Supplement A

Logistic, log-logistic and probit functions

Dose-response is assumed to follow the sigmoid shape. The term dose is used here broadly as a dose-related quantity which demonstrates predictive power for an endpoint of interest. For example, the probability of normal tissue complications, P, may be a function of a mean or maximum dose, or, it can be plotted as a function equivalent uniform dose (EUD). However, incidence of complications can be plotted as a function of V_D, volume receiving at least dose D. The underlying assumption is that this dependence follows a sigmoid shape and there are multiple functions describe this shape. Popular choices are logistic, log-logistic and probit functions (14). For any arbitrary parameter X the shape of the function is governed by model parameters X_{50}, the value at which 50% of patients show response, for example complications, and γ_{50}, normalized slope, which is percent change in response per 1% percent change in parameter value at 50% incidence. In our analysis, incidence of radiation pneumonitis was analyzed as a logistic function of mean lung dose (MLD), and parameter values were D_{50}=6.06 Gy, and γ_{50}=1.19. This means that at MLD=6.06 Gy the model predicts 50% of patients to show complications, and for 1% (0.0606 Gy) change in MLD around 6.06 Gy it predicts the incidence of complications to change by 1.19%.

Commonly used logistic function is:

$$P = \frac{1}{1 + \exp\left[-4\gamma_{50}\left(\frac{X}{X_{50}} - 1\right)\right]}$$

Log-logistic function is:

$$P = \frac{1}{1 + \left(\frac{X_{50}}{X}\right)^{4\gamma_{50}}}$$

Probit function, which is connected to the standard normal distribution, is the foundation of the popular Lyman-Kutcher-Burman (LKB) model (20, 21). The probability of complications as a function of the parameter X:

$$P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{u^2}{2}\right) du$$

where

$$t = (X - X_{50})/mX_{50}$$

Because the error function is readily available in most compilers and spreadsheets it is convenient to recast this function as:

$$P = 0.5 + 0.5\,\mathrm{erf}(r)$$

$$r = t/\sqrt{2}$$

Parameter m governs the slope and is connected to the normalized slope as:

$$\gamma_{50} = \frac{1}{m\sqrt{2\pi}}$$

While these three function follow the sigmoid shape, they do not fall on top of each other. Figure A1 shows these three functions with MLD_{50} and γ_{50} set to values obtain in this paper for the logistic model. Model predictions match at MLD_{50} and diverge at other MLD values. When model fitting is performed the data are mostly concentrated at low probability if it is normal tissue response, or typically high probability for tumor control. If these model are made to fit the data, they will agree in the region defined by the data, and model projections will diverge away from this region. Consequently, each of these models will have own MLD_{50} and γ_{50}.

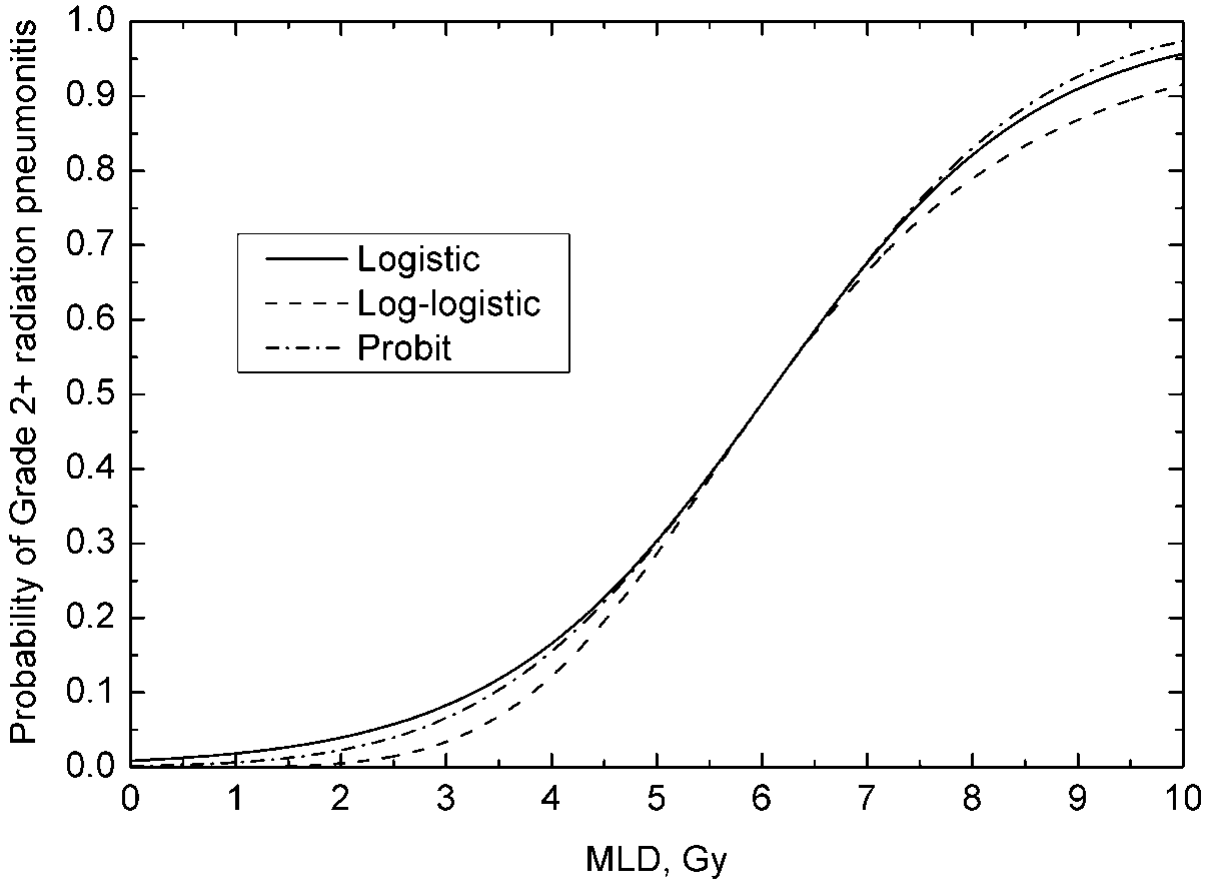


Figure S1. Logistic, log-logistic and probit functions matched on model parameter values, MLD_{50}=6.06 Gy and γ_{50}=1.19.

Supplement B

Relationship between logistic regression and dose-response curves in TCP/NTCP modeling

In logistic regression, the probability P of an event caused by some variables $X=\{x_1,\ldots, x_n\}$ is given by logistic function

$$P(X|\beta) = \frac{1}{1+e^{-\beta_0-\beta_1 \cdot x_1 - \cdots - \beta_n \cdot x_n}} \qquad \text{(Eq. A1)}$$

with the given model parameters $\beta = \{\beta_0, \ldots, \beta_n\}$. This allows consideration of additional factors, not just dose.

For cases of dose-response analysis of RT data where radiation dose is the only considered variable, the relationship between some aspect of the dose distribution and the outcome has often been written as (2):

$$P(D|D_{50,}\gamma_{50}) = \frac{1}{1+e^{4\gamma_{50}\cdot(1-\frac{D}{D_{50}})}} \qquad \text{(Eq. A2)}$$

where D_{50} is the dose required for 50% probability of response and the γ_{50} is the normalized slope. The relationships between the model parameters are:

$$\begin{cases} \gamma_{50} = -\frac{\beta_0}{4} \\ D_{50} = -\frac{\beta_0}{\beta_1} \end{cases} \qquad \text{(Eq. A3a,b)}$$

and equivalently:

$$\begin{cases} \beta_0 = -4\gamma_{50} \\ \beta_1 = \frac{4\gamma_{50}}{D_{50}} \end{cases} \qquad \text{(Eq. A4a,b)}$$

Because the range of values of the logistic curve lies between zero and one, it is suitable to describe the probability of binary outcomes, such as the absence or presence of G2+ RP.

To statistically investigate the potential impact of a predictor of the outcome, the likelihood function *L*

$$L(D_{50}, \gamma_{50}|D_{i,j}) = \prod_{i=1}^{r} P(D_i|D_{50}, \gamma_{50}) \times \prod_{j=r+1}^{n} (1 - P(D_j|D_{50}, \gamma_{50}))$$

is used. Here, the D_i are the doses for the r patients showing toxicity and D_j are the doses for the n-r patients not showing toxicity. The binary endpoint value for each patient is implicitly included by the use of either P or 1-P in the expression above. A visualization of *L* is shown in Figure S2.

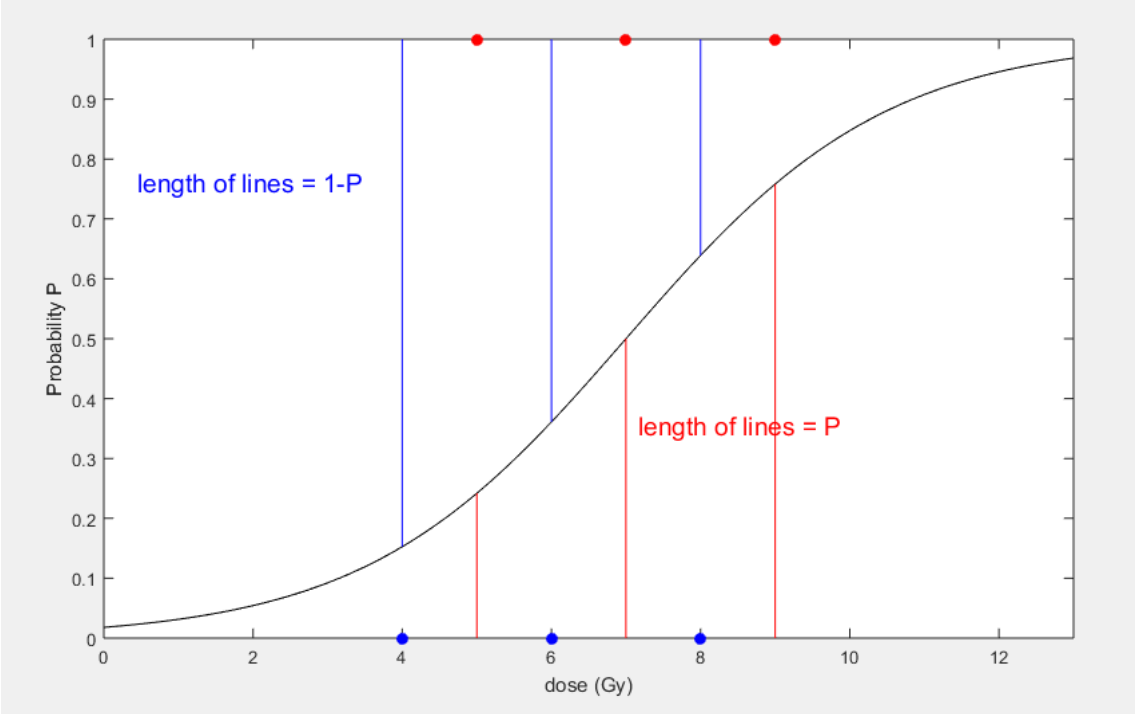


Figure S2. Visual depiction on how to get the likelihood function value from the dose-response curve values P for three patients with and three patients without the outcome. The function value is the product of the length of all red and blue lines. The patients with the outcome in red are pulling the curve upwards and are balanced by the patients without the outcome in blue pulling it downwards.

The parameter combination (D_{50}, γ_{50}) that maximizes the value of *L* best describes the observed outcome. This method is called maximum likelihood estimation (MLE). For computational reasons the log-likelihood function *LL*:

$$LL\left(D_{50},\gamma_{50}\middle|D_{i,j}\right)=\sum_{i=1}^{r}\ln\left(P(D_i|D_{50},\gamma_{50})\right)+\sum_{j=r+1}^{n}\ln\left(1-P\left(D_j|D_{50},\gamma_{50}\right)\right) \quad \text{(Eq. A5)}$$

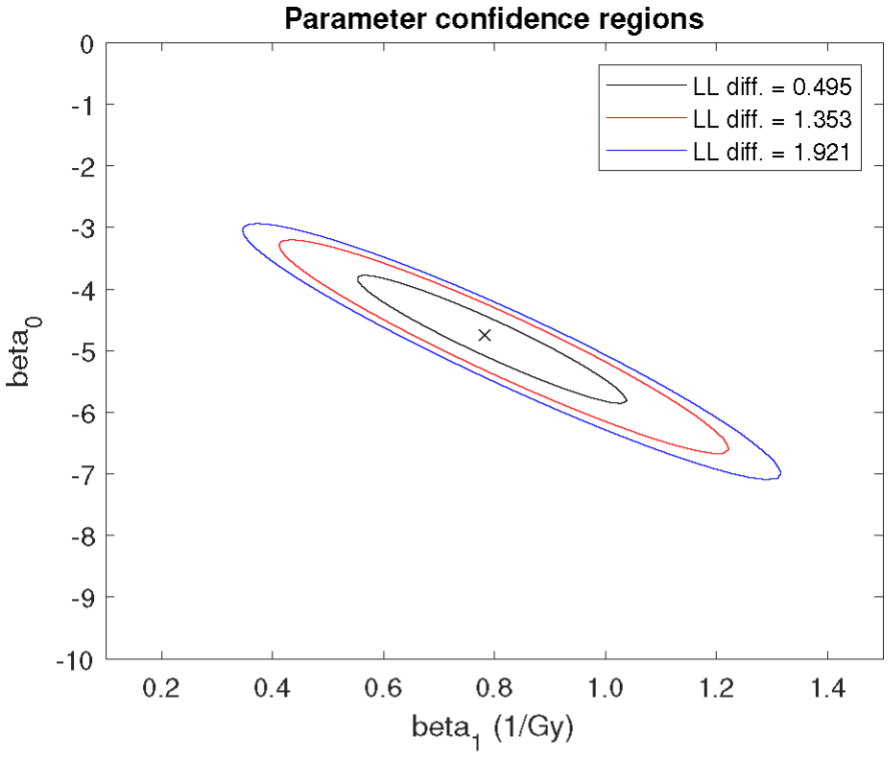
is used instead of *L*. If outcome data are given in the form of stratified data Eq. A5 can be expressed as

$$LL\left(D_{50},\gamma_{50}\middle|D_{k,}\,r_{k,,}n_{k,,}\right)=\sum_{i=1}^{k}\mathrm{r_k}\cdot\ln\left(P(D_k|D_{50},\gamma_{50})\right)+(\mathrm{n_k}-\mathrm{r_k})\cdot\ln\left(1-P(D_k|D_{50},\gamma_{50})\right)$$

(Eq. A6)

where r_k and n_k are the number of responders and total subjects, respectively, at level k.

Finding the optimal parameters according to MLE is an optimization problem that can be solved in statistical software. It is however illustrative to calculate the LL values on a grid of parameter combination values to visualize the *LL* surface. See Figure S3.


Parameter confidence regions
LL diff. = 0.495
LL diff. = 1.353
LL diff. = 1.921
beta0
beta1 (1/Gy)
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
0.2
0.4
0.6
0.8
1.0
1.2
1.4

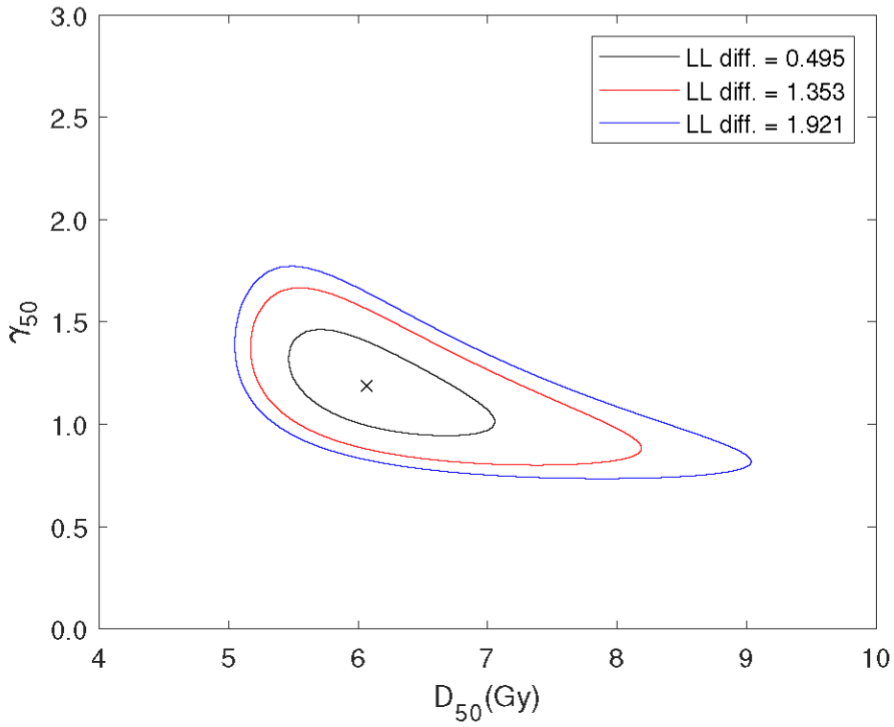

LL diff. = 0.495
LL diff. = 1.353
LL diff. = 1.921
γ50
D50(Gy)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4
5
6
7
8
9
10

Figure S3. Iso-LL contours for the investigated dataset. Maximum likelihood parameters are shown as black x. Upper panel shows iso-LL contours for β_0 and β_1, lower panel for D_{50} and γ_{50}.

The shapes of iso-LL contours for β_0 and β_1 in a projected plan of the *LL* surface are ellipsis (Figure S3, top panel). This ellipsis is transformed by Equation A3a, b to the corresponding isocontour for (D_{50}, γ_{50}). The banana shape, Figure S3, lower panel, originates from the fact that D_{50} is proportional to 1/ β_1 (Eq. A3b).

Supplement C

Bootstrapping

When we analyze the data and build a model for dose- response we base the data we have at our disposal are for a sample of patients. What we really want to know is dose- response for whole population. This is handled by calculating confidence intervals which show, at a certain confidence level (probability), the interval into which the population-based values will fall. There are well-established methods to calculate confidence intervals (CIs) and confidence regions for the estimated parameters. Profile-likelihood method was described above. However, propagating parameter value uncertainties into dose-response curve uncertainty is not trivial. One commonly used method to estimate this uncertainty is bootstrapping. The finite patient dataset we used for our dose-response modeling can be considered a sample from a hypothetical patient population for which we would like to know the dose-response. For the question at hand, we would like to know how the dose-response curve from our studied sample compares to the true population dose-response curve. To empirically estimate this, we consider our sample as the total population and create many new datasets, of the same size as our original, by sampling with replacement. For example, in this paper sample size was 96 patients. Each bootstrap sample consisted of 96 patients. When constructing a bootstrap sample one patient at a time is selected randomly from the original cohort and is replaced back into the cohort remaining available for sampling. This means that in a bootstrap sample some patients from the original cohort can be sampled two, three or even more times, and some not at all. Dose-response parameters and curve obtained for this bootstrap sample will be different from those obtained for the original cohort. To establish CI the process has to be repeated many time. In the example dataset in this paper, 2000 bootstrap samples were used. For each of 2000 bootstrap samples, the model parameter combination (D_{50}, γ_{50}) was estimated by MLE. There are now 2000 corresponding dose-response curves and its 95% CI is formed by excluding the most extreme 2.5% of the values in each direction at each dose level.