Absorbed Dose Calculations for Rapidly Growing Tumors

Roger W. Howell, Venkat R. Narra, and Dandamudi V. Rao

Department of Radiology, Division of Radiation Research, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ 07103

One of the most promising areas for cancer therapy with administered radiopharmaceuticals is the treatment of very small tumors and micrometastases. Small tumors and micrometastases, however, may be rapidly growing at the time of treatment, resulting in a substantial change in mass during the period of irradiation. In this work, the formalism required to calculate the average absorbed dose to rapidly growing tumors is developed and applied to an in vitro tumor model. Further application to in vivo human myeloma tumors reveals that tumor growth may have a significant effect on the average dose delivered to the tumor from incorporated radionuclides. These considerations may assist in establishing dose-response relationships necessary for radiopharmaceutical cancer therapy.

J Nucl Med 1992; 33:277-281

Over the last several years there has been a great deal of interest in employing radiopharmaceuticals such as radiolabeled monoclonal antibodies (*1*), and radiolabeled chemotherapeutic agents (*2,3*) for cancer therapy. This keen interest has elicited a number of considerations regarding calculation of the absorbed dose to the tumor. Tumor dosimetry has largely focused on the issue of inhomogeneity in the intratumor activity distribution (*4-12*). A comprehensive examination of the effects of such inhomogeneities at the macroscopic, multicellular, and subcellular levels was recently presented by Howell et al. (*5*).

A distillation of all the recent work in tumor dosimetry suggests that perhaps the greatest benefit to cancer therapy from radiolabeled agents may be found in the treatment of micrometastases. Micrometastases, however, introduce further complications to an already complex dosimetric problem. In conventional organ dosimetry (*13*), it is appropriately assumed that the mass of the organ remains constant during the period of irradiation. This assumption also has been extended to tumor dosimetry. As pointed out in our recent work (*5*), this may not be appropriate for all tumors. The fact that tumor mass can change quickly is well recognized. Consequently, the role of tumor growth in optimizing the traditional treatment of tumors with chemotherapy and radiotherapy has been discussed extensively (*14-16*). This suggests that the temporal dependence of the tumor mass may influence the calculated tumor dose in radiopharmaceutical therapy. Since knowledge of the dose is central to any radiation therapy, the effect of changing tumor mass should be critically examined.

In the present work, the MIRD Schema (*13*) has been used as a foundation to develop a dosimetric formalism for time-dependent mass. Rapidly growing multicellular spheroids are used as an experimental in vitro model to illustrate the effect of tumor growth on the calculated average absorbed dose to the tumor. In addition, the potential significance of growth is discussed in relation to in vivo tumor dosimetry.

THEORETICAL METHODS

General Formalism: Dosimetry for Time-Dependent Mass

According to the Medical Internal Radiation Dose (MIRD) Committee Schema (*13*), the general form for calculating the average absorbed dose rate $\dot{D}$ to a target region r_k, from radiations emanating from a source region r_h, containing activity A_h, is given by

$$\dot{D}(r_k \leftarrow r_h) = A_h \sum_i \Delta_i \Phi_i(r_k \leftarrow r_h). \qquad \text{Eq. 1}$$

The quantities Δ_i and Φ_i are the equilibrium dose constant and specific absorbed fraction for the i^{th} radiation component of the source radioactivity, respectively. When the target region k is a volume, the quantity Φ_i may be expressed as

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

where m_k is the mass of the target volume, and ϕ_i is the absorbed fraction for the i^{th} radiation component. The above equations are general and make no assumptions regarding the temporal dependence of any quantity including the mass of the target region. Using these definitions, a similarly general expression for the average absorbed dose D (Eq. 3) may be formulated with no

Received June 4, 1991; revision accepted September 4, 1991.

For reprints contact: Roger W. Howell, PhD, Department of Radiology, MSB F-451, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103.

assumptions regarding the temporal dependence of the target mass.

$$D(v_k \leftarrow r_h) = \sum_i \int_{t_1}^{t_2} \frac{A_h(t)\Delta_i\phi_i(v_k \leftarrow r_h, t)}{m_k(t)}\,dt, \qquad \text{Eq. 3}$$

Note that the absorbed fraction $\phi_i(v_k \leftarrow r_h, t)$ is time-dependent because it is a function of the size of the source and target regions.

Absorbed Fractions for Spherical Tumors

For spherical volumes of unit density matter, containing monoenergetic electron or β-emitting activity, the self absorbed fraction $\phi_i(t)$ may be obtained from the MIRD scaled absorbed-dose distributions $F(x/x_{90}, E_0)$ according to the relation (see MIRD Pamphlet 7 (*17*) for details):

$$\phi_i(t) = \int_0^\infty \psi(x, t)F(x/x_{90})(dx/x_{90}). \qquad \text{Eq. 4}$$

The variable x is the distance from a source point P within the sphere, x_{90} is the ninety percentile distance (*17*), and $\psi(x, t)$ is the geometric factor (see below). Alternatively (*7*), the absorbed fraction for electrons may be determined using Cole's (*18*) experimentally determined range-energy relation $X(E_i)$ and energy-loss expression dE/dX:

$$\phi_i(t) = \int_0^\infty \psi(x, t)\,\frac{1}{E_i}\,\frac{dE}{dX}\bigg|_{X(E_i)-x} dx, \qquad \text{Eq. 5}$$

where E_i is the energy of the i^{th} electron radiation component. For x-rays and γ-rays, the absorbed fraction for spherical geometry and unit density matter is given by

$$\phi_i(t) = \int_0^\infty \psi(x, t)\Phi(x, E_i)4\pi x^2\,dx, \qquad \text{Eq. 6}$$

where $\Phi(x, E_i)$ is the point isotropic specific absorbed fraction tabulated by Berger in MIRD Pamphlet 2 (*19*).

The geometric factor $\psi(x, t)$, given by Berger (*20*), is the fraction of the surface of a spherical shell of radius x centered around a source point P that falls within the source sphere of diameter d.

$$\psi(x, t) = 1 - \frac{3}{2}\,\frac{x}{d(t)} - \frac{1}{2}\left(\frac{x}{d(t)}\right)^3. \qquad \text{Eq. 7}$$

The above equation for $\psi(x, t)$ is only valid for determining the self-absorbed fraction $\phi(v_k \leftarrow v_k)$ for spheres containing homogeneously distributed activity, however, Equations 4–6 may be used in conjunction with geometric factors for other geometries.

Temporal Dependence of Tumor Mass

As indicated above, the implications of tumor growth in chemotherapy and conventional radiotherapy have been studied extensively (*14–16*). The Gompertz expression, given by Equation 8, has been one of the most commonly used models to describe the kinetics of tumor growth (*14,21*).

$$m_k(t) = m_k(t = 0)e^{(b/\alpha)(1-e^{-\alpha t})} \qquad \text{Eq. 8}$$

In this model the tumor initially experiences exponential growth with a rate constant b and, subsequently, as the tumor increases in size, its growth rate is in turn damped exponentially with a damping constant α. The constants α and b are characteristic of the tumor and may be determined by a least squares fit to experimental data. It should be noted that regardless of the model for m(t), the average dose to rapidly growing tumors may be determined using Equations 3–7 and an appropriate expression for A(t).

APPLICATION TO AN IN VITRO EXPERIMENTAL MODEL

Multicellular spheroids are a widely used in vitro tumor model for radiation response studies (*22,23*). More recently they have been used as a tool for evaluating the potential of radiopharmaceuticals for cancer therapy. Sutherland et al. (*24*), Kwok et al. (*25*), and McFadden et al. (*26*) have used this tumor model to measure the penetration and binding of radiolabeled monoclonal antibodies and their fragments in spheroids. Kwok et al. (*27*) investigated the therapeutic potential of radiolabeled monoclonal antibodies by monitoring the growth of spheroids as a function of time post-treatment. This assay, where the growth of non-irradiated and irradiated spheroids are monitored over a week or more, is commonly used to assess the effect of radiation on in vitro tumors. Hence, this assay can be used to demonstrate the importance of growth in tumor dosimetry. In this work, the growth of Chinese hamster V79 cell multicellular spheroids is monitored after treatment with tritiated thymidine ^{3}HTdR. This radiochemical was selected not for its therapeutic potential, but rather for its simplicity in its radiation properties. Tritium emits very short range (~ few μm in tissue) β-particles that are essentially all absorbed in the spheroid (i.e., $\phi = 1$). This simplifies the dosimetry by eliminating the complications of time-dependent absorbed fractions, thereby serving as a fine example to illustrate the importance of tumor growth on the calculated dose.

Preparation of Multicellular Spheroids

Chinese hamster V79-513 cells (kindly provided by Dr. R. Athwal, UMDNJ, Newark, NJ) were maintained as monolayers in culture flasks (37°C, and 5% CO_2–95% air) containing minimum essential medium (MEM) supplemented with 10% fetal bovine serum, 50 units/ml penicillin, 50 μg/ml streptomycin, and 2 m*M* L-glutamine. Multicellular spheroids were prepared by transferring 3×10^6 V79 cells to 250 ml erlenmeyer culture flasks containing 100 ml of MEM (preincubated overnight at 37°C, and 5% CO_2–95% air). After capping tightly, the flasks were incubated on an orbital shaker at 37°C for 3 days to allow multicellular spheroids to grow to about 100–150 μm in diameter.

Growth Delay of Multicellular Spheroids

Spheroids, judged to be about 125 μm in diameter, were transferred by pipette to individual wells in a 96 well culture dish. The wells were precoated with a thin layer of 1% Difco agar to prevent attachment, and then loaded with MEM. The initial volume of each spheroid was determined by measuring the diameter (inverted microscope equipped with eyepiece graticule) along two perpendicular axes (d_1, d_2) and calculating the volume

according to the relation $V = (\pi/6)(\sqrt{d_1 d_2})^3$. Various amounts of the radiochemical ^{3}HTdR were then added to the wells in groups of 12 to achieve concentrations of 1850 Bq/ml, 3700 Bq/ml or 7400 Bq/ml and a final volume of 200 μl in the well. The spheroid volumes were measured on various days up to 1 wk postadministration. The radiochemical was present in the culture medium throughout the 1-wk period. In a separate experiment, the kinetics of ^{3}HTdR uptake by the spheroids were monitored. This was accomplished by removing the spheroids from the wells, washing them with phosphate-buffered saline, and determining the incorporated radioactivity with liquid scintillation counting techniques.

Experimental Results and Calculation of the Spheroid Average Absorbed Dose

The average spheroid volume is shown as a function of time in Figure 1. A significant growth delay was observed when the spheroids were exposed to 1850 Bq/ml and 3700 Bq/ml of ^{3}HTdR, while 7400 Bq/ml led to some regression of the tumor volume. The corresponding kinetics of uptake of radioactivity by the spheroids is shown in Figure 2. The uptake pattern was essentially linear for 1850 Bq/ml and 3700 Bq/ml ^{3}HTdR, while a turnover, presumably related to the severe growth delay observed in Figure 1, was observed for 7400 Bq/ml. The uptake data were least squares fitted to $A(t) = \omega t$ and the growth data fitted to the Gompertz equation (Eq. 8). The fitted parameters ω, b, and α, are given in Table 1 for the control spheroids as well as those treated with 1850 Bq/ml and 3700 Bq/ml ^{3}HTdR. Because of the considerable regression in spheroid volume following the treatment with 7400 Bq/ml, a least squares fit with these functional forms was not feasible and therefore, for the sake of simplicity, will not be addressed further.

The average absorbed dose to the spheroids can be calculated by substituting expressions for m(t) and A(t) into Equation 3 and carrying out the integration. With $\phi = 1$ for ^{3}H β-rays, $A(t) = \omega t$, and m(t) given by the Gompertz equation (Eq. 8), Equation 3 may be integrated by parts over the limits 0 to T resulting in

$$D = \sum_i \frac{\Delta_i \omega}{m(t=0)\alpha e^{b/\alpha}} \left(\frac{1}{2}\alpha T^2 + \sum_{n=1}^{\infty} \frac{(b/\alpha)^n}{n \cdot n!} \left(\frac{1}{n\alpha} - \left(T + \frac{1}{n\alpha} \right) e^{-n\alpha T} \right) \right). \quad \text{Eq. 9}$$

With $\Delta = 9.08 \times 10^{-16}$ Gy-kg/Bq-s, $m(t = 0) = 1.04 \times 10^{-9}$ kg (assuming unit density), T = 168 hr, and ω, α, and b from Table 1, the average absorbed doses to the spheroids from the incorporated radioactivity are calculated to be 0.78 Gy and 1.5 Gy for the concentrations 1850 Bq/ml and 3700 Bq/ml, respectively. The contribution to the spheroid absorbed dose from the extra-spheroidal activity is negligible (<0.01 Gy).

Significance of Growth in the Spheroid Absorbed Dose Calculation

The importance of folding tumor growth into the calculation of the spheroid absorbed dose may be examined by ignoring the presence of growth. The functional form for the cumulated activity $\tilde{A}$ in the spheroid over the one week growth period is given by $\omega t^2/2$ for the 1850 Bq/ml and 3700 Bq/ml cases. Hence, the respective cumulated activities for these concentrations are 1.94×10^7 Bq-s and 3.23×10^7 Bq-s. With $m = 1.04 \times 10^{-9}$ kg (initial mass) and T = 168 hr, the respective spheroid average absorbed doses are 17 Gy and 28 Gy. These values are about 20 times larger than those calculated when spheroid growth was taken into account. This suggests that growth can indeed be a significant factor in tumor dosimetry.

APPLICATION TO AN IN VIVO TUMOR

Although tumor growth is clearly an important factor in in vitro tumor dosimetry, its importance in vivo is not obvious. Tumor growth in vivo can also be described by the Gompertz equation as demonstrated by Sullivan and Salmon (*21*). They have determined that for human mye-

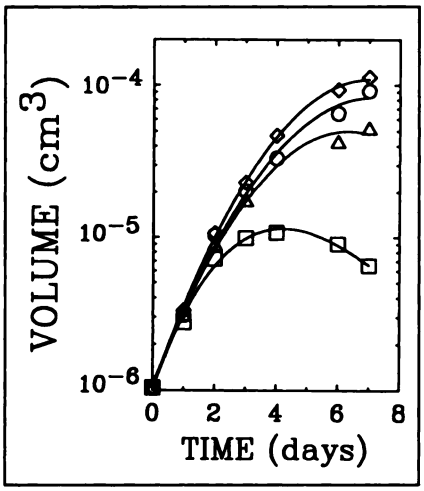

FIGURE 1. Growth of cultured Chinese hamster V79 multicellular spheroids in the presence or absence of tritiated thymidine (^{3}HTdR). The growth curves for spheroids in culture medium containing 1850 Bq/ml, 3700 Bq/ml, and 7400 Bq/ml ^{3}HTdR are indicated by the circles, triangles, and squares, respectively tively. Untreated controls are represented by the diamonds.

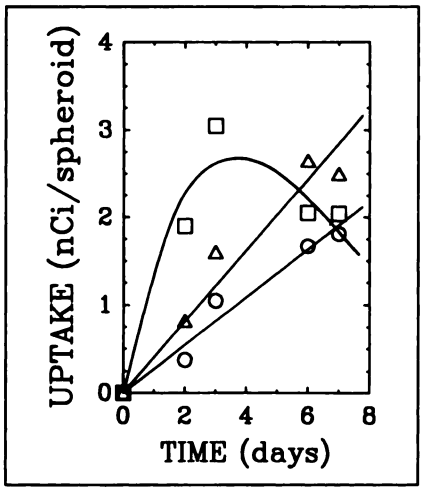

FIGURE 2. Kinetics of incorporation of ^{3}HTdR into rapidly growing cultured V79 multicellular spheroids. The uptake curves are for ^{3}HTdR concentrations of 1850 Bq/ml (circles), 3700 Bq/ml (triangles), and 7400 Bq/ml (squares) in the culture medium.

TABLE 1
Parameters for Spheroid Growth and Uptake of Radioactivity

	ω (Bq/h)	b (h^{-1})	α (h^{-1})
Control	—	0.0690	0.0130
1850 Bq/ml	0.381	0.0575	0.0108
3700 Bq/ml	0.635	0.0623	0.0146

loma tumors the Gompertzian kinetics parameters b and α are 0.3 d^{-1} and 0.011 d^{-1}, respectively. If we assume the radiopharmaceutical is taken up by the tumor instantaneously, and cleared from the tumor exponentially with an effective clearance constant λ, then for $\phi_i = 1$ the average tumor dose is given by

$$D = \sum_i \int_0^T \frac{A(t=0)}{m_k(t=0)} \Delta_i e^{-\lambda t-(b/\alpha)(1-e^{-\alpha t})}\, dt. \qquad \text{Eq. 10}$$

For $\alpha = 0.011\ d^{-1}$ and $0 \le T \le 7$ d, the quantity $(1 - e^{-\alpha t} \sim \alpha t$. Hence, Equation 10 simplifies to

$$D \cong \frac{A(t=0)}{m_k(t=0)} \frac{1}{\lambda + b} \sum_i \Delta_i. \qquad \text{Eq. 11}$$

Therefore, the ratio R of the absorbed dose when growth is ignored to the dose when growth is taken into account is given by

$$R\ (\phi = 1) \sim \frac{\lambda + b}{\lambda} = 1 + \frac{b}{\lambda}. \qquad \text{Eq. 12}$$

The significance of growth for calculating the average dose to human myeloma tumors (b = 0.3 d^{-1}) may now be explored over a range of effective half-lives. For an effective half-life of 1 day (i.e., $\lambda = 0.693\ d^{-1}$), the tumor dose when growth is ignored is about 1.4 times greater than when growth is accounted for. If the effective half-lives are 2 days and 3 days, the ratio increases to 1.9 and 2.3, respectively. Factors of this magnitude are significant and suggest that tumor growth may be relevant to in vivo dosimetry as well as for cultured multicellular spheroids.

DISCUSSION

Tumor dosimetry is already an exceedingly complex problem where the number of factors affecting calculation of the absorbed dose seems to be ever increasing. However, it is essential to address all factors that influence the absorbed dose including changes in tumor mass. Under what circumstances does growth warrant consideration? The examples described above for V79 multicellular spheroids and human myeloma tumors indicate that tumor growth plays an important role in determining the absorbed dose to rapidly growing micrometastases containing radionuclides that emit non-penetrating particulate radiations (i.e., $\phi = 1$). When more penetrating radiations are emitted, such as energetic β-rays from ^{131}I and ^{90}Y, only a fraction of the energy is absorbed in the micrometastasis ($\phi \neq 1$) and the fraction of energy absorbed increases as the tumor mass increases. Since the dose is proportional to ϕ/m, the effect of increasing mass on the dose is somewhat offset by a corresponding increase in ϕ. Consider, for example, a radionuclide that emits 1 MeV electrons. For sphere diameters ranging from 100 μm to 1000 μm, the absorbed fraction is approximately proportional to the sphere diameter. Therefore, for unit density matter it follows that $\phi(t) \propto m(t)^{1/3}$. Substitution of this expression into Equation 3, along with the expressions used above for A(t) and m(t), yields an expression for the tumor dose, which accounts for the time dependence of ϕ. In this case, the ratio R of the absorbed dose when growth is ignored to the dose when growth is taken into account is

$$R(\phi < 1) \sim \frac{\lambda + \frac{2}{3}b}{\lambda} = 1 + \frac{2b}{3\lambda}. \qquad \text{Eq. 13}$$

When the same growth constant implemented above for human myeloma tumors (b = 0.3 d^{-1}) is used, ratios of 1.3, 1.6, and 1.9 are obtained for 1 day, 2 day, and 3 day effective half-lives, respectively. These values are not very different than those obtained above with Equation 12 for $\phi = 1$. This suggests that, depending on the growth rate, it may be necessary to incorporate growth into tumor dosimetry when both low- and high-energy electron emitters are employed in cancer therapy.

The ratios calculated above are only for a representative case. Tumor growth rates are known to fluctuate (*16*) and therefore may have widely variable Gompertz growth parameters (b and α). What values of b and α will substantially influence the calculated absorbed doses? A close examination of Equations 12 and 13 suggests that a good rule of thumb is that tumor growth will play a significant role when the growth constant b is of the order of or greater than the effective clearance constant λ. When $\lambda \gg$ b, tumor growth will not affect the absorbed dose and may therefore be ignored. This rule of thumb is intuitively reasonable since the mass must change significantly during the period of irradiation (dictated by λ) in order for it to have an appreciable effect on the dose.

It should be noted that the primary purpose of this work is to develop a formalism for calculating average absorbed doses to rapidly growing tumors. Accordingly, the method has only been applied to relatively simple examples where the activity is assumed to be uniformly distributed in the tumor and the growth kinetics are not highly complex. Clearly the temporal dependence of the micrometastatic tumor masses during therapy are likely to be far more complex with periods of growth as well as shrinkage. An example of this is provided in Figure 1 (7400 Bq/ml denoted by the squares) where a sufficiently high concentration of the radiopharmaceutical ultimately leads to regression of the spheroid volume. Although such complex patterns have not been addressed here, this dosimetry formalism is completely general and therefore may be used with any functional form for the temporal dependence of the tumor mass.

Central to the success of any radiation therapy is a clear understanding of the relationship between the absorbed dose and the biological response. In the case of external beam therapy the absorbed dose can either be measured or calculated with reasonable accuracy and therefore dose-response relationships have been clearly established for this modality. However, for therapy with incorporated radionuclides, we must rely solely on absorbed dose calculations because direct measurement of the dose is impractical. Hence, the absorbed dose must be calculated with care, taking account of all possible variables affecting the calculation. In radionuclide therapy, the dose is delivered over a period of time during which the volumes of small tumors may change significantly. In that event, the tumor dose may be substantially overestimated unless the change in tumor mass is folded into the calculations. The dosimetry formalism presented above may facilitate calculation of more accurate doses and establishment of meaningful dose-response relationships for experimental radionuclide therapy.

ACKNOWLEDGMENTS

This work was supported in part by New Jersey Cancer Commission grant 688-009, NIH grant 2 S07 RR05393, and USPHS grant CA-32877.

REFERENCES

1. Order SE, Klein JL, Leichner PK. Yttrium-90 antiferritin—a new therapeutic radiolabeled antibody. *Int J Radiat Oncol Biol Phys* 1986;12:277–281.
2. Howell RW, Sastry KSR, Hill HZ, Rao DV. Cis-platinum-193m: its microdosimetry and potential for chemo-Auger combination therapy of cancer. In: Schlafke-Stelson AT, Watson EE, eds. *Proceedings of the Fourth International Radiopharmaceutical Dosimetry Symposium.* Oak Ridge, TN: DOE Conference CONF-851113; 1986; 493–513.
3. Hou D-Y, Hoch H, Johnston GS, *et al. A new* ^{111}*In-bleomycin complex for combined radiotherapy and chemotherapy. J Surg Oncol* 1985;29:91–98.
4. Sastry KSR, Haydock C, Basha AM, Rao DV. Electron dosimetry for radioimmunotherapy: optimal electron energy. *Radiat Prot Dosim* 1985;13:249–252.
5. Howell RW, Rao DV, Haydock C. Dosimetry techniques for therapeutic applications of incorporated radionuclides. In: Adelstein SJ, Kassis AI, Burt RW, eds. *Dosimetry of incorporated radionuclides.* Washington DC: American College of Nuclear Physicians; 1990:215–256.
6. Humm JL. Dosimetric aspects of radiolabeled antibodies for tumor therapy. *J Nucl Med* 1986;27:1490–1497.
7. Howell RW, Rao DV, Sastry KSR. Macroscopic dosimetry for radioimmunotherapy: nonuniform activity distributions in solid tumors. *Med Phys* 1989;16:66–74.
8. Kwok CS, Prestwich WV, Wilson BC. Calculation of radiation doses for nonuniformly distributed beta and gamma radionuclides in soft tissue. *Med Phys* 1985;12:405–412.
9. Makrigiorgos GM, Adelstein SJ, Kassis AI. Limitations of conventional internal dosimetry at the cellular level. *J Nucl Med* 1989;30:1856–1864.
10. Langmuir VK, Sutherland RM. Dosimetry models for radioimmunotherapy. *Med Phys* 1988;15:867–873.
11. Wessels BW, Griffith MH. Miniature thermoluminescent dosimeter absorbed dose measurements in tumor phantom models. *J Nucl Med* 1986;27:1308–1314.
12. Griffith MH, Yorke ED, Wessels BW, DeNardo GL, Neacy WP. Direct dose confirmation of quantitative autoradiography with micro-TLD measurements for radioimmunotherapy. *J Nucl Med* 1988;29:1795–1809.
13. Loevinger R, Berman M. A revised schema for calculating the absorbed dose from biologically distributed radionuclides. In: *MIRD Pamphlet No. 1, revised.* New York: Society of Nuclear Medicine, 1976.
14. Laird AK. Dynamics of growth in tumors and in normal organisms. National Cancer Institute Monograph 30 1969;15–28.
15. Duchting W, Vogelsaenger T. Aspects of modelling and simulating tumor growth and treatment. *J Cancer Res Clin Oncol* 1983;105:1–12.
16. Speer JF, Petrosky VE, Retsky MW, Wardwell RH. A stochastic numerical model of breast cancer growth that simulates clinical data. *Cancer Res* 1984;44:4124–4130.
17. Berger MJ. Distribution of absorbed dose around point sources of electrons and beta particles in water and other media. In: *MIRD Pamphlet No. 7.* New York: Society of Nuclear Medicine, 1971.
18. Cole A. Absorption of 20 eV to 50,000 eV electron beams in air and plastic. *Radiat Res* 1969;38:7–33.
19. Berger MJ. Energy deposition in water by photons from point isotropic sources. In: *MIRD Pamphlet No 2.* New York: Society of Nuclear Medicine, 1968.
20. Berger MJ. Beta-ray dosimetry calculations with the use of point kernels. In: Cloutier RJ, Edwards CL, Snyder WS, eds. *Radiation dose and effects, AEC symposium series no. 20.* Washington, DC: U.S. Atomic Energy Commission; 1970:63–86.
21. Sullivan PW, Salmon SE. Kinetics of tumor growth and regression in IgG multiple myeloma. *J Clin Invest* 1972;51:1697–1708.
22. Durand RE, Sutherland RM. Radiation studies with spheroids. *Cancer Res* 1984;95:103–115.
23. Sutherland RM, Durand RE. Radiation response of multicell spheroids—an in vitro tumor model. *Current Topics Radiat Res Q* 1976;11:87–139.
24. Sutherland R, Buchegger F, Schreyer M, Vacca A, Mach JP. Penetration and binding of radiolabeled anti-carcinoembryonic antigen monoclonal antibodies and their antigen binding fragments in human colon multicellular tumor spheroids. *Cancer Res* 1987;47:1627–1633.
25. Kwok CS, Cole SE, Liao S-K. Uptake kinetics of monoclonal antibodies by human malignant melanoma multicell spheroids. *Cancer Res* 1988;48:1856–1863.
26. McFadden R, Kwok CS. Mathematical model of simultaneous diffusion and binding of antitumor antibodies in multicellular human tumor spheroids. *Cancer Res* 1988;48:4032–4037.
27. Kwok CS, Crivici A, MacGregor WD, Unger MW. Optimization of radioimmunotherapy using human malignant melanoma multicell spheroids as a model. *Cancer Res* 1989;49:3276–3281.