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Title: Graphical Representation of the Effects on Tumor and OAR for Determining the Appropriate Fractionation Regimen in Radiation Therapy Planning

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Abstract

Purpose: We propose a graphical representation of the relation between the effect on the tumor and the damage effect on an organ at risk (OAR) against the irradiation dose, as an aid for choosing an appropriate fractionation regimen.

Methods: The graphical relation is depicted by the radiation effect on the tumor E_1 versus that on an OAR E_0. By observing the features of the E_1 vs. E_0 relation curve, i.e. convex or concave shape, one can judge whether multi-fractionation is better or not. This method is applied to the linear-quadratic model (with α and β parameters) as an example. Further, the method is extended to the general case for non-uniform dose distribution to the OAR, which is frequently seen in clinical situations.

Results: The criterion for selecting multi- or hypo- fractionation is based on the relation between the dose for the OAR and the α/β ratio of the OAR to the tumor. It is also shown that the graphical relation enables us to estimate the final effect after multi-fractionated treatment by plotting a tangent line on the curve.

Conclusions: The graphical representation method is of use for improving planning in radiotherapy by determining the effective fractionation scheme.

Keywords: radiation therapy, radiation effect, dose fractionation, organ at risk,
linear-quadratic model

Introduction

Conventional fractionated radiotherapy typically delivers 60 to 70 Gy in approximately 30 fractions (1.8 to 2.0 Gy per day) for curative treatment. Various altered fractionation regimens have been proposed to improve tumor control without increasing late toxicity to normal tissue (1-3). The superiority of hypo-fractionated radiotherapy for certain situations, which delivers higher radiation dose in a smaller number of fractions, has been especially emphasized in the era of high precision radiotherapy. Many clinical studies have attempted to determine which fractionation regimen would be better in terms of tumor local control and normal tissue toxicity based on randomized trials (4-7).

As an alternative approach, a mathematical evaluation method provides an explicit criterion for deciding which fractionation regimen should be selected (8-10). Traditionally, the multi-target model, introduced in the 1950s (11,12), and its improved model has been used for approximation of radiation response, particularly in high fractional dose treatments (13). The linear-quadratic (LQ) model was introduced in the 1960s and is widely accepted in the regimen of radiotherapy. The LQ model has been successfully applied in clinical situation to calculate biologically effective dose (BED), which gives the same effect on the tumor or organ at risk (OAR) regardless of the fractionation regimens (14-16). It is pointed out, however, that the LQ model may overestimate the biological effect at a high dose per fraction in regard to hypofractionation (17, 18). The universal survival curve (USC), which combines the LQ model in the low dose range with the multi-target model in the high dose range, has been introduced to provide better fit to various experimental data over wide range of doses (19, 20).

Recently, the authors have proposed a simple mathematical method to compare conventional multi-fractionated irradiation and hypo-fractionated irradiation based on the LQ model in terms of minimizing radiation damage to an organ at risk (OAR) while the effect to the tumor tissue is fixed (21). We derived the conclusion that multi-fractionated irradiation

with a constant dose is better when the ratio of α/βs for the OAR and the tumor was less than the ratio of doses to the OAR and the tumor (dose ratio; δ), whereas hypo-fractionated irradiation is better when the ratio of α/βs is greater than δ. Our approach seems to have potential capability to evaluate optimal fractionation regimens although some limitations still remain.

In this study, our previous model is extended so that the incidence of adverse reaction in the OAR and the local control of the tumor can be investigated without assuming the LQ model. A graphical representation is introduced to determine the relation between radiation effects on the tumor and the OAR for selecting the appropriate treatment regimen, i.e., hypo-fractionation or conventional multi-fractionated irradiation. Furthermore, the model is generalized to consider non-uniform dose distribution within the OAR.

Method

Many models for damage effects on living cells in radiation exposure have been reported besides the LQ model currently used in radiation therapy (e.g. universal survival curve (19)). The essential point in radiation therapy is to sterilize the tumor to a requisite level while normal tissues or OARs are preserved intact as much as possible. The radiation effects on the tumor and OARs are in trade-off.

In the present method, we assume that the damage effect on bio-tissues after radiation exposure is accumulated for multi-fractionated irradiations. Although the method does not depend on the model, here we deal with the LQ model as an example for simplicity. The parameters used in the LQ model are α_1, β_1 for the tumor and α_0, β_0 for the OAR.

Uniform dose distribution model

First, let us postulate that the tumor and OAR are irradiated uniformly, where the dose to

the tumor (target dose) is d [Gy] and the dose to the OAR is δd [Gy] with a constant proportionality factor δ. By defining the surviving fractions (SFs) for the tumor $S_1(d)$ and for the OAR $S_{0,\delta}(d)$, we have the effects on both tissues as $E_1(d)=-\ln S_1(d)$ and $E_0(d)=-\ln S_{0,\delta}(d)$, respectively. In the LQ model, the following formulas are provided.

$$S_1(d) = e^{-(\alpha_1 d+\beta_1 d^2)} \tag{1a}$$

$$S_{0,\delta}(d) = e^{-[\alpha_0(\delta d)+\beta_0(\delta d)^2]} \tag{1b}$$

$$E_1(d) = \alpha_1 d + \beta_1 d^2 \tag{2a}$$

$$E_0(d) = \alpha_0(\delta d) + \beta_0(\delta d)^2 \tag{2b}$$

Regarding d as an intermediate parameter, the relations between S_1 and $S_{0,\delta}$, and E_1 and E_0 are illustrated as Fig. 1 and Fig. 2, respectively. Hereafter, we refer to the plot for the relation between E_1 and E_0 in Fig. 2 as the "TO plot" (the effects on Tumor and OAR).

Next, the N-time multi-fractionation is considered with d_1, d_2, ..., d_N fractionated doses. The SFs for the tumor and OAR after irradiation are given by,

$$S_1(d_1,\ldots,d_N) = \prod_{i=1}^{N} S_1(d_i) \tag{3a}$$

$$S_{0,\delta}(d_1,\ldots,d_N) = \prod_{i=1}^{N} S_{0,\delta}(d_i), \tag{3b}$$

and the effects are

$$E_1(d_1,\ldots,d_N) = -\ln \prod_{i=1}^{N} S_1(d_i) \tag{4a}$$

$$E_0(d_1,\ldots,d_N) = -\ln \prod_{i=1}^{N} S_{0,\delta}(d_i). \tag{4b}$$

The relation between E_1 and E_0 is more specifically represented by a vector operation as,

$$\big(E_1(d_1,\ldots,d_N), E_0(d_1,\ldots,d_N)\big) = \sum_{i=1}^{N} \big(E_1(d_i), E_0(d_i)\big). \tag{5}$$

This expression implies that the logarithmic SFs for tumor and OAR are the summations of the damage effect for every irradiation fraction. Particularly, if the dose for every irradiation fraction is constant as d, the next equation is obtained.

$$\left(E_1(d,\ldots,d), E_0(d,\ldots,d)\right) = N\left(E_1(d), E_0(d)\right) \qquad (6)$$

When we consider the therapy in which the effect on the tumor is fixed (e.g., as –ln0.05=2.995732), it would be more favorable that the effect on the OAR is as low as possible. For a single irradiation, we can look up the damage effect for the OAR immediately from the curve in Fig. 1 or Fig. 2. On the contrary, for multi-fractionation, the damage effect on the OAR can be determined by extending the straight line that connects the origin (0, 0) and ($E_1(d)$, $E_0(d)$) to N-fold length from the origin in Fig. 2. As an example, the damage effects on the OAR with *2*- and *10*-fractionations for the case of δ=0.8 are illustrated in Fig. 3. In this case, *10*-time fractionation is better than *2*-time fractionation for mitigating the damage effect on the OAR.

Non-uniform dose distribution model

In the previous subsection, the model for a uniform irradiation to the tumor and OAR was treated. However, in the actual situation in radiotherapy, the dose delivered is non-uniform. Particularly, the local dose to the OAR depends on the position, even if the dose to the tumor is almost uniform by the IMRT (Intensity Modulated Radiation Therapy) procedure. In this subsection, we consider the case of non-uniform dose with the OAR but uniform with the tumor (we can deal with non-uniform dose with the tumor if necessary). For taking account of the variation of the dose for the OAR, we introduce a density probability function $f(\delta)$ as a function of the proportionality factor δ. This function is equivalent to the differential of DVH (of OAR) and satisfies

$$\int_0^\infty f_0(\delta)d\delta = 1, \quad f_0(\delta) \geq 0\,. \qquad (7)$$

First, a single irradiation is assumed for the target (tumor) dose of d as a uniform irradiation. Contrary, a non-uniform dose for the OAR is taken into account by allocating a uniform dose to each functional subunit (FSU) of the OAR (2). The averaged surviving

fraction over the whole FSU of the OAR is expressed with the proportionality factor δ by

$$S_0(d) = \int_0^\infty S_{0,\delta}(d)\, f_0(\delta) d\delta \qquad (8)$$

and the averaged damage effect is

$$E_0(d) = -\ln S_0(d) = -\ln \int_0^\infty S_{0,\delta}(d)\, f_0(\delta) d\delta . \qquad (9)$$

The relation between $S_0(d)$ and $S_1(d)$ can be graphically described (i.e., with the TO plot) in the same manner as in Fig. 2, and the relation between the effects, $E_0(d)$ and $E_1(d)$, holds as well.

Next, we consider a N-time irradiation with target (tumor) dose, $d_1,d_2,...,d_N$, and pay attention to a FSU of the OAR at a relative dose with the proportionality factor δ. The surviving fraction of the entire OAR after the N-time irradiation is given by

$$S_{0,\delta}(d_1,..., d_N) = \int_0^\infty \prod_{i=1}^N S_{0,\delta}(d_i)\, f_0(\delta) d\delta . \qquad (10)$$

Thus, the damage effect on the OAR becomes

$$E_0(d_1,..., d_N) = -\ln S_{0,\delta}(d_1,..., d_N) = -\ln \int_0^\infty \prod_{i=1}^N S_{0,\delta}(d_i)\, f_0(\delta) d\delta , \qquad (11)$$

while the effect on the tumor is as follows,

$$E_1(d_1,..., d_N) = -\ln S_1(d_1,..., d_N) = -\ln \prod_{i=1}^N S_1(d_i) = -\sum_{i=1}^N \ln S_1(d_i) = \sum_{i=1}^N E_1(d_i) . \qquad (12)$$

As an example, let us treat the case of the TO plot ($E_1(d)$, $E_0(d)$) to have a convex shape with the effect on the tumor being –ln0.05. If a single dose to the tumor is $d^{(1)}$ (i.e., $E_1(d^{(1)})$=–ln0.05), the same effect on the tumor by the N-time dose is formulated as $\sum_{i=1}^N E_1(d_i) = -\ln 0.05$. Since $\sum_{i=1}^N E_1(d_i) = E_1(d^{(1)})$ and ($E_1(d)$, $E_0(d)$) have convex shape, we find that the relation of $\sum_{i=1}^N E_0(d_i) \le E_0(d^{(1)})$ holds by comparing ($E_1(d^{(1)})$, $E_0(d^{(1)})$) with $\left(\sum_{i=1}^N E_1(d_i), \sum_{i=1}^N E_0(d_i)\right)$. That is,

$$\int_0^\infty \prod_{i=1}^N S_{0,\delta}(d_i)\, f_0(\delta) d\delta \ge \prod_{i=1}^N \int_0^\infty S_{0,\delta}(d_i)\, f_0(\delta) d\delta \qquad (13a)$$

or

$$E_0(d_1,...,d_N) = -\ln \int_0^\infty \prod_{i=1}^N S_{0,\delta}(d_i) f_0(\delta) d\delta \le -\sum_{i=1}^N \ln \int_0^\infty S_{0,\delta}(d_i) f_0(\delta) d\delta = \sum_{i=1}^N E_0(d_i) \le E_0(d^{(1)}) \tag{13b}$$

is obtained. The latter relation implies that the multi-irradiation treatment decreases the damage effect on the OAR compared to a single irradiation.

Results and Discussion

The present method can be applied to other surviving fraction models that are not necessarily in analytical form. If the relation curve E_1 vs. E_0 exhibits a concave shape, a multi-fractionated treatment is better, while if the curve has a convex shape, a hypo-fractionated treatment is better. It is interpreted that the tangential line of the curve at d=0 provides the damage effect for the infinite-time fractionation case.

This graphical method was applied to the multi-fractionation regimen with the LQ model. In the LQ model, the surviving fractions are given by

$$S_1(d_1,...,d_N) = e^{-\sum_{i=1}^N (\alpha_1 d_i + \beta_1 d_i^2)} \tag{14a}$$

$$S_{0,\delta}(d_1,...,d_N) = e^{-\sum_{i=1}^N [\alpha_0 (\delta d_i) + \beta_0 (\delta d_i)^2]}, \tag{14b}$$

and the effects are

$$E_1(d_1,...,d_N) = -\ln \prod_{i=1}^N S_1(d_i) = \sum_{i=1}^N (\alpha_1 d_i + \beta_1 d_i^2) \tag{15a}$$

$$E_0(d_1,...,d_N) = -\ln \prod_{i=1}^N S_{0,\delta}(d_i) = \sum_{i=1}^N [\alpha_0 (\delta d_i) + \beta_0 (\delta d_i)^2]. \tag{15b}$$

For an N fractionation, the damage effect on the OAR can be determined by extending the straight line that connects the origin (0, 0) and ($E_1(d)$, $E_0(d)$) to N-fold length from the origin. In Figs. 4 and 5, the lines for the cases of 1-10 irradiation fractionations in the LQ model (with α_0=0.04, β_0=0.02, α_1=0.05, β_1=0.005) are presented. Here, Fig. 4 is for δ=0.8 and Fig. 5 is for δ=0.1; that is, Fig. 4 represents a more damaging case for the OAR than Fig. 5. The

lines described in the figures indicate that a larger fractionation number is better with the case (Fig. 4), while a single irradiation raises the minimum damage effect on the OAR (Fig. 5). In general, we can say that if the TO plot has a concave shape, multi-fractionation is better, while a single exposure is better otherwise.

Now, let us derive the condition criterion. By using Eqs.2(a)(b), the relations

$$\frac{dE_0}{dE_1} = \frac{dE_0}{dd}\frac{1}{\frac{dE_1}{dd}} = \frac{\alpha_0\delta + 2\beta_0\delta^2 d}{\alpha_1 + 2\beta_1 d} \tag{16}$$

and

$$\frac{d}{dE_1}\left(\frac{dE_0}{dE_1}\right) = \frac{d}{dd}\left(\frac{dE_0}{dE_1}\right)\frac{1}{\frac{dE_1}{dd}} = \frac{2\alpha_1\beta_0\delta\left(\delta - \frac{\alpha_0/\beta_0}{\alpha_1/\beta_1}\right)}{(\alpha_1 + 2\beta_1 d)^2} \times \frac{1}{\alpha_1 + 2\beta_1 d} = \frac{2\alpha_1\beta_0\delta\left(\delta - \frac{\alpha_0/\beta_0}{\alpha_1/\beta_1}\right)}{(\alpha_1 + 2\beta_1 d)^3} \tag{17}$$

can be obtained. Therefore, a general rule is given as follows:

(i) if $\frac{\alpha_0/\beta_0}{\alpha_1/\beta_1} < \delta$, the TO plot has convex shape

(ii) if $\frac{\alpha_0/\beta_0}{\alpha_1/\beta_1} \geq \delta$, the TO plot has concave shape.

This simple rule is consistent with our previous study (17). It was shown that a multi-fractionated irradiation with a constant dose is better when the ratio of α/β values for the OAR and tumor is less than δ(ratio of dose to the OAR and the tumor), while hypo-fractionation irradiation is appropriate when the ratio is greater than δ.

The graphical method used here is applicable to other surviving fraction models, such as universal survival curve (19) that can describe a surviving fraction properly even at a higher dose region (with a linear shape).

Conclusion

In this paper, we have proposed a graphical method pertaining to the effect on the tumor (E_1) versus the damage effect on the OAR (E_0), and showed that the method is useful for planning radiation therapy. This graphical method is based on the cell surviving (or damage effect) model. However, we can apply this method to any model for multi-fractionation regimen, if the radiation effect occurs independently at each dose in multiple irradiations. It was shown that one can determine whether multi-fractionation is better or not by observing the relation curve E_1 vs. E_0. The relation curve also enables us to estimate the final effect after the multi-fractionated treatment by plotting a tangent line on the curve. Further, the extended method to the case of non-uniform irradiation to an OAR was presented, and the validity of fractionated treatment was discussed.

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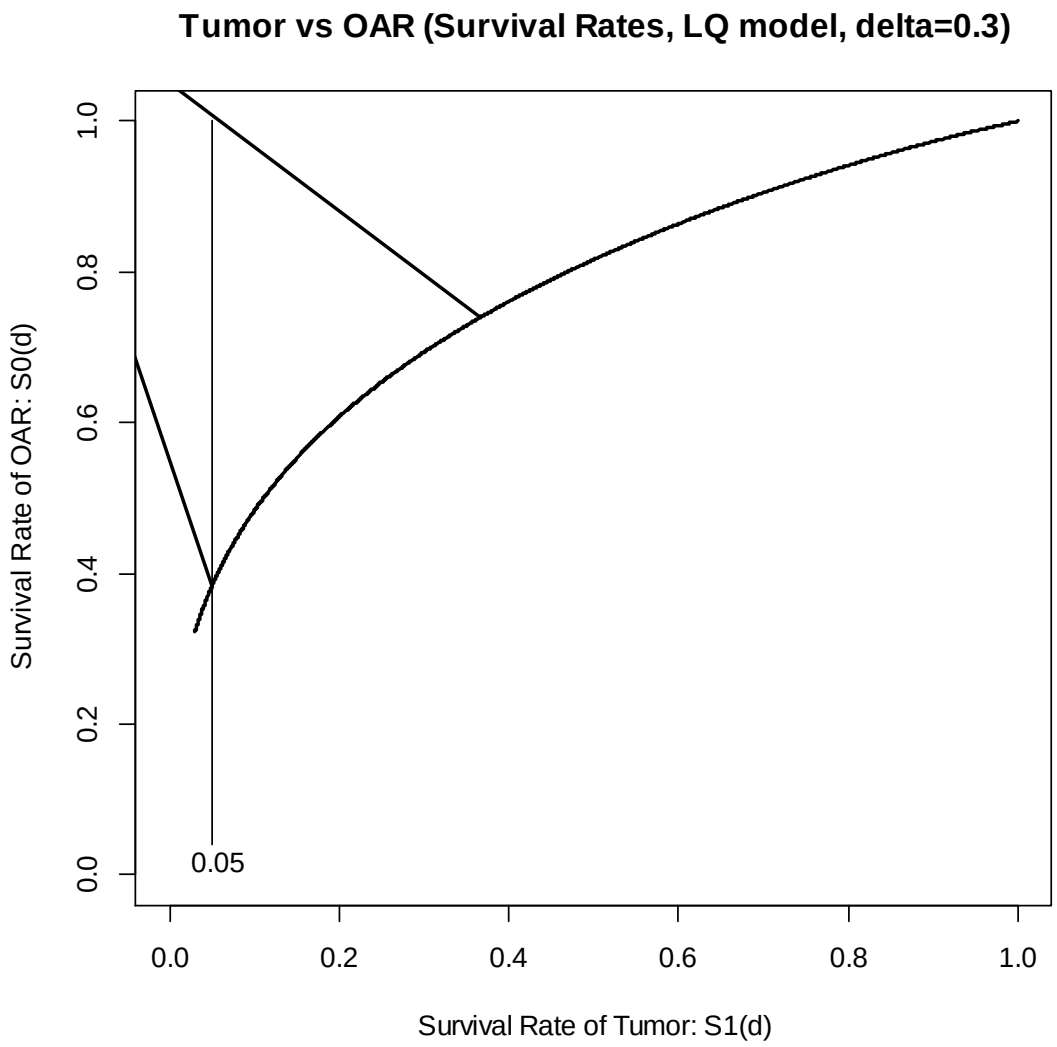

Fig. 1 Graphical representation of the relation between surviving fraction for the tumor S_1 and that for the OAR S_0 .

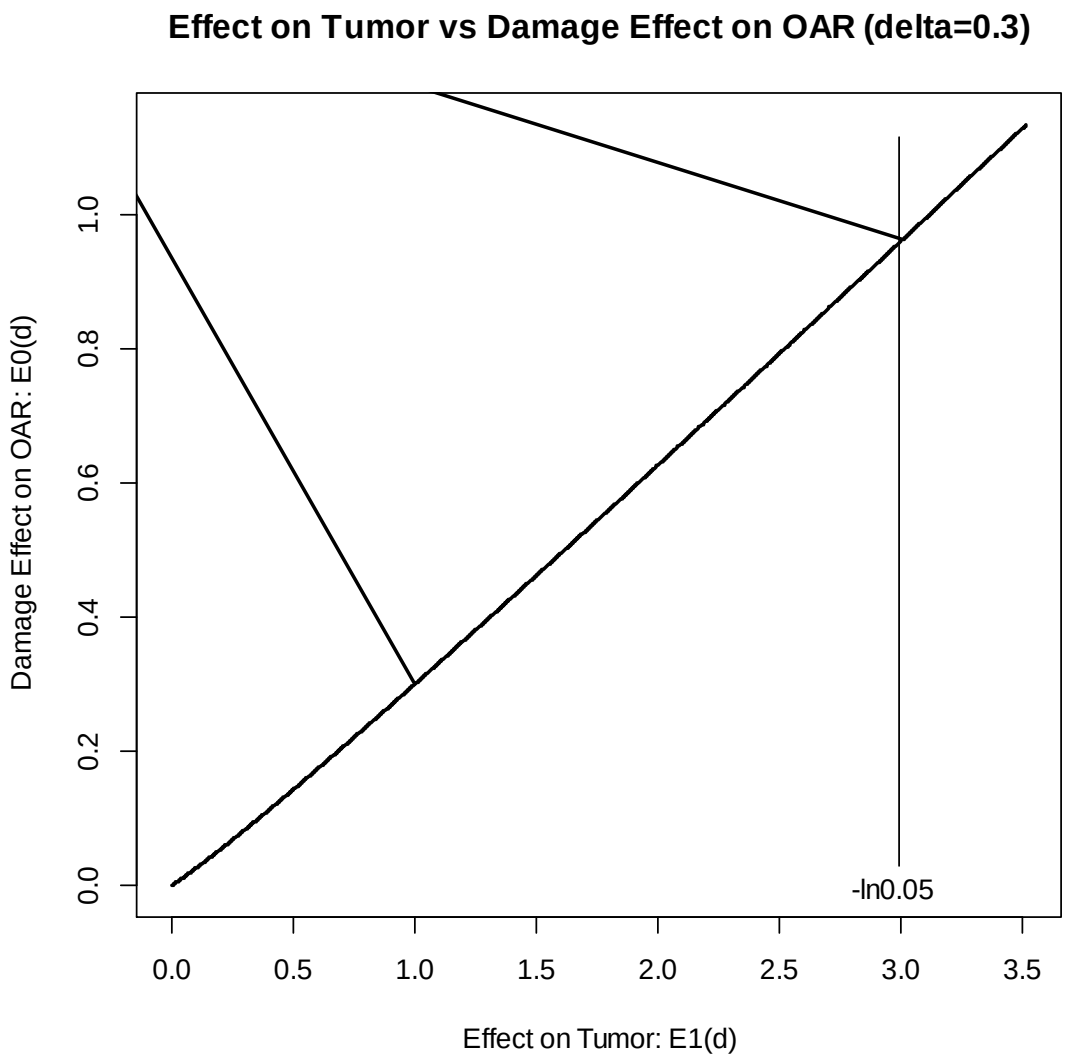

Fig. 2 Graphical representation of the relation between effect on the tumor E_1 and that on the OAR E_0 (TO plot).

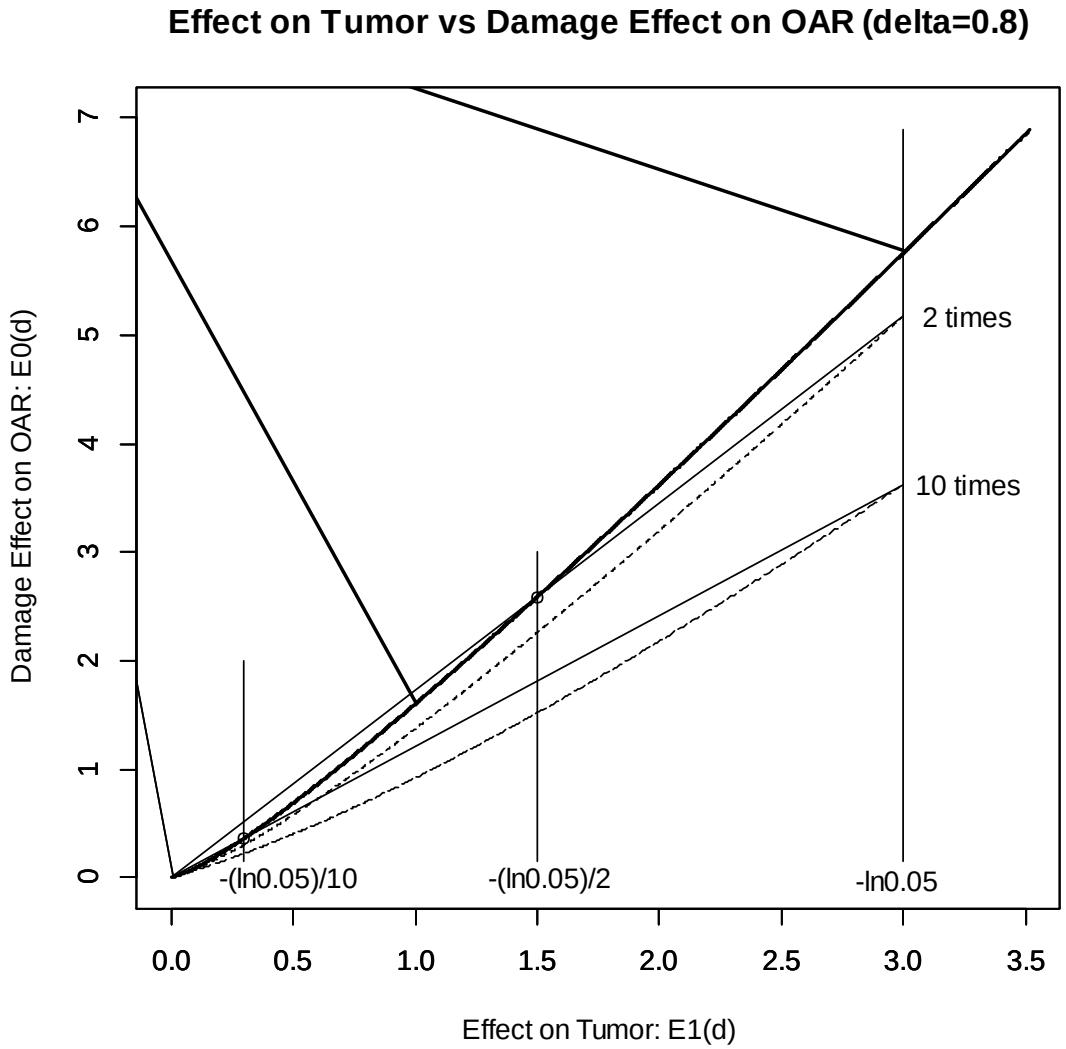

Fig. 3 The damage effects on the OAR with *2*- and *10*-fractionated irradiations, derived graphically using the TO plot with eq.(6).

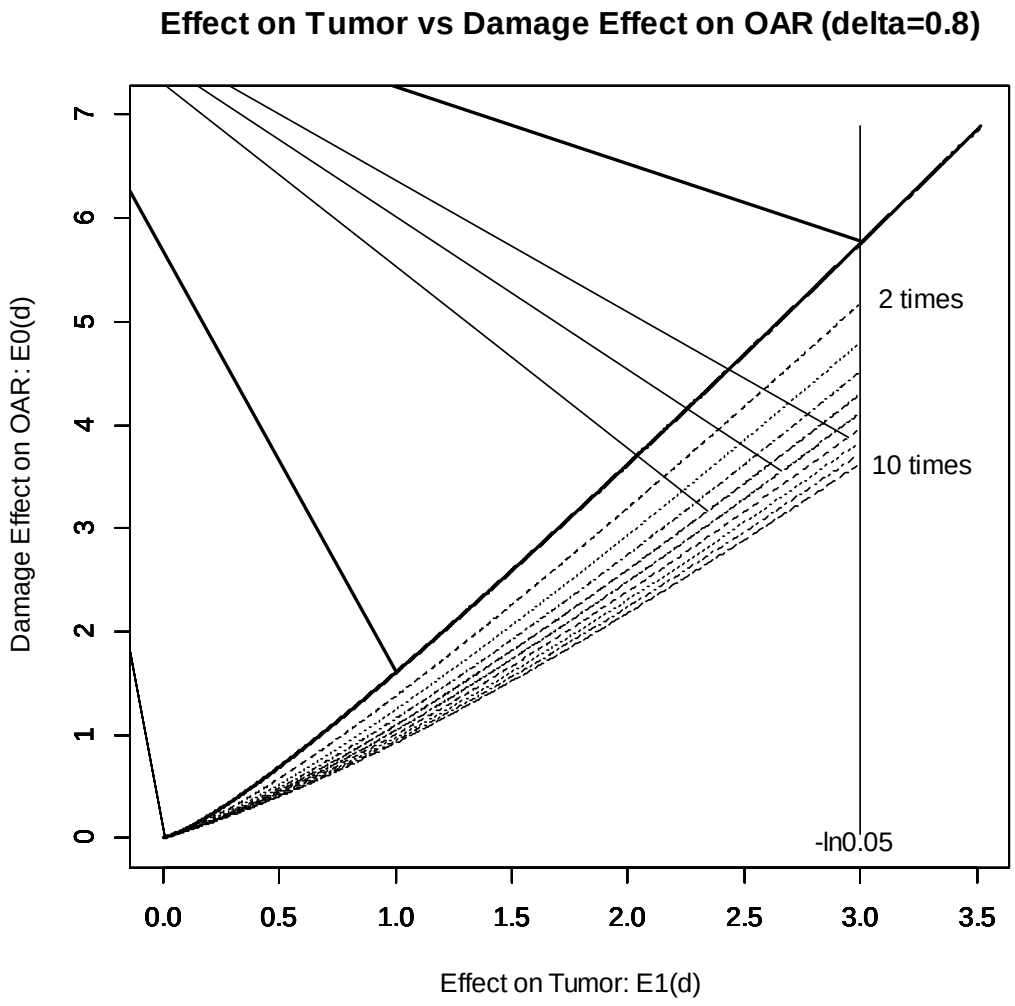

Fig. 4 When δ is large (e.g., δ=0.8), conventional fractionated radiotherapy is better because the damage effect on the OAR decreases as the number of irradiations increases. Here, the solid curve is the TO plot.

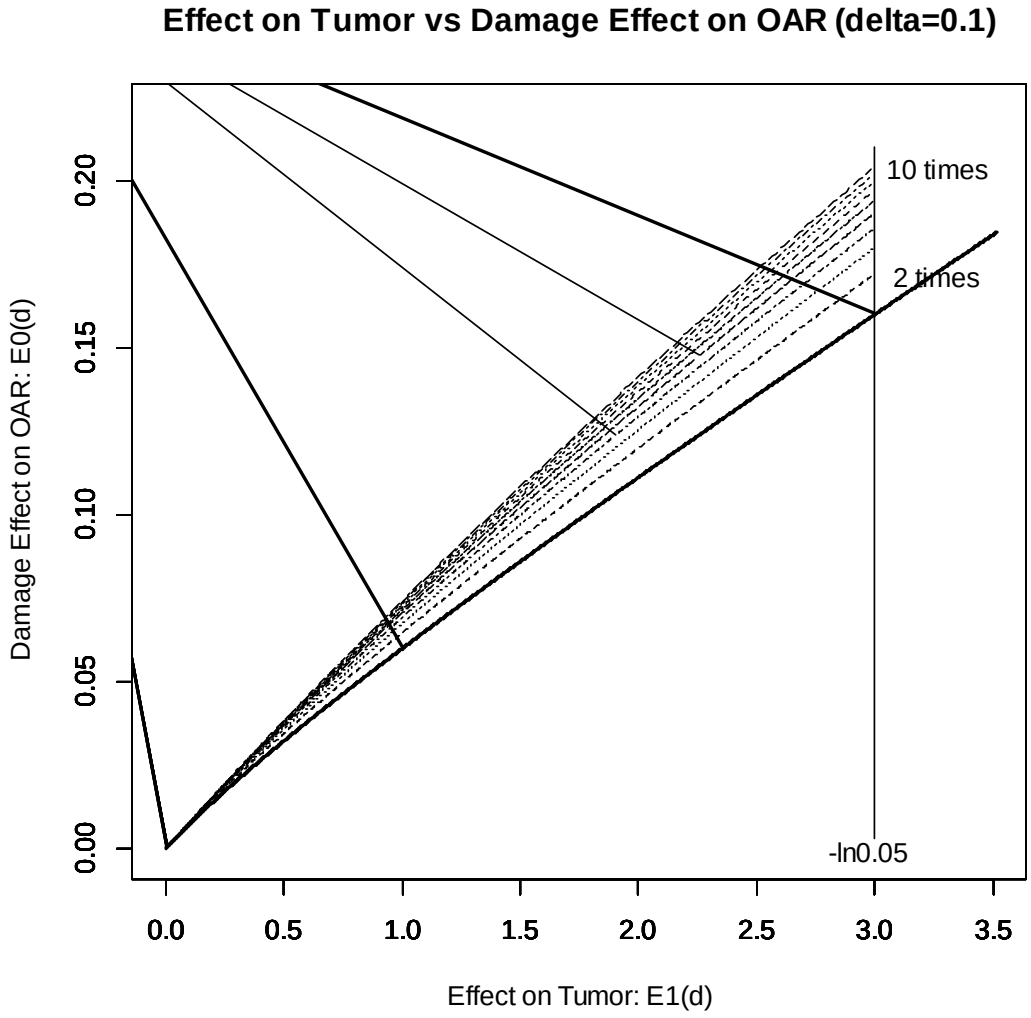

Fig. 5 When δ is small (e.g., δ=0.1), hypo-fractionated radiotherapy is better because the damage effect on the OAR increases as the number of irradiations increases.