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Mass Scaling of S Values for Blood-Based Estimation of Red Marrow Absorbed Dose: The Quest for an Appropriate Method

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As a first step in performing patient-specific absorbed dose calculations, it may be necessary to scale dose conversion factors (e.g., S values in the MIRD system or dose factors in the RADAR system) by patient organ mass. The absorbed dose to active marrow is of particular interest for radionuclide therapy. When using the blood-based model of red marrow (RM) absorbed dose estimation, there are only 2 S values of concern, representing RM self-dose and cross-dose terms. Linear mass scaling has generally been performed for the self-dose term, whereas the cross-dose term is considered to be mass independent. We will illustrate that each radionuclide may need to have its mass-based correction determined to assess whether the conventionally used linear mass scaling is appropriate and should be applied not only to the self-dose S value but also to the cross-dose term.

Key Words: dosimetry; red marrow dosimetry; radionuclide therapy; radioimmunotherapy

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When use of the blood-based model of red marrow absorbed dose estimation is appropriate, there are only 2 S values of concern. They are the red marrow-to-red marrow S value, S(RM←RM), and the total body-to-red marrow S value, S(RM←TB), representing RM self-dose and cross-dose terms, respectively. We will examine the need for and type of mass scaling appropriate for each of these S value terms.

MASS SCALING OF ORGAN SELF-DOSE S VALUE

The S value in the MIRD system (*1*), which gives absorbed dose to a target region r_k from activity uniformly distributed in each source region r_h, is defined as:

$$S(r_k \leftarrow r_h) = \frac{\sum_i \Delta_{i,np}\,\phi_{i,np}\,(r_k \leftarrow r_h) + \sum_i \Delta_{i,p}\,\phi_{i,p}(r_k \leftarrow r_h)}{m_{r_k}},$$

where Δ is the mean energy emitted per nuclear transition, ϕ is the fraction of energy emitted in source region r_h that is absorbed in target region r_k, m_{r_k} is the mass of target region r_k, and np and p refer to nonpenetrating and penetrating types of radiation, respectively.

Mass scaling of this S value was discussed in MIRD Pamphlet No. 5, revised (*2*), and by Snyder (*3*). Their conclusions were that if the source and target organs are identical and the source is distributed uniformly, evidence suggests that the absorbed fraction (AF) for self-irradiation (i.e., $r_h = r_k$ in the preceding equation) for penetrating emissions varies with the cube root of the mass, provided the mean free path of the photon is large compared with the diameter of the organ. No claim to a high degree of accuracy is made; indeed, the authors suggest that the opposite is true. It is evident that only a rough approximation to the absorbed dose is given as Snyder stated that he hoped to "develop other and better methods for taking account of organ mass." In MIRD Pamphlet No. 11 (*1*), it was noted that when r_k and r_h coincide, the dose from photons with energies above 100 keV appears to be proportional to the organ mass raised to the $-2/3$ power ($m_h^{-2/3}$)—that is, absorbed dose, D, is equal to a constant multiplied by the cumulated activity, $\tilde{A}_h$, divided by $m_h^{2/3}$. Because absorbed dose from electrons scales inversely with mass, scaling is no longer simple; photon dose changes with one power of mass and electron dose changes with another. In fact, MIRD Pamphlet No. 11 (*1*), stated that "...there seems to be no scaling procedure which is approximately correct for all energies of particles and masses of organs." Nevertheless, most investigators believe it is reasonably accurate to mass-scale the phantom self-dose S value on a linear basis using the multiplicative factor $(m_{TB-phantom}/m_{TB-patient})$ to arrive at the appropriate S value for an individual patient.

We sought to evaluate this relationship through examination of total body-to-total body (TB-to-TB) S values for 3 radionuclides: ^{131}I, ^{137}Cs, and ^{186}Re. Basic decay data were taken from the MIRD Decay Scheme book (*4*). We assumed that the AF for self-irradiation from "nonpenetrating emissions" was unity ($\phi_{np} = 1$) and used ϕ_p values from

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MIRD Pamphlet No. 3, Table 9 (*5*), which assumed uniform distribution of activity in unit density ellipsoids of various sizes. This homogeneous ellipsoidal model has principal axes in the ratio of 1:1.8:9.27. Loevinger et al. stated in 1956 (*6*) that the human body may be approximated by an ellipsoid of ratio of axes 5:1, which is a ratio of length to maximum diameter; this agrees well with this model, which has a 5.15:1 ratio. We considered only the energy of the most abundant penetrating emission for each radionuclide (364 keV for ^{131}I, 662 keV for ^{137}Cs, and 100 keV for ^{186}Re). Considering ellipsoids of mass 40–160 kg, the TB-to-TB S values for the 3 radionuclides showed the functional dependencies presented in Table 1.

As can be seen in Table 1, the dependence of ϕ_p was not always with the cube root of mass, and S_p dependence did not always vary to the 2/3 power. In addition, as demonstrated by the equations given in the total S value dependence column in Table 1, linear mass scaling for this S value is not necessarily appropriate. Linear scaling appears to work best for ^{186}Re, as the penetrating contribution to the S value is lowest of the 3 radionuclides and is relatively insignificant. As the penetrating-to-nonpenetrating ratio increases, use of linear mass scaling is less accurate. Using the derived total S value mass dependencies given in Table 1 compared with linear mass scaling, the errors over the 40- to 160-kg TB mass range were ^{131}I, ±8%; ^{137}Cs, ±12%; and ^{186}Re, ±0.5%.

Therefore, appropriate mass scaling for each radionuclide's TB self-dose S value, as well as other discrete source organ self-dose S values, may vary from the assumed linear model. The deviation from linearity and the need for a nonlinear approach can only be assessed after performing an analysis such as the above. These variations are admittedly small relative to other possible errors in the dosimetry analysis (e.g., activity quantification, uncertainty in kinetic parameters, organ mass values), but the most correct values always should be used to minimize overall uncertainty in the calculations.

MASS SCALING OF ORGAN CROSS-DOSE S VALUE

Assuming $\phi_{np} = 0$, the S value considering only photon emissions may be defined as:

$$S(r_k \leftarrow r_h) = \frac{\sum_i \Delta_{i,p}\, \phi_{i,p}(r_k \leftarrow r_h)}{m_{r_k}}.$$

In MIRD Pamphlet No. 5 (*7*) it is noted that the AFs (for the penetrating emissions) for a target organ irradiated by another source organ are assumed to vary directly with the mass of that organ, provided the source is outside the region and not too close to its surface. If this assumption is correct, absorbed dose from cross-irradiation will be independent of organ size. Snyder (*3*) showed that for a discrete organ (e.g., a urinary bladder of varying size, whose size was varied by a factor of 2, irradiated by either ovaries or kidneys as the source organ), the absorbed dose was the same regardless of bladder size. Snyder notes that "for the assumption to hold, it is essential that the distance from source to target is not changing by a large percentage of its initial value. In such a case, the inverse-square effect would be expected to override any effect of the change in mass." In MIRD Pamphlet No. 11 (*1*), it was noted that for target organs r_k sufficiently distant from the source organ r_h, one would expect Φ ($r_k \leftarrow r_h$) to be reasonably independent of organ mass. Thus, to a first approximation, this adjustment may be considered to be present. As target region r_k approaches source region r_h, however, this relationship may not hold. The applicability is certainly in doubt for TB as a source region, as the source surrounds the target. Thus, TB-to-target organ–specific AFs may indeed be dependent on TB mass.

Using MIRD Pamphlet 5, revised (*2*), AFs were determined by interpolation for the principal ^{131}I photon energy for several organs when the source was uniformly distributed in the TB. The results are presented in Table 2.

Plotting the AFs given in Table 2 against mass and fitting to a linear function we find:

$$\mathrm{AF} = 0.0059 \times \mathrm{mass\ (kg)}\ (r^2 = 0.995).$$

Thus, AF appears to vary as a linear function of mass and, therefore, the various specific AFs, Φ ($r_k \leftarrow r_{TB}$), and corresponding S values, $S(r_k \leftarrow r_{TB})$, are reasonably mass independent. Thus, no mass scaling of the phantom cross-dose S value appears to be required.

However, the preceding analyses are based on a single mathematic phantom with a TB mass of 70 kg. Interestingly, based on reported S values in MIRDOSE3 (*8*) for adults and 15-, 10-, 5-, and 1-y-old mathematic phantoms, S(RM ← TB) and S(TB ← TB) are virtually identical for ^{186}Re and within 5% of each other for ^{131}I and ^{137}Cs for all mathematic phantoms. Both S values can be obtained for any of the phantoms representing younger individuals by multiplying the adult S values by the TB phantom mass ratios of $(m_{TB-adult\ phantom}/m_{TB-any\ younger\ phantom})$. These results are consistent with the reported TB-to-TB and

TABLE 1
TB-to-TB S Value Dependence for 3 Radionuclides

Radionuclide	ϕ_p dependence	S_p dependence	Total S value dependence
^{131}I	$\phi_p = 0.115 \times \mathrm{mass}^{0.255}$	$S_p = 0.0934 \times \mathrm{mass}^{-0.745}$	$S = 0.44 \times \mathrm{mass}^{-0.895}$
^{137}Cs	$\phi_p = 0.130 \times \mathrm{mass}^{0.227}$	$S_p = 0.166 \times \mathrm{mass}^{-0.774}$	$S = 0.63 \times \mathrm{mass}^{-0.897}$
^{186}Re	$\phi_p = 0.096 \times \mathrm{mass}^{0.301}$	$S_p = 0.0042 \times \mathrm{mass}^{-0.699}$	$S = 0.73 \times \mathrm{mass}^{-0.994}$

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TABLE 2
Absorbed Fractions for TB-to-Various Target Organs for ^{131}I

Organ	Mass (g)	Absorbed fraction
Kidneys	284.2	0.00173
Liver	1,809	0.0107
Lungs	999.2	0.00518
RM	1,500	0.00912
Ovaries	8.27	0.0000508
Spleen	173.6	0.00108
Thyroid	19.63	0.0000917

TB-to-RM S values for any age of these mathematic phantoms. This relationship holds as well for any of the target organs given in Table 2—that is, $S(r_k \leftarrow r_{TB})$ behaves in a similar fashion as $S(r_{TB} \leftarrow r_{TB})$ and $S(r_{RM} \leftarrow r_{TB})$. $S(r_{RM} \leftarrow r_{TB})$ will thus vary with body mass as does $S(r_{TB} \leftarrow r_{TB})$—that is, the TB-to-RM S values are like self-dose S values that require mass scaling rather than cross-dose S values that need no mass correction.

MASS SCALING FOR BLOOD-BASED ESTIMATION OF RM DOSE

The equation for RM absorbed dose estimation when using the blood-based model (*9*) is:

$$D_{RM} = \tilde{A}_{RM}\, S(RM \leftarrow RM)_{phantom} + \tilde{A}_{RB} \times S(RM \leftarrow RB)_{phantom},$$

where RB is remainder of the body and:

$$S(RM \leftarrow RB)_{phantom} = S(RM \leftarrow TB)_{phantom} \times \left(\frac{m_{TB}}{m_{TB} - m_{RM}}\right) - S(RM \leftarrow RM)_{phantom} \times \left(\frac{m_{RM}}{m_{TB} - m_{RM}}\right).$$

The approaches most commonly seen in the literature indicate that it is reasonably accurate to mass-scale the phantom RM-to-RM S value by $(m_{TB-phantom}/m_{TB-patient})$. No mass correction is generally applied to the cross-dose S value. But our analyses indicate that the suitability of linear mass scaling should be evaluated and that it may also be appropriate to mass-scale the phantom TB-to-RM S value.

As a caveat, the appropriateness of this mass correction is dependent on the assumption that the patient's RM mass scales linearly with their TB weight—that is, $m_{RM\text{-}patient} = m_{RM\text{-}phantom} \times m_{TB\text{-}patient}/m_{TB\text{-}phantom}$. Shen et al. (*10*) found little relationship between RM mass and TB mass, but Woodard (*11*), based on measurements in 11 cadavers (6 male, 5 female), suggests that the active marrow percentage of TB weight was 1.37% ± 0.23% in males and 1.16% ± 0.17% in females. Even though further study may indicate a better surrogate than TB weight for estimating patient RM mass, or the need for an age-based mass adjustment, the essential points of this communication remain valid—that is, both terms of the RM absorbed dose equation should be appropriately mass-adjusted, using a linear or nonlinear approach.

CONCLUSION

The first and simplest step in moving from phantom-based to patient-specific dosimetry involves appropriate organ mass scaling. An improvement in dose estimate accuracy is expected as absorbed dose is a measure of absorbed energy per unit mass of tissue. When using the blood-based model of RM absorbed dose estimation, there are only 2 S values of concern: S(RM←RM) and S(RM←TB). There are 3 choices for mass scaling these S values in the required RB-to-RM S value term: (a) no mass correction at all, (b) mass-correcting only the RM-to-RM S value, or (c) mass-correcting both S values.

The entire effect of mass scaling on RM dose estimation occurs for the cross-dose term; the self-dose term is mass independent as the RM cumulated activity is adjusted in such a manner as to cancel the mass dependence. The contribution of the cross-dose term to the total RM dose is dependent on the patient's weight deviation from that of the mathematic phantom as well as the patient's TB-to-RM biokinetic ratio (9).

Mass correction may be adequately accounted for using a linear correction or it may require a nonlinear scaling strategy, depending on the specific radionuclide being studied. Obviously, method (a) is not patient specific but, rather, is only phantom specific, as S(RM←RB) is a constant value and, therefore, gives useful results only for the phantom on which it is based. In addition, this option can be eliminated as at least one of the RB S values (i.e., the RM-to-RM S value) must be multiplied by the mass scaling term. Method (b) is certainly appropriate, based on information in the majority of the literature published to date. But our analyses indicate that the most appropriate choice is method (c), as we and others have alluded to previously (*9,12*). Validation of these conclusions with studies using phantoms of varying TB mass or with datasets involving patient data from radiopharmaceutical therapy studies is needed.

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