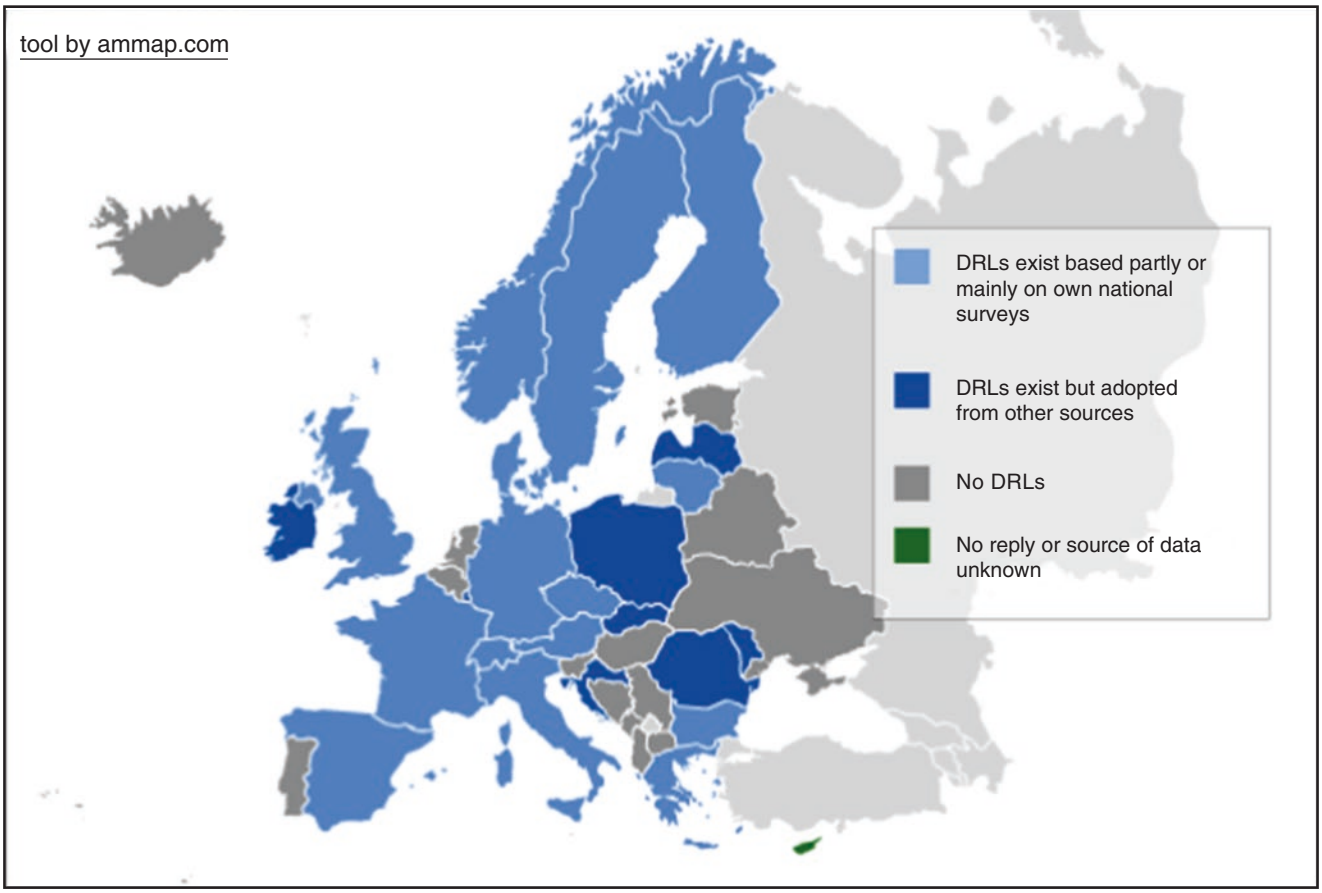

Fig. 2.1 Adoption of national Diagnostic Reference Levels for NM examinations in European countries [7]

Table 2.1 Fraction of adult administered activity for different age groups of children recommended by the Pediatric Task Group of the European Association of Nuclear Medicine [6]

kg	Fraction of adult administered activity	kg	Fraction of adult administered activity	kg	Fraction of adult administered activity
3	0.1	22	0.50	42	0.78
4	0.14	24	0.53	44	0.80
6	0.19	26	0.56	46	0.82
8	0.23	28	0.58	48	0.85
10	0.27	30	0.62	50	0.88
12	0.32	32	0.65	52–54	0.90
14	0.36	34	0.68	56–58	0.95
16	0.40	36	0.71	60–62	1.00
18	0.44	38	0.73	64–66	
20	0.46	40	0.76		

Table 2.2 Minimum amounts of administered activities for children [6]

Radiopharmaceutical	Minimum administered activity for children (MBq)
Gallium-67-citrate	10
I-123-Amphetamine (brain)	18
I-123-Hippuran	10
I-123-Iodide (thyroid)	3
I-123-MIBG	35
I-131-MIBG	35
Tc-99m-albumin (cardiac)	80
Tc-99m-colloid (liver and spleen)	15
Tc-99m-colloid (marrow)	20
Tc-99m-colloid (gastric reflux)	10
Tc-99m-DTPA (kidneys)	20
Tc-99m-DMSA	15
Tc-99m-MDP (phosphonate)	40
Tc-99m-spleen (denatured RBC)	20
Tc-99m-HIDA (biliary)	20
Tc-99m-HMPAO (brain)	100
Tc-99m-HMPAO (WBC)	40
Tc-99m-MAA or microspheres	10
Tc-99m-MAG3	15
Tc-99m-pertechnetate (micturating-cystography)	20
Tc-99m-pertechnetate (first pass)	80
Tc-99m-pertechnetate (Meckel's diverticulum/ectopic gastric mucosa)	20
Tc-99m-pertechnetate (thyroid)	10
Tc-99m-RBC (blood pool)	80

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