

Application of the Linear-Quadratic Model to Radioimmunotherapy: Further Support for the Advantage of Longer-Lived Radionuclides

Roger W. Howell, S. Murty Goddu and Dandamudi V. Rao

Department of Radiology, University of Medicine & Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey

Radioimmunotherapy (RIT), as it is currently practiced, delivers low doses to tumors primarily because of dose-limiting bone marrow toxicity. The biologic effectiveness of RIT depends on the total dose, dose rate and the fractionation schedule of the radiolabeled antibodies administered. **Methods:** An approach based on the linear-quadratic (LQ) model, which is currently used in conventional radiotherapy, is advanced for treatment planning in RIT. This approach incorporates repair rates, radiosensitivity of the tissues, biologic half-lives of the antibodies, physical half-lives of the radionuclides, dose rates and total doses needed for a given biologically effective dose. The concept of a relative advantage factor (RAF) is introduced to quantify the therapeutic gain that can be realized by using longer-lived radionuclides instead of the shorter-lived counterparts currently in use. **Results:** RAFs are calculated for different biologic and physical half-lives, and values as high as 3 to 5 can be attained when longer-lived radionuclides are used. The RAFs predicted by the LQ model reaffirm the authors' earlier conclusion based on the time-dose-fractionation approach that relatively long-lived radionuclides coupled to monoclonal antibodies are indeed more likely to deliver therapeutically effective doses to tumors. Several radionuclides are evaluated in this context. **Conclusion:** The authors maintain that ^{32}P is the most promising isotope and the optimal physical half-life is about two to three times the biologic clearance half-life of the antibodies in the tumor.

Key Words: radioimmunotherapy; linear-quadratic model; dose-rate effects; radionuclide selection; biologically equivalent dose

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There is considerable interest in the evolving field of radioimmunotherapy (RIT) of cancer. The general goal in RIT is to deliver therapeutic doses to tumors without unduly affecting critical organs, such as bone marrow. Current methods that use relatively short-lived radionuclides have met with limited success. This is primarily because, when short-

lived radionuclides are used, the effective uptake half-times ($T_{\text{eu,t}}$, approximately 1-2 days) of the radiolabeled antibodies in human tumors are frequently comparable to the effective tumor clearance half-lives ($T_{\text{e,t}}$, approximately 2-7 days); the effective half-lives in the body $T_{\text{e,B}}$ are approximately 1 to 4 days (1-4). Given these general conditions in RIT, it is desirable to increase the effective half-life in the tumor relative to the effective half-life in the critical organs to improve therapeutic efficacy. Because there is only limited control over the biologic half-life of a given antibody, the effective half-life of the radiolabeled antibody can be lengthened by increasing the physical half-life (T_p). Therefore, the T_p of the radionuclides must be selected judiciously based on the biologic conditions.

When longer-lived radionuclides are used, dose rate effects will play a role in determining the biologic outcome (5,6). The authors' (7) recent work, which used time-dose-fractionation (TDF) methods to account for dose rate effects, showed that longer-lived radionuclides can provide a substantial therapeutic advantage in RIT. Several radionuclides were suggested that meet the criteria for therapeutic applications. In the present work, the advantage of longer-lived radionuclides is reexamined with the linear-quadratic (LQ) model. The LQ model, currently used in radiotherapeutic treatment planning, is adapted for applications in RIT. This approach takes into consideration the radiosensitivity of the tissues, repair rates, dose rates and biologic half-life and T_p to obtain biologically effective doses (BED). The usefulness of the LQ approach in RIT is discussed and illustrated with several examples. To evaluate the merits of longer-lived radionuclides quantitatively, the concept of a relative advantage factor (RAF) is developed and discussed. RAFs are calculated for several radionuclides with different T_p and different combinations of $T_{\text{eu,t}}$, $T_{\text{e,t}}$ and $T_{\text{e,B}}$. The LQ approach utilizes numerous parameters, which are described in Table 1 for ready reference.

LINEAR-QUADRATIC MODEL

LQ Model in Conventional Radiotherapy

The LQ model is commonly used to evaluate and compare different fractionation schedules in radiotherapy, including differ-

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For correspondence or reprints contact: Dandamudi V. Rao, PhD, Department of Radiology, MSB F-451, UMDNJ—New Jersey Medical School, 185 S. Orange Avenue, Newark, NJ 07103.

TABLE 1
Explanation of Symbols

Symbol	Explanation
T_p	Physical half-life of the radionuclide
T_b	Biologic half-life of the radiolabeled antibody
T_e	Effective half-life of the radiolabeled antibody
T_u	Biologic uptake half-time
$T_{b,t}$	Biologic half-life in the tumor
$T_{u,t}$	Biologic uptake half-time in the tumor
$T_{b,B}$	Biologic half-life in the body
T_{eu}	Effective uptake half-time ($T_{eu} = (T_p \times T_u)/(T_p + T_u)$)
τ_e	Effective time ($\tau_e = T_e - T_{eu}$)
$T_{e,t}$	Effective half-life in the tumor
$T_{eu,t}$	Effective uptake half-time in the tumor
$\tau_{e,t}$	Effective time in the tumor
$T_{e,B}$	Effective half-life in the body
r_t	Dose rate to the tumor
r_B	Dose rate to the whole body
r_0	Initial dose rate
$r_{0,t}$	Initial dose rate to the tumor
$r_{0,B}$	Initial dose rate to the whole body
TDF	Time dose fractionation factor
λ	Decay constant of the radionuclide
λ_e	Effective decay constant of the radionuclide
μ	Repair time constant
T_μ	Repair half-time
α/β	Ratio of linear and quadratic coefficients in linear-quadratic model
BED	Biologically effective dose
RE	Relative effectiveness per unit dose
RAF	Relative advantage factor
T/NT	Tumor to nontumor (body) dose rate ratio at peak tumor activity
D_B	Total body dose
D_t	Total tumor dose

ent dose rates utilized in brachytherapy (8-10). The model is generally applicable for conventional therapies that involve multiple fractions of acute external beams of radiations and brachytherapy at constant dose rates and exponentially decaying dose rates. In the LQ model, the fraction of cells that survive a regimen of radiation insults when the fractions are spaced sufficiently to allow for full recovery of sublethal damage is given by $S = e^{-E}$, where (9)

$$E = ND_N(\alpha + \beta D_N). \quad \text{Eq. 1}$$

The quantity N is the number of fractions, D_N is the dose per fraction and α and β are the linear and quadratic coefficients of the dose-response relationship, respectively. The total dose D delivered during the regimen is simply $N \cdot D_N$.

The BED, also known as the extrapolated response dose (ERD) (8,9), is defined as

$$BED = \frac{E}{\alpha} = D \cdot RE, \quad \text{Eq. 2}$$

where RE is the relative effectiveness per unit dose (10). For fractionated external-beam radiotherapy, the relative effectiveness per unit dose is (8-10)

$$RE = 1 + D_N \left(\frac{\beta}{\alpha} \right). \quad \text{Eq. 3}$$

For protracted irradiation, Dale (9) showed that when the irradiation time exceeds 100 hr (as in the case of 60 Gy ^{226}Ra over 7 days), the relative effectiveness is given by

$$RE = 1 + \frac{2r}{\mu} \left(\frac{\beta}{\alpha} \right), \quad \text{Eq. 4}$$

where r is the dose rate and μ is the repair time constant. Similarly, for the complete decay of permanent implants, the RE can be written as (9)

$$RE = 1 + \frac{r_0}{\mu + \lambda} \left(\frac{\beta}{\alpha} \right) = 1 + \frac{r_0}{\ln 2} \left(\frac{\beta}{\alpha} \right) \frac{T_p T_\mu}{T_p + T_\mu}, \quad \text{Eq. 5}$$

where r_0 is the initial dose rate, T_p is the physical half-life and T_μ is the repair half-time.

LQ Model for RIT

When permanent sealed-source implants are used in brachytherapy, the dose rate to the tumor decreases monoexponentially from some initial r_0 . This is not the case in therapeutic modalities that implement internally administered radionuclides (e.g., radioimmunotherapy). In these instances, the dose rate to the tumor rises from an initial value of zero to some maximum value as the radioactivity is taken up by the tumor and then subsequently decreases asymptotically back to a zero dose rate when the radioactivity eventually clears from the tumor. Similar dose rate patterns may also be present for the critical normal organs. Usually, the functional form of the dose rate to the critical organ or tumor is adequately represented by

$$r(t) = r_0(e^{-\ln 2 t/T_e} - e^{-\ln 2 t/T_{eu}}), \quad \text{Eq. 6}$$

where T_e is greater than T_{eu} . The effective clearance half-life T_e is simply $T_p T_b / (T_p + T_b)$, and the effective uptake half-time T_{eu} is $T_p T_u / (T_p + T_u)$, where T_u and T_b are the biologic uptake half-time and clearance half-life, respectively. The quantity r_0 is the *extrapolated* "initial" dose rate (7,11,12). Integration of Equation 6 for complete decay yields the total dose D to the tissue as follows:

$$D = \frac{r_0}{\ln 2} \tau_e, \quad \text{Eq. 7}$$

where the *effective time* $\tau_e = T_e - T_{eu}$. Following the derivation in Appendix 2 of Dale (9), it can be shown that when Equation 6 is used as the functional form for the dose rate, the relative effectiveness per unit dose (RE) is given by

$$RE = 1 + \frac{r_0}{\ln 2} \left(\frac{\beta}{\alpha} \right) \left\{ \frac{2T_\mu^4(T_e - T_{eu})}{(T_\mu^2 - T_e^2)(T_\mu^2 - T_{eu}^2)} + \frac{2T_e T_{eu} T_\mu}{(T_e^2 - T_{eu}^2)} \left(\frac{T_e}{T_\mu - T_e} + \frac{T_{eu}}{T_\mu - T_{eu}} \right) - \frac{T_\mu}{T_e - T_{eu}} \left(\frac{T_e^2}{T_\mu - T_e} + \frac{T_{eu}^2}{T_\mu - T_{eu}} \right) \right\}. \quad \text{Eq. 8}$$

This expression is valid for either tumor or organs. An expression for RE can also be derived for more complex dose rate functions. For instance, if the clearance is multiexponential, the RE can be readily derived using the dose rate function $r(t) = r_0(\sum a_i \exp(-\ln 2 t/T_{e_i}) - \exp(-\ln 2 t/T_{eu}))$, where $\sum a_i = 1$.

If it is assumed that the body is the critical organ and that there

is essentially instantaneous uptake of the radioactivity by the body (i.e., intravenous bolus, $T_{eu} = 0$), followed by monoexponential clearance, then Equation 8 essentially reduces to Equation 5 with T_p replaced with the effective half-life in the body $T_{e,B}$ and r_0 replaced with the initial dose rate to the body $r_{0,B}$.

$$RE_B = 1 + \frac{r_{0,B}}{\ln 2} \left(\frac{\beta}{\alpha} \right) \frac{T_\mu T_{e,B}}{T_\mu + T_{e,B}} \quad \text{Eq. 9}$$

Equations 2 and 6 to 9 are useful to predict required doses in RIT with the LQ model. Experimental tumor kinetics/dose rate data must be fit to Equation 6 to obtain T_e and T_{eu} for Equation 8 to be valid. It should be noted that this formalism does not take into account the proliferation of normal and tumor tissues (13–15), volume effects and macroscopic and microscopic dose nonuniformity in normal and tumor tissues (15–19). These may play a substantial role in the therapeutic outcome. Despite these limitations, this approach should be useful in RIT planning and to evaluate the relative advantage of radionuclides with different physical half-lives. Several examples follow that demonstrate the use of these equations in RIT planning. For the sake of comparison with earlier calculations based on the TDF model (7,11,12), similar examples are illustrated with the LQ model.

Example 1: Calculation of Initial Dose Rates to the Organ/Tumor

Problem. In a ^{131}I -labeled monoclonal antibody (Mab) treatment, it is known that $T_{eu,t} = 1.5$ days and $T_{e,t} = 5.5$ days in the tumor; hence, $\tau_{e,t} = 4$ days. What is the $r_{0,t}$ necessary to deliver a total dose that is biologically equivalent to 60 Gy delivered continuously over 7 days from ^{226}Ra ?

Solution. The dose rate required to deliver 60 Gy in 7 days from ^{226}Ra is 0.357 Gy/hr. If it is assumed that the tumor $\mu = 0.46 \text{ hr}^{-1}$ and $\alpha/\beta = 10 \text{ Gy}$ (5,9), then Equation 4 gives $RE(^{226}\text{Ra}) = 1.155$. Then $BED(^{226}\text{Ra}) = 1.155 \times 60 \text{ Gy} = 69.3 \text{ Gy}$. The $r_{0,t}$ required to deliver a BED of 69.3 Gy from ^{131}I -Mab may be obtained by substituting Equations 7 and 8 into Equation 2. The resulting quadratic equation may be solved for $r_{0,t}$, yielding 0.474 Gy/hr. The tumor dose needed to be biologically equivalent to the ^{226}Ra regimen is $D_t = 1.44 r_{0,t} \tau_{e,t} = 1.44(0.474)(96) = 65.5 \text{ Gy}$. This is only 10% more than the 60 Gy required for ^{226}Ra .

Example 2: Calculation of the Maximum Tolerable Dose

Problem. Assume that the bone marrow dose is the same as the whole-body dose. In ^{90}Y therapy, patients have tolerated a body dose of 2 Gy, and the $T_{e,B}$ is 1 day. What body dose will be tolerated by patients if the Mabs are labeled with ^{131}I , the $T_{e,B}$ of which is determined to be 4 days?

Solution. The initial dose rate from ^{90}Y to the body is 2 Gy/(1.44 × 24) = 0.058 Gy/hr. If $\mu = 0.46 \text{ h}^{-1}$ and $\alpha/\beta = 2.5 \text{ Gy}$ (9) is assumed, $RE_B = 1.036$ is obtained from Equation 9. Hence, $BED_B(^{90}\text{Y}) = 2 \times 1.036 = 2.072 \text{ Gy}$. The $r_{0,B}$ required to deliver a BED_B of 2.072 Gy from ^{131}I -Mab may be obtained by a substitution of Equation 9 and $D_B = 1.44 r_{0,B} T_{e,B}$ into Equation 2. The resulting quadratic equation may be solved for $r_{0,B}$, yielding 0.0149 Gy/hr. The tolerated body dose for ^{131}I is then $D_B = 1.44 r_{0,B} T_{e,B} = 1.44(0.0149)(96) = 2.06 \text{ Gy}$. Therefore, 2.06 Gy from ^{131}I with a $T_{e,B}$ of 4 days is biologically equivalent to 2 Gy from ^{90}Y with a $T_{e,B} = 1$ day.

Example 3: Calculation of Required $r_{0,t}/r_{0,B}$

Problem. A ^{32}P -Mab is to be used for RIT where $T_{e,B} = 2.9$ days, $T_{e,t} = 6.9$ days and $T_{eu,t} = 1.6$ days. Calculate the tumor dose from ^{32}P that is equivalent to 70 Gy in 35 fractions of external photons (2 Gy per fraction). If BED_B must be limited to 3.2 Gy, determine the required ratio of the extrapolated initial dose rates for tumor and body for the therapy to be successful. Compute the tumor dose rate-to-body dose rate ratio (target-to-nontarget or T/NT) that would be observed at the time of maximum uptake in the tumor. Assume that $\mu = 0.46 \text{ hr}^{-1}$ ($T_\mu = 1.5 \text{ hr}$) for both tumor and body and that α/β is 10 Gy and 2.5 Gy for the tumor and body, respectively (5,9).

Solution. For the first calculation, the RE_t for the 2-Gy/fraction regimen, obtained from Equation 3, is 1.2. Hence, the external photon $BED_t = 1.2 (70 \text{ Gy}) = 84 \text{ Gy}$. By a substitution of Equations 7 and 8 into Equation 2 and solving the quadratic equation, the $r_{0,t}$ needed for a BED_t of 84 Gy is 0.434 Gy/hr. The tumor dose that is biologically equivalent to the 70-Gy external photon regimen is then simply $D_t(^{32}\text{P}) = 1.44 r_{0,t} \tau_{e,t} = 1.44(0.434)(6.9 - 1.6)24 = 79.5 \text{ Gy}$. For the second calculation, the $r_{0,B}$ required to deliver a BED_B of 3.2 Gy from ^{32}P may be obtained by a substitution of Equation 9 and $D_B = 1.44 r_{0,B} T_{e,B}$ into Equation 2 and solving the resulting quadratic equation to obtain 0.0312 Gy/hr. Therefore, the required ratio $r_{0,t}/r_{0,B} = 13.9$. For the third calculation, the time at which the tumor uptake is maximum is given by (obtained from the derivative of Equation 6):

$$T_{\max} = \frac{1.44 T_{e,t} T_{eu,t}}{T_{e,t} - T_{eu,t}} \ln \left(\frac{T_{e,t}}{T_{eu,t}} \right).$$

Therefore, $T_{\max} = 4.38$ days. Substitution of T_{\max} into Equation 6 yields $r_t(T_{\max}) = 0.494 \times 0.434 \text{ Gy/hr} = 0.214 \text{ Gy/hr}$ and $r_B(T_{\max}) = 0.351 \times 0.0312 \text{ Gy/hr} = 0.0110 \text{ Gy/hr}$. Hence, the T/NT ratio that would be observed at maximum tumor uptake is $r_t(T_{\max})/r_B(T_{\max}) = 0.214/0.0110 = 19.4$.

RELATIVE ADVANTAGE FACTOR

When sealed sources are implanted in conventional radiotherapy, the total dose delivered is dictated by the initial dose rate and the T_p of the radionuclide. In RIT, however, the total dose delivered depends on the extrapolated “initial” dose rate (Equation 6 and Fig. 1), the T_p of the radionuclide and the biokinetic properties of the antibodies. The extrapolated initial dose rate r_0 is a well-known concept. Obviously, the dose rate to the tumor at time zero is zero (Equation 6 and Fig. 1), yet the parameter r_0 has many interesting and useful characteristics that may be best described by an example. Consider two hypothetical radionuclides that have the same chemical properties and emit the same radiations but have different physical half-lives of 2.67 and 49.5 days. A fixed quantity of antibody is labeled with the same activity of each radionuclide and administered as a bolus intravenous injection. Also assume that the $T_{u,t} = 1.9$ days, the $T_{b,t} = 13.4$ days and the body is the critical organ with a biologic clearance time $T_{b,B} = 3.7$ days. The corresponding effective half-lives are $T_{eu,t} = 1.1$, $T_{e,t} = 2.2$ and $T_{e,B} = 1.5$ days for $T_p = 2.67$ days and $T_{eu,t} = 1.8$, $T_{e,t} = 10.4$ and $T_{e,B} = 3.4$ days for $T_p = 49.5$ days. Substitution of these parameters into Equation 6 yields the dose rate curves in Figure 1. Note that, because

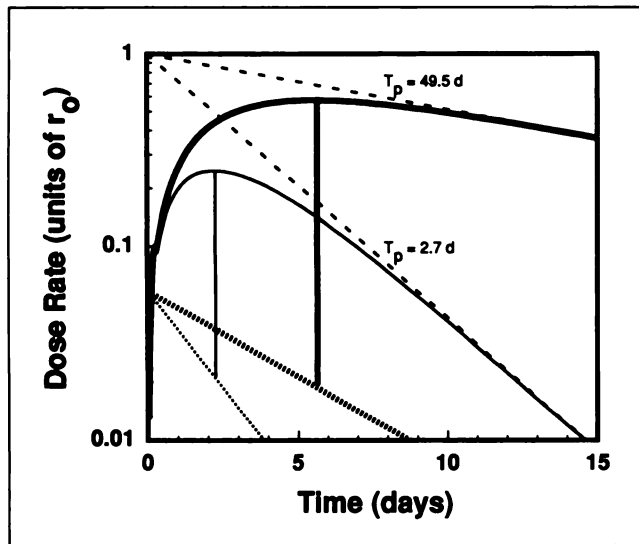


FIGURE 1. Dose rate to tumor (solid lines) and body (dotted lines) as a function of time postadministration for two hypothetical radionuclides with physical half-lives of 2.7 and 49.5 days, respectively. The degree of boldness of the lines reflects the increasing T_p . Each hypothetical radionuclide emits identical radiations, and the same activity is administered of each. It is assumed that Equation 6 describes the dose rates and that $T_{u,t} = 1.9$ days, $T_{b,t} = 13.4$ days, $T_{u,B} = 0$ (instantaneous uptake in the body) and $T_{b,B} = 3.7$ days. Note that, for the same activity injected, the extrapolated initial dose rates, $r_{0,t}$, are the same for both radionuclides, as are the initial body dose rates, $r_{0,B}$. Also note that the ratio of tumor-to-body dose rate at maximum tumor uptake (T/NT ratios) is more favorable for the longer-lived radionuclide.

the injected activity is the same, the extrapolated initial tumor dose rates are the same for both physical half-lives (Fig. 1). Similarly, the initial body dose rates are also equal to one another. Therefore, r_0 carries information regarding the activity injected and the biologic uptake and clearance times. However, as expected, the uptake and clearance patterns of radioactivity in the tumor are different for the two radionuclides, as are the body clearances. Because the same activity is administered, the long-lived radionuclide clearly delivers a much higher total dose to the tumor than does the short-lived nuclide ($D_t = 1.44 r_0 T_{e,t}$). The body dose will also be higher ($D_B = 1.44 r_0 T_{e,B}$). The long-lived radionuclide, however, takes much better advantage of the long biologic half-life in the tumor and the relatively short biologic half-life in the body. This advantage is graphically illustrated in Figure 1 with solid vertical lines that extend from the tumor dose rate at the maximum uptake to the body dose rate at the same time postadministration. The T/NT dose rate ratio at peak tumor activity is substantially larger for the longer-lived radionuclide. In principle, this ratio is independent of the activity administered.

Although this hypothetical example provides some insights into the extrapolated r_0 and the advantage of longer-lived radionuclides, it does not quantitatively examine the capacity of longer-lived radionuclides to deliver a therapeutic dose to the tumor while adverse effects to the critical organs are minimized. Such an analysis must account for

differences in dose rates delivered by radionuclides with different half-lives. When the $r_{0,t}$ is low, the total dose delivered to the tumor must be increased to compensate for dose rate effects. In the authors' (7) previous communication, the biologic effectiveness of different dose rates was taken into account with TDF values. In the LQ model, the BED is used to account for dose rate effects. To examine this, consider a tumor that requires a sterilization $BED_t = 69.3$ Gy (i.e., equivalent to 60 Gy over 1 wk from ^{226}Ra), $\alpha/\beta = 10$ Gy and a $T_\mu = 1.5$ hr (9,14). The tumor is to be treated with an antibody labeled with either the relatively short-lived ^{90}Y ($T_p = 2.67$ days) or the longer-lived $^{114\text{m}}\text{In}$ ($T_p = 49.5$ days). Again assume that $T_{u,t} = 1.9$, $T_{b,t} = 13.4$, and $T_{b,B} = 3.7$ days. The corresponding effective half-lives are therefore $T_{e,u,t} = 1.1$, $T_{e,t} = 2.2$, and $T_{e,B} = 1.5$ days for ^{90}Y and $T_{e,u,t} = 1.8$, $T_{e,t} = 10.4$ and $T_{e,B} = 3.4$ days for $^{114\text{m}}\text{In}$. Also suppose the body is the critical organ with $\alpha/\beta = 2.5$ Gy (9) and $T_\mu = 1.5$ hr (9), and restrict $BED_B = 3.2$ Gy (i.e., equivalent to 3.06 Gy from ^{90}Y). With these assumptions and restrictions, the required $r_{0,t}$ values are computed to be 1.63 Gy/hr and 0.226 Gy/hr for ^{90}Y and $^{114\text{m}}\text{In}$, respectively (Example 1). The respective required values of $r_{0,B}$ are 0.0591 and 0.0268 Gy/hr (Example 2). The required r_0 values reflect the biologic half-life, physical half-life and the dose rate effects by virtue of taking the BED into account. Substitution of these parameters into Equation 6 and plotting the tumor and body dose rates as a function of time yields the curves shown in Figure 2. It is

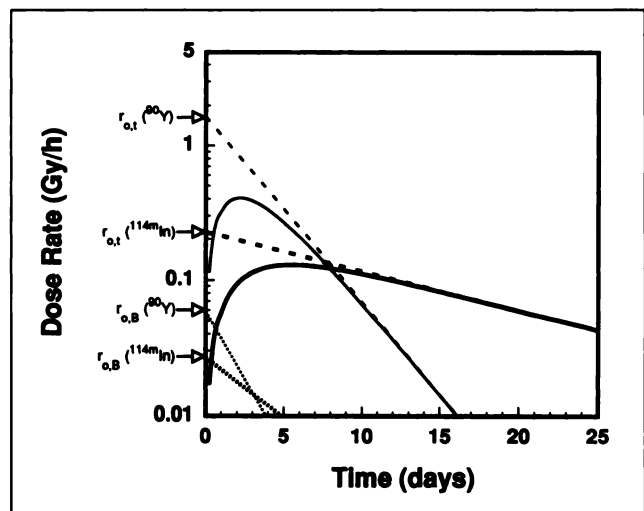


FIGURE 2. Dose rate to tumor (solid lines) and body (dotted lines) as a function of time postadministration of $^{114\text{m}}\text{In}$ (bold lines) and ^{90}Y (regular lines). The cumulative dose in each case is that required to achieve $BED_t = 69.3$ Gy, $BED_B = 3.2$ Gy with $(\alpha/\beta)_t = 10$ Gy, $(\alpha/\beta)_B = 2.5$ Gy, $T_\mu = 1.5$ hr, $T_{u,t} = 1.9$ days, $T_{b,t} = 13.4$ days and $T_{b,B} = 3.7$ days. Extrapolation to the required initial dose rates to the tumor ($r_{0,t}$) are indicated by the dashed lines. Body initial dose rates ($r_{0,B}$) are also denoted. The required values of $r_{0,t}$ and $r_{0,B}$ are substantially higher for ^{90}Y than for $^{114\text{m}}\text{In}$. The ratio of the required $r_{0,t}/r_{0,B}$ is also higher for ^{90}Y , which indicates that therapy with this radionuclide is more difficult to realize than with the longer-lived $^{114\text{m}}\text{In}$.

TABLE 2
Dosimetry Characteristics of Radionuclides with Different Physical Half-Lives*

Characteristic ^a	⁹⁰ Y	¹³¹ I	³² P	⁸⁶ Rb	^{114m} In					
T _{0,B} (days)	1.5	2.5	2.9	3.0	3.4					
T _{0,t} (days)	2.2	5.0	6.9	7.7	10.4					
T _{0,t} (days)	1.1	1.5	1.6	1.6	1.8					
τ _{0,t} = (T _{0,t} - T _{0,t}) for tumor	1.1	3.5	5.3	6.1	8.6					
Theoretic Model	TDF	LQ	TDF	LQ	TDF	LQ	TDF	LQ	TDF	LQ
r _{0,B} (cGy/hr) at TDF _B = 2.0, BED _B = 3.2 Gy	5.9	5.9	4.0	3.6	3.6	3.1	3.5	3.0	3.2	2.7
D _B (cGy), TDF _B = 2.0, BED _B = 3.2 Gy	306	306	346	312	361	313	363	314	376	315
r _{0,t} (cGy/hr), TDF _t = 100, BED _t = 69.3 Gy	176 [‡]	163	66 [‡]	54	47 [‡]	36	42 [‡]	32	32 [‡]	23
D _t (cGy) TDF _t = 100, BED _t = 69.3 Gy	6700	6200	8000	6500	8600	6600	8800	6600	9500	6700
r _{0,t} /r _{0,B} , i.e., ratio of "initial" dose rates to achieve TDF _t = 100, TDF _B = 2.0; BED _t = 69.3 Gy, BED _B = 3.2 Gy	30	28	17	15	13	12	12	10	10	8.4
RAF [†] for TDF _t = 100, TDF _B = 2.0; BED _t = 69.3 Gy, BED _B = 3.2 Gy	1.0	1.0	1.8	1.8	2.3	2.4	2.5	2.6	3.0	3.3

*TDF = 100 is biologically equivalent to BED = 69.3 Gy; TDF = 2 is biologically equivalent to BED = 3.2 Gy.

†RAF is the advantage factor relative to ⁹⁰Y.

‡Initial dose rates for the TDF model were obtained using numerical integration (7,11,12).

§See Table 1 for explanation of symbols.

LQ = linear-quadratic method.

important to understand that these dose rate profiles deliver equal tumor BEDs (69.3 Gy) and body BEDs (3.2 Gy). It is desirable to require only a small ratio of r_{0,t}/r_{0,B}. Conceptually, this is similar to requiring only a small T/NT ratio at peak tumor activity to eradicate the tumor. Although conventional T/NT ratios provide some insight into the likelihood of a successful therapeutic outcome, their values depend on the time postadministration. Therefore, they are not an ideal quantity for comparing the relative efficacy of different radionuclides. The appropriate quantity for this comparison is the ratio, r_{0,t}/r_{0,B}. Consider the case above for ⁹⁰Y and ^{114m}In. The ratios of the required initial dose rates (r_{0,t}/r_{0,B}) for these radionuclides are 27.6 and 8.4, respectively. It is much easier to achieve a dose rate to the tumor that is only 8.4 times higher than the body dose rate. When two different radionuclides are required to deliver the same tumor BED_t and same body BED_B, it is apparent that the benefit of longer-lived radionuclides may be expressed in terms of the required extrapolated initial dose rates as an RAF

$$RAF = \frac{(r_{0,t}/r_{0,B})_s}{(r_{0,t}/r_{0,B})_l} = \frac{(r_{0,t})_s}{(r_{0,t})_l} \cdot \frac{(r_{0,B})_l}{(r_{0,B})_s} \quad \text{Eq. 10}$$

where s denotes short-lived and l denotes longer-lived radionuclides. Hence, the RAF is defined as the factor by which it is more likely to deliver a sterilization dose to the tumor with a longer-lived radionuclide than with a short-lived radionuclide for the same biologically equivalent dose to the critical organ. Therefore, in the example cited earlier, the RAF for ^{114m}In relative to ⁹⁰Y is 3.3.

Advantage of Longer-Lived Radionuclides

To intercompare the relative advantage of several potentially useful radionuclides with different T_ps, the RAFs compared to ⁹⁰Y are given in Table 2 for ¹³¹I, ³²P, ⁸⁶Rb and ^{114m}In. These radionuclides have physical half-lives of 8, 14.3, 18.7 and 49.5 days, respectively. For this analysis, it is again assumed that BED_t = 69.3 Gy (i.e., equivalent to 60 Gy over 7 days from ²²⁶Ra), BED_B = 3.2 Gy, T_μ = 1.5 hr, T_{u,t} = 1.9 days, T_{b,t} = 13.4 days and T_{b,B} = 3.7 days. The corresponding effective half-lives, uptake times and effective times are given in rows 1 to 4 of Table 2. The calculated values of the extrapolated r_{0,B} and r_{0,t} required to achieve BED_t = 69.3 Gy, while restricting BED_B = 3.2 Gy, are given in rows 6 and 8. The corresponding required total absorbed doses for the body and tumor are given in

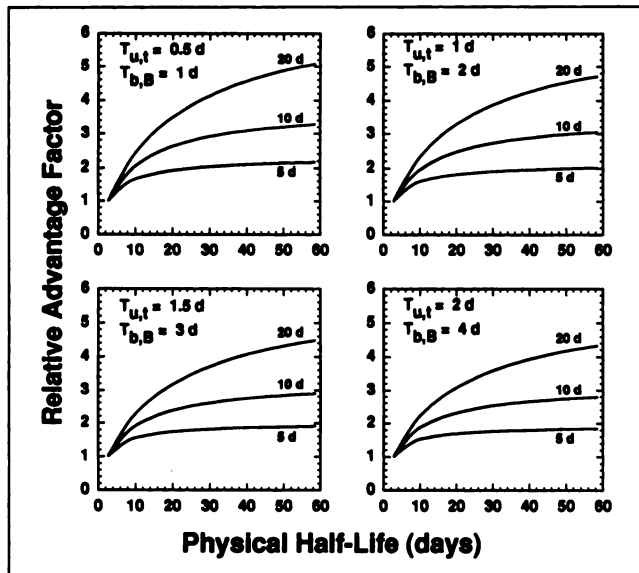


FIGURE 3. Dependence of RAF compared with ^{90}Y on T_p of the radionuclide for four pairs of $T_{u,t}$ and $T_{b,B}$. $T_{b,t}$ of 5, 10 and 20 days are considered for each pair of $T_{u,t}$ and $T_{b,B}$, and the RAF is calculated as a function of the T_p . RAFs increase as the T_p increases in all cases. The rate of increase with T_p is highest for the longest $T_{b,t}$. RAFs reach values as high as approximately 5. The RAF begins to saturate at physical half-lives that are about two to three times the biologic clearance half-life of the antibodies in the tumor.

rows 7 and 9, respectively. As expected, the required values of $r_{0,t}$ and $r_{0,B}$ decrease substantially as the T_p of the radionuclide increases. Finally, the ratio $r_{0,t}/r_{0,B}$ and the RAF values are given in rows 10 and 11 of Table 2, respectively. It is evident that the RAF compared with ^{90}Y ($T_p = 2.67$ days) increases substantially as T_p increases with values of 1.0, 1.8, 2.4, 2.6 and 3.3 for ^{90}Y , ^{131}I , ^{32}P , ^{86}Rb and $^{114\text{m}}\text{In}$, respectively. Hence, longer-lived radionuclides can be in excess of three times more likely than ^{90}Y to succeed in delivering a therapeutic dose to the tumor while an acceptable level of radiotoxicity to the body is maintained. Although this analysis takes ^{90}Y as the reference source, the RAF of a longer-lived radionuclide may be evaluated relative to any reference radionuclide.

The RAF values obtained were based on a single set of BED_t , BED_B , $T_{u,t}$, $T_{b,t}$ and $T_{b,B}$. The dependence of the RAF (compared with ^{90}Y) on T_p for different sets of $T_{u,t}$, $T_{b,t}$ and $T_{b,B}$ is shown in Figure 3 for fixed $\text{BED}_t = 69.3$ Gy and $\text{BED}_B = 3.2$ Gy. The curves in Figure 3 are for $T_{b,t}$ of 5, 10 and 20 days, respectively. Long $T_{b,t}$, coupled with long T_p result in the highest RAF values, as would be expected. In contrast, short $T_{b,t}$ and short T_p lead to RAF values that approach unity. Also, note that increasing T_p beyond a certain point does not have a major impact on the RAF because of the asymptotic nature of the curves. In other words, when the biologic clearance time from the tumor $T_{b,t}$ is short (e.g., 5 days), then the effective half-life in the tumor is not changed substantially by increasing the T_p . Therefore, the RAF also remains largely unchanged. However, when $T_{b,t}$ is long, there is much to be gained by

increasing T_p . Because the RAF may also depend on non-uniformities in activity distribution, caution should be exercised when longer-lived radionuclides are selected. The radionuclides listed in Table 2 of this article and in Tables 5 to 7 of the article by Rao and Howell (7) are medium- to long-range beta emitters, and they were selected with this in mind. It should be noted in passing that longer physical half-lives may introduce some regulatory inconveniences (i.e., decontamination and waste disposal). This is a small price to pay should longer-lived radionuclides be more therapeutically effective.

Dependence of RAF on $T_{u,t}$

One important parameter that influences the RAF is the $T_{u,t}$. Figure 4 shows the RAF compared with ^{90}Y as a function of $T_{u,t}$ for the standard conditions of $\text{BED}_t = 69.3$ Gy, $\text{BED}_B = 3.2$ Gy, $T_\mu = 1.5$ hr, $T_{b,t} = 13.4$ days and $T_{b,B} = 3.7$ days. Note that the RAF increases with $T_{u,t}$, and the rate of increase depends on the T_p . The increasing advantage of longer-lived radionuclides as $T_{u,t}$ increases should now be clear. The reason for this is that when $T_{u,t}$ is long and the T_p is short, then much of the activity decays in the body before it has a chance to reach the tumor. The RAF is accordingly low (7). On the other hand, if $T_{u,t}$ is long, then the RAF is amplified as the T_p increases. Hence, although there is a significant advantage to using longer-lived radionuclides even when $T_{u,t} = 0$, the greatest advantage is realized when the uptake half-time in the tumor is long.

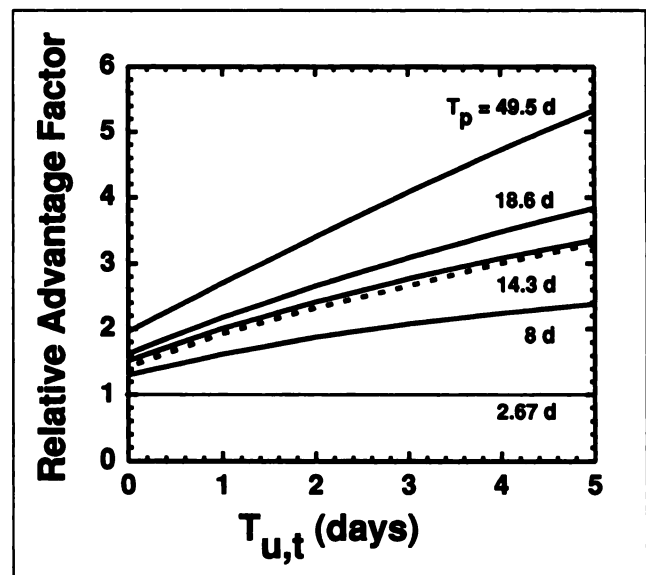


FIGURE 4. RAF compared with that of ^{90}Y as a function of the $T_{u,t}$ for $\text{BED}_t = 69.3$ Gy, $\text{BED}_B = 3.2$ Gy, $T_{u,t} = 1.9$ days, $T_{b,t} = 13.4$ days and $T_{b,B} = 3.7$ days. Solid curves, calculated using the LQ approach, are presented for physical half-lives of 2.67 (^{90}Y), 8 (^{131}I), 14.3 (^{32}P), 18.6 (^{86}Rb) and 49.5 days ($^{114\text{m}}\text{In}$). The RAF increases with $T_{u,t}$ and T_p , with values as high as approximately 5 reached for long $T_{u,t}$ and long T_p . The dashed line was obtained for ^{32}P by the TDF approach. $\text{TDF}_t = 100$ (equivalent to $\text{BED}_t = 69.3$ Gy) and $\text{TDF}_B = 2$ (equivalent to $\text{BED}_B = 3.2$ Gy) (7,11) was assumed. Therefore, the RAF does not depend on the model.

TABLE 3
Relative Advantage Factors as a Function of Tumor and Body Biologically Effective Doses

		⁹⁰ Y	¹³¹ I	³² P	⁸⁶ Rb	^{114m} In
BED _t = 100	BED _B = 2	1.0	1.81	2.32	2.57	3.15
	BED _B = 5	1.0	1.83	2.36	2.62	3.23
	BED _B = 10	1.0	1.86	2.42	2.69	3.32
BED _t = 69.3	BED _B = 2	1.0	1.84	2.37	2.62	3.23
	BED _B = 5	1.0	1.86	2.41	2.68	3.31
	BED _B = 10	1.0	1.89	2.47	2.75	3.41
BED _t = 40	BED _B = 2	1.0	1.87	2.42	2.69	3.34
	BED _B = 5	1.0	1.90	2.47	2.75	3.42
	BED _B = 10	1.0	1.93	2.53	2.82	3.52

t = tumor; B = body; BED = biologically effective dose.

Independence of RAF on BED_t, BED_B, T_μ, α/β and Radiation Spectra

Thus far, emphasis has been placed on BED_t = 69.3 Gy, which is biologically equivalent to 60 Gy from ²²⁶Ra over a 7-day period, and BED_B = 3.2 Gy, which is equivalent to 3.06 Gy from ⁹⁰Y. Depending on the situation (e.g., tumor type or critical organ), it may be necessary to use different BED values. Therefore, it is interesting to examine the dependence of RAF on tumor and body BEDs while all other parameters remain fixed (T_μ = 1.5 hr, T_{u,t} = 1.9 days, T_{b,t} = 13.4 days and T_{b,B} = 3.7 days). Table 3 gives the RAF values for BED_t values of 40, 69.3 and 100 Gy and BED_B values of 2, 5 and 10 Gy. The corresponding total absorbed doses are 37.4, 62.1 and 86.1 Gy for the tumor and 8.77, 4.66 and 1.94 Gy for the body, respectively. It is interesting that despite the large differences in absorbed doses, the RAF remains relatively unaffected (Table 3). In fact, in the extreme, the RAF only changes by approximately 10% when the BEDs are changed from BED_t = 100 and BED_B = 2 Gy to BED_t = 40 and BED_B = 10 Gy. Although not shown, the dependence of RAF on T_μ and α/β is even smaller. For instance, when α/β for the body is increased from 2 to 40 Gy, the RAF value decreases by a maximum of only about 2%. Similarly, varying T_μ from 1.5 to 0.5 hr increases the RAF by only a maximum of approximately 5%. Therefore, it may be concluded that the RAF does not significantly depend on the body or tumor BEDs or on the values of T_μ and α/β. Finally, the RAF also does not depend on the radiation spectra of the radionuclides when the radiations are of low linear energy transfer with similar penetrating abilities in tissue.

LQ Versus TDF Approach

In the authors' (7) earlier communication, the therapeutic advantage of longer-lived radionuclides by the TDF approach was investigated. The TDF model, however, is believed by some to be inadequate (10). Therefore, it is interesting to compare RAFs and required r₀ values and total doses (for the same biologic effect) calculated with the LQ and TDF models (Table 2). The model used for the calculation is indicated in row 5 of Table 2. As before, the standard biologic conditions are T_{u,t} = 1.9, T_{b,t} = 13.4 and

T_{b,B} = 3.7 days. In the TDF approach, it is required that TDF_t = 100 (i.e., equivalent to BED_t = 69.3 Gy or 60 Gy over 7 days from ²²⁶Ra) and TDF_B = 2 (equivalent to BED_B = 3.2 Gy or 3.06 Gy to the body from ⁹⁰Y). The TDF calculations are carried out with Equation 6 as described previously (11,12). Although the required r₀ values calculated with the LQ and TDF models are similar for ⁹⁰Y, they differ by as much as 20% for r_{0,B} (row 6) and 40% for r_{0,t} (row 8) when the longer-lived ^{114m}In is considered. Similar disparities are present for the required total absorbed doses (Table 2, rows 7 and 9). These large differences arise because the TDF model appears to predict much larger dose rate effects than does the LQ model, at least for the conditions examined here. For example, despite the disparate required values of r_{0,t} for ⁹⁰Y and ^{114m}In, the total doses required to deliver a BED_t of 69.3 Gy are 62 Gy and 67 Gy, respectively. The corresponding values from the TDF model are 67 Gy and 95 Gy, respectively. This suggests that the LQ model predicts that large differences in required dose rates between the two radionuclides are of little consequence in terms of their biologic effectiveness. In other words, according to the LQ model, dose rate effects are of relatively little importance in RIT. In contrast, dose rate effects appear to be relatively more important when the TDF model is used.

At present, it is not clear which model should be used in RIT planning to determine required values of r_{0,t} for a given therapeutic regimen. It appears that the LQ approach is favored in conventional radiotherapy (10); however, firm clinical data are needed to establish the usefulness of any model in RIT. In any case, it is critical to point out that the RAF is essentially independent of the approach (TDF or LQ). For comparison, RAF values calculated by both the TDF and LQ approaches are given in row 11 of Table 2. Only small differences are observed between the two approaches; the largest difference in RAF values is about 10% for ^{114m}In. Similarly, when the TDF approach is used to examine the RAF for ³²P (T_p = 14.3 days) as a function of the T_{u,t}, essentially the same functional dependence that was obtained with the LQ model is found (Fig. 4, dashed line). Therefore, the present results, which are based on

the LQ model, provide further support for the authors' (2) TDF-based conclusion that longer-lived radionuclides are more likely to deliver therapeutically effective doses in RIT than the shorter-lived radionuclides currently in use.

The feasibility of RIT with longer-lived radionuclides may be questioned given that the maximum theoretic specific activity decreases as the T_p increases. In the earlier communication (7), in which the TDF approach was used, several relevant quantities were calculated based on the initial dose rates for each radionuclide, including ^{90}Y , ^{131}I , ^{32}P , ^{86}Rb and $^{114\text{m}}\text{In}$ (Table 8, rows 12–16 in reference 7): (1) required activity to achieve $\text{TDF}_B = 2$, (2) required activity per gram of tumor tissue to achieve $\text{TDF}_t = 100$, (3) specific activity relative to ^{90}Y , (4) activity per cell and (5) number of radiolabeled antibodies per cell. The maximum theoretic specific activities were given in Table 8, row 17 of reference 7. It was concluded that the required specific activities could, in principle, be achieved for all of these radionuclides. The same analysis can be performed based on the required r_0 values obtained with the LQ model, and essentially the same conclusions can be drawn. Therefore, we reaffirm that ^{32}P is the most promising beta emitter in terms of its radiation energy, availability, high specific activity, cost and relatively long T_p . Other radionuclides, such as ^{91}Y and $^{114\text{m}}\text{In}$, also merit consideration when the $T_{u,t}$ and $T_{b,t}$ are long (7). As a rule of thumb, it is recommended that the optimal T_p of the radionuclide should be about two to three times that of the biologic clearance half-life of the antibody in the tumor.

As in the authors' (7) previous analysis using the TDF approach, the present calculations with the LQ model assume that the whole body is the dose-limiting organ. It is generally recognized that bone marrow toxicity is the dose-limiting factor in RIT. However, like the TDF approach, the LQ method described in this article is general and can be applied directly to the bone marrow, or any other critical organ for that matter, if appropriate biologic data and reliable methods to calculate the critical organ dose are available.

SUMMARY

The LQ approach for treatment planning in RIT presented in this work incorporates differences in dose rates, biologic half-lives of the antibodies, physical half-lives of the radionuclides, total doses required for a given biologic effect in tumor and normal tissues, repair half-times and radiation response of the tissues. The computational results clearly point out that longer-lived radionuclides will have a definite therapeutic advantage over the shorter-lived radionuclides currently in use when the biologic half-life of the antibodies in the tumor is relatively long compared with the biologic half-life in the critical organ. Furthermore, the advantage is enhanced when the uptake half-time in the tumor is long. These considerations suggest that the optimal T_p should be based on the biologic uptake and clearance times. Considering the biological half-lives

that are generally observed in clinical RIT, the optimal radionuclide appears to be ^{32}P (7). As a general rule, the T_p should be about two to three times the biologic clearance half-life of the antibodies in the tumor.

Not accounted for in this approach are nonuniformities in activity distribution (17–20), volume effects and proliferation of the irradiated tissue (13,14). In bulk tumors, nonuniformities in activity distribution can be a significant problem when the therapeutic outcome is predicted. However, the recent work of Muthuswamy et al. (21) indicates that longer-lived radionuclides are more likely to penetrate into the tumor before decaying in the body than are shorter-lived radionuclides. This implies that dose nonuniformities in the tumor will be smoothed to some extent when longer-lived radionuclides are employed, thereby providing further support for their use in RIT.

It has been suggested by Fowler (5) that a dose rate of 2 to 3 cGy/hr is required just to overcome the proliferation of most types of tumor cells, with the exception of adenocarcinoma of the prostate in which the proliferation is much slower. Therefore, the portion of the total dose that is delivered below this rate is essentially wasted (5,14). For the longest-lived radionuclide and conditions considered in this work, it may be readily calculated that, for a therapeutically effective dose ($\text{BED}_t = 69.3$ Gy), only about 10% of the total dose is delivered at a dose rate of less than 3 cGy/hr. Hence, inclusion of a proliferation term is not expected to have a significant impact on the relative advantage factors calculated here. In any case, the approach presented here can be readily modified (14) to include such effects.

Finally, successful treatment of tumors in RIT with longer-lived radionuclides depends on the ability to develop antibodies that have long biologic half-lives in the tumor and chemically stable radiolabels. These should not be insurmountable problems. Therefore, in view of the limited success with RIT thus far with relatively short-lived radionuclides, the longer-lived radionuclides and treatment planning approaches suggested here and earlier (7) should improve the likelihood of a successful therapeutic outcome.

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