integrate over the rate as a function of time, as initially indicated by Orton (2). Using Orton's (2) numerical constant, we set:

$$\text{TDF(tumor)} = 0.114 \int_0^\infty r(t)^{1.35}\, dt. \qquad \text{Eq. 3}$$

Next, we assumed that the tumor dose rate function could be mathematically modeled as:

$$r(t) = r_0[\exp(-\lambda_1 t) - \exp(-\lambda_2 t)], \qquad \text{Eq. 4}$$

where λ_1 represents the effective rate constant and λ_2 the effective uptake rate constant. A curve such as Equation 4 increases from zero at t = 0, goes through a maximum and returns to the origin at long times as we expect for tumor uptake of a radiotracer. The two rate constants are related to the effective half-times (T) described by Rao and Howell (1) via the usual form: $\lambda = 0.693/T$ whereby each rate constant contained a sum of biological (b) and physical (p) rate constants; e.g., $\lambda_1 = \lambda_{b1} + \lambda_p$.

We have performed several integrations of our Equation 3 using Equation 4 as the rate function. We then compared those results with Rao and Howell's approximation of Equation 1 using the biological kinetic parameters (condition 1) as supplied by those authors (1). The results are given in Table 1. We note that our results are approximately 70% of those given by Rao and Howell (1). Moreover, if we kept the difference of times (τ_e) fixed but allowed $T_{e,t}$ to increase twofold (condition 2), the result of our ^{131}I calculation became only 60% of that shown in Rao and Howell (1). This contradicted the assertion (1) that the TDF depends only on τ_e.

Accepting that tumor dose rate effects are indeed operative with pure beta sources, we are led to several conclusions regarding TDF in radioimmunotherapy. First, we believe that a more general absorbed dose rate integration should be done—using, if available, the actual tumor uptake curve(s) for estimation of TDF. Next, Tables 2, 3, and 4 shown in Rao and Howell (1) are not readily applicable in clinical practice since they depend upon variables which are either unclear (r_0) or incorrect (the time integral of the rate). Finally, although the authors suggest (1) that longer-lived radionuclides should be used in RIT, we would caution that this conclusion depends upon the stability of the bifunctional chelating agent used. We know of no agent which has a zero off rate; i.e., is permanently stable in plasma. Thus, long-lived potential RIT radionuclides such as ^{32}P may be leachable from the antibody leading to altered biodistributions involving increased bone marrow uptake.

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REPLY: We appreciate the interest of Liu et al. in our recent publication (1) on the use of a time-dose-fractionation (TDF) approach to select optimal radionuclides for radioimmunotherapy. Liu et al. seem to be primarily concerned about the use of TDF for therapy with internal beta emitters, as well as our not considering the most general form of the TDF computation for internal emitters.

Liu et al. question the existence of a dose-rate effect for beta emitters, and therefore question the applicability of the TDF approach which was formulated based on clinical brachytherapy data with ^{226}Ra (2). Dose rate effects for low-LET radiations (e.g., β, γ, χ) are well known in radiobiology and have been a topic that has attracted considerable attention in RIT. As pointed out in the introduction of our paper (1), Fowler (3) has used the linear-quadratic model to suggest that dose-rate effects indeed play a role in radioimmunotherapy. This is further substantiated in the recent AAPM Nuclear Medicine Committee Task Group No. 2 Report on Dosimetry of Radiolabeled Antibodies where Langmuir et al. (4) discuss evidence of dose-rate effects for beta emitters. Clearly, only small dose-rate effects are expected for short-lived radionuclides such as ^{90}Y and such effects may be difficult to discern experimentally considering the uncertainties inherent in internal dosimetry. This is supported by our TDF calculations ((1), Table 8, row 8) which show that ^{90}Y can be about as effective as the standard 60 Gy of ^{226}Ra gamma rays delivered over 7 days. However, the same TDF calculations demonstrate that dose-rate effects can be more substantial when effective half-lives are increased through the use of longer-lived radionuclides such as ^{32}P and ^{114m}In.

Liu et al. also expressed concern regarding our use of an approximate form of the TDF expression for incorporated radionuclides. We have chosen this approach for the sake of simplicity without unduly sacrificing accuracy given the uncertainties in determining tumor activity and absorbed dose. This rationale is explained in detail below. The authors are correct in that the most general form of the dose rate function r(t) will provide the most accurate TDF values. Accordingly, Liu et al. have appropriately suggested that the following traditional function for the dose rate be used:

$$r(t) = r_0(e^{-0.693t/T_e} - e^{-0.693t/T_{eu}}), \qquad \text{Eq. 1}$$

where T_e and T_{eu} are the effective clearance half-life and effective uptake half-time in the tissue, respectively, and r_0 is the extrapolated "initial" dose-rate. Given that they have conveniently used r_0 in Equation 1, we fail to understand their lack of appreciation of the definition of the extrapolated "initial" dose-rate. In any case, the total dose D delivered to the tissue is obtained by integrating Equation 1 from 0 to ∞ which yields:

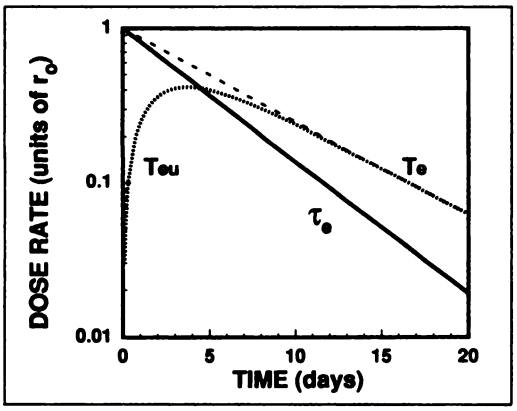

FIGURE 1. Graphic representation of the temporal dependence of the target tissue dose-rate following administration of radiolabeled antibodies. The dotted line is obtained using Equation 1. The dashed line is an extrapolation of the second component (T_e) of the dose-rate curve to time zero which gives the "initial" dose rate r_0. Finally, the solid line represents the time dependence of the "effective" dose rate given by Equation 3 with an effective time $\tau_e = T_e - T_{eu}$. The integral dose under the dotted and solid curves is the same.

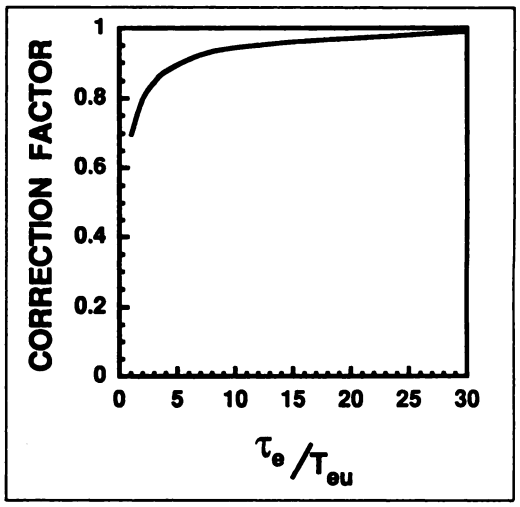

FIGURE 2. The correction factor for TDF values as a function of the ratio of the effective time-(τ_e)-to-the effective uptake time (T_{eu}). The correction factor is the ratio of the TDF value calculated by numerical integration of Equation 1 with Equation 4, to the approximate TDF value calculated using Equation 5. Should a high degree of accuracy be desired, the approximate TDF values presented in Tables 2–4 in Ref. 1 may be adjusted using these correction factors.

$$D = 1.44 r_0 (T_e - T_{eu}). \qquad \text{Eq. 2}$$

The effective time τ_e used in our calculations is defined to be $T_e - T_{eu}$. Of course, integration of

$$r_0 e^{-0.693t/\tau_e}, \qquad \text{Eq. 3}$$

also yields the same total dose given in Equation 2. For the sake of clarity, these concepts and definitions are illustrated in Figure 1. The rationale for our use of τ_e and the extrapolated value r_0 (which Liu et al. use themselves in their Equation 4) should now be apparent. The TDF, as defined by Orton (*2*), is given by

$$TDF = 0.114 \int_0^\infty r(t)^{1.35}\, dt. \qquad \text{Eq. 4}$$

Substitution of Equation 1 into Equation 4 to obtain the general form of the TDF expression for incorporated radionuclides does not result in a closed form and therefore requires numerical integration on a case-by-case basis. An approximate expression for the TDF can be obtained by substituting Equation 3 for r(t) in Equation 4 thereby yielding:

$$TDF = 0.122 r_0^{1.35} \tau_e. \qquad \text{Eq. 5}$$

This is the same expression we used in our TDF calculations (*1*). The above approximation is good when the effective clearance half-life is substantially longer than the effective uptake half-time (i.e., T_e T_{eu} or τ_e/T_{eu} 1). We clearly warned readers that caution should be exercised when the effective half-life in the tumor is short and comparable to the effective uptake half-time (i.e., $T_e \lesssim T_{eu}$ or $\tau_e/T_{eu} \sim 1$). This approximation overestimates the TDF values in these circumstances. Figure 2 shows the dependence of the correction factor on the ratio τ_e/T_{eu}. The correction factor is the ratio of the TDF value numerically calculated using the general form (Equations 1 and 4) to the TDF value calculated using our approximation (Equation 5). At large ratios of τ_e/T_{eu}, which are expected in the case of longer-lived radionuclides (e.g., ^{32}P, ^{114m}In), the correction factors are small. Hence, the tabulations given by Liu et al. are expected.

In the case of ^{90}Y, where T_e = 2.2 days, T_{eu} = 1.1 days, and τ_e = 1.1 days (condition 1 of Liu et al.'s Table), the general form of the TDF gives a value about 30% lower than our approximate value. This may be readily seen in Figure 2. They fail to acknowledge that the errors decrease as the physical half-life of the radionuclide increases (same biological conditions). The approximate TDF is only about 15% and 10% lower for ^{32}P and ^{114m}In, respectively. Most surprising is their choice of effective half-life T_e of 10 days for ^{131}I (condition 2 of Liu et al.'s Table). We wonder how a radionuclide with an 8-day physical half-life can yield a 10-day effective half-life? Furthermore, their choice of effective uptake half-time T_{eu} = 6.5 days implies a biological uptake half-time of 35 days is not appropriate in that any antibody with such biokinetic characteristics would have no use in RIT. Any approximation, when taken to such absurd limits, can lead to large errors.

Our use of the effective time τ_e to approximate the TDF was meant to provide a closed expression for TDF which would facilitate its use in clinical RIT. TDF values can not be calculated using the general form without resorting to numerical integration and TDF values cannot be tabulated readily because the TDF is a function of three variables (r_0, T_e, T_{eu}). Considering the large errors encountered in internal dosimetry (e.g., nonuniform activity distribution, in vivo quantitation, etc.), the relatively small errors introduced by our approximation are a small price to pay considering the simplicity and convenience it offers. Hence, Liu et al.'s comment "Also problematic was the use of a simple time difference" (i.e., $T_e - T_{eu}$) is unjustified. Should the reader desire a greater degree of accuracy than provided by Equation 5 and our TDF Tables (Ref. 1, Tables 2–4), the correction factors provided in Figure 2 may be employed.

A few final remarks are in order. First, Liu et al. indicated that we stated that "the TDF depends only on τ_e." This is simply incorrect. We repeatedly stated in our paper that the TDF value

depends on both r_0 and τ_e, the latter obviously depending on T_e and T_{eu}. Second, Liu et al.'s concern regarding the leachability of the radiolabeled antibodies is obvious and only a restatement of the reservations expressed in our concluding remarks (*1*). Third, if TDF values are calculated using the general TDF form, then a quick analysis suggests that the target-to-nontarget ratios required for short-lived radionuclides (e.g., ^{90}Y, ^{131}I) will be even higher than the values reported in our article (Ref. 1, Fig. 2). This strengthens our arguments for the use of longer-lived radionuclides in RIT. Fourth, if indeed there are no dose-rate effects for internal beta emitters as implied by Liu et al., then longer-lived radionuclides are even more advantageous. Finally, although not addressed by Liu et al., the limitations of the TDF model are pointed out in our original publication. We look forward to comparing our results based on the TDF approach with similar calculations based on the linear-quadratic model.

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Standardized Uptake Values of FDG

TO THE EDITOR: We read with interest the article by Kim et al. (*1*) where the standardized uptake value normalized for the body surface area (SUV_{bsa}) was found preferable to the standardized uptake value normalized for the body weight (SUV_{bw}) for measuring the [^{18}F]-fluorodeoxyglucose (FDG) uptake. We agree that the substitution of weight for body surface area for quantitation of relative tracer uptake in neoplastic (*2,3*) and normal tissues (*4*) may overcome weight dependency associated with the commonly used formula for calculation of SUV_{bw}. In accordance with Kim et al., we have found that SUV_{bw} overestimates FDG (and L-[^{11}C]methionine) uptake in large patients, but feel that a few comments are in order to relate their findings to our observations.

First, we would like to draw attention to the fact that SUV_{bsa} is not a dimensionless parameter. The authors (*1*) report values of 0.056–0.111 with a mean of 0.083 for SUV_{bsa} of liver for patients with abdominopelvic malignancies. It is not clear to us how these absolute values relate to the dimensions and formula given in their paper for calculation of SUV_{bsa} which should result in figures per meter if appropriate unit cancellations are made. In fact, the absolute SUV_{bsa} values for liver in a population of patients with localized breast cancer yields 50–76 m^{-1} suggesting that Kim et al. have used a scaling factor which was not given in their original formula. It is true that this presumed conversion might be convenient for practical purposes but may invalidate comparisons with other studies if appropriate modifications are not reported.

In light of the difference in SUV_{bsa}s between patients with breast and abdominopelvic malignancies it would be interesting to assess the impact of metastatic spread on FDG uptake in liver, which may explain the larger variability in the study of Kim et al. (*1*) in comparison to currently reported values (67 ± 7 m^{-1}). Although Kim et al. do not give the percentage of patients with liver metastases it is tempting to think that their study included several patients with altered liver function and perhaps subclinical disease, bearing in mind the typical pattern of metastatic spread in patients with colorectal and ovarian cancer. It could be further hypothesized that an increase in FDG uptake in liver may preceed clinical metastases. This, of course, should be assessed in a prospective study.

Second, we emphasize that "normalization" of SUV_{bsa} to the mean SUV_{bw} in only one series of patients cannot replace other methods of quantitation—normal SUV can hardly be assessed for tumor tissue. Our examples also suggest that normalization in seemingly healthy tissues may lead to erroneous conclusions in an oncologic patient population at risk of harboring more widespread disease. We feel strongly that absolute values are preferable not only to assess the aggressiveness of the tumor but also to allow meaningful comparisons between different patient populations.

Physicians involved in the use of FDG-PET may feel that SUV_{bsa} is a bit clumsy while SUV_{bw} simply describes the ratio between the accumulation of the tracer in the volume under observation and the whole-body average distribution. Being a dimensionless parameter, on the basis of predicted lean body mass, SUV may be the simplest solution for semiquantitative measurement of the uptake of FDG (*4*).

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REPLY: We thank Drs. Leskinen-Kallio, Minn and Zasadny for raising their concerns and for the opportunity to further discuss this subject.

Leskinen-Kallio et al. correctly pointed that SUV_{bsa} is not a dimensionless parameter. The primary purpose of our study (*1*) was to compare the dependency of SUV_{bw} on body size with that of SUV_{bsa}, but not to define the normal range of SUV_{bsa} for the liver. Of the several steps involved in calculating SUV_{bsa} in our study, the final step was to obtain values directly comparable to