Journal name: Medical Physics
Article type: Research Article

Title: Optimization of the fractionated irradiation scheme considering physical doses to tumor and organ at risk based on dose volume histograms

Authors: Yasutaka Sugano[1], Masahiro Mizuta[2], Seishin Takao[3], Hiroki Shirato[3], Kenneth L. Sutherland[3], Hiroyuki Date[4]

Affiliations: [1]Graduate School of Health Sciences, Hokkaido University, [2]Laboratory of Advanced Data Science, Information Initiative Center, Hokkaido University, [3]Department of Radiation Medicine, Graduate School of Medicine, Hokkaido University, [4]Faculty of Health Sciences, Hokkaido University

Corresponding Author: Hiroyuki Date
Postal Address: Faculty of Health Sciences, Hokkaido University, Kita-12, Nishi-5, Kita-ku, Sapporo 060-0812, Japan
E-mail: date@hs.hokudai.ac.jp **Tel**: +81-11-706-3423 **Fax**: +81-11-706-4916

Conflict of interest: Any actual or potential conflicts of interest do not exist for all authors.

The manuscript has not been published previously nor concurrently submitted for publication elsewhere.

ABSTRACT

Purpose: Radiotherapy of solid tumors has been performed with various fractionation regimens such as multi- and hypo- fractionations. However, the ability to optimize the fractionation regimen considering the physical dose distribution remains insufficient. This study aims to optimize the fractionation regimen, in which we propose a graphical method for selecting the optimal number of fractions (*n*) and dose per fraction (*d*) based on dose volume histograms for tumor and normal tissues of organs around the tumor.

Methods: Modified linear-quadratic (LQ) models were employed to estimate the radiation effects on the tumor and an organ at risk (OAR), where the repopulation of the tumor cells and the linearity of the dose-response curve in the high dose range of the surviving fraction were considered. The minimization problem for the damage effect on the OAR was solved under the constraint that the radiation effect on the tumor is fixed by a graphical method. Here, the damage effect on the OAR was estimated based on the dose volume histogram.

Results: It was found that the optimization of fractionation scheme incorporating the dose volume histogram is possible by employing appropriate cell surviving models. The graphical method considering the repopulation of tumor cells and a rectilinear response in the high dose range enables us to derive the optimal number of fractions and dose per

fraction. For example, in the treatment of prostate cancer, the optimal fractionation was suggested to lie in the range of 8-32 fractions with a daily dose of 6.3-2.2 Gy.

Conclusions: It is possible to optimize the number of fractions and dose per fraction based on the physical dose distribution (i.e., dose volume histogram) by the graphical method considering the effects on tumor and OARs around the tumor. This method may stipulate a new guideline to optimize the fractionation regimen for physics-guided fractionation.

KEYWORDS

fractionated radiotherapy, linear-quadratic (LQ) model, universal survival curve (USC), repopulation of tumor cells, dose volume histogram (DVH)

1. INTRODUCTION

Radiotherapy with external irradiation for the treatment of solid tumors is currently performed by the fractionated irradiation scheme based on the four R's concept (repair, redistribution, repopulation, and reoxygenation) [1]. In standard fractionated radiotherapy, 60-70 Gy (1.8-2.0 Gy per day) is delivered in about 30 fractions for curative treatment. Many studies have examined the effectiveness of various fractionation schemes such as multi-fractionation and accelerated radiotherapy [2-6]. Hypo-fractionated radiotherapy with a high daily dose in a small number of fractions has also drawn attention because it has revealed a capability to eradicate tumors without increasing adverse effects compared to standard multi-fractionation [7-9]. In addition, stereotactic body radiotherapy (SBRT) for lung cancer [10, 11] and hypo-fractionated SBRT for prostate cancer using a precise localization technology [12, 13] are being conducted in which the physical dose distribution is optimized before the selection of a dose fractionation. In these circumstances, the appropriate fractionation regimen in accordance with the prescribed dose to the target region must be determined. Although many studies have attempted to find or predict the appropriate fractionation regimen [14-17], studies to optimize the number of fractions and to discern the applicability of multi- or hypo-fractionation remain insufficient.

Recently, Mizuta et al. have proposed a mathematical method to select a fractionation regimen based on physical dose distribution [18], and relevant investigations into this have been reported subsequently [19-22]. Following the paper [18], the authors also presented a graphical method using a “TO plot” to determine the appropriate fractionation regimen based on the relation between radiation effects on the tumor and an organ at risk (OAR) [23]. These studies have shown explicit criteria for selecting better fractionation methods, which are determined by the physical dose distribution and the α/β value in the linear-quadratic (LQ) model. They concluded that multi-fractionation with constant dose is better when the ratio of α/β values for the OAR and tumor is less than the ratio of doses to the OAR and tumor δ while hypo-fractionated irradiation is better when the ratio of α/β values is greater than δ. However, in these cases, the optimal number of fractionation turned out to be infinite or a single fraction. These optimal numbers of fractionation do not support the clinical results achieving good performance with 30 to 40 fractions in standard irradiation and three to ten fractions in SBRT. The reason for this defect is presumably that they did not consider the repopulation process of the tumor cells and the rectilinear response of the survival curve in the high dose range. In their study, the LQ model was applied to an analytical method, and a graphical method was contrived to illustrate the optimal

condition of the fractionation. However, the LQ model has a tendency to overestimate the radiation effect on tissues in high dose regions [24-27], while this model doesn't explicitly include consideration of the repopulation of tumor cells. Besides, their optimization method has another important limitation, i.e., a uniform irradiation is postulated over the tumor and OARs. For the use of the method in actual clinical practice, it is necessary to improve the method to be able to consider the non-uniform physical dose distribution, particularly for OARs.

In this study, the same methodology as in their previous work is extended to more precise conditions by adopting the cell survival models that consider the effect of repopulation of tumor cells and the rectilinear response in the high dose range as the modified LQ model. We improve the optimization method capable of considering the non-uniform physical dose delivery to OARs based on dose volume histograms (DVHs).

2. METHODS

2.1 The surviving fraction model

First, we define the effect on the tumor $E_1(d)$ and the damage effect on an OAR $E_0(\delta d)$ as follows,

$$E_1(d) = -\ln S_1(d), \quad (1)$$

$$E_0(\delta d) = -\ln S_0(\delta d), \quad (2)$$

where $S_1(d)$ and $S_0(\delta d)$ are the surviving fractions of the tumor and OAR (subscript 1 is for tumor and 0 for OAR), respectively, and δ ($\delta \geq 0$) is the proportional factor representing the dose ratio of the OAR to tumor (i.e., d is the dose to the tumor and δd is the dose to the OAR).

In order to examine the effects on the tumor and OAR in radiation exposure, we adopted the following three models instead of the simple LQ model used in the previous studies [18, 23]: 1) LQ model considering the repopulation of the tumor (LQ-repopulation), 2) Universal survival curve (USC) [28], 3) USC considering the repopulation of the tumor (USC-repopulation).

LQ model considering repopulation of the tumor (LQ-repopulation)

When we define d as the absorbed dose, the surviving fraction $S(d)$ for the LQ-repopulation model is described by

$$S_1(d) = \exp[-(\alpha_1 d + \beta_1 d^2) + \frac{\ln 2}{T_{\text{pot}}}(T - T_{\text{k}})], \quad (3)$$

$$S_0(\delta d) = \exp\{-[\alpha_0(\delta d) + \beta_0(\delta d)^2]\}. \quad (4)$$

Here, T is the total treatment time, T_k is the starting time and T_{pot} is the doubling time for repopulation of tumor cells. By taking the repopulation of tumor cells into account, we expect to be able to estimate the effects of a multi-fractionated radiotherapy.

Universal survival curve (USC)

The concept of USC was introduced in 2008 by Park et al. It is constructed by a combination of the LQ model in the low dose range and the multi-target model in the higher dose range [28]. The surviving fraction with USC is given by

$$S_1(d) = \begin{cases} \exp[-(\alpha_1 d + \beta_1 d^2)] & \text{if } d < D_{t,1} \\ \exp\{-[(\alpha_1 + 2\beta_1 D_{t,1})d - \beta_1 {D_{t,1}}^2]\} & \text{if } d \geq D_{t,1} \end{cases}, \quad (5)$$

$$S_0(\delta d) = \begin{cases} \exp[-(\alpha_0(\delta d) + \beta_0(\delta d)^2)] & \text{if } \delta d < D_{t,0} \\ \exp\{-[(\alpha_0 + 2\beta_0 D_{t,0})(\delta d) - \beta_0 {D_{t,0}}^2]\} & \text{if } \delta d \geq D_{t,0} \end{cases}, \quad (6)$$

where $D_{t,1}$ and $D_{t,0}$ are the transition dose (or boundary dose) from linear-quadratic to purely linear shape. The USC provides a rectilinear description of the surviving fraction in the high dose range above the transition dose while preserving the quadratic nature of the LQ model in the low dose range. It has been reported that the USC is more realistic than the LQ model [28] because it has more success in modelling the outcomes of hypo fractionation with high dose per fraction as in SBRT [29-31]. Taking advantage of the USC in describing a realistic surviving fraction in the high dose range, it is expected to

estimate the effects more accurately for hypo-fractionated radiotherapy because a high dose per fraction is necessary for hypo-fractionation.

USC considering repopulation of the tumor (USC-repopulation)

The surviving fraction in the USC-repopulation is described by

$$S_1(d)=\begin{cases}\exp[-(\alpha_1 d+\beta_1 d^2)+\dfrac{\ln 2}{T_{\mathrm{pot}}}(T-T_{\mathrm{k}})] & \text{if } d<D_{t,1}\\ \exp\{-[(\alpha_1+2\beta_1 D_{t,1})d-\beta_1 {D_{t,1}}^2]+\dfrac{\ln 2}{T_{\mathrm{pot}}}(T-T_{\mathrm{k}})\} & \text{if } d\geq D_{t,1}\end{cases}, \quad (7)$$

$$S_0(\delta d)=\begin{cases}\exp[-(\alpha_0(\delta d)+\beta_0(\delta d)^2)] & \text{if } \delta d<D_{t,0}\\ \exp\{-[(\alpha_0+2\beta_0 D_{t,0})(\delta d)-\beta_0 {D_{t,0}}^2]\} & \text{if } \delta d\geq D_{t,0}\end{cases}. \quad (8)$$

This is a hybrid model having the features of the above two models, which aims for the precise estimation of the effects in both the multi-fractionated and hypo-fractionated irradiation regimens.

2.2 Radiation effects of OARs based on dose volume histogram

In the previous study [23], the doses to the tumor and OAR were assumed to be delivered uniformly for simplicity (i.e., the proportional factor δ was stipulated to be constant). However, in the actual situation in radiotherapy, the dose is delivered non-uniformly. This is true particularly for the dose to the OAR. To take account of the

physical dose distribution of the OAR, we introduce a probability density function $f_0(\delta)$ as a function of δ [23],

$$\int_0^\infty f_0(\delta)d\delta = 1, \quad f_0(\delta) \geq 0. \tag{9}$$

The function $f_0(\delta)$ is equivalent to the differential DVH of the OAR. Thus the formula of the damage effect to the OAR, given in Eq. (2), can be replaced by

$$E_0(\delta d) = -\ln \int_0^\infty S_0(\delta d)\, f_0(\delta)d\delta\,. \tag{10}$$

Here, the dose to the tumor is assumed to be uniform with d Gy assuming that a precise dose delivery to the tumor is achieved by a modern irradiation technique such as intensity modulated radiation therapy (IMRT).

Next, we consider N-time fractionated irradiation with a series of dose delivery (d_1, d_2,…, d_N). If an equally-fractionated dose plan is assumed (the validity of this assumption has been discussed in Ref. [18]), the effects on the tumor and OAR are given as follows:

$$E_1(\mathrm{Reg}(N,d)) = -\ln \int_0^\infty [S_1(\delta d)]^N\, f_1(\delta)d\delta \approx -\ln[S_1(d)]^N = N \times E_1(d)\,, \tag{11}$$

$$E_0(\mathrm{Reg}(N,d)) = -\ln \int_0^\infty [S_0(\delta d)]^N\, f_0(\delta)d\delta\,, \tag{12}$$

where $f(\delta)$ is the differential DVH (subscript 1 is for tumor and 0 for OAR) and Reg(N,d) represents the fractionation regimen with the number of fractions N and the prescribed dose per fraction to the tumor d Gy. The dose to the tumor was assumed to be

approximately uniform as in Eq.(11). These formulae enable us to separately estimate the effect on the tumor and the damage effect on the OAR corresponding to various fractionation regimens in the case of non-uniform dose to the OAR.

2.3 Optimization of fractionation regimen

The essential goal in radiotherapy is to sterilize tumor cells to a requisite level while normal tissues (especially OARs) are preserved intact as much as possible. Although we could deal with the dual problem by attacking the tumor cells as intensely as possible under an acceptable damage level to OAR, the former principle was adopted in the present study. In accordance with this basic policy, we define the fractionation regimen that yields the minimum damage effect on an OAR while the effect on the tumor is fixed (e.g., by 30-time fractionated irradiations with total dose 70 Gy) as the optimal fractionation regimen,

$$E_1(\mathrm{Reg}(N,d)) \rightarrow \text{Fixed},$$

$$E_0(\mathrm{Reg}(N,d)) \rightarrow \text{Minimization}.$$

By regarding the dose (d) as an intervening variable, we can plot a curve to illustrate the relation between $E_1(\mathrm{Reg}(N,d))$ and $E_0(\mathrm{Reg}(N,d))$, which we call a “TO plot” [23].

By the use of the TO plot, the optimal fractionation regimen was sought to minimize the damage effect on the OAR while the effect on the tumor was fixed at a targeted level.

3. RESULTS AND DISCUSSION

As an example, we applied our optimization method to a case of IMRT for prostate cancer with bladder and rectum as OARs. Nowadays, IMRT for prostate cancer may be performed with standard fractionation or hypo-fractionation as in SBRT. However, we have not had any principle to determine the appropriate dose fractionation even with the same dose distribution. Figure 1(a) shows a set of DVH samples created to imitate a typical case of IMRT for prostate cancer. The differential DVH corresponding to $f(\delta)$ is also given in Figure 1(b). Tumor volume and density are described as a function of the ratio (δ) of OAR dose to PTV dose (not directly as a function of the delivered dose). These show that the PTV is well controlled while the dose to the bladder is relatively low and the range of dose to the rectum is spread. We assumed a set of the parameters as: α_1=0.15, β_1=0.015, α_0=0.04, β_0=0.02, T_{pot}=28 day and T_{k}=0 while $D_{t,1}$ and $D_{t,0}$ are fixed at 6 Gy as a typical condition [28]. The effect on the tumor is targeted to the value equivalent to a 30-time irradiation (total dose is 70 Gy) as a conventional fractionation regimen. The damage effects on the OARs and the effect on the tumor based on Eq. (11)

and Eq.(12) can be calculated by numerical integrations.

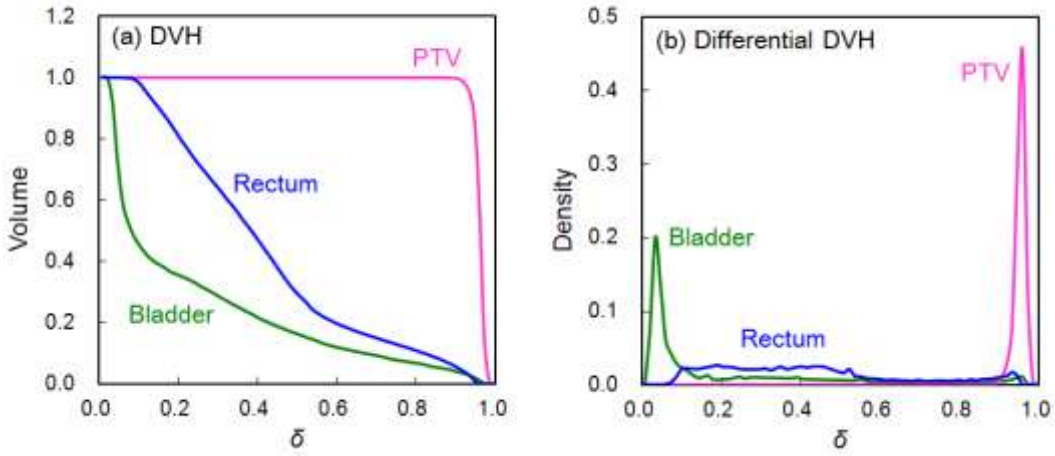

FIG. 1. Example of the dose volume histogram for treatment of prostate cancer: (a) dose volume histograms (DVHs) for bladder, rectum and planning target volume (PTV), (b) differential dose volume histograms for bladder, rectum and PTV.

Table1. Optimal fractionation schemes for organs at risk of prostate cancer

	LQ-repopulation	***USC***	***USC-repopulation***
Bladder			
Number of fractions	1	8	8
Dose per fraction (Gy)	24.0	6.5	6.3
Total dose (Gy)	24.0	52.3	50.7
Rectum			
Number of fractions	32	40*	32
Dose per fraction (Gy)	2.2	1.8	2.2
Total dose (Gy)	70.9	73.0	70.9

*The upper limit of the number of fractions was supposed to be 40 in this case although the optimal number was given to be infinity in the optimization method.

The results of the analysis on the optimal fractionation conditions from the TO plot are presented in Table 1. Here, we have performed the search for the optimal number of fractions from 1 to 40 times (we set 40 times as the maximum fractionation number tentatively, according to a typical clinical condition [32]). The TO plot calculated with the LQ-repopulation model for the bladder and rectum is shown in Figure 2. In this case, the plots show that a single fraction is the best for the bladder whereas 32 fractions is the best for the rectum. By using Eq.(3) and Eq.(4), the relevant optimal daily doses for them are calculated to be 24 Gy and 2.2 Gy, respectively. Figure 3 shows those for the USC model, where the optimal number is 8 fractions for the bladder and 40 fractions for the rectum. From Eq.(5) and Eq.(6), the doses per fraction are 6.5 Gy and 1.8 Gy, respectively. Figure 4 is for the case of the USC-repopulation model. We find that the optimal numbers are 8 fractions for the bladder and 32 fractions for the rectum while the doses per fraction for them are 6.3 Gy and 2.2 Gy, respectively, from Eq.(7) and Eq.(8).

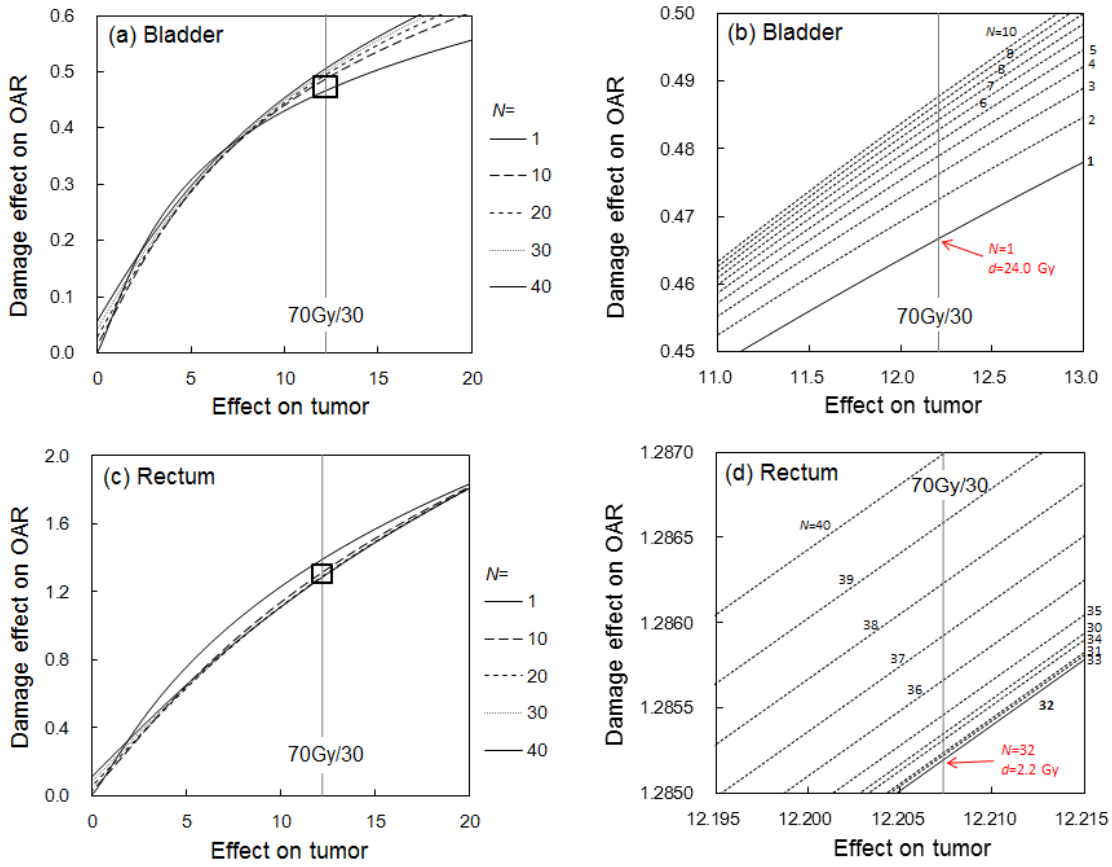

FIG. 2. TO plots for bladder and rectum calculated with LQ-repopulation model. (a) TO plot for bladder, (b) Enlarged view of TO plot for bladder (□ area in (a)), (c) TO plot for rectum, (d) Enlarged view of TO plot for rectum (□ area in (c)). (*N*: Number of fractions)

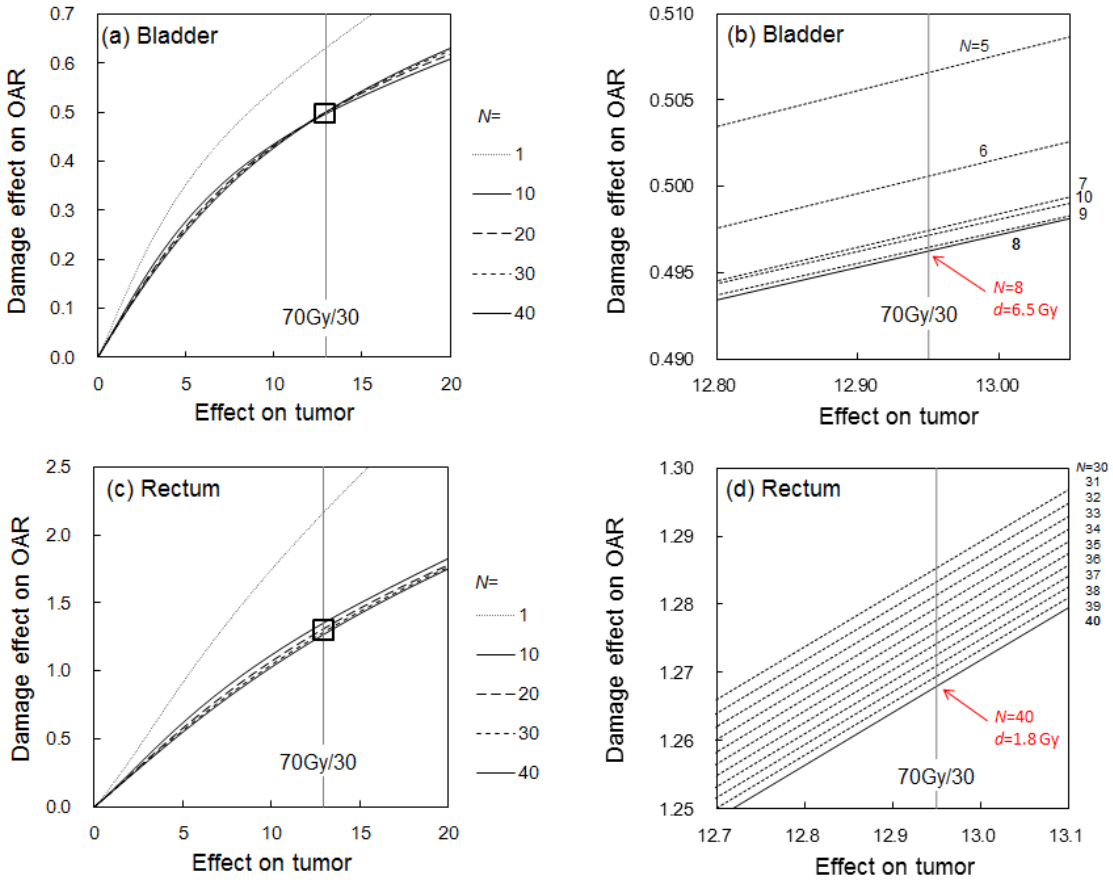

FIG. 3. TO plots for bladder and rectum calculated with USC model.
(a) TO plot for bladder, (b) Enlarged view of TO plot for bladder (□ area in (a)), (c) TO plot for rectum, (d) Enlarged view of TO plot for rectum (□ area in (c)). (*N*: Number of fractions)

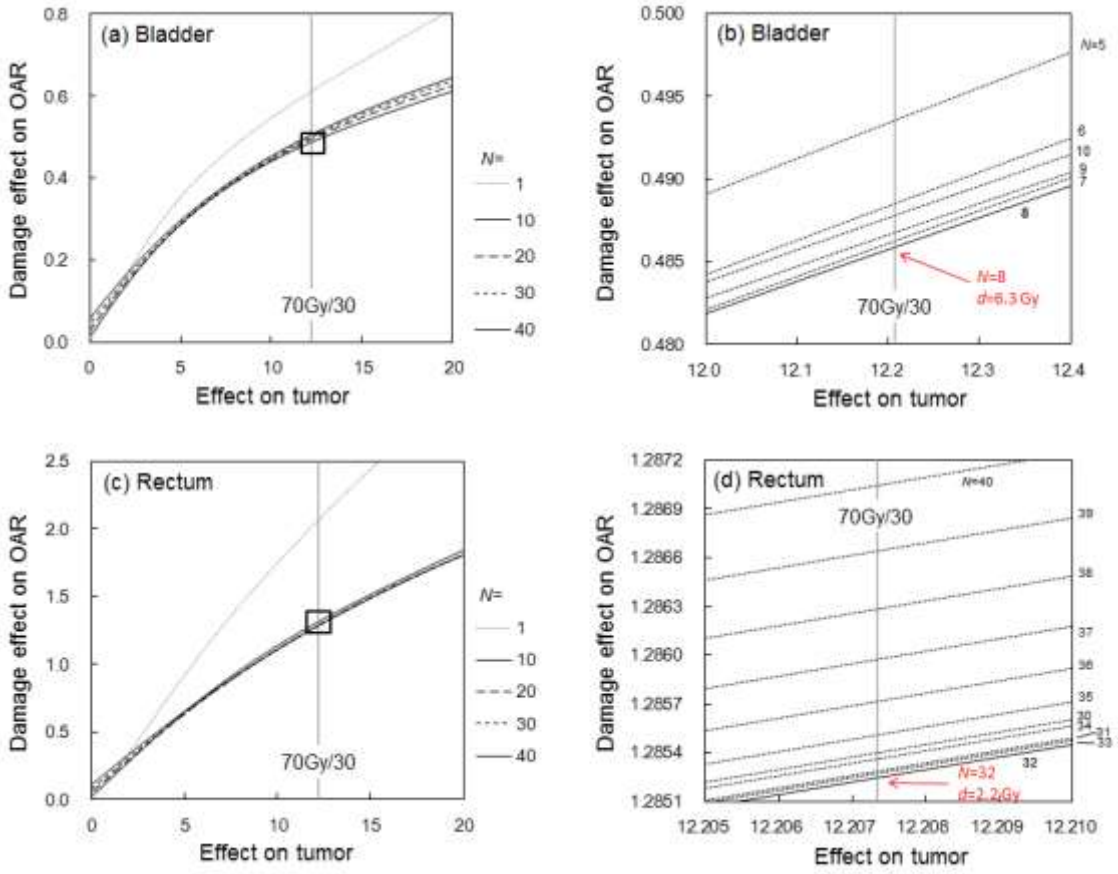

FIG. 4. TO plots for bladder and rectum calculated with USC-repopulation model. (a) TO plot for bladder, (b) Enlarged view of TO plot for bladder (□ area in (a)), (c) TO plot for rectum, (d) Enlarged view of TO plot for rectum (□ area in (c)). (*N*: Number of fractions)

We can summarize the results of this planning case so far as:

(i) If we adopt the LQ-repopulation model, the optimal fraction number *n* is 1 for bladder and 32 for rectum. The result for the bladder 24 Gy per 1 fraction may be underestimated.

(ii) If we adopt the USC model, the optimal fraction number *n* is 8 for bladder and above 40 for rectum.

(iii) If we adopt the USC-repopulation model, the optimal fraction number *n* is 8 for bladder and 32 for rectum.

It may be appropriate to use the USC-repopulation model because it is the most practical model among the three. However, there still remains the crucial problem to determine a unique number of fractions under the condition that *n*=8 is the best for the bladder while 32 is the best for the rectum. In Table 2, we summarize the damage effects on the bladder and rectum for *n*=1, 8, 20, 32 and 40, where *n*=20 is the average of 8 and 32. As is shown in Table 2, *n*=20 seems to be able to provide a well-balanced strategy between the fraction numbers 8 and 32.

Table2. Damage effects on rectum and bladder for USC-repopulation model

n	*Dose par fraction*	*Total dose*	*Effect for Rectum*	*Effect for Bladder*
1	38.70	38.70	2.155	0.607
8	6.34	50.69	1.409	0.490
20	3.21	64.14	1.371	0.499
32	2.22	70.94	1.363	0.505
40	1.86	74.24	1.364	0.508

In the previous studies for physical-guided fractionation (PGF) [18, 23], the radiation effect was estimated based on the LQ model and a simple rule was found: a multi-fractionated irradiation with a constant dose per fraction is better when the ratio of α/β value of the OAR to that of the tumor is less than δ, while a hypo-fractionation irradiation is appropriate when the ratio is greater than δ. However, the optimal number of fractions for the multi-fractionated irradiation was infinity and a single fraction was optimal for the hypo-fractionated irradiation. Infinite number of fractionations can be regarded as a low dose rate irradiation and the success of implanted brachytherapy with the nominal treatment period of 1 to 2 weeks is an example. However, for the treatment period longer than 2 weeks (where we need to consider the repopulation), it is not logical to neglect the effect of repopulation in the LQ-model. In the present study, when we used the LQ-repopulation model, 32 fractions rather than infinite was shown to be optimal. This is consistent with the clinical fact that the standard irradiation with 30 to 40 fractions in 2 months achieves an excellent tumor control and a low complication

rate. Our study suggests that the LQ-repopulation model is more appropriate than the LQ model without consideration of repopulation in standard external radiotherapy.

The TO plot analysis with the LQ-repopulation model predicts that a single fraction is the best for the bladder in the treatment of prostate cancer. However, there have not been any trials which use a single fraction of high dose irradiation. This may be due to emotional fear for serious side effects caused by a single high dose irradiation based on the over-estimation of the curvature of dose response curve in the LQ-model or LQ-repopulation model. In this study, we have shown that the USC model or USC-repopulation models predict that 8 fractions with 6-6.5 Gy as a daily dose is optimal for the bladder in the treatment of prostate cancer, which is quite similar to the dose fractionation regimen actually used in clinical studies of SBRT. This similarity may be just a coincidence but suggests the superiority of the USC-model for the estimation of the rectilinear response in the high dose range. If we adapt the TO plot for the treatment period shorter than 4 weeks in hypo-fractionated irradiation where we need to consider the rectilinear response in the high dose range, the USC model is more appropriate. However, the TO plot using the USC model predicts that 40 fractions is the best in range of 1 to 40 fractions, i.e. that infinite fraction is the optimal for the rectum.

On the other hand, the TO plot with the USC-repopulation model predicts 8 fractions and 32 fractions as the best fractionation for the bladder and rectum, respectively. For covering both of the schemes above (i.e., standard radiotherapy in 2 months and SBRT with high dose per fraction), our results suggest that the USC-repopulation model is the most reasonable model to be used in this analysis as far as the parameters are reasonably pre-determined for these calculations. However, it is another issue whether we should select 8 fractions, 20 fractions or 32 fractions as the optimal fractionation for this particular patient with prostate cancer. It depends on the relative severity of the adverse effect for the bladder and rectum, past medical history of the patient in the bladder and rectum, whether the patient is taking anti-coagulant medication or not, and other complications. The final decision requires clinical decision by physicians at present but the PGF can provide additional guidance for the physician. In the future, the importance of PGF will increase by introducing weighting factors for each OAR. We adopted the USC model as the survival model to consider the linearity of the surviving fraction at high dose range. However, it would not be necessarily unique to the USC model and the similar superiority to the LQ model can be expected even when we use other models such as the nonlethal probability model [33]

In this study, we have paved the way for the TO plot for the optimization of the dose fractionation in actual IMRT using DVH by introducing a probability density function $f(\delta)$. Because $f(\delta)$ is equivalent to the differential DVH, the optimization is possible by incorporating the DVH derived from a three-dimensional treatment planning system.

The present study with three types of the modified LQ model shows a similar tendency that leads to the selection in terms of multi- or hypo- irradiation. In the case of IMRT for prostate cancer, multi-fractionation is better because the rectum corresponds to tissue for which the ratio of α/β is less than δ. On the other hand, hypo-fractionation is better for the bladder because the ratio of α/β is sometimes greater than δ for the bladder. However, the optimal fraction number is estimated not necessarily to be infinity or single when we use the modified LQ models. The survival models associated with the repopulation of tumor cells enable us to derive the optimal number of fractions as a few dozens of times (such as 32 times) rather than infinity for the rectum. In addition, by means of the models considering the linearity of the surviving fraction at high doses, we can derive the optimal number of fractions (such as 8 times) rather than a single fraction for the bladder. In this study, we adopted the USC model as the survival model to consider the linearity of the surviving fraction in the high dose range and confirmed the similar tendency to other models such as the nonlethal probability model [33]. By

taking account of the repopulation of tumor cells and the linearity in the high dose range in the LQ model, the optimization method was improved to be able to derive the optimal fractionation schemes, which supports empirical evidence found in clinical cases.

The previous studies were confined to the case that the dose distribution in the tumor and OAR are uniform. It should be natural to suppose that the local dose to OARs depends on their positions around a tumor while the dose to the tumor is realized almost uniform with a precise dose delivery technique such as IMRT. In this study, the optimization method has been extended to the case of non-uniform dose distribution of OARs by introducing a probability density function $f(\delta)$. Because $f(\delta)$ is equivalent to the differential DVH, the optimization is possible by incorporating the dose volume histogram. The optimization via TO plot using dose volume histograms is a promising method for the determination of the appropriate fractionation regimen in modern radiotherapy, where the physical dose distribution is determined before the selection of dose fractionation.

The actual response of tumor and normal tissues may depend on multiple factors (e.g., reoxygenation and redistribution) that cannot always be included in simplified

mathematical formulae. Therefore, further investigations are required to confirm the true optimal fractionation scheme through prospective clinical trials.

4. CONCLUSIONS

In this study, we have attempted to derive the optimal fractionation condition (the number of fractions, dose per fraction and total dose) by quantifying the effects on the tumor and OAR based on our optimization method. As the results, we came up with the following conclusions:

(1) The graphical method (TO plot) for the radiation effects associated with the repopulation of tumor cells and a rectilinear response in the high dose range enables us to derive the optimal fractionation scheme for IMRT and SBRT of prostate cancer, which may support other appropriate cases in clinical studies.

(2) It is possible to take account of the dose volume histogram as the physical dose distribution in the fractionation schemes to be optimized.

We have improved the TO plot method approaching practical use in physics-guided fractionation, which may lead to a new guideline to optimize the fractionation regimen for radiotherapy planning.

ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI Grant Number 25540008.

REFERENCES

1. H.R. Withers, “The four R’s of radiotherapy,” Adv. Radiat. Biol. **5**, 241-271 (1975).
2. J. Bourhis, J. Overgaard, H. Audry, K.K. Ang, M. Saunders, J. Bernier, J.C. Horiot, A. Le Maître, T.F. Pajak, M.G. Poulsen, B. O'Sullivan, W. Dobrowsky, A. Hliniak, K. Skladowski, J.H. Hay, L.H. Pinto, C. Fallai, K.K. Fu, R. Sylvester, J.P. Pignon “Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis,” Lancet **368**, 843-854 (2006).
3. A.T. Monroe, N. Bhandare, C.G. Morris, W.M. Mendenhall, “Preventing radiation retinopathy with hyperfractionation,” Int. J. Radiat. Oncol. Biol. Phys. **61**, 856-864 (2005).
4. M.I. Saunders, S. Dische, “Radiotherapy employing three fractions in each day over a continuous period of 12 days,” Br. J. Radiol. **59**, 523-525 (1986).
5. S. Dische, M.I. Saunders, “The rationale for continuous, hyperfractionated, accelerated radiotherapy (CHART),” Int. J. Radiat. Oncol. Biol. Phys. **19**,

1317-1320 (1990).

6. M. Saunders, S. Dische, A. Barrett, A. Harvey, G. Griffiths, M. Palmar, "Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: Mature data from the randomized multicentre trial," Radiother. Oncol. **52**, 137-148 (1999).

7. T.J. Whelan, J.P. Pignol, M.N. Levine, J.A. Julian, R. MacKenzie, S. Parpia, W. Shelley, L. Grimard, J. Bowen, H. Lukka, F. Perera, A. Fyles, K. Schneider, S. Gulavita, C. Freeman, "Long-term results of hypofractionated radiation therapy for breast cancer," N. Engl. J. Med. **362**, 513-520 (2010).

8. T. Hijal, A.A. Hamad, T. Niazi, K. Sultanem, B. Bahoric, T. Vuong, T. Muanza, "Hypofractionated radiotherapy and adjuvant chemotherapy do not increase radiation-induced dermatitis in breast cancer patients," Curr. Oncol. **17**, 22-27 (2010).

9. I.S. Vogelius, D.C. Westerly, G.M. Cannon, S.M. Bentzen, "Hypofractionation does not increase radiation pneumonitis risk with modern conformal radiation delivery techniques," Acta. Oncol. **49**, 1052-1057 (2010).

10. R. Timmerman, R. McGarry, C. Yiannoutsos, L. Papiez, K. Tudor, J. DeLuca, M. Ewing, R. Abdulrahman, C. DesRosiers, M. Williams, J. Fletcher, "Excessive

toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer," J. Clin. Oncol. **24**, 4833-4839 (2006).

11. Y. Nagata, J. Wulf, I. Lax, R. Timmerman, F. Zimmermann, I. Stojkovski, B. Jeremic, "Stereotactic radiotherapy of primary lung cancer and other targets: Results of consultant meeting of the International Atomic Energy Agency," Int. J. Radiat. Oncol. Biol. Phys. **79**, 660-669 (2011).
12. E.E. Yeoh, R.J. Botten, J. Butters, A.C. Di Matteo, R.H. Holloway, J. Fowler, "Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: Final results of phase III randomized trial," Int. J. Radiat. Oncol. Biol. Phys. **81**, 1271-1278 (2011).
13. G. Arcangeli, J. Fowler, S. Gomellini, S. Arcangeli, B. Saracino, M.G. Petrongari, M. Benassi, L. Strigari, "Acute and late toxicity in a randomized trial of conventional versus hypofractionated three-dimensional conformal radiotherapy for prostate cancer," Int. J. Radiat. Oncol. Biol. Phys. **79**, 1013-1021 (2011).
14. W. Budach, T. Hehr, V. Budach, C. Belka, K. Dietz, "A metaanalysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of

the head and neck," BMC Cancer **6**, 28 (2006).

15. H. Onishi, H. Shirato, Y. Nagata, M. Hiraoka, M. Fujino, K. Gomi, K. Karasawa, K. Hayakawa, Y. Niibe, Y. Yakai, T. Kimura, A. Takeda, A. Ouchi, M. Hareyama, M. Kokubo, T. Kozuka, T. Arimoto, R. Hara, J. Itami, T. Arai, "Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: Can SBRT be comparable to surgery?" Int. J. Radiat. Oncol. Biol. Phys. **81**, 1352-1358 (2011).
16. N. Stavreva, A. Nahum, K. Markov, R. Ruggieri, P. Stavrev, "Analytical investigation of the possibility of parameter invariant TCP-based radiation therapy plan ranking," Acta. Oncol. **49**, 1324-1333 (2010).
17. Y. Yang, L. Xing, "Optimization of radiotherapy dose-time fractionation with consideration of tumor specific biology," Med. Phys. **32**, 3666-3677 (2005).
18. M. Mizuta, S. Takao, H. Date, N. Kishimoto, K.L. Sutherland, R. Onimaru, H. Shirato, "A mathematical study to select fractionation regimen based on physical dose distribution and the linear quadratic model," Int. J. Radiat. Oncol. Biol. Phys. **84**, 829-833 (2012).
19. J. Unkelbach, D. Craft, E. Salari, J. Ramakrishnan, T. Bortfeld, "The dependence of optimal fractionation schemes on the spatial dose distribution," Phys. Med. Biol. **58**, 159-167 (2013).

20. J. Flanz, T. Bortfeld, “Evolution of technology to optimize the delivery of proton therapy: the third generation,” Semin. Radiat. Oncol. **23**, 142-148 (2013).

21. H. Keller, A. Hope, G. Meier, M. Davison, “A novel dose-volume metric for optimizing therapeutic ratio through fractionation: retrospective analysis of lung cancer treatments,” Med. Phys. **40**, 084101 (2013).

22. J. Unkelbach, C. Zeng, M. Engelsman, “Simultaneous optimization of dose distributions and fractionation schemes in particle radiotherapy,” Med. Phys. **40**, 091702 (2013).

23. M. Mizuta, H. Date, S. Takao, N. Kishimoto, K.L. Sutherland, R. Onimaru, H. Shirato, “Graphical representation of the effects on tumor and OAR for determining the appropriate fractionation regimen in radiation therapy planning,” Med. Phys. **39**, 6791-6795 (2012).

24. J.P. Kirkpatrick, J.J. Meyer, L.B. Marks, “The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery,” Semin. Radiat. Oncol. **18**, 240-243 (2008).

25. M. Astrahan, “Some implications of linear-quadratic-linear radiation doseresponse with regard to hypofractionation,” Med. Phys. **35**, 4161-4172 (2008).

26. G.R. Borst, M. Ishikawa, J. Nijkamp, M. Hauptmann, H. Shirato, G. Bengua, R. Onimaru, A. de Josien Bois, J.V. Lebesque, J.J. Sonke, "Radiation pneumonitis after hypofractionated radiotherapy: evaluation of the LQ(L) model and different dose parameters," Int. J. Radiat. Oncol. Biol. Phys. **77**, 1596-1603 (2010).

27. M. Guckenberger, R.J. Klement, M. Allgäuer, S. Appold, K. Dieckmann, I. Ernst, U. Ganswindt, R. Holy, U. Nestle, M. Nevinny-Stickel, S. Semrau, F. Sterzing, A. Wittig, N. Andratschke, M. Flentje, "Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer," Radiother. Oncol. **109**, 13-20 (2013).

28. C. Park, L. Papiez, S. Zhang, M. Story, R.D. Timmerman, "Universal survival curve and single fraction equivalent dose: Useful tools in understanding potency of ablative radiotherapy," Int. J. Radiat. Oncol. Biol. Phys. **70**, 847-852 (2008).

29. B.M. Wennberg, P. Baumann, G. Gagliardi, J. Nyman, N. Drugge, M. Hoyer, A. Traberg, K. Nilsson, E. Morhed, L. Ekberg, L. Wittgren, J.Â. Lund, N. Levin, C. Sederholm, R. Lewensohn, I. Lax, "NTCP modelling of lung toxicity after SBRT comparing the universal survival curve and the linear quadratic model for

fractionation correction," Acta. Oncol. **50**, 518-527 (2011).

30. B. Wennberg, I. Lax I, "The impact of fractionation in SBRT: analysis with the linear quadratic model and the universal survival curve model," Acta. Oncol. **52**, 902-909 (2013).

31. E.l. Lindblom, A. Dasu, I. Lax, I. Toma-Dasu, "Survival and tumour control probability in tumours with heterogeneous oxygenation: a comparison between the linear-quadratic and the universal survival curve models for high doses," Acta. Oncol. **53**, 1035-1040 (2014).

32. S. Aluwini, F. Pos, E. Schimmel, E. van Lin, S. Krol, P.P. van der Toorn, H. de Jager, M. Dirkx, W.G. Alemayehu., B. Heijmen, L. Incrocci, "Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial," Lancet Oncol. **14**, 70482-70486 (2015)

33. H. Date, K. Wakui, K. Sasaki, T. Kato, T. Nishioka, "A formulation of cell surviving fraction after radiation exposure," Radiol. Phys. Technol. **7**, 148-157 (2014).