# Generalized Approach to Absorbed Dose Calculations for Dynamic Tumor and Organ Masses

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Tumor absorbed dose calculations in radionuclide therapy are presently based on the assumption of static tumor mass. This work examines the effect of dynamic tumor mass (growth and/or shrinkage) on the absorbed dose. **Methods:** Tumor mass kinetic characteristics were modeled with the Gompertz equation to simulate tumor growth and an additional exponential term to accommodate tumor shrinkage that may result as a consequence of therapy. **Results:** Correction factors, defined as the ratio of the absorbed dose, which was calculated by considering tumor mass dynamics, to the absorbed dose, which was calculated by assuming static mass, are presented for 1- and 100-g tumors with different tumor mass kinetics. The dependence of the correction factor on the effective half-life $T_e$ of the radioactivity in the tumor and the tumor shrinkage half-time $T_s$ was examined. The correction factors for the 1-g tumor were > 1 for short $T_s$ and $T_e$. In contrast, the correction factor was less than 1 for long $T_s$ (> 9 days). The dose correction factors for the 100-g tumor were > 1 for all $T_s$ and $T_e$. Finally, the dosimetric method for dynamic masses is illustrated with experimental data on Chinese hamster V79 multicellular spheroids that were treated with $^3H$. **Conclusion:** Correction factors as high as about 10 are likely when $T_e$ and $T_s$ are short. As $T_s$ increases beyond 20 days, the importance of dynamic mass diminishes because most of the activity decays before the mass changes appreciably. In some cases, mass dynamics should be taken into account when the absorbed dose to tumors is estimated.

**Key Words:** dosimetry; tumor growth; tumor shrinkage; multicellular spheroids; micrometastases; radioimmunotherapy

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It is generally assumed in the dosimetry of administered radionuclides that the target mass is static during the period of irradiation (*1*). Although this is usually the case for most normal organs, there are instances in which the mass of the target may be dynamic. For example, the fetus and its constituent organs grow rapidly. Similarly, micrometastatic and gross tumors may also undergo periods of rapid growth (*2–5*). Furthermore, tumors are likely to undergo shrinkage during protracted irradiation. Hence, rapidly growing tumors that are treated with radiolabeled antibodies may have complex tumor mass kinetics in which a period of growth is followed by shrinkage. If the tumor mass doubling time ($T_g$) or tumor shrinkage half-time ($T_s$) is of the order of the effective half-life of the radioactivity in the tumor, then the traditional assumption of static mass can lead to large errors in the absorbed dose estimation.

Recently, Howell et al. (*3*) presented a method to calculate the absorbed dose to rapidly growing target masses that contain radioactivity. In the present work, this method is expanded to include the calculation of absorbed doses to dynamic target masses undergoing growth and/or shrinkage during radionuclide therapy. Such an approach was recently considered by Dale et al. (*6*) for brachytherapy. The method presented here can be useful for improved absorbed dose calculations for dynamic tumor masses and for rapidly growing normal organs such as those found in the fetus. In addition, the approach presented may be useful for laboratory radioimmunotherapeutic protocols that involve small animals that have rapidly changing tumor masses, which can be followed through direct measurement. For convenience, the symbols (and their definitions) that are used in the dosimetry model are listed in Table 1 for ready reference.

## METHODS

The mean absorbed dose $\bar{D}_k$ to target region $r_k$ from source region $r_h$ is given by the MIRD schema (*1*) as follows:

$$\bar{D}(r_k \leftarrow r_h) = \tilde{A}_h \sum_i \Delta_i \Phi_i(r_k \leftarrow r_h), \qquad \text{Eq. 1}$$

where $\tilde{A}_h$ is the cumulated activity in the source region and $\Delta_i$ is the mean energy emitted per disintegration for the ith radiation component. The specific absorbed fraction $\Phi_i$ for target volume $v_k$ is given by the following equation (*1*).

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**TABLE 1**
Explanation of Symbols

| Symbol | Explanation |
|---|---|
| $T_p$ | Physical half-life of the radionuclide |
| $T_e$ | Effective half-life of the radiopharmaceutical in the tumor |
| $T_{eu}$ | Effective uptake half-time of the radiopharmaceutical in the tumor |
| $T_g$ | Initial tumor mass doubling time |
| $T_D$ | Tumor growth rate damping half-time |
| $T_s$ | Tumor shrinkage half-time |
| $a_0$ | Extrapolated activity |
| $m_0$ | Initial mass of the tumor |
| $v_k$ | Volume of target region k |
| $\bar{D}_k$ | Mean absorbed dose to target region k |
| $A_h(t)$ | Activity in source region h at time t |
| $\Delta_i$ | Mean energy emitted per disintegration of the ith radiation component |
| $\Phi_i$ | Specific absorbed fraction for the ith radiation component |
| $\phi_i$ | Absorbed fraction for the ith radiation component |

$$\Phi_i(v_k \leftarrow r_h) = \frac{\phi_i(v_k \leftarrow r_h)}{m_k}. \qquad \text{Eq. 2}$$

The parameter $m_k$ is the mass of the target region, and $\phi_i$ is the fraction of energy emitted from the source region that is absorbed in the target region (absorbed fraction) for the ith radiation component, respectively (*1*).

The general formalism given by Equations 1 and 2 does not consider dynamic target masses. In the authors' previous work (*3*), a general expression for calculation of the mean absorbed dose to targets with dynamic masses was given as follows:

$$\bar{D}(v_k \leftarrow r_h) = \sum_i \int_0^t \frac{A_h(t)\Delta_i\phi_i(v_k \leftarrow r_h, t)}{m_k(t)}\,dt. \qquad \text{Eq. 3}$$

The source activity $A_h(t)$, target mass $m_k(t)$ and absorbed fraction $\phi(t)$ all are time-dependent quantities. Expressions for the absorbed fractions for photons and electrons can be found in Howell et al. (*3*). Activity in the source region may frequently be described by a period of exponential uptake of radioactivity followed by exponential clearance. Hence, the activity in the source region may be written as follows (*7,8*).

$$A_h(t) = a_0(e^{-0.693t/T_e} - e^{-0.693t/T_{eu}}), \qquad \text{Eq. 4}$$

where $T_e$ and $T_{eu}$ are the effective clearance half-life and effective uptake half-time, respectively. The quantity $a_0$ is the extrapolated activity at t = 0 (*8,9*). In the authors' earlier work on rapidly growing tumors (*3*), the Gompertz equation (Eq. 5) was used to model tumor growth.

$$m_k(t) = m_0e^{(b/a)(1-e^{-at})} = m_0e^{(T_D/T_g)(1-e^{-0.693t/T_D})}. \qquad \text{Eq. 5}$$

The Gompertz parameter *b* represents the initial specific growth rate of the tumor during the period of observation, and *a* is the damping constant that exponentially curtails the tumor growth rate as the mass increases (*10*). The initial tumor doubling time during the period of observation is therefore $T_g = 0.693/b$, and the tumor growth rate damping half-time is $T_D = 0.693/a$. This expression, however, does not accommodate tumor shrinkage and therefore requires an additional term for this purpose. If the tumor is assumed to shrink exponentially as a consequence of radionuclide therapy (*6*), Equation 5 can be rewritten as

$$m_k(t) = m_0e^{-0.693t/T_s}e^{(T_D/T_g)(1-e^{-0.693t/T_D})}, \qquad \text{Eq. 6}$$

where $T_s$ is the tumor shrinkage half-time. Substitution of Equations 4 and 6 into Equation 3 gives the mean absorbed dose to a tumor with dynamic mass and dynamic activity.

$$\bar{D}(v_k \leftarrow r_h) = \sum_i \int_0^t \frac{a_0(e^{-0.693t/T_e} - e^{-0.693t/T_{eu}})\Delta_i\phi_i(v_k \leftarrow r_h,t)}{m_0e^{-0.693t/T_s}e^{(T_D/T_g)(1-e^{-0.693t/T_D})}}\,dt \qquad \text{Eq. 7}$$

Equation 7 is numerically integrated with a FORTRAN code running on a UNIX-based HP9000 computer.

In this theoretic analysis, the kinetics of uptake and clearance of the radioactivity in the tumor is assumed to follow Equation 4. Similarly, it is assumed that the mass dynamics can be described by Equation 6. These functions have been selected because they frequently provide an adequate fit to experimental data on radionuclide kinetics and tumor mass dynamics. There may be instances where these equations may not adequately describe the data and, hence, different functions may be required. Regardless of the functional forms that describe the radionuclide kinetics and tumor mass dynamics, the formalism presented above (Eq. 3) can readily be used with appropriate functions that best describe the observed data to calculate the mean absorbed dose to tumors with dynamic mass.

## RESULTS AND DISCUSSION

### Application to an In Vivo Tumor Model

Tumor mass doubling times vary widely for human cancers, depending on the type and size of tumor (*5*). Doubling times that range from as short as 3 days for aggressive Burkitt lymphoma to more than 100 days for adenocarcinoma of the colorectal region have been observed. Figures 1 and 2 show examples of growth curves for representative tumors of initial mass 1 and 100 g, respectively. The 1-g tumor is assumed to have $T_g$ = 7 days ($b$ = 0.10 day$^{-1}$) and $T_D$ = 50 days ($a$ = 0.014 day$^{-1}$), whereas the 100-g tumor is assigned less aggressive growth parameters $T_g$ = 30 days ($b$ = 0.023 day$^{-1}$) and $T_D$ = 70 days ($a$ = 0.01 day$^{-1}$). The effect of these parameters on tumor mass dynamics were examined with Equation 6. For very long tumor shrinkage half-times ($T_s = \infty$), both tumors grow asymptotically to a final mass of approximately 1 kg (Figs. 1 and 2). When shrinkage half-times of 1, 2 and 4 wk are applied, the influence of decreasing $T_s$ is apparent in the lower three curves in Figures 1 and 2. When tumors are in their rapid growth phase (i.e., 1-g tumor), only very short $T_s$ (1 wk) causes no growth and only shrinkage of the tumor (Fig. 1). Longer $T_s$ (2 and 4 wk) may result in initial growth with subsequent decrease in tumor mass. In contrast, $T_s$ as long as 4 wk can shrink the tumor in the case of large slow-growing tumors of 100 g (Fig. 2). In radioimmunotherapy, the radiation dose to the tumor is delivered chronically over a period typically from 1 to 2 wk, depending on the effective half-life of the radiolabeled antibodies. The extent of tumor shrinkage during this period depends on the dose rate and cumulative dose delivered. In the event

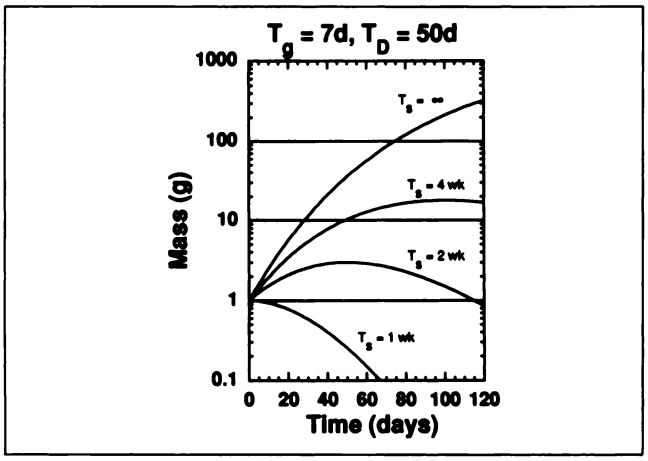


**FIGURE 1.** Mass kinetics for tumor of initial mass $m_0$ = 1 g, $T_g$ = 7 days and $T_D$ = 50 days. Effect of shrinkage half-time $T_s$ on overall tumor mass dynamics was calculated with Equation 6 and illustrated for $T_s$ = 1, 2 and 4 wk. In the absence of shrinkage ($T_s$ = ∞), the tumor grows asymptomatically to a mass of approximately 1000 g.

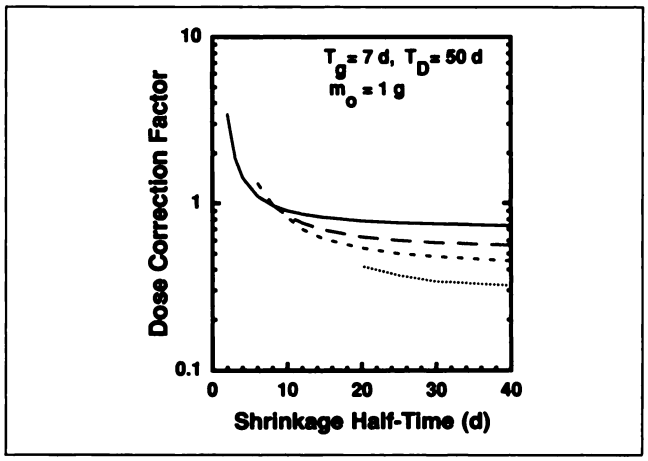


**FIGURE 3.** Dose correction factor as function of $T_s$ for tumor with $m_0$ = 1 g, $T_g$ = 7 days and $T_D$ = 50 days. Influence of the effective half-life of radioactivity $T_e$ in the tumor on the correction factor is illustrated for $T_e$ = 2 days (—), 6 days (——), 10 days (– –) and 20 days (···). Curves appear truncated because it was assumed that $T_s \geq T_e$.

that an insufficient dose rate and/or dose is delivered, the tumor may continue to grow rather than shrink. In either case, it is unlikely that the tumor mass remains constant during the irradiation period. Therefore, if the mass is assumed to be constant for dose calculations, as is currently practiced, the calculated absorbed dose may be very different from the actual dose received by the tumor. It is therefore essential that the growth kinetics of the tumor are taken into account to obtain reliable tumor dose estimates. Reliable estimates are an essential part of the assessment of the efficacy of various radionuclides for cancer therapy.

To examine the effect of growth on absorbed dose to the tumor, the dose was calculated with Equation 7 for different growth characteristics. For this purpose, the dose correction factor was defined as the ratio of the self-absorbed dose to the tumor for dynamic tumors (growth and/or shrinkage) to the self-absorbed dose when the tumor mass was assumed to be static. Figure 3 shows the dose correction factor as a function of $T_s$ for various effective half-lives $T_e$ of a monoclonal antibody labeled with an energetic beta emitter uniformly distributed in a small (1 g), rapidly growing tumor. The effective uptake half-time in the tumor ($T_{eu}$) was assumed to be 1.6 days. In addition, it was assumed that $T_s \geq T_e$. It should be noted that, for short $T_s$ and short $T_e$, the correction factor is greater than 1. On the other hand, for longer $T_s$ (> 9 days), the correction factor is less than 1. Similar calculations for large and slowly growing tumors (100 g) show that the dose correction factor is always greater than 1 for $T_s$ less than 40 days (Fig. 4). In fact, correction factors approaching 10 can be obtained for short $T_e$ and short $T_s$. As $T_s$ increases beyond 20 days, the importance of dynamic mass diminishes because most of the dose is delivered before the tumor mass changes appreciably. These calculations suggest that mass dynamics can indeed play an important role in the determination of the absorbed dose to tumors.

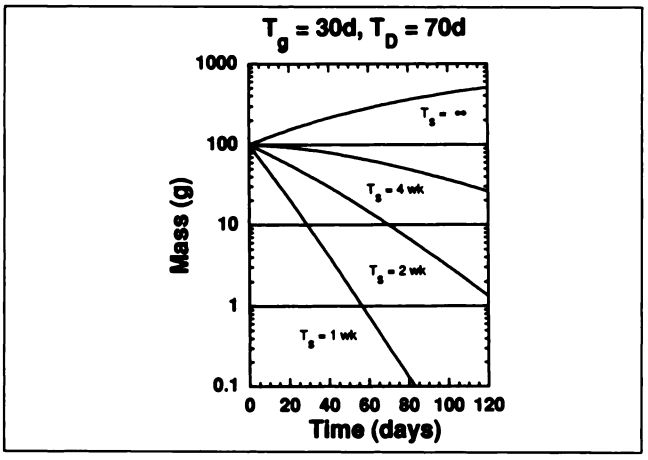


**FIGURE 2.** Mass kinetics for tumor of initial mass $m_0$ = 100 g, $T_g$ = 30 days and $T_D$ = 70 days. Effect of shrinkage half-time $T_s$ on overall tumor mass dynamics was calculated with Equation 6 and illustrated for $T_s$ = 1, 2 and 4 wk. As in the 1-g case, tumor grows asymptomatically to a mass of approximately 1000 g when $T_s$ = ∞ (no shrinkage).

### Application to an In Vitro Tumor Model

Cultured multicellular spheroids have been used widely as an in vitro model to examine the potential of labeled antibodies for radioimmunotherapy (*11–13*). In the authors' earlier report, Chinese hamster V79 multicellular spheroids were used to examine the implications of rapidly growing tumors on absorbed dose calculations (*3*). Spheroids were prepared by inoculation of 100 ml of culture medium into a 250-ml Erlenmeyer flask with $10^6$ V79 cells. After 3 days at 37°C on an orbital shaker, the spheroids were 100 to 150 $\mu$m in diameter. Spheroids that were approximately 125 $\mu$m in diameter were transferred individually to agar-coated wells in a 96-well plate, and tritiated thymidine ($^3$HTdR) was added to the plates to a final con-

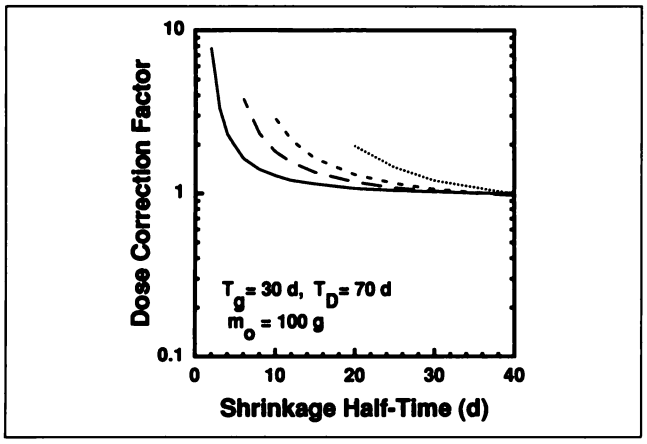


**FIGURE 4.** Dose correction factor as function of $T_s$ for tumor with $m_0$ = 100 g, $T_g$ = 30 days and $T_D$ = 70 days. Effect of $T_e$ on the correction factor is shown for $T_e$ = 2 days (—), 6 days (— —), 10 days (– –) and 20 days (· · ·). It was assumed that $T_s$ can never be less than $T_e$.

centration of 1850, 3700 and 7400 Bq/ml in 200 $\mu$l of culture medium. Spheroid volumes were measured daily for 7 days after the addition of the radiochemical. Separate experiments were carried out to determine the kinetics of uptake of the radiochemical. In the 1850- and 3700-Bq/ml cases, the growth of the spheroids followed simple Gompertz kinetics (Eq. 5), and the uptake of $^3$HTdR was linear during the 7-day observation period [see Figs. 1 and 2 in Howell et al. (*3*)]. After a least-squares fit of the experimental data, the Gompertz parameters and slopes of the radiochemical uptake were determined, and the absorbed doses were calculated (Eq. 3) to be 0.78 and 1.5 Gy, respectively, when mass dynamics were taken into account (*3*). When the dynamics of the spheroid masses were ignored, the calculated absorbed doses were about 20 times greater than the doses given above.

Not addressed in the authors' earlier work (*3*) was the calculation of the absorbed dose delivered to the spheroids that experience an initial growth period followed by shrinkage. These spheroids were incubated at high concentrations of $^3$HTdR (7400 Bq/ml). They did not experience simple Gompertz growth kinetics; instead, the spheroid mass grew quickly for about 4 days and then began to shrink. These data are reproduced in Figure 5, and the curve is the result of a least-squares fit to the new mass kinetics model, which entails periods of both growth and shrinkage (Eq. 6). The fitted parameters are $T_g$ = 0.42 days, $T_D$ = 2.2 days and $T_s$ = 1.8 days, which are extremely short half-times relative to those observed for macroscopic tumors in vivo (*5*). The uptake of $^3$HTdR for the 7400 Bq/ml is reproduced in Figure 6 where the curve represents a least-squares fit of the data to Equation 4. An uptake half-time $T_{eu}$ of 1.6 days, clearance half-life $T_e$ of 4.1 days, and $a_0$ = 280 Bq were obtained. In the calculation of the absorbed dose to the spheroid of unit density with Equation 7 and $m_0 = 10^{-6}$g, the fitted parameters $T_g$ = 0.42 days, $T_D$ = 2.2 days, $T_s$ = 1.8 days, $T_{eu}$ = 1.6 days, $T_e$ = 4.1 days, $a_0$ = 280 Bq and $\phi$ = 1 for the very short-range (< 1 $\mu$m) $^3$H beta particles, one obtains a mean absorbed dose to the spheroid of 6.8 Gy during the 7-day observation period. This is about six times smaller than the 42 Gy obtained when spheroid mass dynamics were ignored. This translates to a dose correction factor of 0.16. Note that the cumulated dose over a 7-day period was calculated in view of the limited data available. Nevertheless, this should serve as an example to illustrate the effect of tumor mass dynamics (growth followed by shrinkage) on the estimated absorbed dose from incorporated radionuclides.

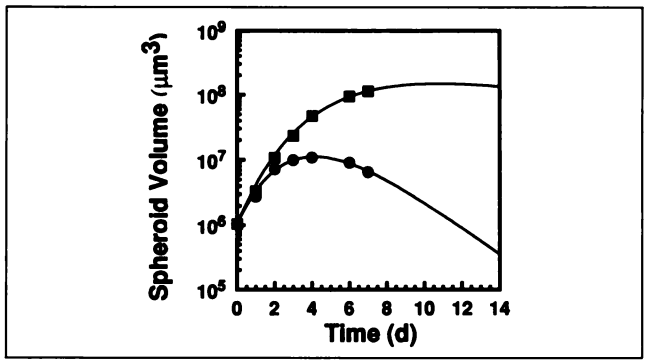


**FIGURE 5.** Growth dynamics of V79 multicellular spheroids during incubation in culture medium (*3*). Squares represent growth kinetics of control spheroids, whereas circles are those incubated in presence of 7400 Bq/ml of $^3$HTdR. Curves are the result of a least-squares fit of data to Equation 6.

## CONCLUSION

The absorbed dose is defined as the energy absorbed per unit mass of tissue. In nuclear medicine, radionuclides deposit energy over an extended period of time that depends on the effective half-life of the radiopharmaceutical in the tissue of interest. In most cases, the mass remains constant during the period of irradiation. In some cases,

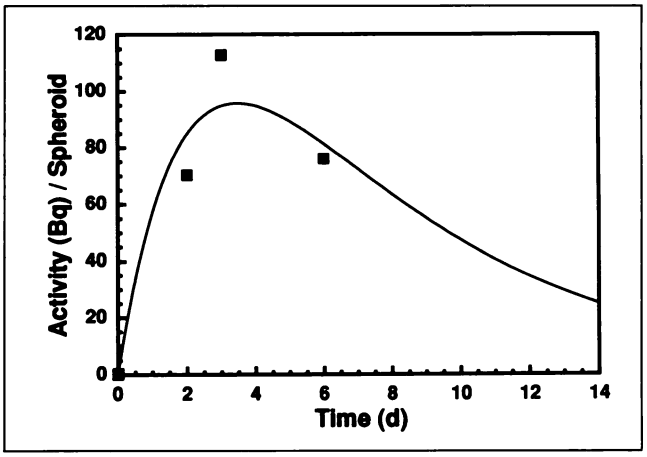


**FIGURE 6.** Kinetics of uptake of $^3$HTdR by Chinese hamster V79 multicellular spheroids as a function of incubation time in culture medium that contained 7400 Bq/ml of activity (*3*). Curve is a least-squares fit of limited data to Equation 4.

however, such as fetal tissue and tumors, the mass is dynamic. If the mass changes at a rate comparable to or more rapidly than the effective decay rate of the radioactivity in the tissue under consideration, then the absorbed dose to the dynamic mass will be substantially different than the absorbed dose to a static mass. This is a consequence of changes in the mass and the absorbed fraction $\phi$, which depends on the mass. To calculate the absorbed dose for dynamic masses, the instantaneous dose rate must be integrated over the irradiation period (Eq. 3).

The problem of dynamic mass is perhaps most pertinent to targeted radionuclide therapy in which tumors may experience changes in mass on a time scale that is of the order of the effective half-life of the radioactivity in the tumor. To evaluate the effectiveness of a given radionuclide therapy, it is imperative that reliable absorbed dose calculations be used to correlate with the biologic response. Hence, the general dosimetry formalism presented above may be useful in these situations. The in vitro multicellular spheroid model serves as an example of the utility of this approach. To utilize this approach in clinical situations, however, it is important to determine the tumor mass dynamics during radionuclide therapy. The general practice of a single tumor mass measurement before therapy may not be adequate for estimation of the absorbed dose to dynamic tumors. It should be noted that nonuniform distribution of activity in the tumor may also play an important role in tumor dosimetry (*14,15*). This can, in principle, also be folded into the dosimetry model.

Based on time-dose fractionation and linear-quadratic (LQ) models, it has recently been suggested that longer-lived radionuclides are likely to offer substantial advantages over the shorter-lived radionuclides currently in use in radioimmunotherapy (*8,9*). When longer-lived radionuclides are used, the need for incorporation of tumor dynamics into absorbed dose calculations is more pronounced because the effective half-life of the radioactivity in the tumor is more likely to be comparable to the tumor growth and shrinkage half-times ($T_g$ and $T_s$). Dale et al. (*6*) has already demonstrated the importance of tumor mass dynamics in brachytherapy in which radionuclides with half-lives of 2.7 to 60 days are implanted in the tumor. Their calculations, also based on the LQ model, also suggest that longer-lived radionuclides offer advantages in tumor therapy. Whether there is an interest in brachytherapy or radioimmunotherapy, it is clear that mass dynamics can play an important role in tumor dosimetry.

## ACKNOWLEDGMENTS

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