Implications of Nonuniform Tumor Doses for Radioimmunotherapy

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This article describes a method of assessing the biologic consequences of nonuniform dose distributions produced in tumors by biologically targeted radionuclide therapy. The analysis is based on a simple mathematical model that assumes all tumor cells are uniformly radiosensitive. **Methods:** Using the linear-quadratic radiobiologic model, it is possible to represent an absorbed dose distribution by a biologically effective dose (BED) volume histogram (BVH). The Laplace transform of the BVH yields an equivalent uniform biologically effective dose. This is a one-number value that fully describes the biologic effect of a nonuniform absorbed dose distribution. In this article, for the purposes of exposition, nonuniform BED distributions are represented by normal distributions. **Results:** Nonuniform absorbed dose distributions are inefficient in sterilizing tumors and become proportionately less effective as the mean dose increases. The loss in effectiveness is most severe for radiosensitive tumors. **Conclusion:** Several approaches may alleviate the consequences of dosimetric nonuniformity. These include the use of smaller targeting molecules, radionuclides with longer emission ranges, fractionated administration of biologically targeted radionuclide therapy and combined modality treatments.

Key Words: heterogeneity; nonuniform dosimetry; fractionation; combined modalities; linear-quadratic model

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Biologically targeted radionuclide therapy for cancer is conceptually appealing, especially in cases in which diffuse or occult disease is present. Although there have been some encouraging clinical results with radiosensitive tumors (*1–3*) and for minimal residual disease (*4,5*), for bulk solid tumors, responses, if any, have been minor.

Several mechanisms may be partly responsible for the failure of targeted radionuclide therapy to produce significant improvements in local control of solid tumors. These include:

1. Limited radiation tolerance of normal tissues.

   The allowable therapeutic intensity is determined by the incidence and severity of normal tissue side effects. Most applications of targeted radionuclide therapy are restricted by bone marrow toxicity and correspond to maximum absorbed doses to red marrow of approximately 2 Gy. This is much less than for local external beam radiotherapy for which tolerance doses to normal tissues can be as high as 60 Gy.
2. Tumor radiosensitivity.

   The spectrum of tumor radioresponsiveness ranges from sensitive (e.g., lymphoma, neuroblastoma) to extremely resistant (e.g., glioblastoma, renal cell cancer). Radiation doses required for local control will vary accordingly (*6–8*). Moreover, because of environmental factors, in particular oxygen tension, there may be local variations in effective radiosensitivity, even for otherwise identical tumor cells.
3. Heterogeneous radionuclide uptake within tumors. (*9–11*).

   This results in nonuniform absorbed doses and dose rates to tumors and a consequent reduction in the effectiveness of treatment (*12–17*).

This article examines the last of these factors, dosimetric nonuniformity. A general method for assessing the biologic effects of nonuniform dose distributions on tumors is described and the implications for treatment design discussed.

METHODS

Overview

The approach described is based on the concept of biologically effective dose (BED). The BED may be calculated using the linear-quadratic (LQ) radiobiologic model and is derived from the absorbed dose-rate profile and the operative radiobiologic factors. The usefulness of this quantity is that the relationship between BED and biologic effect is linear.

A three-dimensional distribution of absorbed dose can be represented as a dose-volume histogram. In an analogous fashion, given data on the temporal variation in dose rates, it may be represented as a BED volume histogram (BVH). If normalized so that the area under the curve is 1, the BVH is the probability density function of BED. A mathematical transformation (Laplace transform) of the BVH enables the derivation of an equivalent uniform biologically effective dose (EUD). The EUD is a one-number value that fully describes the biologic effect of a nonuniform distribution of absorbed dose. This concept has been described in the context of external beam therapy (*18*) but is perhaps of even more value for radioimmunotherapy in which the variation of absorbed dose throughout the tumor volume is significantly greater.

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Calculation of Biologically Effective Dose Using Linear-Quadratic Model

At present, the most commonly used radiobiologic model is the LQ model (*19,20*). This has been applied to a wide range of scenarios, including the analysis of cell survival curves and dose-response relationships for normal tissues and tumors. Originally used for acute high-dose-rate irradiations, the LQ model has been extended to include low-dose-rate treatments, including brachytherapy and biologically targeted radionuclide therapy (*21–25*). The LQ model is so called because of the shapes of survival curves it predicts for single high-dose-rate radiation exposures. For protracted irradiations, irrespective of whether they are delivered by external beam, brachytherapy or biologically targeted radionuclides, the predicted survival curve shapes are not LQ, but more complex. It is perhaps more accurate to consider these as linear-nonlinear. The degree of "linear" cell kill is determined by the dose, D, and by the α radiosensitivity parameter. The degree of "nonlinear" cell kill is determined by the β radiosensitivity parameter, repair rate and temporal pattern of dose delivery, namely, the dose rate and how this varies with time. As the dose rate decreases, the nonlinear component of cell kill decreases and survival curves become more linear. Mathematically, in the limit as dose rate goes to zero, the survival curve is totally linear and is fully defined by α and D.

The computational basis of the LQ model is the BED. The BED is an abstraction and represents the dose delivered at the mathematical limit of low dose rate that would have the same biologic effect as the dose actually experienced. This means that all the "nonlinear" dependency of cell kill (e.g., the D^2 term) and all the dose-rate dependency of cell kill is incorporated into the definition of the BED. Procedures for calculating BED from the actual irradiation parameters have been described (*21–25*); however, this aspect is not explicitly discussed here.

The relationship between surviving fraction (sf) and BED is given by

$$sf = \exp(-\alpha\, BED)\,. \qquad \text{Eq. 1}$$

The slope of the survival curve is a measure of the radiosensitivity of the cells and is characterized by the parameter α (Gy^{-1}). It has been observed that a correlation exists between the in vitro radiosensitivity of tumor cells and the in vivo radioresponsiveness of tumors of the same type (*6,7*). For in vitro tumor cell culture, average values of α are approximately 0.35 Gy^{-1}, values approximately 0.5 Gy^{-1} correspond to radiosensitive tumor cells and values approximately 0.2 Gy^{-1} correspond to radioresistant tumor cells (*6,7*).

Calculation of Equivalent Uniform Biologically Effective Dose

With the LQ model, an absorbed dose distribution can be represented by a BED distribution or BVH (*26,27*). The differential BVH, normalized such that the area under the curve is 1.0, is the probability density function, $P(\psi)$ of the BED, ψ. By definition the surviving fraction for a given value of ψ is

$$sf = \exp(-\alpha\psi)\,. \qquad \text{Eq. 2}$$

The overall surviving fraction for the nonuniform distribution $P(\psi)$ is then

$$SF(\alpha) = \int_0^\infty P(\psi)\exp(-\alpha\psi)d\psi\,, \qquad \text{Eq. 3}$$

which is the Laplace transform of the BVH.

This enables the definition of the EUD as the uniform value of BED that would produce the same surviving fraction as the nonuniform distribution,

$$EUD = -\frac{1}{\alpha}\ln(SF(\alpha)) = -\frac{1}{\alpha}\ln\left(\int_0^\infty P(\psi)\exp(-\alpha\psi)d\psi\right). \qquad \text{Eq. 4}$$

RESULTS

Given that a BVH can be constructed from a set of three-dimensional absorbed dose rate and kinetic data, the EUD may be derived. Figure 1 illustrates a hypothetical example of a BVH experienced by a population of tumor cells. This is represented by a normal distribution with a mean of 40 Gy and a fractional SD of 0.175 (Fig. 1A). For each value of BED, the probability of cell survival is given

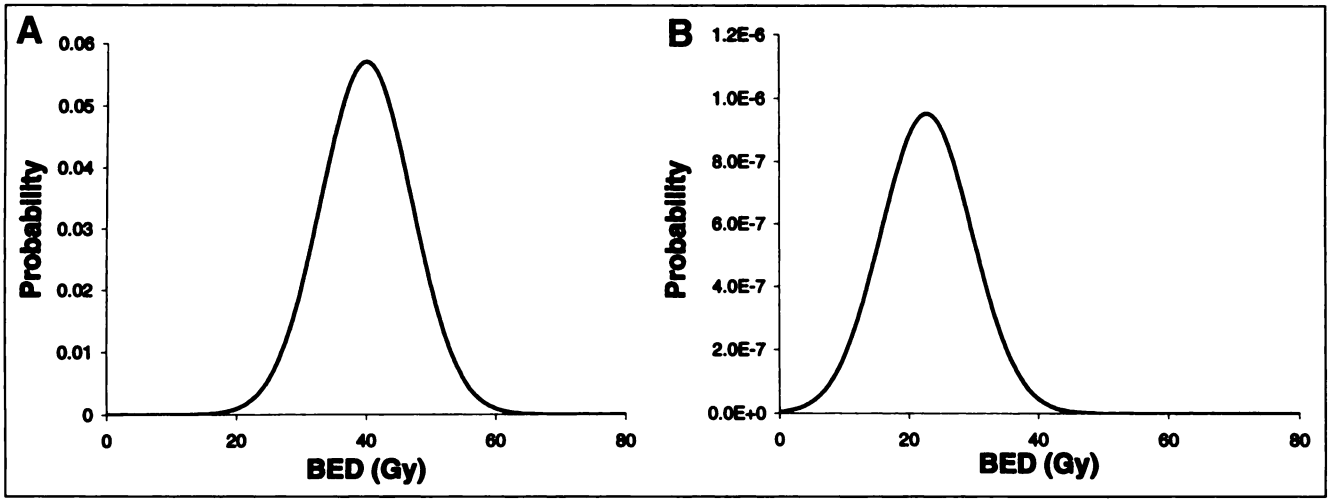

FIGURE 1. (A) Nonuniform distribution of BED to tumor cell population is represented by normal distribution with mean of 40 Gy and fractional SD of 0.175. (B) Resulting distribution of survival probability (calculated for tumor radiosensitivity parameter α of 0.35 Gy^{-1}) is displaced to left compared with (A). Total survival probability is area under curve. Equivalent uniform BED of 31.4 Gy would produce same surviving fraction as nonuniform BED distribution.

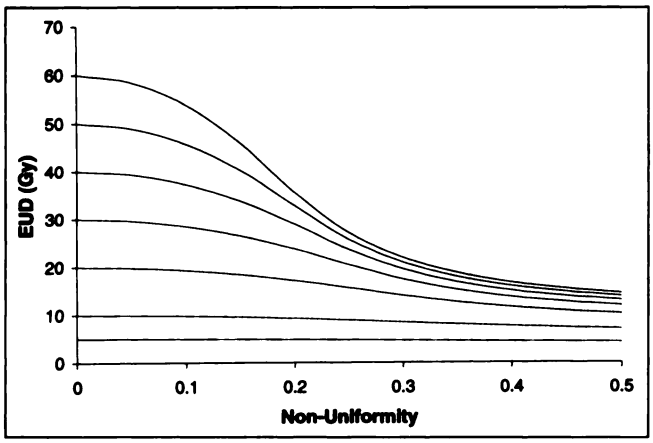

FIGURE 2. EUD as function of mean (individual curves) and fractional SD (x-axis) of BED distribution, calculated for $\alpha = 0.35$ Gy^{-1}. As distribution becomes less uniform, EUD decreases. Loss of effectiveness is worse for larger mean BED. All values of EUD on any one curve correspond to same mean effective dose (value when nonuniformity = 0).

by multiplying the probability of a cell experiencing that BED by the corresponding surviving fraction. The resulting distribution of survival probability, calculated using an α value of 0.35 Gy^{-1}, is shown in Figure 1B. It is apparent that this distribution is displaced to the left (i.e., to lower values of BED) with respect to Figure 1A. This indicates that the tumor cells most likely to survive are those that experience lower values of BED. In contrast, tumor cells that experience a higher BED than the rest are "overkilled" in the sense that their number has become insignificant compared with the total number of survivors. The surviving fraction is the area under the curve of Figure 1B. As discussed in the methods section, this corresponds to the Laplace transform of the BED distribution. When the appropriate numerical values are used, it can be shown that the EUD in this case is 31.4 Gy. This uniform value of BED would have the same biologic effect on the tumor cell population as the normal distribution mean of 40 Gy and fractional SD of 0.175. This suggests that the EUD is less than the mean BED. For this example, the loss in therapeutic effect corresponds to 8.6 Gy of 40 Gy or 21%.

It is possible to simulate variations in the degree of nonuniformity by changing the fractional SD of the BED distribution. Fractional SDs varied between 0 (corresponding to a uniform BED) and 0.5. The distribution means varied between 5 and 60 Gy. Figure 2 shows how the EUD changes as a function of these parameters. Each individual EUD curve corresponds to the same mean BED.

Two features of Figure 2 are apparent:

1. As the distribution becomes more nonuniform, the EUD (i.e., the therapeutic effect) decreases.
2. The loss of therapeutic effectiveness depends on the mean BED and is proportionately worse for greater values.

The intrinsic tumor cell radiosensitivity is an important factor and has a significant impact. Figure 3 shows families of EUD curves calculated in a similar manner to those of Figure 2. Figure 3A is for an α value of 0.2 Gy^{-1}, corresponding to a radioresistant tumor, and Figure 3B is for $\alpha = 0.5$ Gy^{-1}, corresponding to a radiosensitive tumor. It is apparent that the loss in effectiveness is more pronounced for the radiosensitive tumor. For example, with a mean BED of 60 Gy and a fractional SD of 0.25, the calculated EUD values are 38.4 Gy (for $\alpha = 0.2$ Gy^{-1}), 27.0 Gy (for $\alpha = 0.35$ Gy^{-1}) and 20.5 Gy (for $\alpha = 0.5$ Gy^{-1}).

DISCUSSION

These findings have important implications for tumor therapy using biologically targeted radionuclides. Nonuniform absorbed dose distributions are inefficient in sterilizing tumors. They are characterized by "underdosing" some elements of the tumor cell population and "overkilling" others. The greater the nonuniformity, the less effective therapy becomes. Moreover, a nonuniform dose distribution becomes proportionately less effective as the mean dose increases, assuming the relative nonuniformity remains similar. This means that simple "dose escalation" may not lead to a significant increase in tumor responses. It was also shown that the negative impact of dosimetric nonuniformity will be most severe for radiosensitive tumors. These are, of course, the very tumors in which targeted radionuclide therapy would be anticipated to have the greatest likelihood of success.

There are several possible approaches that may help to alleviate the problems associated with nonuniform dosimetry. The first is obvious—reduce the nonuniformity directly. Smaller targeting molecules (e.g., antibody fragments, haptens) may be more freely diffusible than larger molecular weight species, such as intact antibodies, and consequently

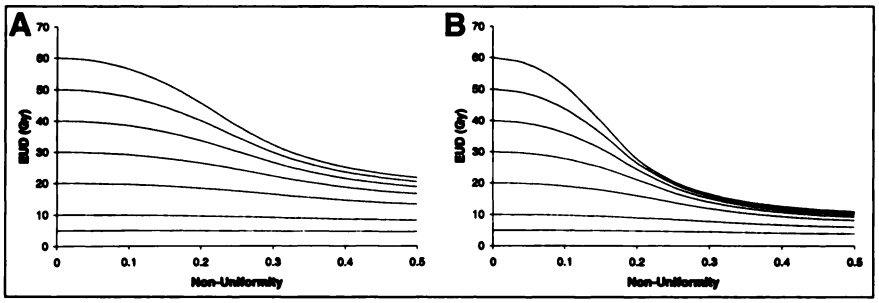

FIGURE 3. Illustration of effect of tumor cell radiosensitivity. EUD is plotted as function of nonuniformity for different values of mean BED. (A) Radioresistant tumor cells ($\alpha = 0.2$ Gy^{-1}) and (B) radiosensitive tumor cells ($\alpha = 0.5$ Gy^{-1}). Loss in therapeutic effectiveness is proportionately worse for radiosensitive population.

produce a more homogeneous pattern of uptake. The use of radionuclides with longer emission ranges (e.g., ^{90}Y, ^{188}Re) will increase cross-fire radiation and absorbed doses in low-activity regions but are inappropriate for microscopic disease (*28*). Other methods of addressing nonuniform dosimetry are less obvious. These include fractionation (i.e., delivery of multiple administrations) of biologically targeted radionuclide therapy and the use of combined modality treatments.

Fractionation may have a therapeutic advantage if different administrations target different subpopulations of tumor cells. This could occur through time-dependent changes in tumor capillary blood flow or modifications to tumor architecture caused by the biologic effects of preceding administrations. In terms of the model described above, the potential advantage of fractionation derives from the finding that dosimetric nonuniformity has less impact when the mean BED is smaller. For example, the calculated EUD ($\alpha = 0.35\ Gy^{-1}$) for a mean BED of 40 Gy with a fractional SD of 0.3 is 19.5 Gy. For a mean BED of 5 Gy with an identical fractional SD, it is 4.6 Gy. If each fraction produces equal biologic effects, then the EUD for eight fractions of 5 Gy would be 36.9 Gy. The difference in tumor cell kill between these two values of EUD is greater than 2.5 logs (i.e., a factor of more than 400).

The assumption of equal effects per fraction is important. To be valid, this requires a randomization of the absorbed dose distribution within tumors for each treatment fraction. Although the exact nature of intratumor absorbed dose distributions will be unknown, we can consider two extreme scenarios. The first is when uptake is essentially random throughout the tumor from one fraction to another. The second is when the pattern of tumor uptake is exactly the same from one fraction to the next. In the latter case, a single high-actvity administration would be expected to be more effective because it entails a higher average dose rate delivered over a shorter time.

In reality, the therapeutic advantage of fractionation (if any) will depend on how much the pattern of tumor uptake varies between individual fractions. Studies in animal models suggest that fractionated radioimmunotherapy is both intrinsically more tumoricidal and less toxic to bone marrow than a single administration (*29–31*). Clinical studies of fractionated radioimmunotherapy have begun at this institution.

The most likely clinical scenarios in which combined modalities may be appropriate are those in which a relatively large (i.e., measurable) primary tumor or metastatic deposit presents, along with numerous smaller metastases, some of which may not be clinically detectable. The main potential benefit of targeted radionuclide therapy will be for the smaller tumor deposits, for which external beam treatment is generally not appropriate. For larger tumors, targeted radionuclide treatment is likely to be suboptimal, as a result of low tumor uptake or heterogeneous distributions. The existence of these diverse configurations of tumor cells in an individual patient is the most important reason why combined modality treatments are indicated.

However, a collateral benefit of combining treatment modalities is the possible reduction of the impact of dosimetric nonuniformity in bulky tumors. Consider, for example, a radionuclide therapy that delivers a nonuniform tumor BED distribution with a mean of 30 Gy and a fractional SD of 0.2. This is combined with a course of external beam therapy that delivers a uniform BED of 30 Gy. The combination has a mean of 60 Gy and a fractional SD of only 0.1. Thus, not only does the mean BED increase but the relative level of dosimetric nonuniformity has also been reduced.

Animal model studies have shown that combining radioimmunotherapy with fractionated external beam radiotherapy can increase the therapeutic effect without increasing normal tissue toxicity (*31–33*).

CONCLUSION

The method of quantifying the biologic effects of dosimetric nonuniformity described in this article is general. Normal distributions were used in the numerical examples for computational convenience. It is not suggested that, in reality, nonuniform BED or dose distributions will be normal. The method can be applied to arbitrary BED distributions, including normal log-normal or even nonanalytic variants. The two important features that determine the loss of cell killing efficacy are the mean BED and the dispersion of the distribution round the mean. In almost all circumstances, and certainly for therapeutic dose levels, it is the dispersion from the mean to the lowest doses experienced that is important. BED values greater than the mean result in a relatively negligible degree of tumor cell survival (i.e., overkill). For log-normal distributions the long high-dose "tails" result in even more overkill than in the normal distribution case. The low-dose "tails" are, however, shorter, i.e., the lowest doses experienced for a log-normal distribution will be generally greater than those due to a normal distribution of the same mean and with a visually similar degree of dispersion from the mean toward lower doses. This means the loss in therapeutic effectiveness will be less severe for log-normal distributions.

More important, although the numbers may change, the general features of the analysis still hold for log-normal distributions, i.e., more heterogeneity is bad and the effect is relatively worse for higher mean values and radiosensitive tumor cells.

In a real clinical application, BVHs would be generated from three-dimensional absorbed dose or BED distributions.

In principle, it would be possible to calculate EUDs for normal tissues irradiated by nonuniform BED distributions. In this case, the calculated EUD would reflect the overall survival level of normal cells or functional subunits within the volume of interest. However, the relationship between this quantity and functional impairment will vary from one organ to another. For organ systems with a "parallel"

architecture (e.g., liver), the method may be appropriate. For others with "serial" structure (e.g., spinal cord), the functional response is likely to be determined by hot spots in the BED distribution. The method described in this article would not be appropriate for these cases.

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