Can Current Models Explain the Lack of Liver Complications in Y-90 Microsphere Therapy?

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Abstract

Normal liver complications have not been observed in Y-90 microsphere therapy of hepatic tumors [selective internal radiation (SIR)], despite clinical studies reporting estimated absorbed doses to normal liver between 100 and 150 Gy.

The purpose of the study was to see whether predictions of normal tissue complication probability (NTCP) models for liver based on clinical data from external beam therapy are consistent with clinical results of SIR.

Liver NTCP was calculated using a parallel architecture model and normal liver dose-volume histograms that have been proposed for SIR. A parallel model including internal functional subunit structure is also proposed. Dose rate effects are incorporated. A criterion for comparing model calculations with clinical data is presented.

For the parallel architecture model, the predicted NTCP is sensitive to the dose distribution in normal liver and to the model parameters, particularly the repair time. With reasonable assumptions about the microsphere distribution, the parallel model with parameters deduced from external beam therapy outcome analysis is consistent with the observed lack of liver complications. Inclusion of FSU structure widens the range of assumptions under which consistency is found.

The parallel model can be consistent with the clinically observed lack of liver complications in SIR. More information about the activity distribution and the radiobiology of normal liver under conditions typical of microsphere therapy should be sought.

Introduction

Hepatic tumors present a challenge to radiation therapy because the liver is a vital yet quite radiosensitive organ. Most estimates of NTCP for the potentially fatal complication of radiation hepatitis are derived from clinical experience in fractionated external beam therapy at 1.8–2 Gy per fraction. For uniform irradiation of the whole liver, these data are consistent with a rapid rise in incidence of radiation hepatitis for doses above 30 Gy with the 50% complication dose, occurring at approximately 40 Gy. (1-9).

In external beam studies, NTCP for radiation hepatitis depends strongly on the volume of liver irradiated (10, 11). It has been estimated (4) that the 50% complication dose for uniform irradiation of one-third of the liver while the remainder receives zero dose (partial organ irradiation) is increased to 55 Gy. Recent data using DVHs from CT-based, three-dimensional conformal radiation therapy (9, 12) suggest an even stronger volume effect. Several models incorporate volume dependencies into external beam planning and allow NTCP to be calculated from DVHs. A parallel architecture model (13-16), which postulates that organ function is carried out by multicellular groupings called FSUs acting in parallel, has recently been proposed for liver.

The intra-arterial injection of microspheres impregnated with the β emitter Y-90 is an internal emitter therapy under investigation. It is sometimes called SIR. Both animal and clinical studies have been reported (17-26). Depending on the manufacturing process, the microspheres range from 18 to 32 μm in diameter and from 10 to several hundred Bq in activity. They are injected into the hepatic artery and ultimately lodge in the microvasculature of the liver and tumor, remaining for the complete decay of the Y-90. A peculiarity of hepatic circulation is exploited to deposit microspheres preferentially in the tumors, with fewer going to normal liver (27). The mean energy/disintegration of Y-90 β particles is 0.937 MeV, and the effective range in soft tissue is 8 mm. Because of the short range, the T:NT ratio is the main determinant of the therapeutic dose ratio. The T:NT ratio has been assessed by various techniques including direct biopsy (19, 20), gamma camera imaging of Tc-99m albumin microspheres (17, 24, 25), bremsstrahlung imaging (17, 24) and intraoperative dosimetry with a solid state probe (19, 24, 25). T:NT ratios ranging from 1:1 to more than 10:1 have been reported in clinical studies (17, 19, 24).

It is difficult to determine the absorbed dose to normal liver in SIR. Reported estimated liver doses frequently exceed 50 Gy (20) and may be as high as 150 Gy for a single infusion (17, 25). One clinical study reports normal liver doses of several hundred Gy cumulated over three to five infusions delivered several times. (1-9).
months apart (25). Despite these high doses, no liver complications were reported.

Most reported normal liver doses are calculated with the assumption of uniform activity distribution in the normal liver (17, 18–20, 23, 24). However, autoradiographs of normal liver tissue (21) show a nonuniform distribution of the microspheres. The activity distributions and the resulting calculated dose distributions are therefore nonuniform.

The microsphere dose distributions can be easily incorporated into NTCP calculations with the parallel model. The parallel model parameters are obtained from a recent external beam implementation (14), despite the fact that both the time and spatial dependence of irradiation in SIR and external beam differ greatly. We used these parameters partly because we believe that the same mechanisms govern radiation damage for the two situations and partly because these are the only parameters presently available. Dose rate effects for the exponentially decaying Y-90 radiation (half-life of 64 h) are incorporated using an approach developed for brachytherapy (28). We then examine the consistency of the observed lack of liver complications with the model predictions.

Materials and Methods

The factors that affect NTCP predictions for SIR are the assumed dose distribution, the model used for the calculations, and dose rate effects. Our approach to these factors and our criterion for evaluating consistency with clinical data are described below.

Normal Liver Dose Estimates Assuming Uniform Activity Distribution

In most clinical studies, it is assumed that the activity that resides in the normal liver rapidly attains a uniform distribution (i.e., uniform specific activity) and that the microspheres remain in place throughout the decay of the Y-90. The normal liver dose calculated with this assumption is denoted by D, in all following work. Two different procedures for calculating D, are used and reported in the literature.

The simplest estimates of D, assume that the total injected activity, A, is uniformly distributed over the entire liver. This is equivalent to setting the T:NT ratio to unity, despite the fact that the intra-arterial injection of Y-90 labeled microspheres is designed to preferentially target tumor microvasculature and produce a large T:NT ratio. If M is the total liver mass (including tumor), D, is given by the equation:

$$D_0 = (\ln 2)^{-1} \cdot A \cdot \frac{t_{1/2}}{M}$$

(A)

Here \(\Delta\) and \(t_{1/2}\) are the equilibrium dose constant and half-life of Y-90, respectively. \(\Delta\) is equal to 1.5 \times 10^{-13} \text{kg Gy/Bq sec} (1.99 g rad/\muCi h), and \(t_{1/2}\) = 64 h. Human liver doses up to 150 Gy as calculated from Eq. A have been reported (17).

If microsphere therapy achieves its goal of a high T:NT ratio, Eq. A overestimates the absorbed dose to normal liver. For a two-compartment model with different uniform specific activities in the normal liver and the tumor, \(D_n\) is given by the equation:

$$D_n = (\ln 2)^{-1} \cdot \Delta \cdot A_0 \cdot t_{1/2}/[(M + (r - 1) \cdot M_t)]$$

(B)

where \(M_t\) is the tumor mass, and \(r\) is the T:NT ratio. If \(r = 3\) and \(M_t/M = 0.1\), the dose to normal liver calculated with Eq. B is 83% of that predicted by Eq. A. Accounting for the mass of the tumor and the T:NT ratio reduces the estimated dose to normal liver, even if the activity is uniformly distributed within the normal liver compartment.

Direct determination of the average normal liver specific activity has been performed through the combined use of a solid state intraoperative \(\beta\) radiation detection probe and counting of biopsy samples (18, 19, 22, 25). In many of these studies, patients received estimated single infusion normal liver doses above 50 Gy.

Normal Liver DVHs

Biopsy Samples. Biopsy samples of normal liver show a nonuniform microsphere distribution. This implies a nonuniform dose distribution in the normal liver.

The microsphere distribution measured in serial autoradiographs of normal human liver samples was used to calculate the normal liver DVH shown in Fig. 1 (21). The dose contribution (in Gy) of a single microsphere of activity A (MBq) a distance \(x\) mm away is \(d(x)\). It was calculated with an approximation (29) to Berger’s (30) point source function:

$$d(x) = 989 \cdot A \cdot (1 - x/R)/x^2$$

for \(x \leq R\)

(C)

$$d(x) = 0$$

for \(x > R\).

Here \(R\), the effective range of Y-90 \(\beta\) particles, was taken as 8 mm. The total dose at any point is the sum of the contributions of all microspheres. In Fig. 1, the dose is normalized to \(D_n\), the dose with the same activity uniformly distributed. Increasing the activity per microsphere increases \(D_n\) proportionally without altering the microsphere distribution.

Computer Simulations. The microspheres in these autoradiographs were deposited in small arteries of approximate length 1 mm (21). Computer simulations of the dose distribution from such an activity distribution were performed. A chosen number of infinite linear structures (“arteries”) of equal activity per unit length were randomly positioned and oriented in a cube of 24 mm on a side. The linear activity was adjusted so that \(D_n\) for the activity contained in the cube was approximately 50 Gy.
a dose representative of medium-activity clinical studies. Eq. C was integrated to obtain the dose distribution of a line source. At each evaluation point, the dose contributions from all of the line sources were summed. To eliminate artifacts due to the finite β particle range, the evaluation points were restricted to an inner cube of 8 mm on a side. To smooth the effects of statistical fluctuations, calculations were repeated up to 100 times with different randomly chosen artery positions and orientations. These data were averaged to obtain a mean DVH. We used DVHs from simulations with 10 and 100 arteries per 24 mm cube for NTCP calculations.

**Consideration of FSU Structure.** In parallel architecture models, the function of the organ is carried out by FSUs, which act in parallel so that the loss of a significant fraction of these multicellular structures can be tolerated without complication. It has been proposed that the basic functional units of the liver are the lobules (8, 27).

The liver lobule has a roughly hexagonal cross-section that is threaded by a central vein. Measured diameters of human liver lobules range from 0.5 to 3 mm (8, 29). In external beam applications of the parallel model, it is appropriately assumed that dose variation on the length scale of an FSU is negligible. However, β emitters may produce dose gradients on a length scale comparable to that of the lobule. For Y-90, 50% of the energy of the average decay is deposited within a 2-mm-radius sphere (31). The microspheres are preferentially deposited in arteries at the periphery of the lobule (29), whereas the site of the critical radiation damage is believed to be the central vein (29, 32). It was pointed out that this reduces the dose to the central vein (29). Further protection is provided to a central vein if some of its neighboring arteries do not contain activity.

To explore the possible effect of FSU structure on predicted NTCP for the parallel model, we simulated the dose distribution at the central veins using a structured lattice model variant of the linear artery model. Instead of being randomly oriented, the activity-filled linear arteries were oriented parallel to each other. They were allowed to randomly occupy the vertices of a square lattice in a plane perpendicular to the artery direction. Unoccupied vertices represent unfilled arteries. A critical structure (e.g., a central vein) was assumed to be located at the center of each lattice square. The arteries and square lattice lie in a cube of side 24 mm, but doses were calculated only at lattice centers in the inner 8 × 8 mm to avoid finite range effects. The average dose at a central vein depends on $D_\alpha$ and the lattice spacing. This relationship is derived in the Appendix.

For each $D_\alpha$, lattice spacing, and number of filled arteries, a dose fraction of central veins histogram was generated by choosing different random occupations of the square lattice by filled arteries until the dose at 6400 lattice centers had been calculated. This histogram was used to calculate NTCP together with the parallel model as described below. Lattice spacings of 1 and 2 mm, consistent with the lobule size, and 10- and 100-artery configurations, as small and large artery density limits, were considered.

**The Parallel Architecture Model**

In the parallel architecture model, NTCP is an increasing function of the number of FSUs inactivated by radiation. The probability that a dose $D$ inactivates an FSU is $p(D)$. For a given DVH the fraction, $f$, of inactivated FSUs is the sum over the dose bins:

$$f = \sum_v p(D_v)$$

where $D_v$ and $v$ are the average dose and the volume fraction in the $i$th dose bin, respectively, and $f$ is called the fractional damage (14). The complication of radiation hepatitis does not occur unless at least a threshold fraction of the FSUs—the functional reserve—is destroyed by radiation. To fit the parallel architecture model to clinical data, expressions for both $p(D)$ and the statistical distribution of functional reserves over the patient population are required (13, 33).

In (14), the maximum likelihood method was used to obtain a four-parameter fit of the parallel architecture model to the complications and DVH data of a group of 93 patients who had received three-dimensional treatment planning for external beam treatment of hepatic tumors. They took $p(D)$ to be a logistic function:

$$p(D) = \frac{1}{1 + (D_{1/2}/D)^k}$$

Half of the FSUs are destroyed at $D_{1/2}$, and $k$ is proportional to the slope of the dose-response curve at $D_{1/2}$. A gaussian distribution of functional reserves with mean $v_{50}$ and SD ($\sigma$) was assumed. NTCP for a general DVH was calculated from the equation:

$$\text{NTCP} = \int_0^\infty \exp\left[ -\frac{(v - v_{50})^2}{2\sigma^2} \right] dy / (2\pi \sigma^2)^{1/2}$$

The mean values and the 68% confidence limits for each model parameter were presented (14). There was a strong anticorrelation between $D_{1/2}$ and $v_{50}$. These parameters, derived from external beam studies, are the only ones available for liver. Therefore, despite the spatial and temporal differences in irradiation, we will apply them to the analysis of NTCP in microsphere therapy. The mean parallel model parameters are as follows: $D_{1/2} = 41.62 \pm 3.5$ Gy; $k = 1.95 \pm 0.77$; $v_{50} = 0.497 \pm 0.043$; and $\sigma = 0.047 \pm 0.027$ (14).

For applications to the structured lattice model, for each 6400-lattice-center dose fraction of central vein histogram, Eqs. D–F and the parallel model parameters were used to calculate NTCP. The average NTCP and the standard deviations reported below are based on 10 such simulations for each value of $D_\alpha$.

**Incorporation of Dose Rate**

In Ref. 14, dose fractionation was accounted for by using the linear-quadratic model as applied to acute irradiation (34). For SIR, the dose rate decays exponentially with the half-life of Y-90. An expression for the BED corresponding to a total dose $D$ delivered by exponentially decaying radiation ($t_{1/2}$) in the presence of repair of sublethal damage with half-time $t_{rep}$ has been derived and applied to examples in brachytherapy (28), and its use was also suggested for microsphere therapy (22). We rewrite this expression in terms of the total dose and the half-times as follows:

$$\text{BED} = D \cdot (1 + \beta/\alpha) \cdot D \cdot t_{rep} (t_{1/2} + t_{rep})$$
In the parallel model, the fractional damage is the volume-weighted sum of \( p(D) \) over the dose bins (Eq. D). We evaluated \( p(D) \) in two ways: (a) physical doses were used for both the reference dose, \( d_{l/2} \), and the mean dose, \( D_v \), in each dose bin. This is equivalent to setting \( \beta \) to 0. There is no sublethal damage and therefore no dose rate effect. (b) Eq. G was used to calculate the BED corresponding to the mean dose in each dose bin of the DVH. Because \( d_{l/2} \) was calculated in Ref. 14 for a dose per fraction of 1.5 Gy using the LQ model (34), we calculate BED\(_{l/2}\) in the same way:

\[
\text{BED}_{l/2} = d_{l/2} \cdot (1 + 1.5 \cdot \beta/\alpha)
\]

The ratio of doses in the function \( p(D) \) was taken between the BED of a dose bin, calculated by Eq. G with \( D = D_v \), and BED\(_{l/2}\), calculated with Eq. H. Because BED\(_{l/2}\) is larger than \( d_{l/2} \), letting \( t_{\text{rep}} \) tend to 0 in Eq. G and applying this procedure, which is equivalent to assuming that repair is too slow to overcome sublethal damage for standard fraction external beam irradiation, predicts a lower NTCP than the use of purely physical doses.

As in Ref. 14, we took \( \beta/\alpha = 0.5 \text{ Gy}^{-1} \). Data for the repair time of liver are not available. To assess the effect of repair in the model, calculations were done for \( t_{\text{rep}} \) of 0.5, 1, and 2 h, times that are characteristic of late normal tissue complications (35). The shortest late tissue repair time of 0.55 h given in the Table 3.6 of Ref. 35 is for lung doses delivered at low dose rate.

**Consistency of Clinical Results and Model Predictions**

The models are constrained by the fact that radiation hepatitis has not been reported in clinical use of SIR. Binomial statistics were used to estimate limits on model predictions of NTCP, which are consistent with the observed lack of normal liver complications reported in Ref. 17. They present a table that includes 14 patients for whom a nominal normal liver dose, calculated according to Eq. A, exceeds 100 Gy. They give the means and standard deviations of the T:NT ratio for each patient but not the ratios of tumor to normal liver masses (\( M/T/M \)). The mean T:NT ratios ranged from 1.72 to 4.52. We assumed \( M/T \) equal to either 0.1 or 0.2 for all patients and then used Eq. B with each patient’s mean or maximum T:NT ratio (maximum = mean + SD) to calculate \( D_v \). The dose distribution in normal liver was assumed to be given by Fig. 1, and this DVH was scaled by each patient’s calculated \( D_v \). The NTCP was calculated for each patient with different combinations of parallel model parameters and \( t_{\text{rep}} \). A similar exercise was then performed with the structured lattice model.

The probability, \( P \), of observing zero complications in a group of \( v \) patients (such as that described above) with calculated NTCPs of NTCP\(_1\), NTCP\(_2\), ..., NTCP\(_v\), is approximately:

\[
P = \prod (1 - \text{NTCP}/100)
\]

We call a model inconsistent with the data if the predicted NTCPs are high enough for complications to be seen with 95% confidence (i.e., \( P < 5\% \)). We only considered single infusion trials because of problems in dealing with repair between several SIR treatments spaced months apart, such as the treatments reported in Ref. 25.

**Results**

In this section, we describe the DVHs used as input for NTCP model calculations and present the model predictions. Consistency with clinical data is then discussed.

**DVHs.** Fig. 2 shows three DVHs, all scaled so that \( D_v \) is 50 Gy. These are obtained from the 10- and 100-artery simulations and the normal liver autoradiograph data of Fig. 1. The 100-artery simulation is more nearly uniform than the other two. A large fraction of normal liver (e.g., 86% for the autoradiograph) receives a lower dose than \( D_v \). There must then be a small high-dose volume beyond the maximum of the plotted DVH. This arises from the inverse square dependence of the point source function of Eq. C, which produces very high doses to small high-dose volume beyond the maximum of the plotted DVH. This results in the inverse square dependence of the point source function of Eq. C, which produces very high doses to small volumes of tissue near a microsphere. In our calculations, this volume was assumed to receive the maximum dose in the DVH, which is much higher than \( d_{l/2} \). All of the FSUs in this volume are destroyed, resulting in the same calculated NTCP as if the “true” DVH had been used. Had the maximum DVH dose been comparable to \( d_{l/2} \), our calculations would have provided an underestimate of NTCP.

**Parallel Model.** The model results are characterized by describing the doses, \( D_v \), at which 5 and 50% NTCP are predicted. For concise notation, we will refer to these doses as \( \{D_v,5\} \) and \( \{D_v,50\} \).

To emphasize the striking effect of introducing the nonuniform dose distributions that may be typical of SIR, note that for a uniform distribution, the parallel model with the mean parameters of (14) predicts \( \{D_v,5\} \approx 35 \text{ Gy} \) and \( \{D_v,50\} \approx 41.4 \text{ Gy} \). Incorporating dose rate effects with \( t_{\text{rep}} = 1 \text{ h} \) increases these doses to 45.5 and 51.7 Gy, respectively, and with \( t_{\text{rep}} = 0.5 \text{ h} \) to 51.3 and 58.8 Gy.

Introducing the nonuniform dose distributions shifts the predicted NTCP to higher values of \( D_v \). Fig. 3 shows the parallel model prediction of NTCP as a function of \( D_v \) for the DVH of Fig. 1. The mean values of the model parameters from Ref. 14 are used for the three left-most curves and the curve labeled with \( \times \). In all cases, \( \{D_v,5\} \) and \( \{D_v,50\} \) are increased by more than 50 Gy compared to the uniform dose distribution with the same model parameters.
Fig. 3 also demonstrates significant dose rate effects for the nonuniform DVH. For calculations using physical doses (leftmost curve), \(D_{n,50} \approx 75 \text{ Gy} \) and \(D_{n,50} \approx 95 \text{ Gy} \). With long repair times \(t_{rep} = 2 \text{ h} \), equivalent complications occur at similar or even lower doses. For shorter repair times, \(t_{rep} = 1 \text{ h} \), triangles, equivalent complications are predicted at higher doses: \(D_{n,50} \approx 94 \text{ Gy} \) and \(D_{n,50} \approx 116 \text{ Gy} \). For the shortest repair time considered, \(0.5 \text{ h} \), \(D_{n,50} \approx 106 \text{ Gy} \) and \(D_{n,50} \approx 132 \text{ Gy} \) with the mean parallel model parameters.

Predicted NTCP is somewhat affected by changing the parallel model parameters within the 68% confidence limits of Ref. 14. Increasing either \(v_{50} \) or \(d_{1/2} \) fixed or \(d_{1/2} \) with \(v_{50} \) fixed makes the model liver more resistant to radiation damage, with \(v_{50} \) having a stronger effect. The correlation ellipse derived in Ref. 14 for these parameters constrains the way in which \(d_{1/2} \) and \(v_{50} \) can be changed. Varying them as the correlation allows can increase \(D_{n,50} \) and \(D_{n,50} \) by 10–15 Gy relative to the mean value curves with the same values of \(t_{rep} \). This is shown by the two curves indicated by circles in Fig. 3. For these graphs, \(d_{1/2} = 38 \text{ Gy} \), \(v_{50} = 0.558 \), and \(t_{rep} = 1 \text{ h} \) and 0.5 h were used. These values of \(d_{1/2} \) and \(v_{50} \) were found with a coarse grid search within the correlation ellipse. Decreasing \(\sigma \) (a narrower distribution of functional reserves) sharpens the model dose response (not shown). The NTCP is insensitive to \(k \), which was kept at 1.95. Below, we refer to the parameter set \(d_{1/2} = 38 \text{ Gy} \), \(v_{50} = 0.558 \), \(\sigma = 0.047 \), \(k = 1.95 \) as the best set.

To examine the effect of the DVH on the predictions of the parallel model, NTCP was calculated for the DVHs of Fig. 2 with \(D_{n} = 50 \text{ Gy} \) with the mean model parameters. For a uniform dose of that size, NTCP would exceed 50%. Both the DVH of Fig. 1 and the 10-artery DVH lead to zero predicted NTCP. The 100-artery DVH, which represents a more uniform dose distribution, results in a predicted NTCP of 62.5% for physical doses, 45.8% for \(t_{rep} = 2 \text{ h} \) and 3.2% for \(t_{rep} = 1 \text{ h} \).

**Structured Lattice Model.** The structured lattice model predicts lower NTCP than the parallel model because the target of radiation damage is spatially removed from the Y-90 activity. The average dose at a critical central structure (see Appendix) is independent of the number of arteries and decreases as the lattice separation, \(s \), increases. The average central doses (Eq. A2) are 0.83\(D_{n} \) for \(s = 1 \text{ mm} \) and 0.68\(D_{n} \) for \(s = 2 \text{ mm} \). The computer simulation demonstrates the additional protective effect of randomly distributed unfilled arteries. Some arteries contain no activity, which reduces the dose to a neighboring central structure. This effect is lost for a high density of filled arteries, as in the 100-artery case. As with the parallel model, the lowest NTCP is predicted with shorter repair times.

Fig. 4 shows the average NTCP versus \(D_{n} \) calculated with the most radiosensitive parameters in the structured lattice simulations: 10 arteries, \(s = 2 \text{ mm} \), and \(t_{rep} = 1 \text{ h} \) and 0.5 h. Results are shown for both the mean and the best parallel model parameters. For the mean parameters with \(t_{rep} = 1 \text{ h} \), \(D_{n,50} \) is between 100 Gy and 110 Gy and \(D_{n,50} \) is between approximately 140 Gy. It is notable that for mean parameters and \(t_{rep} = 0.5 \text{ h} \), and for the best parameters, \(D_{n,50} \) exceeds 150 Gy.

**Consistency of Clinical Results and Model Predictions.** The criterion described in "Materials and Methods" was used to evaluate the consistency of the models with clinical data of (17). Sixteen of the patients reported in (17) received nominal liver doses over 100 Gy. None developed radiation hepatitis. For 14 of these patients, key information was tabulated in Ref. 17, including liver volume, administered activity, the mean and SD of the T:NT ratio, and the prescribed and calculated nominal absorbed liver doses. Tumor to normal liver mass ratios were not reported; we took them to be either 0.1 or 0.2 for all of the patients. From these data, we calculated the \(P \) value of observing zero complications with Eq. 1. Consistency was defined as \(P > 5\% \). We calculated \(D_{n} \) with either Eq. A or Eq. B. We then calculated NTCP for each patient with both the parallel model (and the DVH of Fig. 1) and the 10-artery structured lattice model. The mean and best FSU parameters were used.

When \(D_{n} \) was calculated with Eq. A, no model calculations
The 10-artery structured lattice model was consistent with Ref. 17 for the combinations of model parameters, Eq. B, and the DVH of Fig. 1. A sample is shown in Table 1. The last column, $P$, is the calculated probability of no complications. The most important factors for consistency are a short repair time, a high T:NT ratio, and a larger tumor to liver mass ratio, $M/M$.

The 10-artery structured lattice model with $M/M = 0.1$, patient mean T:NT ratio, and mean parallel parameters was consistent with Ref. 17, with $t_{rep} = 1$ h ($P = 8\%$). Additionally, the 10-artery structured lattice model was consistent with Ref. 17 for the combinations of model parameters, $t_{rep}$, and T:NT (shown in Table 1 for the parallel model).

**Discussion**

To explain the observed high normal liver tolerance for Y-90 microsphere therapy, three factors must be understood and incorporated into model calculations. These are the dose distribution in normal liver, the NTCP model and its parameters, and the time scale for repair of radiation damage in the liver.

Normal liver absorbed doses calculations should not assume uniform specific activity throughout the liver, as this can lead to substantial overestimate of the normal liver dose. Using each patient’s mean T:NT ratio and Eq. B with $M/M = 0.1$ for the 14 high-dose patients of Ref. 17 reduced the calculated $D_n$ by an average of 15% compared to $D_n$ calculated from Eq. A. As a result, some implementations of the parallel model were found to be consistent with the observed lack of radiation hepatitis. Future clinical studies would be enhanced by providing information about the gross partitioning of activity between tumor and normal liver.

Different dose distributions with the same $D_n$ lead to radically different NTCP predictions. The parallel model predicts lower NTCP for more nonuniform distributions where only small volumes of tissue are at high dose, such as the autoradiograph DVH of Fig. 1 or the 10-artery simulated DVH. Tissue sample studies are needed to obtain reliable normal liver DVHs.

NTCP estimates depend critically on the model and parameters used as shown in Figs. 3 and 4. We used parallel model parameters derived from analysis of external beam data (14) partly because we believe that the same mechanisms govern radiation damage to the FSUs for Y-90 therapy and partly because they are the only ones available. Table 1 shows that for short repair times, these parameters are consistent with the data of Ref 17.

If the FSU structure separates the microspheres from a critical portion of the FSU, the normal liver may have greater resistance to short-range $\beta$ emissions. The structured lattice model is an idealized attempt to deal with this effect. It is consistent with the observed lack of complications for a wider range of parameters than the ordinary parallel model. Studies of tissue samples from livers treated with SIR and better knowledge of the nature of radiation damage to liver lobules are required to develop a more realistic structured lattice model.

The response of the normal liver to exponentially decaying radiation is an important factor in NTCP calculations for SIR. We incorporated dose rate effects using Dale’s elaboration of the linear-quadratic model (28) in which sublethal damage is exponentially repaired. The predicted NTCP is very sensitive to the repair time, $t_{rep}$. Only for short repair times ($\leq 1$ h) were our models consistent with the clinical data. To extend biologically based NTCP models to continuous radiation situations requires better knowledge of repair. Of course, if mechanisms of damage differ for SIR and external beam, models and parameters that are unconstrained by external beam data will be required.

We did not consider the Lyman model (36) in this study. Despite its wide application in external beam therapy, it is not suitable for estimating NTCP for SIR because of its sensitivity to small high-dose regions.

As additional patients receive SIR, the resulting complications and dose distribution data will be helpful in elucidating differences in liver damage mechanisms between external beam and SIR and in developing sound, radiobiologically based models for NTCP in the liver.

**Appendix**

**Average Central Dose in the Structured Lattice Model.**

Assume the activity is contained in a water equivalent, unit density cube of side $L$ meters. It is shown in Ref. 29 that complete decay of a uniformly distributed initial activity of $A_0$ Bq of Y-90 delivers a dose $D_n$, Gy if:

$$A_0 = 2.01 \times 10^{20}D_n \cdot L^3$$

(A1)

If the activity is equally divided among $N$ linear arteries, each of length $L$, the activity per artery is $A_0/N$. The arteries are randomly placed at the vertices of a square lattice containing $N_{int}$ points. Some lattice points are occupied, others empty. The dose at a distance $x$ from the center of a line source of unit activity is $g(x)$. The average dose at the midpoint, $r_0$, of a lattice square, is estimated by assuming that each lattice point, $r_i$, is occupied by a linear source, calculating its dose contribution to the midpoint of the central square in the lattice, $A_0 g(|r_0 - r_i|)/N$, and weighting this dose contribution by the probability of occupation of a lattice point, $N/N_{int}$. The average dose at the midpoint is the sum over all of the lattice points:

$$D = \sum (A_0/N) \cdot (N/N_{int}) \cdot g(|r_0 - r_i|)$$

$$= \sum [2.01 \times 10^{20}D_n/L^3/N_{int}] \cdot g(|r_0 - r_i|)$$

(A2)

The average dose is independent of the number of arteries because the activity per linear artery (thus the dose contribution per line source) is proportional to $1/N$, whereas the occupation probability is proportional to $N$. 

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**Table 1** Conditions under which the parallel model is consistent with clinical data

<table>
<thead>
<tr>
<th>$M/M$</th>
<th>T:NT</th>
<th>Parallel parameters</th>
<th>$t_{rep}$ (h)</th>
<th>$P$ (%)</th>
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</thead>
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<td>Patient mean</td>
<td>Mean</td>
<td>0.5</td>
<td>7.7</td>
</tr>
<tr>
<td>0.1</td>
<td>Patient mean</td>
<td>Best</td>
<td>0.5</td>
<td>42</td>
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$P$ is the calculated probability of no instances of radiation hepatitis.
References
Can Current Models Explain the Lack of Liver Complications in Y-90 Microsphere Therapy?

Ellen D. Yorke, Andrew Jackson, Richard A. Fox, et al.

*Clin Cancer Res* 1999;5:3024s-3030s.

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