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Small-Scale Dosimetry: Challenges and Future Directions

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The increased specificity of targeting agents has resulted in an interest in the use of radionuclides that emit particulate radiation: alpha particles, beta particles and Auger electrons. The potential advantage of these radionuclides is the ability to deliver therapeutic doses to individual tumor cells while minimizing the dose to the surrounding normal tissues. However, the dosimetry of these radionuclides is challenging because the dose must be characterized on a scale that is comparable to the range of these emissions, ie, millimeters for beta particles, micrometers for alpha particles, and nanometers for Auger electrons to. In this review, each class of particulate emitter is discussed along with the associated dosimetric techniques unique to calculating dose on these scales. The limitations of these approaches and the factors that hinder the clinical use of small-scale dosimetry are also discussed.
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In recent years, there has been increasing interest in combining biologically specific targeting agents (ie, antibodies, peptides, etc.) with short-range particulate radiation emitters (alpha particles, beta particles, Auger electron emitters).[1-9] This therapeutic combination offers the potential of delivering lethal doses of radiation to individual tumor cells while minimizing the volume or normal tissue irradiated. Dosimetrically, these advances present a significant challenge. In the past, absorbed dose in nuclear medicine was often estimated at the organ level based on idealized models.[10-12] Calculation of absorbed dose on this scale has been sufficient for photon emitters used in imaging applications. However, for particulate emitters in therapeutic applications, the dose needs to be determined on a scale that is comparable with the range of emission. This scale is on the order of millimeters for beta particles, micrometers for alpha particles, and nanometers for Auger electrons. Although the formalism established by the Medical Internal Radiation Dose (MIRD) Committee may be adapted to these dimensions,[13,14] other factors also need to be considered. These factors include the effects of tissue heterogeneities,[15-17] stochastic variations in the amount of energy deposited in subcellular targets,[18-20] and the geometry of the target itself (ie, DNA).[21-24] In this review, we describe the calculational techniques used for short-range particulate radiation. Following a discussion of the MIRD method, each particulate radiation type is presented along with the specific calculational approaches that are unique to the emission. The limitations of these approaches along with the opportunities and future directions are discussed.

MIRD Method

In 1968, the MIRD Committee established the formalism for dose calculation from internally deposited radionuclides reducing the complex nature of the absorbed dose calculation into a simple mathematical form.[10] The MIRD schema provides methods for calculating the absorbed dose from the source-activity distribution and the physical properties of the radionuclide. This calculation is simply the conversion of activity in a source organ into the energy absorbed per unit mass in the target organ. In the MIRD schema, the mean absorbed dose, $\bar{D}$, within the k^{th} target from the i^{th} source is defined as:

$$\bar{D} = \tilde{A}_i \sum \Delta_j \frac{\phi_j\,(k \leftarrow i)}{m_k} \qquad (1)$$

where $\tilde{A}_i$ is the cumulated activity from the i^{th} source, Δ_j is the mean energy emitted per nuclear transition from the j^{th} transition, ϕ_j is the absorbed fraction, representing the fraction of

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energy emitted from the i^{th} source which is absorbed by the k^{th} target, and m_k is the mass of the target.[10] In this equation, Δ_j depends only on the decay properties of the radionuclide of interest and is given as the product of the number of particles (photons or electrons) of type j (n_j), and the mean energy per particle (E_j) of type j such that:

$$\Delta_j = K\, n_j E_j \quad (2)$$

where K is a proportionality constant with a value that depends on the units chosen for Δ_j and E_j. The absorbed fraction ϕ_j has values between 0 and 1 for penetrating radiations (photons) and is typically assigned to be equal to 1.0 for so-called "nonpenetrating" radiations (eg, alpha particles, Auger electrons, beta particles).

To further simplify the MIRD calculations, all physical data can be combined into single parameter known as the S value, which represents the mean dose deposited per unit cumulated activity,

$$S = \sum \Delta_j\, \phi_j(k \leftarrow i)/m_k. \quad (3)$$

Thus, the mean absorbed dose to the k^{th} organ, based on the MIRD schema, can be written as follows:

$$\bar{D} = \sum \tilde{A}_i S(k \leftarrow i). \quad (4)$$

Equation 4 can subsequently be rearranged as follows:

$$\bar{D} = A_0 \tau \sum S(k \leftarrow i) \quad (5)$$

where τ is the residence time which can be defined as the "average" or "effective" life of the initial activity (A_0) in the source organ. MIRD Pamphlet 11 characterized the S values for 117 radionuclides and many source/target organ pairs based on the MIRD anthropomorphic model.[11] Almost 20 years later, Stabin and Siegel published a compendium of nuclear medicine dose factors (an equivalent quantity to the S value as suggested by the authors) for 816 radionuclides.[25] This report used the most current decay data and phantoms for internal dose calculations.

Small-Scale Dosimetry

The development of the S value tables for a wide range of source/target organs and radionuclides have simplified internal dosimetry calculations. Moreover, the MIRD method is sufficiently general such that it can be applied to source/targets of any dimension (organs to subcellular regions).[13,14] However, the accuracy of these calculations is limited by the size of the source region that can be accurately quantified. Until the late 1970s, planar imaging was primarily used, and the MIRD method was only applied to organ-level dosimetry.[26-30] Suborgan dose calculations were made possible with positron emission tomography (PET) in the late 1970s and with single-photon emission computed tomography (SPECT) imaging in the early 1980s. These suborgan models included a multi-region heart[31] and kidney models.[12,32]

Quantification of nonuniform time-dependent activity (via PET or SPECT) with a resolution of 3 to 6 mm increased the accuracy of the MIRD method, thus allowing for voxel-based dosimetry. Dosimetry at this level is of interest in radioimmunotherapy, radioiodine therapy, and intratumoral radiopharmaceutical injections. MIRD Pamphlet 17 provides tabulated S values for 3 and 6 mm voxels from a nonuniform activity distribution for five of the most commonly used radionuclides.[33] This work has subsequently been expanded to voxel phantoms for internal dosimetry.[34] A comparison of internal radiation doses estimated by MIRD Pamphlet 17 and voxel techniques for a family of realistic phantoms was published in 2000.[35] These realistic phantoms were based on computed tomography (CT) images of humans. Because of the individual anatomical differences, some disagreements between these models and the MIRD model values were observed. Zankl and coworkers reported similar conclusions, including very large variations among voxel models for low-energy photon emitters.[34]

As more highly specific targeting strategies are developed that use short-range emissions (alphas, betas, Auger electrons), it is evident that the average dose at the organ or voxel level is less meaningful. For example, the mean organ or tumor dose alone does not correlate well with the biological effects observed with Auger electron emitters.[36] Within a group of cells, there is also considerable evidence that the dose individual cells receive may vary largely along with the associated biological response.[37] Thus, cellular and subcellular dosimetry has many applications in therapeutic studies where knowledge of the absorbed dose to individual cells and their nuclei is required. These applications include radiolabeled blood cells, ascites, isolated cells in an organ that preferentially incorporate a radiopharmaceutical, and cultured cells in the laboratory.

In 1997, the MIRD schema was extended to provide S values to calculate dose at the cellular level.[38] A simple cellular model was proposed consisting of two concentric homogenous spheres of unit density representing cell and cell nucleus. Figure 1 depicts the MIRD cell model showing the nucleus, cytoplasm and cell surface compartments. Typical cell diameters (R_C) and the corresponding cellular nucleus diameters (R_N) ranged from 6 to 20 μm and 4 to 18 μm, respectively. The activity was assumed to be uniformly distributed in one of the cellular compartments (ie, whole cell, cytoplasm, or nucleus). Cellular S values for emitters of mo-

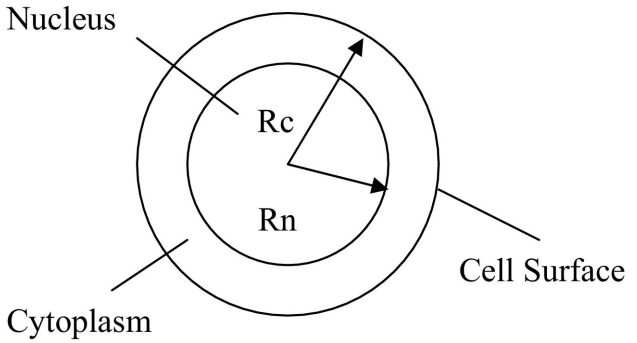

Figure 1 MIRD cell model (adapted from ref. 38) consisting of 2 concentric spheres representing the nucleus, cytoplasm and cell surface compartment modeled.

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