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INTERNAL RADIATION DOSIMETRY FOR
CLINICAL TESTING OF RADIOLABELED
MONOCLONAL ANTIBODIES

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ABSTRACT

In gauging the efficacy of radiolabeled monoclonal antibodies in cancer treatment, it is important to know the amount of radiation energy absorbed by tumors and normal tissue per unit administered activity. This paper describes methods for estimating absorbed doses to human tumors and normal tissues, including intraperitoneal tissue surfaces, red marrow, and the intestinal tract from incorporated radionuclides. These methods use the Medical Internal Radiation Dose (MIRD) scheme; however, they also incorporate enhancements designed to solve specific dosimetry problems encountered during clinical studies, such as patient-specific organ masses obtained from computerized tomography (CT) volumetrics, estimates of the dose to tumor masses within normal organs, and multicellular dosimetry for studying dose inhomogeneities in solid tumors. Realistic estimates of absorbed dose are provided within the short time requirements of physicians so that decisions can be made with regard to patient treatment and procurement of radiolabeled antibodies. Some areas in which further research could improve dose assessment are also discussed.

INTRODUCTION

Ionizing radiation induces molecular changes leading to biological damage. The relationship between radiation dose and biological effectiveness is therefore one of the most important associations in radiation research. Reliable absorbed-dose calculations in radioimmunotherapy are essential for the assessment of tumor response to absorbed dose, evaluation of normal-tissue toxicity, and for treatment-planning [1].

Physicians treating cancer need to know the radiation absorbed dose (or "average" dose) to tissues of interest*. The amount of energy imparted to tissue may be calculated by integrating the time-activity curves through complete radioactive decay or biological clearance. These values are estimated from data obtained by quantitative gamma-camera imaging and/or direct counting of excised tissues or samples of systemic fluids or excreta at several time points. Cross-organ irradiation by penetrating radiations must also be considered. Accounting for all sources of energy, the shape and density of organs, and the changing concentrations of activity in all organs and tissues, can become a rather complex task. The quality and reliability of dose estimates for administered radiolabeled antibodies depend on the quality of the measurement data and the methods used to calculate doses from those data; uncertainties in both measurements and dose calculations can be reduced by improvements in technique. Unfortunately, the more accurate methods for obtaining dosimetry information can also be the more invasive, time-consuming, discomforting (to the patient) and expensive techniques. To support a clinical research program, therefore, it is important to find a reasonable balance between dosimetric simplicity and complexity, while providing timely and reliable results. This paper describes methods we have found successful for meeting clinical research needs within the limitations described above. They involve assessment of absorbed doses to major normal organs and the whole body, red marrow, tumors, the peritoneal region, and the bladder.

DOSIMETRY OF NORMAL ORGANS AND THE WHOLE BODY

The general methods recommended by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine [2-4] are used to estimate normal organ and whole-body doses from intravenously administered radiolabeled antibodies. These methods account for both penetrating and non-penetrating radiations. Penetrating radiation includes photons and x-rays having energy greater than 10 keV; non-penetrating radiations include electrons, beta-particles, and gamma-or x-rays having less than 10 keV in energy. Non-penetrating radiations are assumed to be totally absorbed in the source region, and no energy is assumed to be imparted to neighboring regions. The fraction of penetrating radiation emitted in a source region and imparted to any target region is obtained from prior Monte Carlo calculations using anthropomorphic mathematical phantoms [2]. These absorbed fractions are used in the software MIRDOSE2 (Oak Ridge Associated Universities, Oak Ridge, Tennessee) to estimate the cross-organ and self-organ contributions to the absorbed dose in target tissues.

* The absorbed or "average" dose (D) is the quotient of the amount of energy (e) imparted by ionizing radiation to matter and the mass of the organ or tissue (m) over which the energy is imparted; thus, $D = e/m$.

The two major sources of uncertainty in absorbed-dose calculations are 1) the quantitative measurements of activity in organs and tissues and 2) the assumption that the dosimetric model is representative of the patient. Organ uptake and retention are often estimated from test administrations of antibody labeled with low-level tracer amounts of radionuclide because count rates from therapy levels are usually too high for patient imaging. Trace-labeled antibody is administered to the patient, and quantitative planar imaging is performed at selected times post-injection to obtain biodistribution data and time-activity curves for major organs (usually the lungs, liver, kidneys, spleen, and imageable tumors) [5]. Whole-body retention is measured using data either from gamma camera images taken 5 meters from the patient or from constant regions of interest in images of "remainder" organs or tissues. Samples of blood and excreta (urine and feces) may also be collected and counted to obtain information for dosimetry.

A residence time (or integral cumulated activity) is calculated for each source organ or the remainder tissues from measurement data. The residence time is proportional to the total number of nuclear transformations that occur within the organ for as long as the radionuclide is present. The percent administered activity over time in each source region is plotted and fitted to a mathematical function or series of functions. The uptake of administered activity by source organs is usually quite rapid and is followed by exponential clearance with a characteristic clearance half-time. Source-organ residence times, (τ_h), are estimated from the cumulated activity (\tilde{A}_h) in source organ h from:

$$\tilde{A}_h = \int_0^{\infty} A_h(t) dt, \quad (1)$$

and

$$\tau_h = \tilde{A}_h / A_o, \quad (2)$$

where $A_h(t)$ is the effective retention of activity in the organ with time t and A_o is the total administered activity. The long-term retention is estimated by fitting exponential functions to the organ retention data. Figure 1 shows three typical examples of decay-corrected retention curves for (a) immediate uptake, typical of the whole body, blood, and some major organs, (b) slow or transient uptake, typical of the kidneys, and (c) continuous uptake, typical of tumor tissues. The cumulated activity for (a) immediate uptake is given by:

$$\tilde{A}_h = \int_0^{\infty} A_h(0) \exp(-\lambda t) dt, \quad (3)$$

where λ is the long-term "effective" clearance constant,

$$\lambda = (\ln 2)(T_{1/2, \text{eff}}), \quad (4)$$

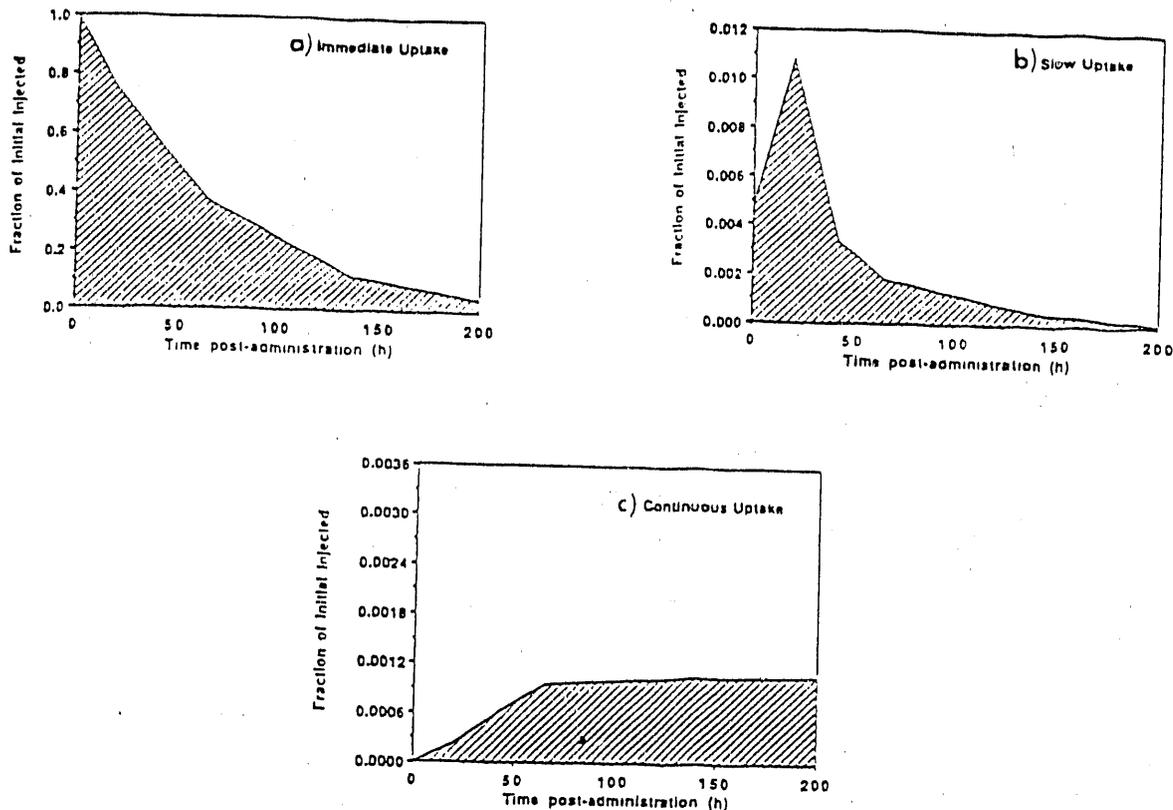


Figure 1. Typical Examples of Radiolabeled Antibody Uptake in Tissues: (a) immediate, (b) slow or transient, and (c) continuous. The shaded areas are equivalent to the residence time, τ_h .

and

$$T_{k,eff} = (\ln 2)/\lambda \quad (5)$$

The time-activity curve for kidneys is often characterized by gradually increasing concentrations followed by exponential clearance (Figure 1, b). The cumulated activity is therefore:

$$\bar{A}_h = \int_0^{t_1} A_h(t) dt + \int_{t_1}^{\infty} A_h(t) \exp(-\lambda t) dt. \quad (6)$$

If the decay-corrected time-activity curve is typical of Figure 1(c), the cumulated activity is determined by a linear fit to the data and disappearance is assumed to occur by radioactive decay only. The cumulated activity is therefore:

$$\bar{A}_h = \int_0^{tf} A_h(t) dt + \int_{tf}^{\infty} A_h(tf) \exp(-\lambda_p t) dt, \quad (7)$$

where tf is the final time point and λ_p is the physical decay constant.

Corrections are made for patient weight and organ mass when actual organ weights are known from CT-imaging. For individual organs, the correction is made by multiplying the source-organ residence time, τ_h , by the ratio of the defined reference man or reference woman organ mass to the known organ mass:

$$\tau_a = \tau_h (m_{\text{MIRD}}/m_{\text{actual}}). \quad (8)$$

The whole body mass in MIRDOSE2 may also be set equal to the actual patient weight. Calculated residence times for each source organ and remainder tissues are entered into MIRDOSE2 to estimate normal organ and whole-body doses (in rad/mCi or mGy/MBq administered) for each patient.

The uncertainty in an absorbed dose estimate is not known. Two major sources of uncertainty in absorbed dose calculations are the quantitative measurements of activity in organs and tissues of the individual patient, and the assumption that the dosimetric MIRD model is representative of the individual patient. The physics of energy transport and deposition are well known, and therefore, the MIRD system can be used for calculation of precise doses to a representative human subject using the mathematical model. What is not known is how well the model represents the individual patient.

TUMOR DOSIMETRY

Tumor dosimetry falls into three categories: 1) absorbed dose estimates for individual tumors in various locations throughout the body, 2) absorbed dose estimates for tumors that develop within normal organs, and 3) localized variations in absorbed dose within tumors due to nonuniform distributions of radiolabeled antibodies at the multicellular level. Each of these categories is discussed below.

Measurement data needed to quantify the time-concentration of radiolabeled antibodies in tumors are obtained from direct imaging and biopsies [5,6]. As with organ volumetrics, estimates of tumor volumes *in situ* are obtained by CT-imaging, contour slicing, and volume summation [7]. The beta-particle absorbed dose (in Gy) to a tissue of mass m for an initial activity A (in μCi) and time t (in days) is:

$$D_h = (1/m) 0.512 A Y E_\beta \int_0^{\infty} A_h(t) dt, \quad (9)$$

When absorbed doses are determined for tumors in various places within the body, the MIRDOSE system may be used by selecting a representative organ of similar mass and location in the body to represent the tumor. For example, the ovaries may be selected to represent mesenteric lymph node tumors, and the thyroid may be selected to represent a neck tumor. The percentage of the total administered activity per gram of tumor tissue (%ID/g) is integrated over infinite time to estimate the residence time, τ_{tumor} . A correction is made to account for the differences between the masses of the tumor and the representative organ:

$$\tau_h = \tau_{\text{tumor}} (m_{\text{tumor}}/m_{\text{organ}}) \quad (10)$$

The residence time, τ_h , may then be used in MIRDOSE2 to calculate an estimated tumor dose. Specific absorbed fractions for tumors of mass and position not easily represented by MIRDOSE organs may be calculated directly using Monte Carlo photon absorption codes, such as MCNP [8] or Johnson's MABDOS [9].

Because many tumors invade normal organs (typically metastatic cancer in liver or lung tissues), a method for obtaining S-values for tumors within organs has been developed [10]. This method applies the point-source specific absorbed fractions for an infinite water medium [11] to a rectangular host organ of arbitrary dimensions that contains a rectangular tumor of arbitrary dimensions and position within the host organ. This method permits calculation of the dose to the host organ from the tumor and *vice versa*. The photon contributions from all other source organs and remainder tissues are obtained using MIRDOSE models.

It is well known that radiolabeled monoclonal antibodies distribute nonuniformly in tumors and that the variation in dose delivered within tumors may have significant therapeutic implications [12]. If the physician needs to know more about the variation in the "localized" absorbed dose, multicellular dosimetry is appropriate. An example of multicellular dosimetry is the analysis of variation in absorbed dose within nodular lymphoma. Immunoperoxidase-stained lymph node biopsy sections (obtained from cancer patients at 48 h post-infusion with ^{131}I -labeled MB-1 antibody [6]) were autoradiographed to show the biodistribution of labeled antibody in follicles and interfollicular areas. Photomicrographs of tissue specimens were analyzed to determine the diameters of follicles, the interfollicular spacing, and the statistical variance in diameters and spacing, as well as whether the spatial arrangement of follicles was regular or random. The relative activity concentrations of ^{131}I -labeled MB-1 antibody were estimated, and absorbed dose distributions were calculated [13]. The ratio of activity in follicles compared to interfollicular spaces was 10:1. Figure 2 shows the variation in absorbed dose at points in tumor tissue as a function of distance (in three dimensions) from the center of a follicle. The mean tumor dose in this example is 40 Gy. Figure 2 also shows the maximum and minimum doses at points in tumor tissue with distance from the center of the follicle.

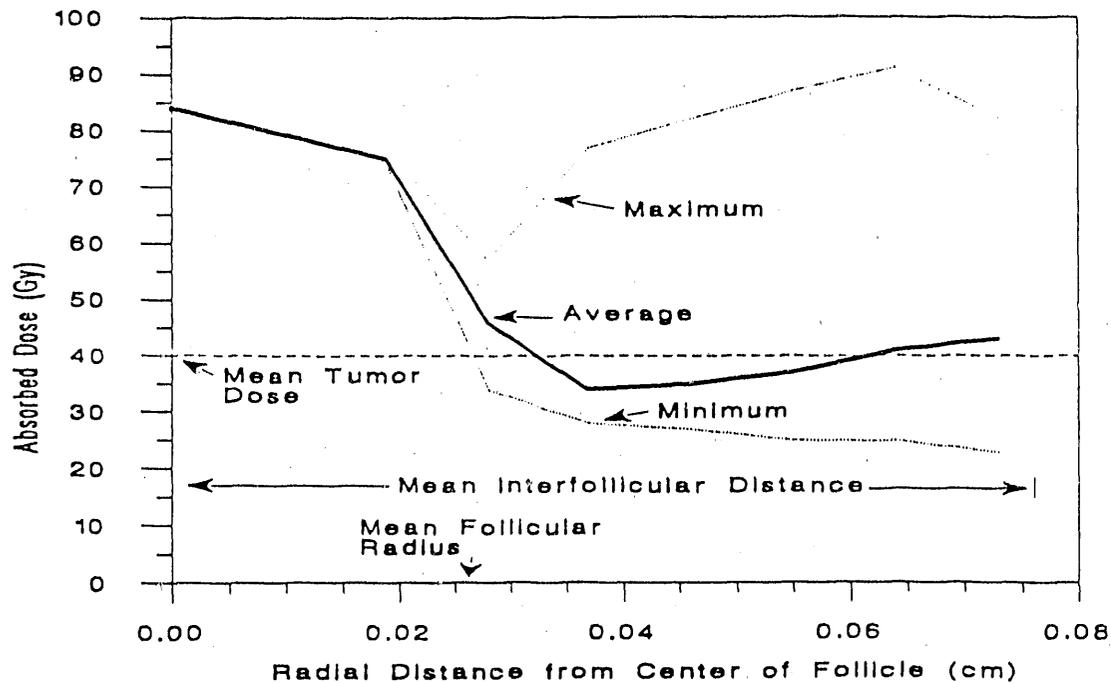


Figure 2. Dose to Points at Various Distances from the Center of a Lymphoma Follicle, Compared to the Mean Tumor Dose. The mean follicular radius (0.026 cm) and interfollicular distance (0.076 cm) are also shown.

For this example, the fraction of the total tumor volume receiving various doses was also calculated; 72% of the tumor tissue received less than the mean tumor dose of 40 Gy.

INTRAPERITONEAL DOSIMETRY

The administration route for radiolabeled antibodies is usually intravenous. However, for treatment of ovarian cancer, intraperitoneal administration has been tested clinically. After intraperitoneal administration, radiolabeled antibodies are taken up by tissues in the peritoneum and absorbed into blood and lymphatics. Absorbed doses are evaluated for the peritoneal region, individual major organs (including the gastrointestinal tract), peritoneal tumors, and the whole body. The initial dose rate to peritoneal tissue surfaces and the cumulative dose from administration to complete disappearance are also estimated.

The model of Watson *et al.* [14] is used to estimate the absorbed dose to the peritoneal cavity, small intestine, and upper large intestine. This model provides a means for calculating specific absorbed fractions for cross-organ photon

irradiation of organs by standard Monte Carlo techniques. These fractions are used to calculate S-values intraperitoneally administered radionuclides. Absorbed doses to other major organs are estimated using MIRDOSE2 with the residence time for activity in the peritoneum assigned for mathematical convenience to the small intestine.

The concentration of activity in peritoneal fluids is determined at various times after administration. Activity in the peritoneum clears by natural decay, absorption into lining tissues and organs (including tumors), and absorption into systemic body fluids. All of these processes act to decrease the activity concentration. The injection fluid is also assimilated, a process that increases the activity concentration. The net change in activity concentration is highly variable from one measurement to the next, but the trend usually appears as a net decrease in concentration with time post-injection. Average doses to peritoneal tissues surfaces and initial dose rates are estimated from the fluid concentration by numerical integration of Berger's [11] scaled absorbed dose distributions for beta-emitting point sources in water. The absorbed dose, $D(x)$, at distance x from a beta point source of average energy, E_β , is:

$$D(x) = \frac{A Y k E_\beta F_\beta(x/X_{90})}{4 \pi \rho X_{90}}, \quad (11)$$

where A is the source activity, Y is the beta yield per disintegration, k is an energy conversion constant, $F_\beta(x/X_{90})$ is the scaled absorbed dose distribution (a function of the distance from the source to the point of measurement as a ratio of the distance to the X_{90} distance), and ρ is the density of the absorbing medium. The initial dose rate and cumulative dose to peritoneal tissue surfaces are obtained by integration of Equation (9).

RED MARROW DOSIMETRY

Red marrow has been regarded clinically as either a target organ or a source organ for dosimetry. When there are no specific uptake and retention data on antibody concentration in red marrow, the red marrow is sometimes included as a target organ in the MIRDOSE system to estimate the absorbed dose. This approach assumes that the concentration of activity in red marrow is the same as in the remainder tissues and clears with the same half-time as the whole body. However, this method generally underestimates the true marrow dose because the activity concentration in marrow is typically higher than remainder tissues. A better approach is to estimate a residence time for marrow and treat marrow as a source organ. Marrow biopsy counts (percent administered activity per gram) are used when available to estimate red marrow time-activity functions. In the future, it may be possible to directly quantify the marrow activity concentrations from patient images.

When direct counting data are not available for marrow, the residence time may be estimated from blood serum counts if two parameters are known: 1) the relative concentration in red marrow relative to circulating blood, and 2) the relative clearance half-time of radiolabeled antibody from red marrow compared to circulating blood. The concentration of radiolabeled antibody in serum is evaluated and an exponential function is fit to the data. An example of the serum clearance of Re-186-labeled NR-LU antibody is shown in Figure 3. The concentration in whole blood is then estimated from the patient hematocrit. The concentration of radiolabeled antibody in red marrow compared to circulating blood depends on the antibody involved and its specificity for hematopoietic tissues, but a value of 0.2 to 0.4 has been recommended [15]. A value of 0.25 is currently being used for all antibodies, based on expert opinion and experience. The residence time for red marrow, τ_{marrow} is therefore:

$$\tau_{\text{marrow}} = (a_0)(\ln 2)(T_{1/2}^{\text{eff}})(m_{\text{marrow}})(0.25), \quad (12)$$

where a_0 is the y-axis intercept of the least-square's fit of the whole-blood activity concentration, and m_{marrow} is the MIRD-recommended red marrow mass (1120 g for reference man and 1050 g for reference woman). Values other than 0.25 for the radiolabeled antibody concentration should be used if justifiable data are available.

INTESTINAL TRACT DOSIMETRY

Some radiolabeled antibodies (such as the ^{99m}Tc - and ^{186}Re -NR-LU-10 whole and the NR-CO-02 $\text{F(ab}')_2$ antibodies) are catabolized in the liver, from which a significant fraction (~15%) of the administered activity is excreted via the biliary pathway into the small intestine. Intestinal activity is notably visible on many gamma camera images. Cathartics are administered to decrease intestinal hold-up times and to reduce the absorbed dose to the walls of the intestinal tract; however, voiding intervals are highly variable. Residence times (τ_h) for the small intestine, upper-large intestine, and lower-large intestine are calculated for activity passing through the intestinal tract. For absorbed dose calculations, the removal constant (λ) for each compartment of the ICRP gastrointestinal tract model [16] is increased by a factor of 2 to account for the observed clearance due to cathartics.

BLADDER WALL DOSIMETRY

To limit the absorbed dose to the bladder, patients receiving radiolabeled antibodies are instructed to urinate frequently, and absorbed dose estimates are not usually requested by the attending physician. Voiding intervals of 2.0 h are assumed when bladder wall doses are requested. Standard MIRD methods are used to estimate absorbed doses to bladder [2].

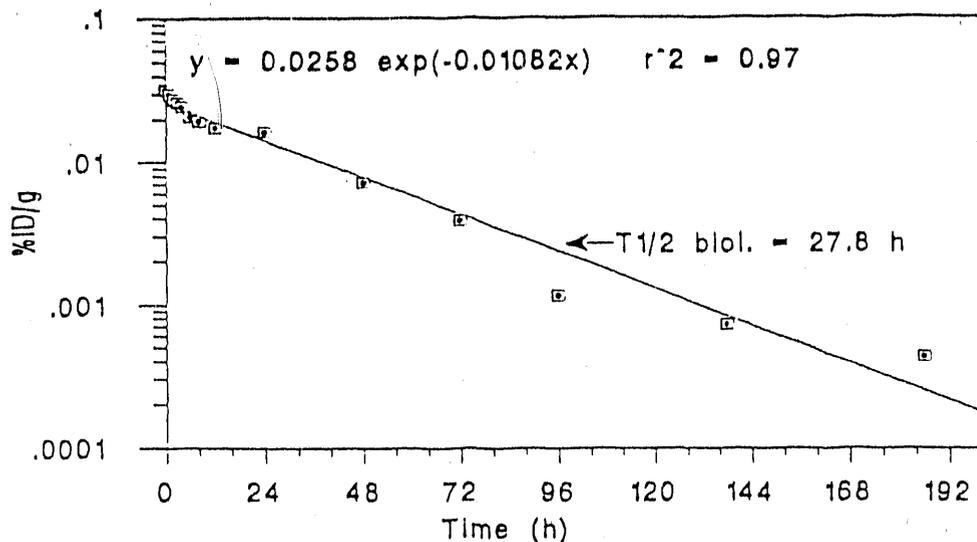


Figure 3. Concentration of Re-186-labeled NR-LU Antibody in Blood Serum of a Typical Cancer Patient.

SPECIALIZED DOSIMETRY FOR LABORATORY ANIMALS

Mice, dogs, and monkeys are routinely used in radioimmunotherapy research. However, the MIRD methods cannot be reliably extended to laboratory animals without modifications related to organ size and position. We have, therefore, developed methods for calculating absorbed doses to organs, tumors, and the whole body for various laboratory animals, but these are beyond the scope of this article. The MIRD system is not applicable to the mouse, which is too small for S-factors to have practical significance for photon-emitters. However, a model for calculating absorbed doses to mouse organs, which takes into account the cross-organ beta-particle contributions to organ dose, has been developed and tested and will be described in a future publication.

CONCLUSIONS AND SUMMARY

Specialized dosimetric tools and computational methods are needed to support the dosimetry needs of a clinical research program. The most important quantity needed by physicians for treatment planning and assessment of therapeutic effectiveness of radiolabeled antibodies in clinical studies is a reliable estimate of the absorbed (or average) dose to the organ, tumor, or tissue of interest. Average tumor doses are extremely useful, even though it is well understood that antibody biodistribution at the multicellular level is not uniform. Localized dosimetry of tumors and other tissues is useful for evaluating the variation in absorbed dose from the mean, but interpretations need to remain fairly simple. Doses to normal organs and red marrow are also

necessary for evaluating dose-limiting radiation toxicities and patient response. Turn-around times for dosimetric results must be compatible with physicians' needs so that decisions can be made with regard to patient treatment and procurement of radionuclides.

Because of the complexity of the human body, the nonuniform biodistribution of radiolabeled antibodies among and within organs, tumors, other tissues and body fluids, and the multiplicity of interrelated elements contributing to the absorbed dose and the localized dose, it is important that research on improved methods for internal dosimetry to be encouraged and supported. For example, the concentrations of activity in red marrow at various times post-administration are known with only limited accuracy. There is a need for further improvements to be made in marrow dosimetry because marrow is usually the most radiosensitive normal tissue involved and, in many cases, becomes the limiting tissue for therapy. There is also need to gain a better understanding of the uncertainties associated with internal dose estimates for individual patients.

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