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Proliferation and the advantage of longer-lived radionuclides in radioimmunotherapy

Roger W. Howell, S. Murty Goddu, and Dandamudi V. Rao^{a)}

Department of Radiology, UMDNJ-New Jersey Medical School, Newark, New Jersey 07103

Abstract

In our previous study we used the linear-quadratic model [J. Nucl. Med. **35**, 1861 (1994)] to confirm our initial finding, based on the time-dose-fractionation model [J. Nucl. Med. **34**, 1801 (1993)], that longer-lived radionuclides (e.g., ³²P, ⁹¹Y) can offer a substantial therapeutic advantage over the shorter-lived radionuclides presently used in radioimmunotherapy (e.g., ⁹⁰Y). The original calculations using the linear-quadratic (LQ) model did not account for proliferation of the tumor and critical bone marrow tissues. It has been suggested that inclusion of a proliferation term in the LQ model can have a substantial impact on the biologically effective dose (BED). With this in mind, we have reexamined the therapeutic efficacy of longer versus short-lived radionuclides using the LQ model replete with proliferation terms for tumor and bone marrow. Relative advantage factors (RAF), which quantify the overall therapeutic advantage of a long-lived compared to short-lived radionuclide, were calculated accordingly. While the extrapolated initial dose rate required to achieve a given BED can be affected by the inclusion of proliferation terms for both the tumor and marrow, *the relative advantage factors for the longer-lived radionuclides were not significantly affected*. Longer-lived radionuclides such as ^{114m}In and ⁹¹Y are about three times more therapeutically effective than the shorter-lived ⁹⁰Y which is currently used in RIT. In other words, for a given therapeutic effect in the tumor, a longer-lived radionuclide can result in a lower deleterious effect to the bone marrow than a short-lived radionuclide. Given that bone marrow is generally considered to be the dose-limiting organ, these results have important implications for radioimmunotherapy.

Keywords

linear-quadratic model; radioimmunotherapy; dosimetry; proliferation

INTRODUCTION

The goal in radioimmunotherapy (RIT) is to deliver therapeutic doses to tumors without compromising the function of the critical organs such as bone marrow. To date, the use of relatively short-lived radionuclides such as ⁹⁰Y has resulted in limited therapeutic success for a number of reasons. Among the reasons are: (i) the absolute uptake of radioactivity per gram of tumor is too low to yield a tumorcidal dose, and (ii) the uptake of radioactivity in the tumor is nonuniform thereby delivering a nonuniform dose to the tumor. Furthermore, when short-lived radionuclides are used, the effective uptake half-times ($T_{eu,t} \sim 1 - 2$ d) of the radiolabeled antibodies in human tumors are frequently comparable to the effective tumor clearance half-times ($T_{e,t} \sim 2 - 7$ d), while the effective half-times in the body $T_{e,B}$ are $\sim 1 - 4$ d.

¹⁻⁴ Under these conditions, much of the radioactivity decays in normal tissues before it has an opportunity to be taken up by the tumor, resulting in relatively high doses to normal tissues and low doses to tumors. Given these general conditions in RIT, it is desirable to increase the effective half-time in the tumor relative to the effective half-time in the critical organs to improve therapeutic efficacy. For a given antibody, the effective half-time of the radiolabeled antibody can in principle be lengthened by increasing the physical half-life of the radionuclide (T_p). Therefore, the physical half-life of the radionuclides should be matched to the biological conditions.

Radionuclides irradiate tissues chronically with dose rates that vary exponentially with time. Hence, dose rate effects play a role in the biological outcome.^{5,6} Our recent work which used the time-dose-fractionation (TDF) and linear-quadratic (LQ) models to account for dose rate effects showed that longer-lived radionuclides can provide a substantial therapeutic advantage in RIT.^{7,8} Our initial approach with the LQ model took into consideration the radiosensitivity of the tissues, repair rates, dose rates, and biological and physical half-lives to obtain biologically effective doses (BED) delivered to the tumor and bone marrow.⁸ The present work builds upon our past modeling by including the proliferation of these tissues and examines the impact of tumor radiosensitivity. Relative advantage factors (RAF) are calculated for several radionuclides with different physical half-lives and compared with the values obtained in our earlier calculations.^{7,8}

THEORETICAL MODELING

Linear-quadratic model

The linear-quadratic model is generally applicable for conventional therapies involving multiple fractions of acute external beams of radiations, as well as brachytherapy at constant dose rates and exponentially decaying dose rates.⁹⁻¹¹ In this model the fraction of cells surviving a fractionated regimen of acute radiation insults is given by $S = e^{-E}$, where¹⁰

$$E = ND_N(\alpha + \beta D_N). \quad (1)$$

The quantity N is the number of fractions, D_N 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 $N \cdot D_N$.

The biologically effective dose (BED) has been defined as¹⁰

$$\text{BED} = \frac{E}{\alpha} = D \cdot \text{RE} \quad (2)$$

where RE is the relative effectiveness per unit dose.¹¹ For fractionated external beam radiotherapy, the relative effectiveness per unit dose is⁹⁻¹¹

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

For protracted irradiation as a result of the complete decay of permanent implants, Dale¹⁰ has shown that the RE can be written as

$$RE = 1 + \frac{r_0}{\ln 2} \left(\frac{\beta}{\alpha} \right) \frac{T_p T_\mu}{T_p + T_\mu}, \quad (4)$$

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

In the case of brachytherapy with permanent sealed-source implants, the dose rate to the tumor decreases monoexponentially from some initial value. However, in RIT the dose rate to the tumor rises from an initial value of zero to a maximum value as the radioactivity is taken up by the tumor, and then decreases exponentially as the radioactivity decays and clears from the tumor. Similar dose rate patterns are frequently observed for the critical normal organs as well. The functional form of the dose rate to the critical organ or tumor can typically be represented by¹²

$$r(t) = r_0 (e^{-\ln 2(t/T_d)} - e^{-\ln 2(t/T_i)}), \quad (5)$$

where T_d is the dose rate decrease half-time during the clearance phase of the radionuclide from the organ, and T_i is the dose rate increase half-time during the uptake phase of the radionuclide by the organ with the provision that $T_d > T_i$. The quantity r_0 is now the *extrapolated* initial dose rate.^{7,8,12-14} When the dose rate decrease and increase half-times are well represented by the effective clearance and uptake half-times (T_e and T_{eu}), the dose rate at time t is given by^{8,12}

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

The effective clearance half-time T_e is given by $T_p T_b / (T_p + T_b)$ and the effective uptake half-time T_{eu} is given by $T_p T_u / (T_p + T_u)$, where T_u and T_b are the biological uptake half-time and clearance half-time, respectively.

The relative effectiveness per unit dose for *incomplete* decay of radioactivity with dose rate kinetics specified by Eq. (6) can be derived by following the steps outlined in Appendix II of Dale.¹⁰ In Appendix II, Dale derives RE for incomplete decay of a radioactive source with $r(t) = r_0 \exp(-\lambda t)$. By substituting Eq. (6) for $r(t) = r_0 \exp(-\lambda t)$ throughout Dale's¹⁰ derivation, it can be shown that the RE for *incomplete* decay of radioactivity with dose rate kinetics specified by Eq. (6) is given by

$$\begin{aligned} RE(t) = 1 + & \frac{2r_0\beta}{\alpha} \frac{1}{\frac{1}{\lambda_e} (1 - e^{-\lambda_e t}) - \frac{1}{\lambda_{eu}} (1 - e^{-\lambda_{eu} t})} \\ & \times \left\{ \left(\frac{1}{(\lambda_e - \mu)} - \frac{1}{(\lambda_{eu} - \mu)} \right) \cdot \left(\frac{1}{(\mu + \lambda_e)} (1 - e^{-(\mu + \lambda_e)t}) - \frac{1}{(\mu + \lambda_{eu})} (1 - e^{-(\mu + \lambda_{eu})t}) \right) \right. \\ & + \left(\frac{1}{(\lambda_e - \mu)} + \frac{1}{(\lambda_{eu} - \mu)} \right) \left(\frac{1}{(\lambda_e + \lambda_{eu})} (1 - e^{-(\lambda_e + \lambda_{eu})t}) \right) - \frac{1}{2\lambda_e(\lambda_e - \mu)} (1 - e^{-2\lambda_e t}) \\ & \left. - \frac{1}{2\lambda_{eu}(\lambda_{eu} - \mu)} (1 - e^{-2\lambda_{eu} t}) \right\}, \quad (7) \end{aligned}$$

where $\lambda_e = \ln 2/T_e$, $\lambda_{eu} = \ln 2/T_{eu}$, and $\mu = \ln 2/T_\mu$. This expression is valid for either tumor or normal tissue.

Linear-quadratic model with proliferation (LQP model)

As stated earlier,⁸ Eqs. (2) (6), and (7) are useful for predicting required extrapolated initial dose rates and total doses in radioimmunotherapy using the LQ model. However, the above formalism does not take into account the proliferation of normal and tumor tissues.^{15–17} Proliferation can play a substantial role in the therapeutic outcome. Dale¹⁵ and Ling¹⁶ have described methods to include a proliferation term in the linear-quadratic model. When proliferation is taken into consideration, the biologically effective dose at any time t can be written as:

$$BED(t) = D(t) \cdot RE(t) - \begin{cases} 0 & t \leq T_{rd} \\ \frac{\ln 2(t - T_{rd})}{\alpha T_g} & t > T_{rd} \end{cases}, \quad (8)$$

where t is the time postinjection of the radioactivity, T_{rd} is the regrowth delay time, and T_g is the potential doubling time. For chronic irradiation, the regrowth delay time is the time delay between the beginning of the irradiation and the initiation of the proliferation response. The potential doubling time is the time required for the tissue to double its cell population. Thus Eq. (8) is essentially the linear-quadratic model with the addition of a proliferation term, henceforth referred to as the LQP model.

Relative advantage factor

It has been shown earlier that when one requires that two different radionuclides deliver the same biologically effective dose to the tumor BED_t and the same deleterious biologically effective dose to the bone marrow BED_B , the benefit of longer-lived radionuclides can be expressed in terms of the *required* extrapolated initial dose rates as a *relative advantage factor* (RAF)⁸

$$RAF = \frac{(r_{0,t}/r_{0,B})_s}{(r_{0,t}/r_{0,B})_l} = \frac{(r_{0,t})_s}{(r_{0,t})_l} \cdot \frac{(r_{0,B})_l}{(r_{0,B})_s}, \quad (9)$$

where s denotes short-lived and l denotes longer-lived radionuclide. 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 effective dose to the critical organ.*⁸

Input parameters

To compare the impact of proliferation on the relative advantage of longer-lived radionuclides in radioimmunotherapy, calculations are carried out using the same “standard” input parameters used in our previous calculations.^{7,8} Hence, it is assumed that a biologically effective dose to the tumor BED_t of 69.3 Gy is required to be delivered. In these calculations, where proliferation is an issue, this corresponds to the maximum BED_t achieved which occurs at the nadir of the tumor cell survival curve. This is equivalent to a ^{226}Ra regimen of 60 Gy over 7 d, or a TDF = 100. Similarly, the biologically effective dose to the bone marrow BED_B is restricted to a value of 3.2 Gy at the nadir for bone marrow cell survival. The biological clearance half-times in the tumor $T_{b,t}$ and bone marrow $T_{b,B}$ are assumed to be 13.4 d and 3.7 d, respectively. The biological uptake half-time in the tumor $T_{u,t}$ and bone marrow $T_{u,B}$ are taken to be 1.9 d and 0 d (instantaneous uptake), respectively.

The proliferation parameters, namely the regrowth delay T_{rd} and potential doubling time T_g , were taken from animal and cell culture data. For bone marrow, our murine data indicate that $T_{rd,B} \sim 8$ d, $T_{g,B} \sim 2$ d, and $\alpha_B \sim 1.5 \text{ Gy}^{-1}$. These values are in agreement with those of Wu and Lajtha.¹⁸ For cultured human LS174T tumor cells, our preliminary data give $T_{g,t} = 1.5$ d, and the data of Wong *et al.*¹⁹ give $\alpha_t = 0.56 \text{ Gy}^{-1}$ and $T_{rd,t} \sim 4$ d at therapeutic doses. These parameters are given in Table I. While the above parameters represent “standard” conditions, calculations are also performed for various values of BED_t , α_t , and $T_{b,t}$.

RESULTS AND DISCUSSION

Relative advantage of longer-lived radionuclides

To compare the relative advantage of several potentially useful radionuclides with different physical half-lives, the RAFs compared to ^{90}Y are given in Table II for ^{32}P and ^{114m}In . As stated earlier, these three radionuclides have physical half-lives of 2.7 d, 14.3 d, and 49.5 d, respectively. As in our past analyses, it is required that $BED_t = 69.3 \text{ Gy}$, $BED_B = 3.2 \text{ Gy}$, $T_\mu = 1.5 \text{ h}$, $T_{u,t} = 1.9 \text{ d}$, $T_{b,t} = 13.4 \text{ d}$, and $T_{b,B} = 3.7 \text{ d}$. However, the BEDs are now required to be achieved at the nadir as opposed to the previous requirement of complete decay.⁸ The proliferation parameters given in Table I were used in this analysis. The effective uptake and clearance half-times are given in rows 1–3 of Table II for each radionuclide. The calculated values of the extrapolated initial dose rates $r_{0,B}$ and $r_{0,t}$, required to achieve $BED_t = 69.3 \text{ Gy}$, while restricting $BED_B = 3.2 \text{ Gy}$, are given in rows 5 and 7 for each of the radiobiological models (time dose fractionation: TDF,⁷ linear quadratic: LQ,⁸ and linear quadratic with proliferation: LQP). The corresponding required total absorbed doses for the bone marrow and tumor are given in rows 6 and 8, respectively. As expected, the required values of $r_{0,t}$ and $r_{0,B}$ decrease substantially as the effective clearance half-time of the radiolabeled antibody increases. The ratios $r_{0,t}/r_{0,B}$ are given in row 9 of Table II. These ratios indicate that the extrapolated initial dose rate to the tumor must be about 30 times higher than the extrapolated initial dose rate to the marrow to achieve a $BED_t = 69.3 \text{ Gy}$ and a marrow sparing $BED_B = 3.2 \text{ Gy}$ with ^{90}Y . In contrast, the tumor dose rate only has to be about 10 times higher than the marrow dose rate in the case of ^{114m}In to achieve the desired BEDs. A ten-fold tumor to nontumor ratio is clearly easier to accomplish than a thirty-fold ratio. Finally, the relative advantage of each radionuclide compared to ^{90}Y is given in row 10 of Table II. It is evident that the RAF compared to ^{90}Y ($T_p = 2.67 \text{ d}$) increases substantially as T_p increases with RAF values of 2.2 and 3.0 for ^{32}P and ^{114m}In , respectively, even when proliferation is included. Hence, longer-lived radionuclides can be at least three times more likely than ^{90}Y to succeed in delivering a therapeutic dose to the tumor while maintaining an acceptable level of radiotoxicity to the bone marrow. As predicted in our earlier report,⁸ the results clearly show that inclusion of proliferation has little impact on the RAFs. The extrapolated initial dose rates and total doses required, however, are substantially higher for the LQP model than the LQ model.⁸ Interestingly, the extrapolated initial dose rates and total doses required by the LQP model are similar to those obtained with the TDF model.⁷

Dependence of relative advantage factor on $T_{g,t}$ and $T_{rd,t}$

In the above calculations which examine the effect of proliferation on the relative advantage of longer-lived radionuclides in RIT, it is assumed that the tumor regrowth delay time $T_{rd,t} = 4$ d, tumor potential doubling time $T_{g,t} = 1.5$ d, marrow regrowth delay time $T_{rd,B} = 8$ d, and marrow potential doubling time $T_{g,B} = 2$ d. These assumptions imply that the tumor is proliferating faster than the marrow which is likely when the tumor is very small. When bulk tumors are present, the above proliferation parameters may be unrealistic. To examine the advantage of longer-lived radionuclides for slowly proliferating tumors, the relative advantage factors are calculated assuming $T_{rd,t} = 8$ d, $T_{g,t} = 4$ d, and all other tumor and

marrow parameters remaining the same as in Table I. The RAF values compared to ^{90}Y for this slowly proliferating tumor are calculated to be 2.4 and 3.4 for ^{32}P and $^{114\text{m}}\text{In}$, respectively. In comparison, the RAF values for rapidly proliferating tumors are 2.2 and 3.0, respectively (see Table II). This suggests that longer-lived radionuclides are even more advantageous when the tumor proliferates slowly. However, in bulk tumors, our ability to predict the biological response for a given treatment regimen is complicated by the fact that the radionuclide is likely to be distributed nonuniformly^{20–22} and much of the tumor is poorly oxygenated.^{21,22}

Dependence of relative advantage factor on α_t , $(\alpha/\beta)_t$

The RAF values calculated in Table II use parameters for a relatively radiosensitive tumor having $(\alpha/\beta)_t = 10 \text{ Gy}$, and $\alpha_t = 0.56 \text{ Gy}^{-1}$. The dependence of the RAF on radiosensitivity of the tumor can be examined by varying α_t accordingly. Figure 1 shows that the RAF does indeed decrease as the tumor becomes more resistant, however, the advantage of longer-lived radionuclides remains substantial even for very resistant tumors. The decrease in the RAF occurs because the proliferation term in the BED expression is inversely proportional to α [see Eq. (8)] which means that the proliferation term plays a greater role in determining BED for resistant tumors (tumors with small α) than sensitive tumors. In order to overcome the increased importance of proliferation in resistant tumors, higher extrapolated initial dose rates and total doses are necessary compared to relatively more sensitive tumors. Consequently, the RAF values are somewhat less for resistant tumors.

Dependence of relative advantage factor on BED_t

The RAF values presented in Table II assume that a therapeutic dose ($\text{BED}_t = 69.3 \text{ Gy}$) can be delivered to the tumor in radioimmunotherapy. When therapeutic doses cannot be realized, the tumor may receive a BED substantially lower than 69.3 Gy. Figure 2 shows the dependence of the relative advantage of longer-lived radionuclides on BED_t . It can be seen that when BED_t drops to 20 Gy, the advantage of longer-lived radionuclides in RIT is still maintained, albeit to a lesser degree. However, as BED_t decreases from 20 Gy to 0 Gy, the RAF drops rapidly to 1. This drop is due to the fact that at low BED_t values, a larger portion of the dose delivered is utilized to overcome proliferation of the tumor. These results suggest that even when RIT is used as an adjuvant therapy with BED_t values in the range of 20–30 Gy, longer-lived radionuclides still offer a substantial advantage over the shorter-lived radionuclides currently in use.

Dependence of relative advantage factor on $T_{b,t}$

The RAF values obtained in Table II were calculated using the “standard” parameters in Table I. The “standard” biological half-time in the tumor $T_{b,t}$ is assumed to be 13.4 d which corresponds to effective half-times in the tumor $T_{e,t}$ of 2.2 and 5.0 d for ^{90}Y and ^{131}I , respectively, for these two commonly used radionuclides in RIT. Lower values of $T_{b,t}$ have also been observed and it is therefore instructive to examine the dependence of the RAF on $T_{b,t}$ (Fig. 3). As expected, Fig. 3 shows a marked decrease in RAF as $T_{b,t}$ decrease to a value equal to the biological half-time in the body $T_{b,B}$. A significant advantage is maintained even for short $T_{b,t}$ because of the relatively slow biological uptake half-time in the tumor $T_{u,t} = 1.9 \text{ d}$. If $T_{u,t} = T_{u,B}$ and $T_{b,B} = T_{b,t}$, then the $\text{RAF} \rightarrow 1$, thereby indicating that all physical half-lives are essentially equivalent for RIT under these conditions.

CONCLUSIONS

The linear-quadratic model, replete with a proliferation term, is used to examine the advantage of longer-lived radionuclides in radioimmunotherapy. The model incorporates differences in dose rates, biological half-times of the antibodies, physical half-lives of the

radionuclides, total doses required for a given biological effect in tumor and normal tissues, repair half-times, *proliferation* and radiation response of the tissues. Like our earlier results with the TDF⁷ and simple LQ model,⁸ the present results show that longer-lived radionuclides such as ^{114m}In or ⁹¹Y can have a substantial therapeutic advantage over shorter-lived radionuclides such as ⁹⁰Y (Table II). These results are supported by the theoretical work of Dale²³ and Britton *et al.*²⁴ More importantly, the recent work of Shen *et al.*²⁵ with ⁶⁴Cu ($T_p = 13$ h) and ⁶⁷Cu ($T_p = 59$ h) labeled BAT-Lym-1 antibodies in humans shows that the therapeutic index (tumor dose/marrow dose) is higher for the longer-lived radionuclide ⁶⁷Cu than the shorter-lived radionuclide ⁶⁴Cu. This provides experimental evidence of the advantage of longer-lived radionuclides over shorter-lived radionuclides, consistent with the theoretical predictions of the LQ model. Another noteworthy observation is that when proliferation is folded into the LQ model, the predicted extrapolated initial dose rates and total doses are very similar to the values predicted by the empirical TDF model (Table II). Finally, as shown in our earlier publication,⁷ selection of the physical half-life of the radionuclide should be based on the biological uptake and clearance times of the antibody with the optimal physical half-life being about 2–3 times the biological clearance half-time of the antibody in the tumor. Physical half-lives greater than 2–3 times the biological clearance half-time provide little additional gain in the RAF because further increase in the physical half-life has little impact on the effective half-time.

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References

1. Macey DJ, Denardo SJ, Denardo GL, Goodnight JK, Unger MW. Uptake of indium-111 labeled monoclonal antibody ZME-018 as a function of tumor size in a patient with melanoma. *Am. J. Physiol. Imag* 1988;3:1–6.
2. Order SE, Klein JL, Ettinger D, Alderson P, Siegelman S, Leichner P. Phase I–II study of radiolabelled antibody integrated in the treatment of primary hepatic malignancies. *Int. J. Radiat. Oncol., Biol., Phys* 1980;6:703–710. [PubMed: 6256319]
3. Breitz HB, Weiden PL, Vanderheyden J-L, Applebaum JW, Bjorn MJ, Fer MF, Wolf SB, Ratliff BA, Seiler CA, Foisie DC, Fisher DR, Schroff RW, Fritzberg AR, Abrams PG. Clinical experience with rhenium-186-labeled monoclonal antibodies for radioimmunotherapy: Results of phase I trials. *J. Nucl. Med* 1992;33:1099–1112. [PubMed: 1597723]
4. Goldenberg DM, Horowitz J, Sharkey RM, Hall TC, Murthy S, Goldenberg H, Lee RE, Stein R, Siegal JA, Izon DO, Burger K, Swayne LC, Belisle E, Hansen HJ, Pinsky CM. Targeting, dosimetry, and radioimmunotherapy of B-cell lymphomas with iodine-131-labeled LL2 monoclonal antibody. *J. Clin. Oncol* 1991;9:548–564. [PubMed: 2066752]
5. Fowler JF. Radiobiological aspects of low dose rates in radioimmunotherapy. *Int. J. Radiat. Oncol., Biol., Phys* 1990;18:1261–1269. [PubMed: 2347734]
6. Langmuir VK, Fowler JF, Knox SJ, Wessels BW, Sutherland RM, Wong JYC. Radiobiology of radiolabeled antibody therapy as applied to tumor dosimetry. *Med. Phys* 1993;20(Pt. 2):601–610. [PubMed: 8492769]
7. Rao DV, Howell RW. Time dose fractionation in radioimmunotherapy: Implications for selecting radionuclides. *J. Nucl. Med* 1993;34:1801–1810. [PubMed: 8410301]
8. Howell RW, Goddu SM, Rao DV. Application of the linear-quadratic model to radioimmunotherapy: Further support for the advantage of longer-lived radionuclides. *J. Nucl. Med* 1994;35:1861–1869. [PubMed: 7965170]
9. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *Int. J. Radiat. Oncol., Biol., Phys* 1982;8:1981–1997. [PubMed: 6759484]

10. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br. J. Radiol* 1985;58:515–528. [PubMed: 4063711]
11. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br. J. Radiol* 1989;62:679–694. [PubMed: 2670032]
12. Howell RW, Goddu SM, Rao DV. Design and performance characteristics of an experimental Cs-137 irradiator to simulate internal radionuclide dose rate patterns. *J. Nucl. Med* 1997;38:727–731. [PubMed: 9170437]
13. Rao DV, Howell RW. On the modeling of the tumor uptake to determine the time-dose-fractionation (TDF) effect in radioimmunotherapy (reply to letter). *J. Nucl. Med* 1994;35:1562–1564.
14. Liu A, Williams LE, Demidecki AJ, Raubitschek AA, Wong JYC. On the modeling of the tumor uptake to determine the time-dose-fractionation (TDF) effect in radioimmunotherapy (letter). *J. Nucl. Med* 1994;35:1561–1562. [PubMed: 8071711]
15. Dale RG. Radiobiological assessment of permanent implants using tumour repopulation factors in the linear-quadratic model. *Br. J. Radiol* 1989;62:241–244. [PubMed: 2702381]
16. Ling CC. Permanent implants using Au-198, Pd-103 and I-125: Radiobiological considerations based on the linear quadratic model. *Int. J. Radiat. Oncol., Biol., Phys* 1992;23:81–87. [PubMed: 1572833]
17. Wessels BW, Rogus RD. Radionuclide selection and model absorbed dose calculations for radiolabeled tumor associated antibodies. *Med. Phys* 1984;11:638–645. [PubMed: 6503879]
18. Wu C-T, Lajtha LG. Haemopoietic stem-cell kinetics during continuous irradiation. *Int. J. Radiat. Biol* 1975;27:41–50.
19. Wong JYC, Williams LE, Demidecki AJ, Wessels BW, Yan XW. Radiobiologic studies comparing yttrium-90 irradiation and external beam irradiation in vitro. *Int. J. Radiat. Oncol., Biol., Phys* 1991;20:715–722. [PubMed: 2004948]
20. Humm JL, Cobb LM. Nonuniformity of tumor dose in radioimmunotherapy. *J. Nucl. Med* 1990;31:75–83. [PubMed: 2295944]
21. 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. [PubMed: 4033585]
22. Howell RW, Rao DV, Sastry KSR. Macroscopic dosimetry for radioimmunotherapy: Nonuniform activity distributions in solid tumors. *Med. Phys* 1989;16:66–74. [PubMed: 2921982]
23. Dale RG, Jones BJ, Coles IP. The effect of tumour shrinkage on biological effectiveness of permanent brachytherapy implants. *Br. J. Radiol* 1994;67:639–645. [PubMed: 8061998]
24. Britton KE, Mather SJ, Granowska M. Radiolabeled monoclonal antibodies in oncology. III. Radioimmunotherapy. *Nucl. Med. Commun* 1991;12:333–347. [PubMed: 2067740]
25. Shen S, DeNardo GL, DeNardo SJ, Salako Q, Morris G, Banks D, Yuan A, DeNardo DA. Dosimetric evaluation of copper-64 in copper-67- 2IT-BAT-Lym-1 for radioimmunotherapy. *J. Nucl. Med* 1996;37:146–150. [PubMed: 8543984]

FIG. 1.

Dependence of relative advantage factor (RAF) on tumor radiosensitivity α_t for ^{90}Y (dotted), ^{32}P (dashed), and $^{114\text{m}}\text{In}$ (solid). The value of α/β is maintained at 10 Gy and the parameters are as given in Table I. A substantial therapeutic advantage is maintained by the use of longer-lived radionuclides even for radioresistant tumors.

FIG. 2.

Dependence of relative advantage factor (RAF) on biologically effective dose to the tumor BED_t for ^{90}Y (dotted), ^{32}P (dashed), and ^{114m}In (solid). With the exception of BED_t , all parameters are as given in Table I. Note that the RAF decreases as BED_t decreases.

FIG. 3.

Dependence of relative advantage factor (RAF) on biological half-time in the tumor $T_{b,t}$. The dotted, dashed, and solid curves are for physical half-lives corresponding to ^{90}Y , ^{32}P , and $^{114\text{m}}\text{In}$, respectively. With the exception of $T_{b,t}$, all “standard” parameters are as given in Table I. The curves are terminated at $T_{b,t} = T_{b,B} = 3.7$ d.

TABLE I

Input parameters for LQ model calculations.

Description	Symbol	Tumor	Bone marrow
Ratio of LQ coefficients	α/β	10 Gy	2.5 Gy
LQ linear coefficient	α	0.56 Gy ⁻¹	1.5 Gy ⁻¹
Repair half-time	T_μ	1.5 h	1.5 h
Biologic clearance time	T_b	13.4 d	3.7 d
Biologic uptake time	T_u	1.9 d	0
Regrowth delay time	T_{rd}	4 d	8 d
Potential doubling time	T_g	1.5 d	2 d
Biologically effective dose	BED	69.3 Gy	3.2 Gy

TABLE II

Dosimetry characteristics of radionuclides with different physical half-lives.^a

		⁹⁰ Y	³² P	^{114m} In
1	$T_{e,B}$ —effective clearance half-time tumor (d)	1.5	2.9	3.4
2	$T_{e,t}$ —effective clearance half-time tumor (d)	2.2	6.9	10.4
3	$T_{e,u,t}$ —effective tumor uptake half-time (d)	1.1	1.6	1.8
4	Theoretical model			
		TDF ⁷	LQ ⁸	LQ ⁸
5	$r_{o,B}$ —initial bone marrow dose rate (cGy/h), TDF _B = 2.0, BED _B = 3.2 Gy	5.9	5.8	3.6
6	D_B —total bone marrow dose (cGy), TDF _B = 2.0, BED _B = 3.2 Gy	306	301	361
7	$r_{o,t}$ —initial tumor dose rate (cGy/h), TDF _t = 100, BED _t = 69.3 Gy	176 ^b	181	36
8	D_t —total tumor dose (cGy) TDF _t = 100, BED _t = 69.3 Gy	6700	6800	9340
9	$r_{o,t}/r_{o,B}$ —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	31	12
10	RAF ^c for TDF _t = 100, TDF _B = 2.0; BED _t = 69.3 Gy, BED _B = 3.2 Gy	1.0	1.0	2.2
			2.3	3.0
			2.4	3.3
			2.5	3.4
			2.6	3.5
			2.7	3.6
			2.8	3.7
			2.9	3.8
			3.0	3.9
			3.1	4.0
			3.2	4.1
			3.3	4.2
			3.4	4.3
			3.5	4.4
			3.6	4.5
			3.7	4.6
			3.8	4.7
			3.9	4.8
			4.0	4.9
			4.1	5.0
			4.2	5.1
			4.3	5.2
			4.4	5.3
			4.5	5.4
			4.6	5.5
			4.7	5.6
			4.8	5.7
			4.9	5.8
			5.0	5.9
			5.1	6.0
			5.2	6.1
			5.3	6.2
			5.4	6.3
			5.5	6.4
			5.6	6.5
			5.7	6.6
			5.8	6.7
			5.9	6.8
			6.0	6.9
			6.1	7.0
			6.2	7.1
			6.3	7.2
			6.4	7.3
			6.5	7.4
			6.6	7.5
			6.7	7.6
			6.8	7.7
			6.9	7.8
			7.0	7.9
			7.1	8.0
			7.2	8.1
			7.3	8.2
			7.4	8.3
			7.5	8.4
			7.6	8.5
			7.7	8.6
			7.8	8.7
			7.9	8.8
			8.0	8.9
			8.1	9.0
			8.2	9.1
			8.3	9.2
			8.4	9.3
			8.5	9.4
			8.6	9.5
			8.7	9.6
			8.8	9.7
			8.9	9.8
			9.0	9.9
			9.1	10.0
			9.2	10.1
			9.3	10.2
			9.4	10.3
			9.5	10.4
			9.6	10.5
			9.7	10.6
			9.8	10.7
			9.9	10.8
			10.0	10.9
			10.1	11.0
			10.2	11.1
			10.3	11.2
			10.4	11.3
			10.5	11.4
			10.6	11.5
			10.7	11.6
			10.8	11.7
			10.9	11.8
			11.0	11.9
			11.1	12.0
			11.2	12.1
			11.3	12.2
			11.4	12.3
			11.5	12.4
			11.6	12.5
			11.7	12.6
			11.8	12.7
			11.9	12.8
			12.0	12.9
			12.1	13.0
			12.2	13.1
			12.3	13.2
			12.4	13.3
			12.5	13.4
			12.6	13.5
			12.7	13.6
			12.8	13.7
			12.9	13.8
			13.0	13.9
			13.1	14.0
			13.2	14.1
			13.3	14.2
			13.4	14.3
			13.5	14.4
			13.6	14.5
			13.7	14.6
			13.8	14.7
			13.9	14.8
			14.0	14.9
			14.1	15.0
			14.2	15.1
			14.3	15.2
			14.4	15.3
			14.5	15.4
			14.6	15.5
			14.7	15.6
			14.8	15.7
			14.9	15.8
			15.0	15.9
			15.1	16.0
			15.2	16.1
			15.3	16.2
			15.4	16.3
			15.5	16.4
			15.6	16.5
			15.7	16.6
			15.8	16.7
			15.9	16.8
			16.0	16.9
			16.1	17.0
			16.2	17.1
			16.3	17.2
			16.4	17.3
			16.5	17.4
			16.6	17.5
			16.7	17.6
			16.8	17.7
			16.9	17.8
			17.0	17.9
			17.1	18.0
			17.2	18.1
			17.3	18.2
			17.4	18.3
			17.5	18.4
			17.6	18.5
			17.7	18.6
			17.8	18.7
			17.9	18.8
			18.0	18.9
			18.1	19.0
			18.2	19.1
			18.3	19.2
			18.4	19.3
			18.5	19.4
			18.6	19.5
			18.7	19.6
			18.8	19.7
			18.9	19.8
			19.0	19.9
			19.1	20.0
			19.2	20.1
			19.3	20.2
			19.4	20.3
			19.5	20.4
			19.6	20.5
			19.7	20.6
			19.8	20.7
			19.9	20.8
			20.0	20.9
			20.1	21.0
			20.2	21.1
			20.3	21.2
			20.4	21.3
			20.5	21.4
			20.6	21.5
			20.7	21.6
			20.8	21.7
			20.9	21.8
			21.0	21.9
			21.1	22.0
			21.2	22.1
			21.3	22.2
			21.4	22.3
			21.5	22.4
			21.6	22.5
			21.7	22.6
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			21.9	22.8
			22.0	22.9
			22.1	23.0
			22.2	23.1
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			22.5	23.4
			22.6	23.5
			22.7	23.6
			22.8	23.7
			22.9	23.8
			23.0	23.9
			23.1	24.0
			23.2	24.1
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			23.5	24.4
			23.6	24.5
			23.7	24.6
			23.8	24.7
			23.9	24.8
			24.0	24.9
			24.1	25.0
			24.2	25.1
			24.3	25.2
			24.4	25.3
			24.5	25.4
			24.6	25.5
			24.7	25.6
			24.8	25.7
			24.9	25.8
			25.0	25.9
			25.1	26.0
			25.2	26.1
			25.3	26.2
			25.4	26.3
			25.5	26.4
			25.6	26.5
			25.7	26.6
			25.8	26.7
			25.9	26.8
			26.0	26.9
			26.1	27.0
			26.2	27.1
			26.3	27.2
			26.4	27.3
			26.5	27.4
			26.6	27.5
			26.7	27.6
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			26.9	27.8
			27.0	27.9
			27.1	28.0
			27.2	28.1
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			27.4	28.3
			27.5	28.4
			27.6	28.5
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			27.9	28.8
			28.0	28.9
			28.1	29.0
			28.2	29.1
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			28.5	29.4
			28.6	29.5
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			28.9	29.8
			29.0	29.9
			29.1	30.0
			29.2	30.1
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			29.5	30.4
			29.6	30.5
			29.7	30.6
			29.8	30.7
			29.9	30.8
			30.0	30.9
			30.1	31.0
			30.2	31.1
			30.3	31.2
			30.4	31.3
			30.5	31.4
			30.6	31.5
			30.7	31.6
			30.8	31.7
			30.9	31.8
			31.0	31.9
			31.1	32.0
			31.2	32.1
			31.3	32.2
			31.4	32.3
			31.5	32.4
			31.6	32.5
			31.7	32.6
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			31.9	32.8
			32.0	32.9
			32.1	33.0
			32.2	33.1
			32.3	33.2
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			32.5	33.4
			32.6	33.5
			32.7	33.6
			32.8	33.7
			32.9	33.8
			33.0	33.9
			33.1	34.0
			33.2	34.1
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			33.5	34.4
			33.6	34.5
			33.7	34.6
			33.8	34.7
			33.9	34.8
			34.0	34.9
			34.1	35.0
			34.2	35.1
			34.3	35.2
			34.4	35.3
			34.5	35.4
			3	