Practical Determination of Patient-Specific Marrow Dose Using Radioactivity Concentration in Blood and Body

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Accurate determination of red marrow radiation is important because myelotoxicity is often dose limiting in radioimmunotherapy. The S-value methodology assumes a fixed red marrow mass as defined by the standard Medical Internal Radiation Dose (MIRD) mathematic phantom. Substantial error can be introduced in marrow radiation estimates because red marrow mass varies from patient to patient. In this work we describe a patient-specific marrow dosimetry methodology that does not require an explicit estimate of marrow mass. **Methods:** Photon radiation to marrow from all sources can be considered as the total body to marrow. Based on photon radiation from body and electron radiation from blood, a patient-specific marrow dose can be determined by counting blood and total body radioactivity and measuring body weight. **Results:** The deviation in marrow dose calculation using total body to represent all photon radiation was 3.9% in 66 patients administered ^{131}I-labeled antibodies and was 9.1% in 18 patients administered ^{67}Cu-labeled antibodies. The differences between this patient-specific approach and estimates based on standard anatomy were considerable, ranging from −35% to 88%. The differences were greater when patients' weights differed substantially from the MIRD reference man phantom. **Conclusion:** For radiopharmaceuticals that do not bind marrow, patient-specific marrow dosimetry can be independent of the actual marrow mass of a patient. Patient-specific marrow dosimetry can be determined using radioactivity concentration in blood and body.

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

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The use of Medical Internal Radiation Dose (MIRD) S values based on population-averaged organ masses (reference man) provides a convenient approach for computation of radiation dose for individual patients (*1*). However, the use of fixed organ dimensions can introduce substantial deviation in radiation dose estimates because organ size can vary substantially among patients. In a ^{131}I-Lym-1 study, 12 of 48 lymphoma patients had spleen volume 4–17 time greater than the spleen volume of MIRD reference man phantom (*2*). Consequently, spleen radiation would be overestimated 4–17 times in these 12 patients if the MIRD spleen S value was used. Therefore, accurate dosimetry requires patient-specific organ mass. Patient-specific S values for most organs can be readily obtained by adjusting the organ mass (*3*) or by interpolating the existing MIRD data for photon (or penetrating) and electron (or nonpenetrating) radiation (*4,5*).

Accurate radiation dosimetry for marrow is important because bone marrow has been identified as the dose-limiting organ in radioimmunotherapy in the absence of bone marrow reconstitution (*6*). However, current standard methods for marrow dose estimation use the S value of reference man (*1,3,6–8*) and assume a red marrow (RM) mass of 1500 g (*1*) or 1120 g (*7*) for individual patients. One of the major challenges in developing patient-specific marrow dosimetry has been determination of the RM mass for individual patients. Although, MRI shows promise as a method to determine RM mass (*9*), total body MRI is required for that purpose.

In this study, we show that, for therapeutic radiopharmaceuticals that do not specifically bind to marrow, absorbed dose to marrow may be obtained without the need to estimate the total marrow mass of a patient. A simple, practical approach is proposed to determine marrow radiation doses for individual patients receiving systemic radionuclide therapies such as radioimmunotherapy.

MATERIALS AND METHODS

Standard MIRD Approach

In the standard MIRD approach, the general expression for RM absorbed dose is (*10*):

$$D_{RM} = \tilde{A}_{RM} \times S(RM \leftarrow RM) + \Sigma \tilde{A}_h \times S(RM \leftarrow h) + \tilde{A}_{RB} \times S(RM \leftarrow RB), \quad \text{Eq. 1}$$

where D_{RM} is the mean absorbed dose in RM. $\tilde{A}_{RM}$, $\tilde{A}_h$ and $\tilde{A}_{RB}$ are cumulated radioactivity in RM, other organ sources (h) and the remainder of body (RB), respectively; m_{RM}, m_h and m_{RB} are the mass of RM, h and RB, respectively; S(RM←RM), S(RM←h) and S(RM←RB) are the S values from RM, h and RB to RM,

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respectively. The S(RM←RB), as described by Coffey and Watson (*11*), is given by:

$$S(RM \leftarrow RB) = S(RM \leftarrow TB) \times m_{TB}/m_{RB} - S(RM \leftarrow RM) \times m_{RM}/m_{RB} - \Sigma S(RM \leftarrow h) \times m_h/m_{RB}, \quad \text{Eq. 2}$$

where h is other organ sources excluding RM, m_{TB} is the mass of the total body (TB) and S(RM←TB) is the S value from TB to RM.

For radiopharmaceuticals that do not specifically bind to marrow, the $\tilde{A}_{RM}$ is often derived from radioactivity in the blood and the RM-to-blood concentration ratio (RMBLR) (*6,12*):

$$\tilde{A}_{RM} = RMBLR \times C_{blood} \times m_{RM}, \quad \text{Eq. 3}$$

where C_{blood} is the concentration of cumulated radioactivity in blood. RMBLR ranges from 0.2 to 0.4 (*6*). A general value of 0.36 for RMBLR is based on a hematocrit of 0.47 and red marrow extracellular fluid fraction of 0.19 (*12*). A reference man m_{RM} of 1500 g is used in MIRD S values (*1*) and 1120 g in the MIRDOSE3 program (*7*).

Patient-Specific Approach

All Photon Radiation Sources Represented by Total Body. In radioimmunotherapy, radiolabeled antibodies are broadly distributed in the body and large portions of the radiation from therapeutic radionuclides are nonpenetrating radiation from β particles, internal conversion electrons or Auger electrons (electron contribution). The sum of penetrating radiation from x-rays, γ rays (photon contribution) from individual sources (h) can be simply represented by photons from TB. Therefore, the MIRD schema for D_{RM} can be simplified to become the sum of electron and photon contributions:

$$D_{RM} = \tilde{A}_{RM} \times S_{electron}(RM \leftarrow RM) + \tilde{A}_{TB} \times S_{photon}(RM \leftarrow TB), \quad \text{Eq. 4}$$

where $S_{electron}(RM \leftarrow RM)$ reflects the electron part of the S value from RM to RM. $S_{photon}(RM \leftarrow TB)$ reflects the photon part of S value from TB to RM.

The S value is a product of the equilibrium dose constant (Δ) and the absorbed fraction (ϕ) divided by the mass. By going one step back from S values using MIRD schema, Equation 4 can be rewritten through the following series of equations:

Considering RB as TB − RM, Equation 2 equals:

$$S(RM \leftarrow RB) = S(RM \leftarrow TB) \times m_{TB}/m_{RB} - S(RM \leftarrow RM) \times m_{RM}/m_{RB}. \quad \text{Eq. 5}$$

This general relationship should be true for the electron part of the S value:

$$S_{electron}(RM \leftarrow RB) = S_{electron}(RM \leftarrow TB) \times m_{TB}/m_{RB} - S_{electron}(RM \leftarrow RM) \times m_{RM}/m_{RB}. \quad \text{Eq. 6}$$

As a general rule of MIRD schema (*10*):

$$S_{electron}(RM \leftarrow RB) = 0. \quad \text{Eq. 7}$$

Then, Equation 6 can be represented as:

$$S_{electron}(RM \leftarrow TB) = S_{electron}(RM \leftarrow RM) \times m_{RM}/m_{TB}, \quad \text{Eq. 8}$$

where $S_{electron}(RM \leftarrow RM)$ is the electron part of the S value from RM to RM. By definition:

$$S_{electron}(RM \leftarrow RM) = \Delta_{electron} \times \phi_{electron}(RM \leftarrow RM)/m_{RM}, \quad \text{Eq. 9}$$

where $\Delta_{electron}$ is the total mean energy emitted per nuclear transition for electron radiation and $\phi_{electron}(RM \leftarrow RM)$ is the absorbed fraction of electron radiation from RM to RM. Using Equation 9 in Equation 8:

$$S_{electron}(RM \leftarrow TB) = \Delta_{electron} \times \phi_{electron}(RM \leftarrow RM)/m_{RM} \times m_{RM}/m_{TB} = \Delta_{electron} \times \phi_{electron}(RM \leftarrow RM)/m_{TB}. \quad \text{Eq. 10}$$

By MIRD definition:

$$S_{photon}(RM \leftarrow TB) = S(RM \leftarrow TB) - S_{electron}(RM \leftarrow TB). \quad \text{Eq. 11}$$

Using Equation 10:

$$S_{photon}(RM \leftarrow TB) = S(RM \leftarrow TB) - \Delta_{electron} \times \phi_{electron}(RM \leftarrow RM)/m_{TB}. \quad \text{Eq. 12}$$

Using Equations 9 and 12 in Equation 4:

$$D_{RM} = \tilde{A}_{RM} \times \Delta_{electron} \times \phi_{electron}(RM \leftarrow RM)/m_{RM} + \tilde{A}_{TB} \times S(RM \leftarrow TB) - \tilde{A}_{TB} \times \Delta_{electron} \times \phi_{electron}(RM \leftarrow RM)/m_{TB}, \quad \text{Eq. 13}$$

Therefore,

$$D_{RM} = \Delta_{electron} \times \phi_{electron}(RM \leftarrow RM) \times |\tilde{A}_{RM}/m_{RM} - \tilde{A}_{TB}/m_{TB}| + \tilde{A}_{TB} \times S(RM \leftarrow TB), \quad \text{Eq. 14}$$

$\Delta_{electron}$ can be found in MIRD Pamphlet 10 (*13*). $\phi_{electron}(RM \leftarrow RM)$ is an exception from the general rule of $\phi_{electron}(h \leftarrow h) \equiv 1$ because the sizes of the trabecular bone and marrow cavities are comparable to the range of the β particles (*1*). $\phi_{electron}(RM \leftarrow RM)$ can be derived by subtracting the photon part of the S value (*13,14*), $S_{photon}(RM \leftarrow RM)$, from S(RM←RM) of MIRD Pamplet 11 (*1*). Values for $\Delta_{electron}$ and $\phi_{electron}(RM \leftarrow RM)$ based on MIRD data are provided for some common therapeutic radionuclides (Table 1).

The magnitude of the deviation introduced by the above simplified approach (TB to represent all photon sources) from that of standard MIRD approach was analyzed in patients using masses and S values of reference man in both approaches (*1*). The difference in RM dose using Equations 14 and 1 was compared in 54 lymphoma patients treated with ^{131}I-Lym-1 (*15*), 12 breast cancer patients treated with ^{131}I-ChL6 (*16*) and 18 lymphoma

TABLE 1
Electron (Nonpenetrating) Radiation Part of Mean Energy Emitted per Transition, $\Delta_{electron}$ and Absorbed Fraction $\phi_{electron}(RM \leftarrow RM)$ Derived from Existing MIRD Data*

	^{131}I	^{67}Cu	^{188}Re	^{90}Y
$\Delta_{electron}$ (g-rad/μCi-h)	0.409	0.334	1.69	1.98
(Gy-kg/Bq-s)	3.08E-14	2.53E-14	1.28E-13	1.49E-13
$\phi_{electron}(RM \leftarrow RM)$	0.77	0.82	0.66	0.65

*Data from (*1,12,16*).
MIRD = Medical Internal Radiation Dose; RM = red marrow.

patients treated with ^{67}Cu-2IT-BAT-Lym-1 (*17*). Lym-1 is a mouse immunoglobulin (IgG2a) monoclonal antibody and ChL6 contains a human IgG1 constant region and the variable region of mouse L6 (IgG2a). ^{131}I and ^{67}Cu are therapeutic radionuclides that have a large fraction of electron radiation. In this analysis, $\tilde{A}_{RB}$ was obtained by subtracting $\tilde{A}_{RM}$, $\tilde{A}_{liver}$, $\tilde{A}_{spleen}$, $\tilde{A}_{lung}$ and $\tilde{A}_{kidney}$ from $\tilde{A}_{TB}$ and $\tilde{A}_{liver}$, $\tilde{A}_{spleen}$, $\tilde{A}_{lung}$, $\tilde{A}_{kidney}$ and $\tilde{A}_{TB}$ were determined by quantitative imaging. $\tilde{A}_{RM}$ was determined using Equation 3, assuming a value of 0.36 for RMBLR.

Marrow Dosimetry for Individual Patients. For therapeutic radionuclides, such as ^{131}I, ^{67}Cu, ^{188}Re or ^{90}Y, the values of S(RM←TB), S(liver←TB), S (spleen←TB) and S(kidney←TB) are almost identical, despite substantial differences in mass and geometry between RM, liver, spleen or kidneys (*1*). Furthermore, the difference between S(RM←TB) and S(TB←TB) value is only 10% for ^{131}I, 12% for ^{67}Cu and 0% for ^{90}Y (pure β emitter) or ^{188}Re (*1*). Therefore, S(RM←TB), like S(TB←TB), is not sensitive to the target mass or geometry of RM but is sensitive to the mass of TB. Patient-specific S(RM←TB) can be readily obtained by adjusting the S(RM←TB) of reference man for the patient's actual body weight. From these considerations and Equation 3, Equation 14 can be simplified as:

$$D_{RM} = \Delta_{electron} \times \phi_{electron}(RM \leftarrow RM) \times \left[RMBLR \times C_{blood} - \tilde{A}_{TB}/m_{TB}\right] + \tilde{A}_{TB} \times S_{ref\ man}(RM \leftarrow TB) \times 69{,}880/m_{TB}, \quad \text{Eq. 15}$$

where $S_{ref\ man}$(RM←TB) and 69,880 g is TB S value and mass of MIRD reference man phantom (*1*). m_{TB} is patient-specific body mass determined by patient weight (g).

$\phi_{electron}$(RM←RM) is sensitive to the size of the marrow cavity and not to the total RM mass (*18*). For an ^{131}I radiopharmaceutical that does not bind to marrow, the patient-specific marrow dose (rad or cGy) can be estimated by:

$$D_{RM}\ (rad/mCi) = 0.313 \times RMBLR \times C_{blood} + 0.456 \times \tilde{A}_{TB}/m_{TB}, \quad \text{Eq. 16}$$

where RMBLR can be determined using the patient's hematocrit and RM extracellular fluid fraction (*12*). C_{blood} is cumulated radioactivity concentration (μCi-h/mL) of the blood. $\tilde{A}_{TB}$ is cumulated radioactivity (μCi/h) determined by counting body radioactivity using a survey meter or gamma camera. m_{TB} is patient's actual body weight (g).

RESULTS

Patient-Specific Approach

All Photon Radiation Sources Represented by Total Body. Small differences were found in RM absorbed dose calculated by standard MIRD approach (Eq. 1) and by representing all photon sources using TB (Eq. 15) (Table 2). In the analysis of 66 patients receiving ^{131}I-Lym-1 or ^{131}I-ChL6, a mean deviation from standard MIRD approach was 3.9% in RM dose. For metal radionuclide ^{67}Cu-2IT-BAT-Lym-1, a mean deviation in RM dose of 9.1% was observed because of the higher uptake of ^{67}Cu in liver (Table 2). A maximum deviation in RM dose of 13.9% was found in 1 patient whose liver uptake was 48% of the total cumulated ^{67}Cu in the body.

TABLE 2
Deviation in Red Marrow Dose Using Total Body to Represent All Photon (Penetrating) Radiation from That of Standard MIRD Approach

	^{131}I-Lym-1 (n = 54)	^{131}I-ChL6 (n = 12)	^{67}Cu-2IT-BAD-Lym-1 (n = 18)
Marrow dose deviation (%)	4.4 ± 2.9	1.7 ± 0.9	9.1 ± 2.8
Range	0.1–10.6	0.6–3.3	3.3–13.9
$\tilde{A}_{liver}/\tilde{A}_{TB}$ (%)	9.8 ± 4.4	5.5 ± 3.7	32.6 ± 7.6
Range	3.0–19.0	1.6–15.5	15.6–47.8
$\tilde{A}_{RM}/\tilde{A}_{TB}$ (%)	2.5 ± 1.4	3.0 ± 1.1	2.2 ± 0.9
Range	0.1–7.0	1.4–4.9	1.2–4.8

MIRD = Medical Internal Radiation Dose; $\tilde{A}_{liver}$ = cumulated radioactivity in liver; $\tilde{A}_{TB}$ = total body cumulated radioactivity; $\tilde{A}_{RM}$ = cumulated radioactivity in red marrow.

S values and organ masses of MIRD reference man were used in both approaches. Marginally greater deviations in marrow dose for ^{67}Cu were associated with higher liver uptake as reflected by ratio of cumulated radioactivity for liver-to-total body ($\tilde{A}_{liver}/\tilde{A}_{TB}$). Ratios of cumulated radioactivity for red marrow-to-total body ($\tilde{A}_{RM}/\tilde{A}_{TB}$) were similar in these three studies.

Marrow Dosimetry for Individual Patients. Example of calculation. Question: A patient treated with ^{131}I-ChL6 had a body weight of 55,900 g. The C_{blood} was 6.36 μCi-h/mL/mCi (22.9 MBq-s/mL/MBq) determined by counting ^{131}I in the blood and $\tilde{A}_{TB}$ was 108,000 μCi-h/mCi (389,000 MBq-s/MBq) determined by total body imaging from immediate to 7 d after ^{131}I-ChL6 injection (*16*). Hematocrit was 0.30 from blood tests. What is the radiation dose to RM? Solution: Based on a hematocrit of 0.30 and a baseline value of 0.19 for RM extracellular fluid fraction (*12*), RMBLR was calculated to be 0.27. From Equation 16, the marrow dose of this patient is:

$$D_{RM} = 0.313 \times 0.27 \times 6.36 + 0.456 \times 108{,}000/55{,}900 = 1.42\ rad/mCi\ (0.384\ Gy/GBq). \quad \text{Eq. 17}$$

The mean patient weight for 84 patients (54 ^{131}I-Lym-1, 12 ^{131}I-ChL6, 18 ^{67}Cu-2IT-BAT-Lym-1) in this analysis was 75 kg and ranged from 48 to 132 kg. The differences between the patient-specific approach (Eq. 15) and MIRD standard approach (Eq. 1) were considerable if patient body weights were substantially different from the MIRD reference man (Fig. 1). If MIRD standard approach was used, an overestimation of 88% in RM dose was found in a patient whose body weight w as 132 kg and an underestimation of 35% was found in another patient whose body weight was 48 kg.

DISCUSSION

Patient-specific dosimetry for radioimmunotherapy has attracted considerable attention. Although RM has been recognized as the dose-limiting organ in nonmyeloablative therapy (*6*) and RM mass varies with patient size and age

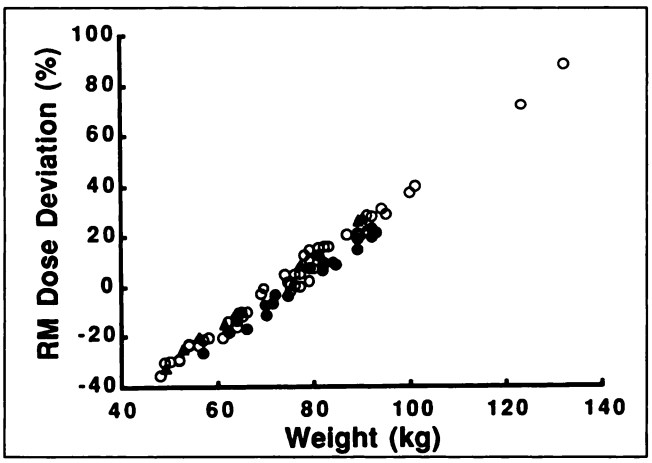

FIGURE 1. Red marrow (RM) dose determined by using standard MIRD reference man approach (Eq. 1) was compared with that using patient-specific approach (Eq. 15) in 54 ^{131}I-Lym-1 (○), 12 ^{131}I-ChL6 (▲) and 18 ^{67}Cu-2IT-BAT-Lym-1 (●) patients. Deviation in RM dose was mainly associated with differences between actual patient body weights and that of MIRD reference man phantom (69.88 kg).

(*9*), a method for patient-specific marrow dosimetry has not yet been described. One major challenge for patient-specific marrow dosimetry is the measurement of marrow mass for individual patients.

For radiopharmaceuticals that do not specifically bind to marrow, cumulated radioactivity in RM is generally determined by counting radioactivity in blood samples (*6,12*). Although DeNardo et al. (*8*) used the S value of MIRD reference man phantom to compute ^{131}I photon radiation to RM, ^{131}I electron radiation dose to RM from blood was independent of the actual RM mass. If marrow cumulated radioactivity is determined by blood sampling, the marrow mass cancels out during the calculation of electron radiation dose to RM (*8*). However, because $\phi_{electron}$(RM←RM) has not been readily available in the literature and a portion of total radiation to RM is photon radiation from other sources for ^{131}I-labeled antibodies, the MIRD approach based on reference man's S value is still widely accepted as standard (*3,6,7*).

In this study, marrow radiation dose was calculated by moving a step back from the S value. Using the Δ and ϕ, we have shown that patient-specific marrow dose can be obtained without knowing the actual RM mass of the patient (Eq. 15).

The absorbed fraction $\phi_{electron}$(RM←RM) of reference man can be derived from MIRD Pamphets 5, 10 and 11 (*1,13,14*). The electron absorbed fraction is only dependent on the microenvironment and not on the overall mass of the organ. The overall mass is used for establishing a radioactivity concentration of the organ. $\phi_{electron}$(RM←RM) is dependent on geometry (chord lengths) of trabeculae and marrow cavities and not on total RM mass (*18*). Eckerman (*18*) reported that $\phi_{electron}$(RM←RM) in lumbar vertebra of a 44-y-old man was 0.935 and 0.757 for electrons of 100 keV and 1000 keV, respectively. On the other hand, $\phi_{electron}$(RM←RM) in lumbar vertebra of a 20-mo-old child was 0.892 and 0.708 for electrons of 100 keV and 1000 keV, respectively. Similar $\phi_{electron}$(RM←RM) values were also found in parietal bone between a 44-y-old man and a 20-mo-old child, despite the vast difference in body and marrow mass. Therefore, the deviation of $\phi_{electron}$(RM←RM) in individual adult patients from that of reference man (Table 1) is expected to be inconsequential for RM dose estimation assuming a similar marrow distribution in the skeleton. The $\phi_{electron}$(RM←RM) derived from MIRD data were based on work of Spiers and is conservatively high (*1*). An improved bone marrow model has been developed by Eckerman (*7,18*) and improved $\phi_{electron}$(RM←RM) values can be used in Eq. 15 when these data are easily accessible.

Computation of the photon radiation from RM and other major organs to RM is challenging for individual patients in a clinical setting. In this study, we showed that all photon radiation to RM can be represented by TB to RM and can be adjusted by body weight to be patient specific. Because therapeutic radionuclides have a large portion of electron radiation and radiolabeled antibodies are relatively broadly distributed in the body, photon radiation from TB is a good approximation for the standard MIRD approach, wherein photon radiation dose contributions from each source are estimated separately. In the present analysis of 84 adult patients receiving ^{131}I and ^{67}Cu, a mean deviation of 5.0% was found for marrow dose if all photon radiation sources were included as TB (Table 2). Because S values in the MIRD table are significant to two digits, the numeric uncertainties by these values themselves are ranged from 0.5% to 4.5%. The deviation introduced by TB representation of all photon radiation sources was inconsequential for marrow dose estimation for above patients.

In a similar previous analysis (*5*), we found that all nontarget sources can be represented by the remainder of the body for therapeutic radionuclides. In 59 patients receiving ^{131}I and ^{67}Cu, a mean 1.1% deviation in radiation dose estimates from the standard MIRD approach was found for liver, spleen, lungs or kidneys as the target, if all nontarget sources were included in the remainder of the body. The slightly greater deviation for RM dose (5.0% compared with 1.1%) found in this analysis was associated with the lower cumulated radioactivity in marrow compared with that in the liver, spleen, lungs and kidneys. A slightly greater deviation for marrow dose in ^{67}Cu compared with ^{131}I was associated with the larger liver uptake of ^{67}Cu because 33% of total cumulated ^{67}Cu of the body was in the liver (Table 2). It is important that the radiopharmaceuticals not all be concentrated in any one or two particular organs so that use of photon contribution of TB to RM S value is appropriate. The deviation in marrow absorbed dose using TB to represent all photon radiation sources can be significant if some tissues have exceptionally large uptake and prolonged retention. In this study, a maximum of 13.9% deviation in marrow dose was found in 1 patient with liver uptake of 47.8% of the total

cumulated ^{67}Cu. For ^{90}Y and ^{188}Re, there will be no or insignificant deviation, even if radiopharmaceuticals are highly localized in one organ (in the special case of a peptide or fragment highly localized in the kidneys). Therefore, these unusual situations can be dealt with only on a case by case basis.

For radiopharmaceuticals that bind to marrow elements, radioactivity in RM cannot be estimated accurately from radioactivity in blood, and Equation 15 is not applicable. In such situations, radioactivity in RM can be estimated by imaging methods such as sacral (*19*) or lumbar vertebral imaging (*20*). The representation of total RM by sacral or lumbar vertebral can be complicated because marrow metastases are generally nonuniformly distributed. In addition, marrow uptake is nonuniform in the skeleton (*21*). These problems need to be addressed in future research designed to further develop patient-specific RM dosimetry for radiopharmaceuticals that bind marrow elements.

CONCLUSION

This study illustrates that all photon radiation sources can be included in the TB as one photon radiation source to RM in radionuclide therapy. A simple and practical approach is proposed to estimate patient-specific RM dose without knowing the actual marrow mass of individual patients. For radiopharmaceuticals that do not specifically bind to marrow, patient-specific marrow doses can be obtained by measuring blood and total body radioactivity and patient body weight.

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