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Title: A MATHEMATICAL STUDY TO SELECT FRACTIONATION REGIMEN BASED ON PHYSICAL DOSE DISTRIBUTION AND THE LINEAR-QUADRATIC MODEL

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Abstract

Purpose: Hypofractionated irradiation is often used in precise radiotherapy instead of conventional multi-fractionated irradiation. We propose a novel mathematical method for selecting a hypofractionated or multi-fractionated irradiation regime based on physical dose distribution adding to biological consideration.

Methods and Materials: The linear quadratic (LQ) model was employed for the radiation effects on tumor and normal tissues, especially OARs. Based on the assumption that the OAR receives a fraction of the dose intended for the tumor, the minimization problem for the damage effect on the OAR was treated under the constraint that the radiation effect on the tumor is fixed.

Results: For an N-time fractionated irradiation regime, the constraint of tumor lethality was described by an N-dimensional hypersphere. The total dose of the fractionated irradiations was considered for minimizing the damage effect on the OAR under the hypersphere condition. It was found that the advantage of hypofractionated or multi-fractionated irradiation therapies depends on the magnitude of the ratio of α/β parameters for the OAR and the tumor in the LQ model and the ratio of the dose for the OAR and the tumor.

Conclusions: The present mathematical method shows that the multi-fractionated irradiation

with a constant dose is better if the ratio of α/β for the OAR and the tumor is less than the ratio of the dose for the OAR and the tumor, while hypofractionated irradiation is better otherwise.

Key words: radiotherapy, radiobiology, dose fractionation, linear-quadratic model, hypersphere

INTRODUCTION

Radiotherapy plays an important role in the treatment of solid tumors. Fractionated irradiation is performed in most clinical cases to kill tumor cells effectively based on the "4Rs" concept (1) and to reduce radiation-induced normal tissue toxicity. A typical multi-fractionated irradiation schedule is 1.8 to 2.0 Gy per day to a total of 60 to 70 Gy. Many studies have discussed alternative treatment regimens, e.g. varying the number of fractions or dose per fraction for various tumor sites and types in actual clinical cases. The effectiveness of hyperfractionated, hypofractionated, or accelerated radiotherapy has been investigated in head and neck cancer (2, 3) and breast cancer (4). Continuous hyperfractionated accelerated radiotherapy (CHART) was introduced in the 1980s. The superiority of CHART compared to conventional radiotherapy has been reported (5-7). In terms of biological effects, hypofractionated radiotherapy has advantages in tumor cell killing due to an increase in dose per fraction and a decrease in treatment duration. Recently, it has become possible to irradiate higher dose to the tumor region while minimizing unwanted radiation exposure to surrounding normal tissue due to advances in high-precision radiotherapy. This trend makes hypofractionated radiotherapy feasible without increasing toxicity of normal tissue (8, 9). However, there is still some controversy with this issue clinically (10).

In other approaches, many investigations have been made to study appropriate treatment regimens based on radiobiological models. The linear quadratic (LQ) model, which was

introduced in the 1960s and widely spread in the 1980s, is one of the most frequently used models (11-15). Fowler *et al*. examined biological effective dose, tumor control, and late effects for normal tissues in various treatment schedules using the LQ model (16). They also investigated the robustness of the LQ model against parameter variations (17). Yang and Xing analyzed optimal treatment strategies based on the LQ model considering tumor proliferation (18). However, there seems to be no report discussing the influence of tumor size, location, and distance to organs at risk (OARs) in determining treatment regimen. For example, hypofractionated irradiation may be preferred to multi-fractionated irradiation for the tumor located far from an OAR in terms of OAR sparing. Existing radiobiological models are unable to deal with such situations.

In this study, we propose a novel mathematical approach to calculate the optimal dose fractionation. The problem is defined as the minimization of the damage effect on normal tissues subject to radiation effect on the tumor based on the LQ model. We approached this problem mathematically as a constrained optimization problem and evaluated what treatment schedule, i.e. hypofractionated or multi-fractionated irradiation, is appropriate.

METHODS AND MATERIALS

The basic assumption in this study relies on the LQ model for both tumors and normal tissues, including organs at risk (OARs); that is, the formula $E(d) = \alpha d + \beta d^2$ is employed

for the effect $E(d)$ as a function of absorbed dose d where α, β are parameters. We use the notation α_1, β_1 for the tumor and α_0, β_0 for the OAR as the parameters, respectively.

Let us consider the damage effect on the OAR exposed to irradiation to yield a radiation effect on the tumor to be E_1 (this is predefined based on the intent to treat radically or palliatively, e.g. –ln0.01 or –ln0.05). Assuming that the tumor and OAR are exposed to the same irradiation field, it should be reasonable to consider that the dose for the OAR is proportional to the dose for the tumor, i.e. the dose for the OAR is given by δd, where the dose for the tumor is d and the proportionality factor δ satisfies $0 \le \delta$ (Fig.1).

For multi-fraction radiation therapy with N-fraction doses $(d_1, d_2, ..., d_N)$, the radiation effect on the tumor is represented by $\sum_{i=1}^{N}(\alpha_1 d_i + \beta_1 d_i^2)$ and is fixed as E_1, that is

$$E_1 = \sum_{i=1}^{N}(\alpha_1 d_i + \beta_1 d_i^2). \qquad (1)$$

Since the doses for the OAR are denoted as $\delta d_1, \delta d_2, ..., \delta d_N$, the damage effect on the OAR (E_0) by N times exposure is given by

$$E_0 = \sum_{i=1}^{N}[\alpha_0(\delta d_i) + \beta_0(\delta d_i)^2]. \qquad (2)$$

Thus, the problem for the fractionation regimen can be handled mathematically as an optimization problem,

$$\sum_{i=1}^{N}[\alpha_0(\delta d_i) + \beta_0(\delta d_i)^2] \rightarrow \text{Min}$$

under the constraint of Eq.(1). If the damage effect on the OAR in formula (2) is smaller with an increase in the number of fractions, multi-fractionated irradiation is better. If the damage

effect on the OAR in formula (2) is larger with an increase in the number of fractions, hypofractionated irradiation is better.

RESULTS

From Eq.(1), we have the following equation,

$$\sum_{i=1}^{N} d_i^2 = \frac{1}{\beta_1}\left(E_1 - \alpha_1 \sum_{i=1}^{N} d_i \right). \tag{3}$$

The formula (2) can be transformed as follows.

$$\begin{aligned} E_0 &= \sum_{i=1}^{N} (\alpha_0 \delta d_i + \beta_0 \delta^2 d_i^2) \\ &= \alpha_0 \delta \sum_{i=1}^{N} d_i + \beta_0 \delta^2 \sum_{i=1}^{N} d_i^2 \\ &= \alpha_0 \delta \sum_{i=1}^{N} d_i + \beta_0 \delta^2 \frac{1}{\beta_1}\left(E_1 - \alpha_1 \sum_{i=1}^{N} d_i \right) \\ &= \left(\alpha_0 \delta - \beta_0 \delta^2 \frac{\alpha_1}{\beta_1} \right) \sum_{i=1}^{N} d_i + \frac{\beta_0 \delta^2}{\beta_1} E_1 \\ &= \frac{\alpha_1 \beta_0 \delta}{\beta_1} \left(\frac{\beta_1 \alpha_0}{\alpha_1 \beta_0} - \delta \right) \sum_{i=1}^{N} d_i + \frac{\beta_0 \delta^2}{\beta_1} E_1 \\ &= \frac{\alpha_1 \beta_0 \delta}{\beta_1} \left(\frac{\alpha_0 / \beta_0}{\alpha_1 / \beta_1} - \delta \right) \sum_{i=1}^{N} d_i + \frac{\beta_0 \delta^2}{\beta_1} E_1 . \end{aligned} \tag{4}$$

Then, this formula is interpreted as follows;

(a) if $\frac{\alpha_0}{\beta_0} \Big/ \frac{\alpha_1}{\beta_1} \geq \delta$, the lower $\sum_{i=1}^{N} d_i$ is, the lower the damage effect on the OAR is.

(b) if $\frac{\alpha_0}{\beta_0} \Big/ \frac{\alpha_1}{\beta_1} < \delta$, the larger $\sum_{i=1}^{N} d_i$ is, the lower the damage effect on the OAR is.

Next, we move to the problem of the minimization or maximization of $\sum_{i=1}^{N} d_i$. From Eq. (1), we have

$$\sum_{i=1}^{N}\left(d_i^2 + \frac{\alpha_1}{\beta_1} d_i \right) = \frac{E_1}{\beta_1}$$

$$\sum_{i=1}^{N}\left[d_i^2 + \frac{\alpha_1}{\beta_1} d_i + \left(\frac{\alpha_1}{2\beta_1} \right)^2 \right] = \frac{E_1}{\beta_1} + N\left(\frac{\alpha_1}{2\beta_1} \right)^2$$

$$\sum_{i=1}^{N}\left(d_i + \frac{\alpha_1}{2\beta_1} \right)^2 = \frac{E_1}{\beta_1} + N\left(\frac{\alpha_1}{2\beta_1} \right)^2 . \qquad (5)$$

The set of fractionated doses $(d_1, \cdots, d_N)$ satisfying the above equation represents an N-dimensional hypersphere $(d_1 \geq 0, \cdots, d_N \geq 0)$, where the center is $\left(-\frac{\alpha_1}{2\beta_1}, \cdots, -\frac{\alpha_1}{2\beta_1} \right)$ and the radius is $\sqrt{\frac{E_1}{\beta_1} + N\left(\frac{\alpha_1}{2\beta_1} \right)^2}$, as depicted in a two-dimensional plane in Fig.2.

In Fig.2, the circle represents the condition of Eq. (5) (for radiation effect on tumor, E_1), and the lines (with minus one inclination) correspond to the values of $\sum_{i=1}^{N} d_i$. Under the reservation $d_i \geq 0$, $\sum_{i=1}^{N} d_i$ is maximized when the line is tangent to the circle, while $\sum_{i=1}^{N} d_i$ is minimized when the line crosses the points that the circle intersects the axes. Therefore, we can summarize the conditions as: $\sum_{i=1}^{N} d_i$ is maximized when $d_1 = \cdots = d_N$, and $\sum_{i=1}^{N} d_i$ is minimized when one of $d_1, \cdots, d_N$ is positive and the others are zero (i.e., single exposure). Ultimately, the adjudication can be described as follows:

(i) if $\frac{\alpha_0}{\beta_0} \Big/ \frac{\alpha_1}{\beta_1} \geq \delta$, hypofractionated irradiation is better than multi-fractionated irradiation.

(ii) if $\frac{\alpha_0}{\beta_0}\Big/\frac{\alpha_1}{\beta_1} < \delta$, multi-fractionated irradiation with a constant dose is better.

The result does not depend on the value E_1, nor the parameters, $\alpha_0, \beta_0, \alpha_1, \beta_1$, but the ratio $\frac{\alpha_0}{\beta_0}\Big/\frac{\alpha_1}{\beta_1}$ and δ.

DISCUSSION

Conventionally, multi-fractionated irradiation has been performed in order to minimize the damage effect on the normal tissue that is preserved intact by taking advantage of the difference of susceptibilities to radiation between the tumor and late-responding normal tissues. The value of α_0/β_0 (for OARs or late-responding normal tissues) has been reported to be usually smaller than α_1/β_1 (for tumors) (11, 12). On the other hand, the dose fraction, δ, for OARs is governed by the configuration of the tumor and the irradiation geometry in the human body, which should be reduced as small as possible.

Now let us suppose $\alpha_0/\beta_0 \approx 2$ and $\alpha_1/\beta_1 \approx 10$ which are taken from a typical clinical condition; then we have $\frac{\alpha_0}{\beta_0}\Big/\frac{\alpha_1}{\beta_1} \approx 0.2$ (19). At the same time, the radiation effect on the tumor is set to be –ln0.05 as a trial. If the dose fraction δ is smaller than 0.2, a single exposure is better than a multi-fractionated exposure, in which the damage effect on OAR is minimized under the constraint of the radiation effect on tumor, as illustrated in Fig.2. Contrary to this, if δ is larger than 0.2, a multi-fractionation regimen with a constant dose per fraction leads to the minimizing damage effect on OAR. The maximization of $\sum_{i=1}^{N} d_i$ with $d_1 = \cdots = d_N$ in

the latter case means that a multiple (*N*) exposure with a constant dose per fraction is favorable for obtaining a low effect on OAR. For example, if $\alpha_1/\beta_1 = 10$ is given by $\alpha_1 = 0.05$ and $\beta_1 = 0.005$, the relation of $\sum_{i=1}^{N}(\alpha_1 d_i + \beta_1 d_i^2) = -\ln 0.05$ is satisfied by $N = 25$ with $d_1 = \cdots = d_N = d = 2.0$ Gy, where $d = 2.0$ Gy is a typical dose in a multi-fractionation regimen. The total accumulated dose is 50 Gy in this case with daily dose of 2.0 Gy, while *d*=20 Gy is required for a single exposure (*N*=1) as an extreme example (as another example, the total dose is 30 Gy for *N*=3) to achieve the same biological effect. Although the total dose $\sum_{i=1}^{N} d_i$ in the multi-fraction irradiation is much larger than that of the hypofractionated irradiation, the effect on the OAR can be smaller than the effect resulting from the hypofractionated irradiation, when $\frac{\alpha_0}{\beta_0} \Big/ \frac{\alpha_1}{\beta_1} < \delta$. This condition is probable when 0.2 < δ for an OAR near the tumor with $\alpha_0/\beta_0 \approx 2$ (e.g., from $\alpha_0 = 0.04$ and $\beta_0 = 0.02$ (19)). It should be emphasized that the decision whether to choose a hypofractionated irradiation or a multi-fractionation in radiation therapy depends on the ratio $\frac{\alpha_0}{\beta_0} \Big/ \frac{\alpha_1}{\beta_1}$ and the dose fraction for the OAR (δ), while the total dose is determined by the values (α_1 and β_1) and the dose per fraction (d) to yield a certain degree of radiation effect on the tumor.

In figure 3, the damage effect on OAR versus the number of fractions is exemplified for two cases, δ=0.1 and δ=0.8, respectively, keeping the radiation effect on the tumor to be –ln0.05. In practice, hypofractionation of 3-5 times rather than single fractionation is often used expecting to increase reoxygenation for hypoxic cells. Figure 3(a) suggests that

hypofractionated irradiation (e.g., 3-5 times) provides less damage effect on OAR than multi-fractionated irradiation (30 times) when δ=0.1 (i.e., OAR receives 10% of tumor dose) and $\frac{\alpha_0}{\beta_0}\Big/\frac{\alpha_1}{\beta_1} \approx 0.2$. Figure 3(b) suggests that multi-fractionated irradiation provides less damage effect on OAR than hypofractionated irradiation when δ=0.8 (i.e., OAR receives 80% of tumor dose) and $\frac{\alpha_0}{\beta_0}\Big/\frac{\alpha_1}{\beta_1} \approx 0.2$.

In actual situations, the value α/β for a tumor or a specific organ (or tissue) may vary depending on its volume due to the oxygen effect (20) and other factors such as the cell cycle. Modification for treatment time in the LQ model alters the result to some extent. However, as far as the simple assumption mentioned earlier holds, the present study can provide us with a criterion for the validity of the hypofraction or the multi-fractionation regimen as Eqs.(1) and (2).

The clinical feasibility of this model can be examined assuming two lung tumors with the same volume of 2.0 cm but situated at different locations; for example peripheral lung tissue and central lung. The organs at risk are normal lung tissue, spinal cord, brachial plexus, pulmonary artery, heart, esophagus, and the proximal bronchial tree (21, 22). We can assume that the complication probabilities of OARs other than the proximal bronchial tree are negligible for both tumors whether a single or fractionated schedule is employed. α_0/β_0 of the proximal bronchial tree is very likely to be smaller than α_1/β_1 of squamous cell carcinoma so that we can assume $\frac{\alpha_0}{\beta_0}\Big/\frac{\alpha_1}{\beta_1}$ is smaller than 1.0. In the treatment of peripheral

lung tumors, the proximal bronchial tree, which is far from the tumor, does not receive any dose (δ=0.0). In the treatment of central lung tumors, on the other hand, the proximal bronchial tree, which is quite close to the tumor, receives the same dose as the target volume (δ=1.0). Consequently, the model predicts that hypofractionated radiotherapy is preferable for the peripheral tumor and multi-fractionated irradiation is preferable for the central tumor. These preferences are consistent with clinical findings and recent recommendations in the treatment guideline for stereotactic body irradiation (SBRT) of stage I squamous cell carcinoma of lung (23, 24).

On the other hand, for the treatment of prostate cancer adjacent to the rectal wall, α_0/β_0 is reported to be larger than α_1/β_1, or $\frac{\alpha_0}{\beta_0}\Big/\frac{\alpha_1}{\beta_1}$ is higher than 1.0 (25). In this scenario, even though the OAR receives dose equivalent to the tumor dose (δ=1.0), the model predicts that hypofractionation will be preferable over multi-fractionation. This is consistent with recently published randomized trials where hypofractionated radiotherapy was better than conventional radiotherapy for prostate cancer (26, 27). Previous radiobiological models predicted that hypofractionation is optimal for prostate cancer based on the fact that α_0/β_0 is larger than α_1/β_1; in other words, δ was set at 1.0. The unique point of the present study is that δ does not need to be 1.0. Dose distribution can thus be considered in order to determine the optimal fractionation.

The justification for applying a constant dose per fraction in the multi-fractionation

regimen is also presented from a mathematical point of view. The model for a single tumor as the target and a single OAR is treated here based on the assumption that each organ is irradiated uniformly. However, the method can be extended to the condition for a non-uniform irradiation to OARs such as in intensity modulated radiation therapy.

The real interest of the present approach would be the determination of the optimum solution for N in clinical practice. However, this requires a better modeling of cellular dynamics following each fraction, incorporating the 4 Rs.

CONCLUSION

In this paper, we have discussed the validity of the multi-fractionation regimen in radiotherapy, based on the LQ model for both tumors and normal tissues (OARs). The problem of minimizing the radiation effect on OAR was solved under the constraint of prescribed effect on the tumor, in which a multi-dimensional hypersphere representing the constraint was taken into account. The result shows that a multi-fractionated irradiation with a constant dose is better when the ratio of α/β values for OAR and tumor is less than δ (ratio of doses to the OAR and the tumor), while hypofractionation irradiation is appropriate when the ratio is greater than δ.

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Figure Legends

Figure 1. Doses for tumor and OAR.

Figure 2. Maximum and minimum conditions of $\sum_{i=1}^{N} d_i$ under the constraint for the radiation effect on tumor.

Figure 3. Damage effect on OAR versus the number of fractionation (N) keeping the radiation effect on tumor (E_1) in Eq.(1) is set to be –ln0.05: (a) for δ=0.1 and (b) for δ=0.8. Here, the dose per fraction (d) was assumed to be constant, and obtained from the constraint of E_1=–ln0.05. The damage effect on OAR (E_0) was then determined by Eq.(2) with $\alpha_0 = 0.04$, $\beta_0 = 0.02$ and the value d for every fractionation number (N).

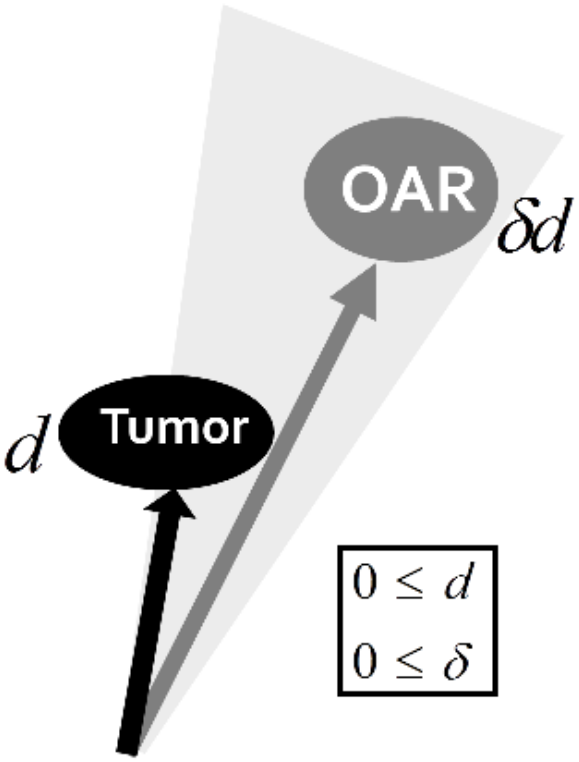

Fig.1

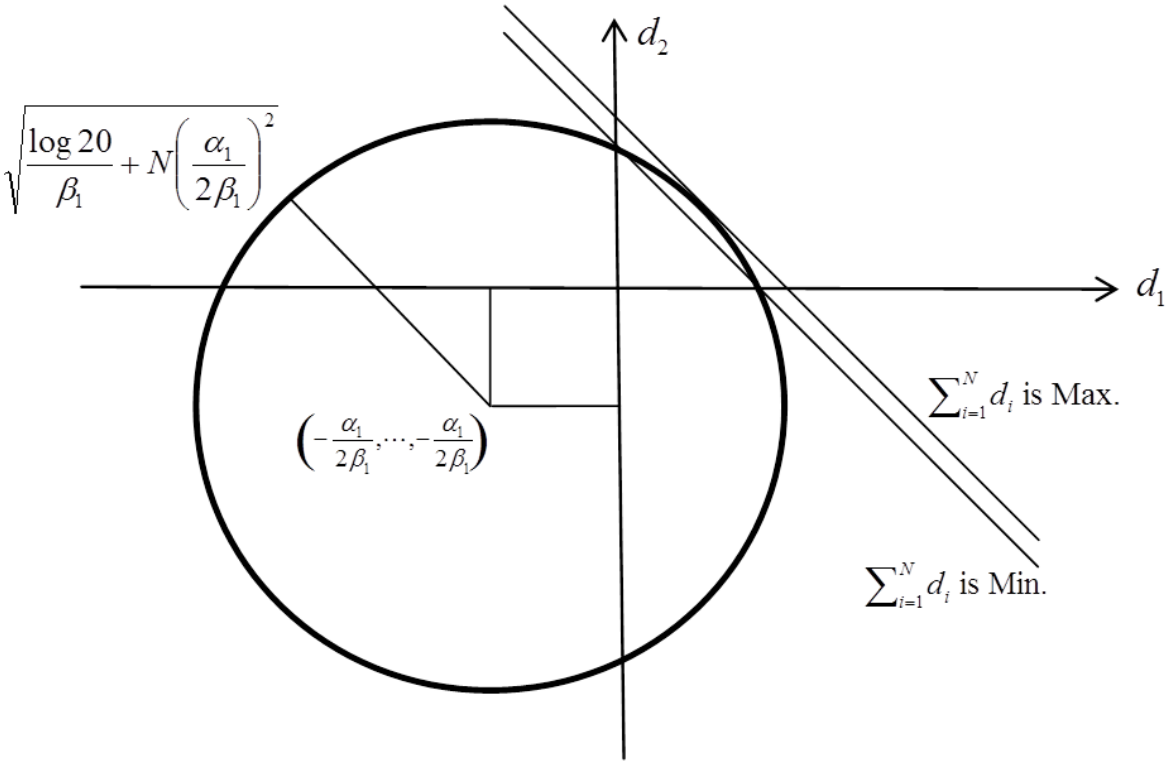
d_2
$\sqrt{\frac{\log 20}{\beta_1}+N\left(\frac{\alpha_1}{2\beta_1}\right)^2}$
d_1
$\left(-\frac{\alpha_1}{2\beta_1},\cdots,-\frac{\alpha_1}{2\beta_1}\right)$
$\sum_{i=1}^{N} d_i$ is Max.
$\sum_{i=1}^{N} d_i$ is Min.

Fig.2

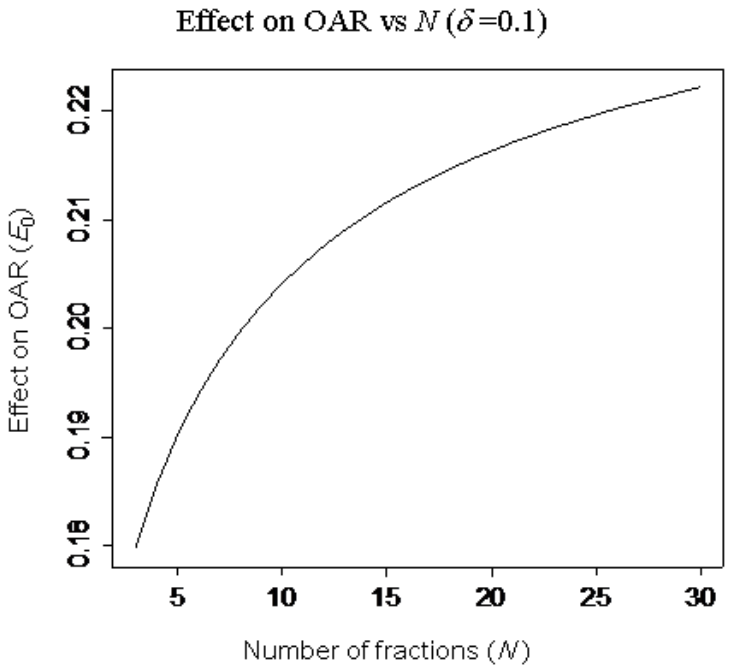
Effect on OAR vs N (δ=0.1)
Effect on OAR (E_0)
0.18
0.19
0.20
0.21
0.22
5
10
15
20
25
30
Number of fractions (N)

Fig.3(a)

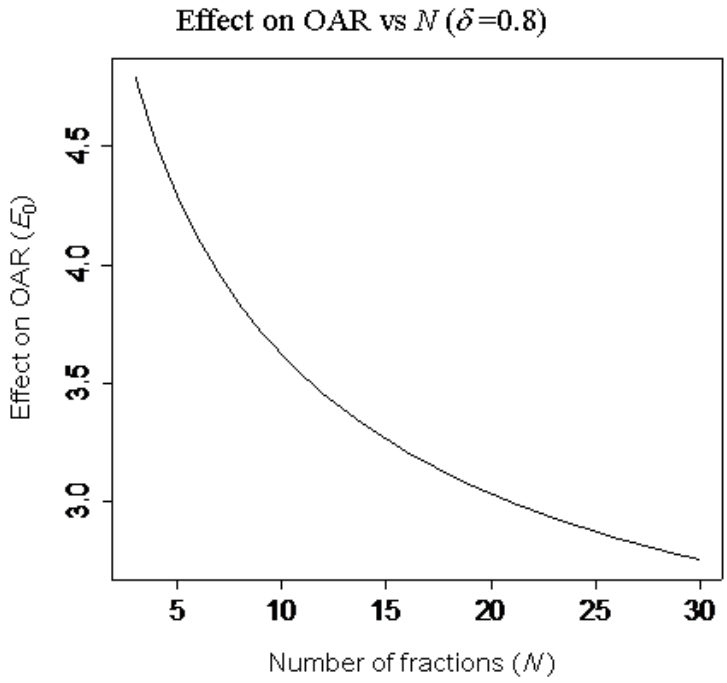
Effect on OAR vs N (δ=0.8)
Effect on OAR (E_0)
3.0
3.5
4.0
4.5
5
10
15
20
25
30
Number of fractions (N)

Fig.3(b)