Reconciliation of Tumor Dose Response to External Beam Radiotherapy versus Radioimmunotherapy with $^{131}$Iodine-labeled Antibody for a Colon Cancer Model

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Abstract

Reported doses of external beam radiotherapy and radioimmunotherapy (RIT) to produce equivalent therapeutic effects are inconsistent, with many proposed causes. Calculations of effective dose were performed for the case of LS174T human colon cancer xenografts, where a $^{60}$Co single fraction exposure (6 Gy) was matched with $^{131}$I-labeled 17-1A monoclonal antibody therapy (300 pCi injection, 19 ± 2 Gy using the Medical Internal Radiation Dose Uniform isotropic model). Measured three-dimensional dose-rate distributions were used to form a time-dependent description of the dose-rate nonuniformity. Included in the calculation of RIT effective dose was energy loss, dose nonuniformity, dose-rate dependence, hypoxic fraction, and cell proliferation. The calculations assumed the linear quadratic model for cell survival with $\alpha = 0.3$ Gy$^{-1}$, $\alpha/\beta = 15$ to 25 Gy, and $\mu = 0.46$ h$^{-1}$. The biologically effective dose for the single fraction $^{60}$Co exposure was 7.4 to 8.4 Gy. Estimates of dose efficiency factors consecutively applied to the RIT dose estimate were: (a) energy loss external to the tumor ($\times 0.85$); (b) effect of dose nonuniformity on cell survival ($\times 0.65$); and (c) effect of correlation of dose nonuniformity with cell proliferation rate ($\times 1.08$). The resulting effective dose for RIT was 11.4 Gy for tumor regrowth. This analysis substantially reconciles external beam radiotherapy/RIT dose-response results for this tumor model to within experimental uncertainties.

Introduction

Comparisons of therapeutic effects and doses of EBRT$^{3}$ and RIT have been reported by many groups. Recent reviews discuss the inconsistency of the results and list many possible causes for the discrepancies (1, 2). The relative efficiency of tumor growth delay ranged between factors of 0.3 to 3. Potential causes noted were: (a) dose nonuniformity; (b) dose-rate effects; (c) RIT preferentially targeting rapidly proliferating cells; (d) enhanced reoxygenation with RIT; (e) cell geometric effect; (f) cell cycle redistribution with accumulation in the radiosensitive G2 phase; and (e) RIT contribution to increased tumor vascular permeability. Because these factors probably affect each EBRT/RIT experimental model differently, it is useful to investigate the effects for each model independently. Here we address athymic nude mice bearing LS174T human colon cancer xenografts treated with i.p. $^{131}$I-labeled 17-1A monoclonal antibody (3).

3D activity density distributions were determined, each specific to the time of tumor resection. Since for the present model the activity distribution was time dependent (4), we used activity distributions from 22 tumors resected at 5 time points after injection to construct a mathematical description of spatial and temporal dependencies.

Materials and Methods

Activity Density Reconstruction. Athymic nude mice bearing LS174T human colon cancer xenografts were treated with i.p. injections of 300 pCi $^{131}$I-labeled 17-1A monoclonal antibody. The tumors were resected and sectioned. Serial-section radiographs were converted to activity density distributions using gelatin calibration standards and a laser densitometer. The activity density distributions were aligned to reconstruct the 3D tumor activity density distribution. Detailed procedure descriptions appear elsewhere (4–6).

Tumor Model. Tumors averaged approximately 1 cm in diameter (range, 0.5–1.7 cm). Tumor growth delay for a 300 pCi 17-1A monoclonal antibody injection RIT was found to correspond to a single $^{60}$Co EBRT exposure of 6 Gy (3). The dose calculated using the uniform isotropic model described by the Medical Internal Radiation Dose formalism (7), assuming total absorption, resulted in a calculated dose of 19 ± 2 Gy for RIT. The contribution in the mouse due to the $\gamma$ components was negligible (<2%) and was not included. The contribution from the $\beta$ component due to other organs was also negligible because of the tumor location (hind flank) and the average range of the $^{131}$I $\beta$ particles (~0.4 mm). The calculational uncertainty was derived from the experimental variations in tumor uptake measurements (3). Improved dose and effective dose calculations used the wealth of information available for this model, including the biodistribution data (3), 3D reconstructions of the activity densities at several time points (4–6), and a summation scheme for deriving total dose distributions while approximately retaining the pattern of time-dependent uptake heterogeneity.

Dosimetry Model. Activity density distributions for 22 tumors covering five time points after injection were reconstructed. Three-dimensional dose-rate distributions were calculated for each tumor. Since each tumor had a unique geometrical shape, the dose-rate distributions were not directly averaged or summed.

The predominant data characteristic was high tumor surface uptake at early times and a slow movement of the activity toward the center at later times (5, 8). The main features of the data were retained by averaging/summing surface or central dose rates separately. This was performed by expressing each tumor as a function of fractional radius. Each of 30 radial segments was defined as a constant fraction of the distance from the tumor center of mass to the tumor surface. The activity or dose-rate distribution for each segment was expressed as a histogram, normalized to reflect a spherical tumor with 1 cm diameter. For each time point, the histograms for each fractional radius were averaged to obtain a single representative dose-rate distribution. The result was five distributions with 30 histograms each, representing the dose-rate distribution characteristic of each radial increment. The averaged dose-rate distributions for days 1 and 4 after injection of 300 pCi of $^{131}$I are shown in Fig. 1.

The spatially and temporally varying description of the dose rate used the measured tumor uptake curve (Fig. 2) and the associated radially dependent dose-rate distributions. The tumor uptake curve (Fig. 2) averaged previously reported whole organ measurements (3) and the whole organ measurements for the activity-reconstructed tumors. An exponential extrapolation was performed for times beyond day 10. To ensure data consistency, the averaged dose-rate distribution for each time point was renormalized to reflect the activity of the decay corrected tumor uptake curve. The portion of the uptake curve assigned to each measured spatial distribution was determined according to the number of tumors used to form the average. For example, the averaged distribution representing 4 days after injection and 7 tumors was assigned a larger time interval of the tumor uptake curve compared to the distribution representing 3 days after injection and 2 tumors. The averaged data represented an idealized history of a representative tumor.

The tumor model description included a prescription for summing dose rates
RECONCILIATION OF TUMOR DOSE RESPONSE TO EBRT vs. RIT

Fig. 1. Radial dependence of dose rate for 300 μCi injection of 131I-labeled 17-1A monoclonal antibody in LS174T xenografts. Plotted are histograms for each of 30 radial increments (tumor center = 0; tumor surface = 30; for a 10-mm diameter tumor, each radial increment represented 0.167 mm). Each histogram represents the number of cubic voxels experiencing dose rates within a radial interval (dose-rate volume histograms). Voxel dimensions were 0.2 or 0.25 mm on a side. A and B, 1 and 4 days after injection, respectively. Data for 3, 7, and 10 days after injection are not shown.

over time. Dose rates for each radial increment were summed over time assuming the approximation of maximum heterogeneity. That is, the partial volume with the highest dose rates were summed, the partial volume with the next highest dose rates were summed, etc. (8). This procedure was equivalent to monotonically spreading the dose rates over spherical shells and summing the shells by aligning the highest dose rate points for each sphere. The present approach to the dosimetric model was designed to be consistent with the Medical Internal Radiation Dose formalism. The calculations for the uniform isotropic model used the area under the tumor uptake curve to calculate the integral of activity-time. The present model used the same uptake curve, with the time-dependent dose-rate nonuniformity as supplemental information.

Effective Dose. The effective dose was defined as the uniform absorbed dose required to produce the same fractional cell survival (S), assuming a linear dose response:

\[ D_{\text{eff}} = \frac{1}{\alpha} \ln(S) \]  

(A)

where \( \alpha \) is the linear dose-response coefficient. For a spatially varying dose distribution:

\[ S = \frac{1}{V} \int \exp[-\alpha D(\vec{r})] \, d^3r \]  

(B)
where the integral is performed over the volume $V$ and $D(\vec{r})$ is the spatially varying dose distribution. $D_{\text{eff}}$ was also expressed as:

$$D_{\text{eff}} = D \times RE$$

where $D$ is the physical absorbed dose and $RE$ is the relative effectiveness factor. Using the linear quadratic model, the $RE$ for a single fraction of EBRT was (9):

$$RE = 1 + \frac{D}{\alpha/\beta}$$

where $\alpha/\beta$ are the linear and quadratic dose-response coefficients. The relative effectiveness factor for RIT was taken from Millar (10):

$$RE = 1 + \frac{D \times OER}{\alpha/\beta}$$

where $OER$ is the oxygen enhancement ratio, $H$ represents hypoxic, and $O$ represents oxic. The above equations for the hypoxic fraction move the cell loss versus dose-curve relative to the oxic fraction by multiplying the dose axis by the $OER$. The surviving fraction was recalculated using:

$$S(\vec{r}, t) = \exp \left( -\alpha \int \int R(\vec{r}, t')dt' \cdot RE(\vec{r}, t) \right)$$

where the $RE(\vec{r}, t)$ values were calculated for each radius and time by performing the indicated integrals over the dose rates, $R(\vec{r}, t)$. The 3D spatial dependence of $R(\vec{r}, t)$ was represented by the histograms at each radius, configured for a 1-cm diameter tumor. These integrals (or sums) were performed assuming the approximation of maximum heterogeneity, as if the tumors were configured for a 1-cm diameter tumor. These integrals (or sums) were performed assuming the approximation of maximum heterogeneity, as if the tumor size of 1 cm diameter (0.5 g mass), the fraction of necrotic tissue was taken to be the average observed value (30%). The vascular density was closely associated with the initial antibody uptake. The average measured activity density distribution at 1 day after injection was assumed proportional to the vascular density distribution. The hypoxic and necrotic fractions as a function of radius were calculated by folding the fractional volume function with the vascular density function. The constant of proportionality was adjusted to yield a 0.30 fractional necrotic volume. The calculation resulted in a net hypoxic fractional volume of 0.10. The cell oxygenation status curves as a function of radius are shown in Fig. 4.

A prediction of the outcome of radiation therapy with dose may be described using fractional cell survival. Presumably, the hypoxic cells are more difficult to sterilize and may be described with different parameters ($\alpha_H/\beta_H$) such that:

$$\alpha_H = \alpha_O/OER$$

$$\alpha_H/\beta_H = (\alpha_O/\beta_O) \times OER$$

where $OER$ is the oxygen enhancement ratio, $H$ represents hypoxic, and $O$ represents oxic. The above equations for the hypoxic fraction move the cell loss versus dose-curve relative to the oxic fraction by multiplying the dose axis by the $OER$. The surviving fraction was recalculated using:

$$S(\vec{r}, t) = \exp \left( -\alpha_H \int \int R(\vec{r}, t')dt' \cdot RE_H(\vec{r}, t) \right)$$

$$S(\vec{r}, t) = \exp \left( -\alpha_O \int \int R(\vec{r}, t')dt' \cdot RE_O(\vec{r}, t) \right)$$

$$S(\vec{r}, t) = 0$$

where $RE_H(\vec{r}, t)$ and $RE_O(\vec{r}, t)$ are the relative effectiveness factors for hypoxic and oxic fractions, respectively.

**Correlation with Cell Proliferation Rate.** The antibody delivery route (circulating blood) produces a natural correlation of the activity density with tumor cell oxygenation and cell proliferation rate, since the blood delivers both oxygen and the radiolabeled antibodies. Monoclonal antibody targeting of antigen sites in tumor has been observed to be highly correlated with vascular density (11, 12). This implies a correlation of absorbed dose with cell proliferation rate. Because the vasculature is primarily concentrated at the tumor periphery, along with interior pockets in some tumors (13), rapid cell proliferation and maximum dose rates are near the surface or, less frequently, in small interior volumes.

For tumors of the size studied (~1 cm diameter), there were partial volumes of necrosis, estimated from our data to range between 10 to 40% of the tumor volume and consistent with reported values for the LS174T cell line (13).
RECONCILIATION OF TUMOR DOSE RESPONSE TO EBRT vs. RIT

Results

Estimated doses and effective doses are given in Table 1. Correction factors are applied sequentially to allow a comparison of their relative magnitudes. $RE$ (Eq. D) for a single fraction EBRT varied from 1.24 to 1.40, depending on the $\alpha/\beta$ ratio. The effective dose for EBRT was 7.4 to 8.4 Gy. For RIT, the fraction of energy retained inside of the tumor was calculated by comparing the average tumor dose to the dose assuming the uniform isotropic model. The average fraction of energy retained was 0.85. The effective dose calculated using the surviving fraction of cells (Eq. B) was 0.65 times the average dose. The effect of cell status (Eq. H.4 with $RE = 1.0$) was negligible. The effect of dose rate (Eq. F) using $\alpha = 0.3 \text{ Gy}^{-1}$, $\alpha/\beta = 15$ or 25 Gy, and $\mu = 0.46 \text{ h}^{-1}$ was small (2–4%). The inclusion of cell oxygenation status (Eq. H.4) to the dose-rate calculation also produced a negligible change. The calculated effective dose was 10.6 to 10.8 Gy.

Additional insight can be gained by including cell proliferation due to the relatively long exposure times for RIT. The dose, fractional cell survival, and effective dose are time dependent, as illustrated in Fig. 5. The average dose initially increased rapidly, then more slowly, and finally exponentially approached the maximum dose value. The frac-

Table 1 Parameters used for effective dose calculations including cell proliferation

<table>
<thead>
<tr>
<th>Cell composition</th>
<th>$\alpha/\beta = 15 \text{ Gy}$</th>
<th>$\alpha/\beta = 25 \text{ Gy}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniform</td>
<td>$\alpha = 0.3 \text{ Gy}^{-1}$</td>
<td>$\alpha = 0.3 \text{ Gy}^{-1}$</td>
</tr>
<tr>
<td>Oxic</td>
<td>$t_d = 3.0 \text{ days}$</td>
<td>$t_d = 3.4 \text{ days}$</td>
</tr>
<tr>
<td>Hypoxic/Necrotic</td>
<td>$\alpha_1 = 0.26 \text{ Gy}^{-1}$</td>
<td>$\alpha_2 = 0.26 \text{ Gy}^{-1}$</td>
</tr>
<tr>
<td>Hypoxic</td>
<td>$\alpha_1 = 0.13 \text{ Gy}^{-1}$</td>
<td>$\alpha_1 = 0.13 \text{ Gy}^{-1}$</td>
</tr>
<tr>
<td>Hypoxic</td>
<td>$\beta_H = 0.0003 \text{ Gy}^{-2}$</td>
<td>$\beta_H = 0.0006 \text{ Gy}^{-2}$</td>
</tr>
<tr>
<td>Necrotic</td>
<td>$t_d = 3.0 \text{ days}$</td>
<td>$t_d = 3.4 \text{ days}$</td>
</tr>
</tbody>
</table>

where $F_i(r)$ is the fraction of cells at position $r$ of type $i$ and $N$ represents necrotic regions. The surviving fractions of oxic, hypoxic, and necrotic cells were calculated separately and then summed to yield the total surviving fraction. An oxygen enhancement ratio of 2.0 for low-dose rate irradiation (14) was used.

Cell proliferation was represented by exponential cell growth of the well-oxygenated cell population (16).

$$S_n(r, t) = \exp\left(-\alpha \int_0^t R(t', r) dt' + Re\left(\alpha_0, t \right) + \lambda t \right)$$

where $\lambda$ is the cell proliferation constant. The tumor doubling time, $t_d$, equals $(\ln 2)/\lambda$. The hypoxic fraction was assumed dormant with no reoxygenation.

Parameter Determination. Typical parameters used for the present model were $\alpha = 0.3 \text{ Gy}^{-1}$, $\alpha/\beta = 15$ to 25 (17, 18), and $\mu = 0.46 \text{ h}^{-1}$ (9, 10). Since the primary purpose of the present work was to compare EBRT to RIT effective dose calculations, parameters used for each were kept consistent.

Buchbaum et al. (3) quoted the regrowth time delay to LS174T tumor doubling to be 15 ± 3 days (300 $\mu$Ci $^{131}$I-17-1A) and 15 ± 1 day (6 Gy $^{60}$Co). Doubling time estimates taken from unirradiated or irradiated tumor growth curves near the 1-cm tumor diameter size were ~4 days. This implies a time to regrowth of 11 days. The doubling time during earlier stages of regrowth was presumably shorter due to lesser fractions of hypoxic/necrotic tissues. Given $\alpha = 0.3 \text{ Gy}^{-1}$ and a regrowth time of 11 days for 6 Gy $^{60}$Co exposure, the implied mean doubling time was $t_d = (\ln 2)/\lambda = 3.4 \text{ days}$ ($\alpha/\beta = 25 \text{ Gy}$) or 3.0 days ($\alpha/\beta = 15 \text{ Gy}$). These values are similar to the doubling time of 3.3 days measured by Leith et al. (19) for LS174T. The same values of $\alpha/\beta$ and $t_d$ were used for the EBRT and RIT calculations. Small adjustments in the parameters had a minimal effect on the EBRT/RIT comparison.

With the inclusion of the hypoxic/necrotic volumes, an average value of $\alpha = 0.3 \text{ Gy}^{-1}$ was retained. The $\alpha_0$ and $\alpha_H$ values were determined using the relative volumes of oxic (60%), hypoxic (10%), and necrotic (30%) cells.

Parameters used for the cell proliferation calculations are given in Table 1.

Table 2 RIT versus EBRT dose and effective dose estimates

<table>
<thead>
<tr>
<th>EBRT</th>
<th>Correction factor</th>
<th>Dose or effective dose, Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniform absorbed dose</td>
<td>1.00</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Dose Rate

| $\alpha = 0.3 \text{ Gy}^{-1}$, $\alpha/\beta = 15 \text{ Gy}$ | 1.40 | 8.4$^a$ |
| $\alpha = 0.3 \text{ Gy}^{-1}$, $\alpha/\beta = 25 \text{ Gy}$ | 1.24 | 7.4$^a$ |

RIT Uniform isotropic model

| 3D dose distribution (energy loss) | 0.85 | 16.0 |

Dose nonuniformity

| $\alpha = 0.3 \text{ Gy}^{-1}$ with cell status | 0.65 | 10.4$^a$ |
| $\alpha = 0.3 \text{ Gy}^{-1}$ with cell status | 1.00 | 10.5$^a$ |

Dose rate

| $\alpha/\beta = 15 \text{ Gy}$ | 1.04 | 10.8$^a$ |
| $\alpha/\beta = 25 \text{ Gy}$ | 1.02 | 10.7$^a$ |
| $\alpha/\beta = 15 \text{ Gy}$ with cell status | 1.00 | 10.8$^a$ |
| $\alpha/\beta = 25 \text{ Gy}$ with cell status | 1.00 | 10.6$^a$ |

Proliferation

| $\alpha/\beta = 15 \text{ Gy}$ | 0.99 (0.42)$^b$ | 10.7 (4.5)$^b$ |
| $\alpha/\beta = 25 \text{ Gy}$ | 0.97 (0.45) | 10.5 (4.8)$^b$ |
| $\alpha/\beta = 15 \text{ Gy}$ with cell status | 1.05 (0.52) | 11.4 (5.6)$^b$ |
| $\alpha/\beta = 25 \text{ Gy}$ with cell status | 1.08 (0.56) | 11.4 (5.9)$^b$ |

$^a$ Effective dose.

$^b$ Values in parentheses represent endpoint for tumor cure probability.

Fig. 5. Time dependence of dose, effective dose, and fractional cell survival (S). The calculations used the spatial average of the cumulated dose $D(r, t)$, the time-dependent expression for $S$ (Eq. I), and $D_{eff}$ (time-dependent version of Eq. A).
tional cell survival decreased to near zero and rebounded. The effective dose initially rose more rapidly than the average dose, then less rapidly, and reached a peak value before cell proliferation predominated. A negative $D_{\text{eff}}$ represented an increased number of tumor cells compared to those initially present (at $t = 0$).

The fractional cell survival was replotted on a log scale in Fig. 6 and compared to the corresponding curve for EBRT. For the parameters that reproduce the tumor regrowth curve for EBRT (i.e., tumor regrowth in 11 days), the RIT curve predicted regrowth in 15 days. To match the RIT curve to the experimental results (dashed curve), the effective dose must be divided by a factor of 1.44. If the useful effective dose up to the time for regrowth only was included, the effective dose was 11.4 Gy (see values used in Table 2). The ratios between EBRT and RIT effective doses were 1.54 ($\alpha/\beta = 15$ Gy) or 1.36 ($\alpha/\beta = 25$ Gy). These ratios are in approximate agreement with the 1.44 factor noted above.

The effective dose for tumor cure probability (fractional cell survival curve minimum and effective dose curve maximum) is considerably less than the effective dose for tumor regrowth delay and are listed in brackets in Table 2 (5.6–5.9 Gy). This difference is due to the choice of end point. There was a smaller time interval (and less physical dose deposited) to the cell survival curve minimum than to the tumor regrowth point.

The EBRT/RIT comparison of effective doses for regrowth was 7.4–8.4 Gy EBRT versus 11.4 Gy RIT (36 to 54% difference). Given the experimental uncertainty in the tumor uptake curve (11%) and the uncertainty of matching tumor growth delay curves for EBRT versus RIT (~20%), these effective dose values are consistent. This analysis appears to reconcile EBRT/RIT results to within experimental uncertainties.

### Discussion

The proposed causes for the discrepancy of EBRT/XRT efficacy will be discussed below.

**Dose Nonuniformity.** For a uniform dose deposition, tumor control is made more difficult with a heterogeneous cell response. Likewise, tumor control is more difficult with a nonuniform dose deposition compared to a uniform dose for the same average value. This may be illustrated by noting that the functional form describing cell survival is not linear in dose but exponential. The average of an exponential function of a variable is less than the average of the variable. Differences between the effective dose and the average physical dose are dependent on the magnitude of the nonuniformity and can be large. Here we calculate an efficiency factor of 0.65.

**Dose Rate.** Dose-rate corrections are dependent on the $\alpha/\beta$ ratio and the repair constant ($\mu$). Dose rates for the present model were low (<10 cGy/h average). As expected (9, 10), dose-rate corrections were small, since the half-time for repair (1.5 h) was small compared to the effective half-life of the radioactivity.

**Preferential Targeting of Rapidly Proliferating Cells.** This mechanism implies an advantage derived from correlating the larger doses with the highest cell proliferation rate. The present model does show this effect but is limited to less than 10% of the effective dose for the regrowth end point.

As pointed out above, there are several ways of expressing the dose effect of proliferation. Assuming a uniform cell status, the $D_{\text{eff}}$ decreased because it tended to increase the difference between the low- and high-dose rate regions. When cell oxygenation status was included, increased dose rates and cell losses in the most rapidly proliferating regions increased the $D_{\text{eff}}$ rate 5–8%. However, the greatest effect was on the $D_{\text{eff}}$ for tumor cure potential ($D_{\text{eff}}$ curve maximum). $D_{\text{eff}}$ decreased by approximately a factor of two by changing the end point. This loss in effect was due to the dose rate used to offset the effect of cell proliferation rate early in treatment and that portion was entirely discounted when the cell proliferation rate predominated (after the curve maximum). These estimates of the decrease in $D_{\text{eff}}$ due to cell proliferation are consistent with those presented by O’Donoghue (16). Note that the effect of preferential targeting of rapidly proliferating cells (with status included) increased $D_{\text{eff}}$ by ~24% using tumor cure potential as the end point.

**Enhanced Reoxygenation with RIT.** A reoxygenation half-time of less than ~5 days could affect fractional cell kill efficiency. However, for the present model, the impact on the effective dose calculation would be small because the surviving hypoxic and oxic fractions are approximately the same magnitude. This effect may be greater with a more aggressive therapy (i.e., higher doses) and/or a more resistant cell line, where the probability of cure is limited primarily by the initially hypoxic clonogenic cell population.

**Cell Geometric Effect.** The cell geometric effect was discussed by Humm and Cobb (20). The cell nucleus is assumed to be the target, and the activity is assumed to predominantly reside on the cell surface. This effect for the present tumor model is negligible (<2%) due to the relatively long range of the $^{131}$I particles. If a large fraction of the activity remained unbound in the interstitial spaces, as is the case here, this effect would be even more diluted (closer to unity).

**Cell Cycle Redistribution (G2 Block).** Repair and repopulation by surviving tumor cells may be an important effect for low-dose-rate radiation treatments, such as RIT. Mitchell et al. (21) demonstrated the correlation between the dose-rate that inhibited growth and the length of mitotic delay after acute radiation. Dillehay et al. (22) documented the rise of the G2+M phase under continuous low-dose-rate radiation and obtained increased cell kill when methylxanthines were used for cell cycle redistribution (unblocking the G2 phase). The enhanced cell killing observed by unblocking the G2 phase provides evidence that G2 blocking effects may be significant. For a 6 cGy/h dose rate delivered for 3 days, unblocking increased log cell kill relative to control samples by factors of 1.2 to 1.8 in a hepatoma cell line. This implies a dose efficiency factor of approximately 0.7 for continuous low-dose-rate irradiation due to the G2 block effect in a radioresistant cell line. The magnitude of this effect will vary with cell type. Since the LS174T cell line is radiosensitive and the dose rates for the present case were low (<10 cGy/h), this effect was expected to be minimal (18).

**RIT Contribution to Tumor Vascular Permeability.** The RIT contribution to increased tumor vascular permeability is included in...
the measured data, both the tumor uptake curves and the 3D activity reconstructions.

Uncertainty Analysis. Primary sources of calculational uncertainty are: (a) use of the linear-quadratic model (Eq. F) or the time-dependent linear-quadratic model (Eq. I) and the uncertainty in \(\alpha/\beta\); (b) the method of summing the 3D dose-rate distributions; and (c) the model used for calculating cell oxygenation status.

Deviations from the linear-quadratic model may be present and would encompass cell cycle redistribution effects. In addition, the assumption of exponential regrowth is probably too simplistic (23). However, keeping model parameters constant while comparing EBRT/RIT calculations minimized uncertainties. Two values of \(\alpha/\beta\) were included to demonstrate the magnitude of uncertainty generated. Tumor doubling time parameters and the value of \(\alpha\) used were correlated because they were required to reproduce the time to tumor regrowth while using values similar to those used by others (9, 10, 17, 18). The results were relatively insensitive to modest parameter variations. The uncertainty in the \(\alpha/\beta\) value had the greatest impact on the EBRT \(D_{eq}\).

The sum of the 3D dose rates may overestimate the dose-rate nonuniformity by averaging results for many tumors. The advantage of avoiding a change in geometry with a change in time was accepted with the disadvantage of broadening the range of dose rates. The shift in the dose-rate profiles from one time-integration region to the next tended to underestimate the dose-rate nonuniformity. Finally, the assumption of maximum heterogeneity for each radial increment tended to underestimate the dose-rate nonuniformity. However, the present estimates are superior to other means of estimating a nonuniform dose rate, such as a mathematical model (24), or a one-section, one-time point measurement (25).

The model used to calculate cell oxygenation status apparently underestimated the hypoxic fraction. This inference is consistent with comparisons of Krogh's model for oxygen transport to a model using measured vascular architecture (26). Both high and low vascular density regions have a greater proportion of hypoxic cells than is predicted by Krogh's cylindrical model due to the chaotic nature of the vessels (26). Although a more accurate model can be used, the effect on the present calculations would be minimal. This issue may be of greater importance at higher dose rates where probability for cure is limited by the hypoxic fraction and/or dependent on the time for reoxygenation.

Conclusions. The largest correction factors for RIT \(D_{eq}\) were energy loss (0.85), dose nonuniformity (0.65), and correlation of dose rate with cell proliferation rate (1.08 for tumor regrowth or 1.24 for tumor cure potential). We present no information on the effects of cell cycle redistribution but expect its effect to be minimal for the present case. The comparison of effective doses for RIT compared to EBRT ranged from 1.36 to 1.54, depending on the calculation assumptions. This difference is on the same order as the experimental uncertainty estimate in the tumor uptake curve (11%) and the uncertainty of matching tumor growth delay curves for RIT versus EBRT (20%).

Use of an effective dose model successfully resolved the apparent dose discrepancy between EBRT and \(^{131}\)I-labeled 17-1A antibody RIT tumor regrowth experiments using the LS174T colon cancer xenograft model.

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References

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