Journal of Radiation Research, Vol. 59, No. S1, 2018, p. i32–i39
doi: 10.1093/jrr/rrx084
Advance Access Publication: 4 January 2018
Special Issue – Approaches to Select Advanced External Radiotherapy

Comparison of the average surviving fraction model with the integral biologically effective dose model for an optimal irradiation scheme

Ryo Takagi[1], Yuriko Komiya[2], Kenneth L. Sutherland[3], Hiroki Shirato[3,4], Hiroyuki Date[5] and Masahiro Mizuta[2,*]

[1]Graduate School of Information Science and Technology, Hokkaido University, Kita-14, Nishi-9, Kita-ku, Sapporo, 060-0814, Japan
[2]Laboratory of Advanced Data Science, Information Initiative Center, Hokkaido University, Kita-11, Nishi-5, Kita-ku, Sapporo, 060-0811, Japan
[3]Global Station for Quantum Medical Science and Engineering, Global Institution for Collaborative Research and Education (GI-CoRE), Hokkaido University, Kita-15, Nishi-8, Kita-ku, Sapporo, 060-0815, Japan
[4]Department of Radiation Medicine, Faculty of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo, 060-8638, Japan
[5]Faculty of Health Sciences, Hokkaido University, Kita-12, Nishi-5, Kita-ku, Sapporo, 060-0812, Japan
*Corresponding author. Information Initiative Center, Hokkaido University, Kita-11, Nishi-5, Kita-ku, Sapporo, 060-0811, Japan.
Tel: +81-11-706-3755; Fax: +81-11-706-4854; Email: mizuta@iic.hokudai.ac.jp
(Received 12 October 2017; revised 14 November 2017; editorial decision 4 December 2017)

ABSTRACT

In this paper, we compare two radiation effect models: the average surviving fraction (ASF) model and the integral biologically effective dose (IBED) model for deriving the optimal irradiation scheme and show the superiority of ASF. Minimizing the effect on an organ at risk (OAR) is important in radiotherapy. The biologically effective dose (BED) model is widely used to estimate the effect on the tumor or on the OAR, for a fixed value of dose. However, this is not always appropriate because the dose is not a single value but is distributed. The IBED and ASF models are proposed under the assumption that the irradiation is distributed. Although the IBED and ASF models are essentially equivalent for deriving the optimal irradiation scheme in the case of uniform distribution, they are not equivalent in the case of non-uniform distribution. We evaluate the differences between them for two types of cancers: high α/β ratio cancer (e.g. lung) and low α/β ratio cancer (e.g. prostate), and for various distributions i.e. various dose–volume histograms. When we adopt the IBED model, the optimal number of fractions for low α/β ratio cancers is reasonable, but for high α/β ratio cancers or for some DVHs it is extremely large. However, for the ASF model, the results keep within the range used in clinical practice for both low and high α/β ratio cancers and for most DVHs. These results indicate that the ASF model is more robust for constructing the optimal irradiation regimen than the IBED model.

Keywords: linear–quadratic model; universal survival curve; radiosensitivity; dose–volume histogram

INTRODUCTION

Minimizing the effect on an organ at risk (OAR) is important in radiotherapy. However, the precise mathematical definition of 'effect' is essential for planning the optimal regimen. The biologically effective dose (BED) model is widely used to estimate the effect on the tumor or on the OAR, for a fixed value of the dose [1]. However, this is not always appropriate because the dose is not a single value but is distributed. Thus, the integral BED (IBED) model was proposed under the assumption that irradiation to tissues is distributed [2–4]. Another model, the average surviving fraction (ASF) model, was also proposed under the same assumption. It is based on the expectation of the surviving proportion of the whole tumor or of the whole OAR [5, 6]. It is easy to prove that IBED and ASF are essentially equivalent for deriving the optimal irradiation scheme in the case of a single-value dose or uniformly distributed dose. However, in the case of non-uniform distribution, they are not equivalent and we must investigate the difference between them.

Both ASF and IBED are based on the LQ model [7]. However, the LQ model does not fit well in the high-dose range. Thus, the universal survival curve (USC), which is identical to the LQ model curve in the low-dose range but is linear in the high-dose range, was proposed as an extension of the LQ model [8, 9]. The USC has advantages as it reduces the overestimated effects in the high-dose range compared with the LQ model, resulting in a more realistic effect on the target site. The ASF and IBED models can be defined based on the USC.

Both the LQ and the USC models require the same parameters, such as α and β. The values of α and β describe linear and quadratic irradiation damage, respectively, and the α/β ratio represents radiosensitivity. The ratios for most cancers are regarded to be relatively high compared with normal tissues, whereas the ratios for some cancers (e.g. prostate cancer) have a similar value to normal tissues.

In this paper, we compare two effect models: the ASF and IBED models, for various values of the α/β ratio based on the LQ and the USC models, and for various types of DVHs.

MATERIALS AND METHODS

We begin with the definition of the effect for multiple-fractions on the tumor or OARs whose dose is a single value or is distributed uniformly (uniform DVHs). In this situation, the dose to the tumor is d [Gy] and the dose to the OAR is δd [Gy] with a constant of proportionality factor δ [10]. Hereafter, N denotes the number of fractions.

We first describe the SF models for the tumor and the OAR based on the LQ model with tumor repopulation (LQ-R). The surviving fractions on the tumor $SF_1(d, N)$ and on the OAR $SF_0(d, N)$ are defined as follows:

$$SF_1(d, N) = \exp\left[-N(\alpha_1 d + \beta_1 d^2) + \frac{\ln 2}{T_{\text{pot}}}(T - T_k)\right], \quad (1)$$

$$SF_0(d, N) = \exp[-N(\alpha_0 \delta d + \beta_0 (\delta d)^2)], \quad (2)$$

where α_1, β_1 are parameters for the tumor, α_0, β_0 are parameters for the OAR, T is the total treatment time, and T_k and T_{pot} are the starting time, and the doubling time for the tumor, respectively [11, 12]. We assume that the radiation is performed once a day, so $T - T_k$ takes the value of N.

The BED models based on the LQ-R for the tumor $BED_1(d, N)$ and for the OAR $BED_0(d, N)$ are defined as follows:

$$BED_1(d, N) = Nd\left(1 + \frac{d}{\alpha_1/\beta_1}\right) - \frac{\ln 2}{\alpha_1 T_{\text{pot}}}(T - T_k), \quad (3)$$

$$BED_0(d, N) = N\delta d\left(1 + \frac{\delta d}{\alpha_0/\beta_0}\right). \quad (4)$$

We present formulas for the SF and BED models based on the USC with tumor repopulation (USC-R) in multiple-fractions on the tumor and the OAR. The SF models based on the USC-R are defined as follows:

$$SF_1(d, N) = \begin{cases} \exp\left[-N(\alpha_1 d + \beta_1 d^2) + \frac{\ln 2}{T_{\text{pot}}}(T - T_k)\right] & \text{if } d < D_{t,1} \\ \exp\left\{-N[(\alpha_1 + 2\beta_1 D_{t,1})d - \beta_1 D_{t,1}^2] + \frac{\ln 2}{T_{\text{pot}}}(T - T_k)\right\} & \text{if } d \geq D_{t,1} \end{cases}, \quad (5)$$

$$SF_0(d, N) = \begin{cases} \exp[-N(\alpha_0 \delta d + \beta_0 (\delta d)^2)] & \text{if } \delta d < D_{t,0} \\ \exp\{-N[(\alpha_0 + 2\beta_0 D_{t,0})\delta d - \beta_0 D_{t,0}^2]\} & \text{if } \delta d \geq D_{t,0} \end{cases}, \quad (6)$$

and the BED models based on the USC-R are defined as follows:

$$BED_1(d, N) = \begin{cases} Nd\left(1 + \frac{d}{\alpha_1/\beta_1}\right) - \frac{\ln 2}{\alpha_1 T_{\text{pot}}}(T - T_k) & \text{if } d < D_{t,1} \\ N\left(d + \frac{2D_{t,1}d - D_{t,1}^2}{\alpha_1/\beta_1}\right) - \frac{\ln 2}{\alpha_1 T_{\text{pot}}}(T - T_k) & \text{if } d \geq D_{t,1} \end{cases}, \quad (7)$$

$$BED_0(d, N) = \begin{cases} N\delta d\left(1 + \frac{\delta d}{\alpha_0/\beta_0}\right) & \text{if } \delta d < D_{t,0} \\ N\left(\delta d + \frac{2D_{t,0}\delta d - D_{t,0}^2}{\alpha_0/\beta_0}\right) & \text{if } \delta d \geq D_{t,0} \end{cases}, \quad (8)$$

where $D_{t,1}$ and $D_{t,0}$ are transition doses to the tumor and the OAR, respectively [11].

The effect on the tumor $E_{1,SF}(d, N)$ and the effect on the OAR $E_{0,SF}(d, N)$ with the SF model [11] are as follows:

$$E_{1,SF}(d, N) = -\ln[SF_1(d, N)], \quad (9)$$

$$E_{0,SF}(d, N) = -\ln[SF_0(d, N)]. \quad (10)$$

Similarly, the effect on the tumor $E_{1,BED}(d, N)$ and the effect on the OAR $E_{0,BED}(d, N)$ with the BED model are defined as follows:

$$E_{1,BED}(d, N) = BED_1(d, N), \quad (11)$$

$$E_{0,BED}(d, N) = BED_0(d, N) \quad (12)$$

The effects with the SF and BED models are essentially the same when SF and BED are used in uniform DVHs.

Based on these definitions, we define the effects in multiple-fractions on the OAR with non-uniform dose distribution. We assume the dose to the tumor is distributed uniformly. On the contrary, typical DVHs of radiation for the OAR distribute non-uniformly in general. The effects are calculated with ASF and IBED for the optimal irradiation scheme based on the LQ-R and based on the USC-R.

First, we define the effects with ASF and with IBED based on the LQ-R in the case of non-uniform OAR DVHs. ASFs based on the LQ-R for the tumor $ASF_1(d, N)$ and for the OAR $ASF_0(d, N)$ are defined by

$$ASF_1(d,\,N) = \exp\left[-N(\alpha_1 d + \beta_1 d^2) + \frac{\ln 2}{T_{\rm pot}}(T - T_k)\right], \quad (13)$$

$$\begin{aligned} ASF_0(d,\,N) &= \int_0^\infty \exp[-N(\alpha_0\delta d + \beta_0(\delta d)^2)]f_0(\delta)\,{\rm d}\delta \\ &\approx \tfrac{1}{M}\textstyle\sum_{i=1}^{M}\exp[-N(\alpha_0\delta_i d + \beta_0(\delta_i d)^2)], \end{aligned} \quad (14)$$

where M is the number of cells or the number of functional subunits, δ_i is the ratio of the OAR dose to the tumor dose for i-th cell or i-th functional subunit, $f_0(\delta)$ is a differential DVH for the OAR, and $\int_0^\infty f_0(\delta)\,{\rm d}\delta = 1$ [11].

IBEDs based on the LQ-R for the tumor $IBED_1(d,\,N)$ and for the OAR $IBED_0(d,\,N)$ are defined by

$$IBED_1(d,\,N) = Nd\left(1 + \frac{d}{\alpha_1/\beta_1}\right) - \frac{\ln 2}{\alpha_1 T_{\rm pot}}(T - T_k), \quad (15)$$

$$\begin{aligned} IBED_0(d,\,N) &= N\int_0^\infty \delta d\left(1 + \frac{\delta d}{\alpha_0/\beta_0}\right)f_0(\delta)\,{\rm d}\delta \\ &\approx N\frac{1}{M}\textstyle\sum_{i=1}^{M}\left[\delta_i d\left(1 + \frac{\delta_i d}{\alpha_0/\beta_0}\right)\right]. \end{aligned} \quad (16)$$

Next, we show formulas for the ASF and IBED models based on the USC-R in multiple-fractions on the tumor and the OAR whose dose is distributed (non-uniform DVH). ASFs based on the USC-R are defined as follows:

$$ASF_1(d,\,N) = \begin{cases} \exp\left[-N(\alpha_1 d + \beta_1 d^2) + \frac{\ln 2}{T_{\rm pot}}(T - T_k)\right] & if\ d < D_{t,1} \\ \exp\left\{-N[(\alpha_1 + 2\beta_1 D_{t,1})d - \beta_1 D_{t,1}^2] + \frac{\ln 2}{T_{\rm pot}}(T - T_k)\right\} & if\ d \ge D_{t,1} \end{cases}, \quad (17)$$

$$\begin{aligned} ASF_0(d,\,N) &= \int_0^{\frac{D_{t,0}}{d}} \exp[-N(\alpha_0\delta d + \beta_0(\delta d)^2)]f_0(\delta)\,{\rm d}\delta \\ &+ \int_{\frac{D_{t,0}}{d}}^\infty \exp\{-N[(\alpha_0 + 2\beta_0 D_{t,0})\delta d - \beta_0 D_{t,0}^2]\}f_0(\delta)\,{\rm d}\delta \\ &\approx \tfrac{1}{M}\textstyle\sum_{\delta_i < \frac{D_{t,0}}{d}}\exp[-N(\alpha_0\delta_i d + \beta_0(\delta_i d)^2)] \\ &+ \tfrac{1}{M}\textstyle\sum_{\delta_i \ge \frac{D_{t,0}}{d}}\exp\{-N[(\alpha_0 + 2\beta_0 D_{t,0})\delta_i d - \beta_0 D_{t,0}^2]\}, \end{aligned} \quad (18)$$

and IBEDs based on the USC-R for the tumor and the OAR are defined by

$$IBED_1(d,\,N) = \begin{cases} Nd\left(1 + \frac{d}{\alpha_1/\beta_1}\right) - \frac{\ln 2}{\alpha_1 T_{\rm pot}}(T - T_k) & if\ d < D_{t,1} \\ N\left(d + \frac{2D_{t,1}d - D_{t,1}^2}{\alpha_1/\beta_1}\right) - \frac{\ln 2}{\alpha_1 T_{\rm pot}}(T - T_k) & if\ d \ge D_{t,1} \end{cases}, \quad (19)$$

$$\begin{aligned} IBED_0(d,\,N) &= N\int_0^{\frac{D_{t,0}}{d}} \delta d\left(1 + \frac{\delta d}{\alpha_0/\beta_0}\right)f_0(\delta)\,{\rm d}\delta \\ &+ N\int_{\frac{D_{t,0}}{d}}^\infty \left[\delta d + \frac{2D_{t,0}\delta d - D_{t,0}^2}{\alpha_0/\beta_0}\right]f_0(\delta)\,{\rm d}\delta \\ &\approx N\frac{1}{M}\textstyle\sum_{\delta_i < \frac{D_{t,0}}{d}}\left[\delta_i d\left(1 + \frac{\delta_i d}{\alpha_0/\beta_0}\right)\right] \\ &+ N\tfrac{1}{M}\textstyle\sum_{\delta_i \ge \frac{D_{t,0}}{d}}\left[\delta_i d + \frac{2D_{t,0}\delta_i d - D_{t,0}^2}{\alpha_0/\beta_0}\right]. \end{aligned} \quad (20)$$

For the case of non-uniform OAR DVHs, the effect on the tumor $E_{1,ASF}(d,\,N)$ and the effect on the OAR $E_{0,ASF}(d,\,N)$ with the ASF model [11] are as follows:

$$E_{1,ASF}(d,\,N) = -\ln[ASF_1(d,\,N)], \quad (21)$$

$$E_{0,ASF}(d,\,N) = -\ln[ASF_0(d,\,N)]. \quad (22)$$

Similarly, for the non-uniform OAR DVHs, the effect on the tumor $E_{1,IBED}(d,\,N)$ and the effect on the OAR $E_{0,IBED}(d,\,N)$ with the IBED model are defined as follows:

$$E_{1,IBED}(d,\,N) = IBED_1(d,\,N), \quad (23)$$

$$E_{0,IBED}(d,\,N) = IBED_0(d,\,N). \quad (24)$$

The effects with the ASF and IBED models are not the same when ASF and IBED are used in non-uniform OAR DVHs.

We must achieve two contrasting objectives: (i) preserve OARs as much as possible and (ii) irradiate sufficient dose to the tumor. We attempt to minimize the effect on OARs, whereas the effect on the tumor is fixed. For uniform DVHs, the effects are calculated as in Eqs. (9–12) for the tumor and the OAR. Note that for serial OARs, it is recommended that the maximum dose be used [4]. The use of the maximum dose means that the dose to the OAR is a single value. For non-uniform DVHs, we use the effects calculated as shown in Eqs. (21–24) for tumor and the OAR, respectively.

With the effects, we derive irradiation regimens using the previously proposed method for five patterns of DVHs with ASF and IBED. Dose–volume histograms (DVHs) for prostate cancer with OARs rectum and bladder are used as reported [11]. We assume that the parameter sets of α_1 and β_1 are different in each of three risk groups [13]. They proposed that the values for the parameters are $\alpha_1 = 0.010$, $\beta_1 = 0.017$ in the high-risk group, $\alpha_1 = 0.036$, $\beta_1 = 0.021$ in the intermediate-risk group and $\alpha_1 = 0.044$, $\beta_1 = 0.028$ in the low-risk group (Table 1). We set the parameters for prostate cancer to $\alpha_0 = 0.04$, $\beta_0 = 0.02$, $T_k = 0$, $T_{\rm pot} = 28$, and $D_{t,1} = D_{t,0} = 6$. We derived the irradiation regimen, irradiating the tumor with a total of 70 Gy in 30 fractions, while minimizing the effect on the OARs.

Figure 1a shows DVHs for lung cancer treated with photon beams. The differential DVH for lung cancer is described in Fig. 1b. These indicate that some OARs [spinal cord (SC), trachea, and esophagus] are irradiated with a low dose over large volumes, but

others [bronchus, aorta, pulmonary artery (PA) and lung] are irradiated to high doses over small volumes. We assume the dose distributions are non-uniform. We set the parameters to $\alpha_1 = 0.15$, $\beta_1 = 0.015$, $\alpha_0 = 0.04$, $\beta_0 = 0.02$, $T_k = 0$, $T_{pot} = 15$ and $D_{t,1} = D_{t,0} = 6$. The deriving irradiation regimens were composed to irradiate to the tumor a total of 70 Gy in 30 fractions while minimizing the effect on the OARs.

We also composed three artificial DVHs (Fig. 2) as follows: the whole OAR is irradiated with a low dose when the distance between the OAR and tumor is sufficiently large (Type 1); the OAR is irradiated gradually from low dose to high dose (Type 2); and half the volume of the OAR is irradiated with a low dose while the remaining is irradiated with a very high dose (Type 3). In these situations, we derive the irradiation regimens for high- and low- α/β ratio cancer, and we assume that each tumor is irradiated uniformly. For high α/β cancer, we set the parameters to $\alpha_1 = 0.15$, $\beta_1 = 0.015$ ($\alpha_1/\beta_1 = 10$), $T_{pot} = 15$, $D_{t,1} = D_{t,0} = 6$, and for low α/β ratio cancer to $\alpha_1 = 0.010$, $\beta_1 = 0.0167$ ($\alpha_1/\beta_1 = 0.6$), $T_{pot} = 28$, $D_{t,1} = D_{t,0} = 6$. The irradiation regimens consist of irradiation to the tumor a total of 70 Gy in 30 fractions while minimizing the effect on the OARs. In addition, we investigate the influence of the doubling time for deriving the optimal regimens in the case of $\alpha_1 = 0.15$, $\beta_1 = 0.015(\alpha_1/\beta_1 = 10)$. We set the value of the doubling time for the tumor, varying from 1 to 50, and calculated the optimal number of fractions for each value with other parameters set the same as above.

Table 1. Parameter settings α, β and α/β, for prostate cancer in three risk groups

	Risk group[a]		
parameter	High	Mid	Low
α (Gy^{-1})	0.010	0.036	0.044
β (Gy^{-2})	0.0167	0.0212	0.0275
α/β (Gy)	0.6	1.7	1.6

[a]We consider the parameters of α and β for prostate cancer are different in their risk groups [13]. All sets of parameters are lower than those for normal tissues that we set in this study.

RESULTS

We choose prostate cancer as a special case because of its low value for the α/β ratio. The α/β ratios for the three risk groups are; $\alpha_1/\beta_1 = 0.6$ for high risk, $\alpha_1/\beta_1 = 1.7$ for intermediate risk and $\alpha_1/\beta_1 = 1.6$ for low risk (Table 1). The results for prostate cancer are shown in Table 2. The optimal numbers of fractions with ASF and IBED based on the LQ-R for bladder and rectum are the same in each risk group. For bladder, the optimal number of fractions is almost the same in ASF and IBED based on the USC-R, and the results for rectum are the same in each risk group. The results are almost the same for prostate cancer calculated with ASF and IBED, regardless of risk groups. Thus, the regimens with either ASF or IBED suggest that hypofractionated radiotherapy is better for this case.

We next derived the irradiation regimens for lung cancer ($\alpha/\beta = 10$). The results are shown in Table 3. The derived regimens are almost the same for spinal cord, trachea and esophagus, with ASF and IBED based on the LQ-R or the USC-R. However, the results with ASF and IBED are different for other OARs. ASF suggests that hypofractionated radiotherapy is better, but IBED recommends hyperfractionated radiotherapy. Taken together, some OARs clearly require a hypofractionated regimen while others show the benefit of either hypo- or hyper-fractionated irradiation. The result depends only on the choice of ASF or IBED.

Finally, we derived the irradiation regimens for three artificial DVHs, whose results are shown in Table 4. The results suggest that the derived irradiation regimens with ASF and IBED are almost the same for low α/β ratio cancers. On the contrary, the optimal number of fractions can be extremely large if we use IBED for high α/β cancers, as shown in Type 2 and Type 3 with IBED. In Type 1, the optimal number of fractions for both high and low α/β ratio cancer is almost the same, with ASF or IBED based on either the LQ-R or the USC-R.

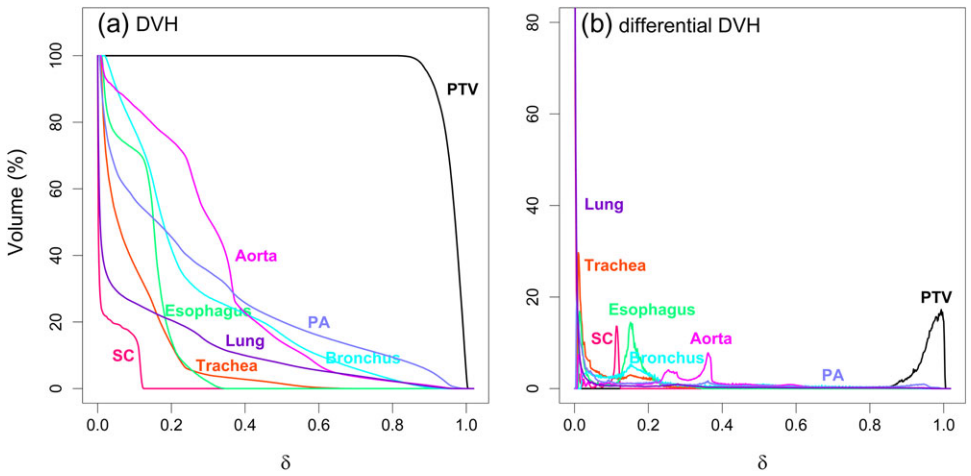

Fig. 1. Example of dose–volume histograms for lung cancer. (a) and (b) describe the dose–volume histogram and differential dose–volume histogram, respectively, for the organs at risk and the planning target volume.

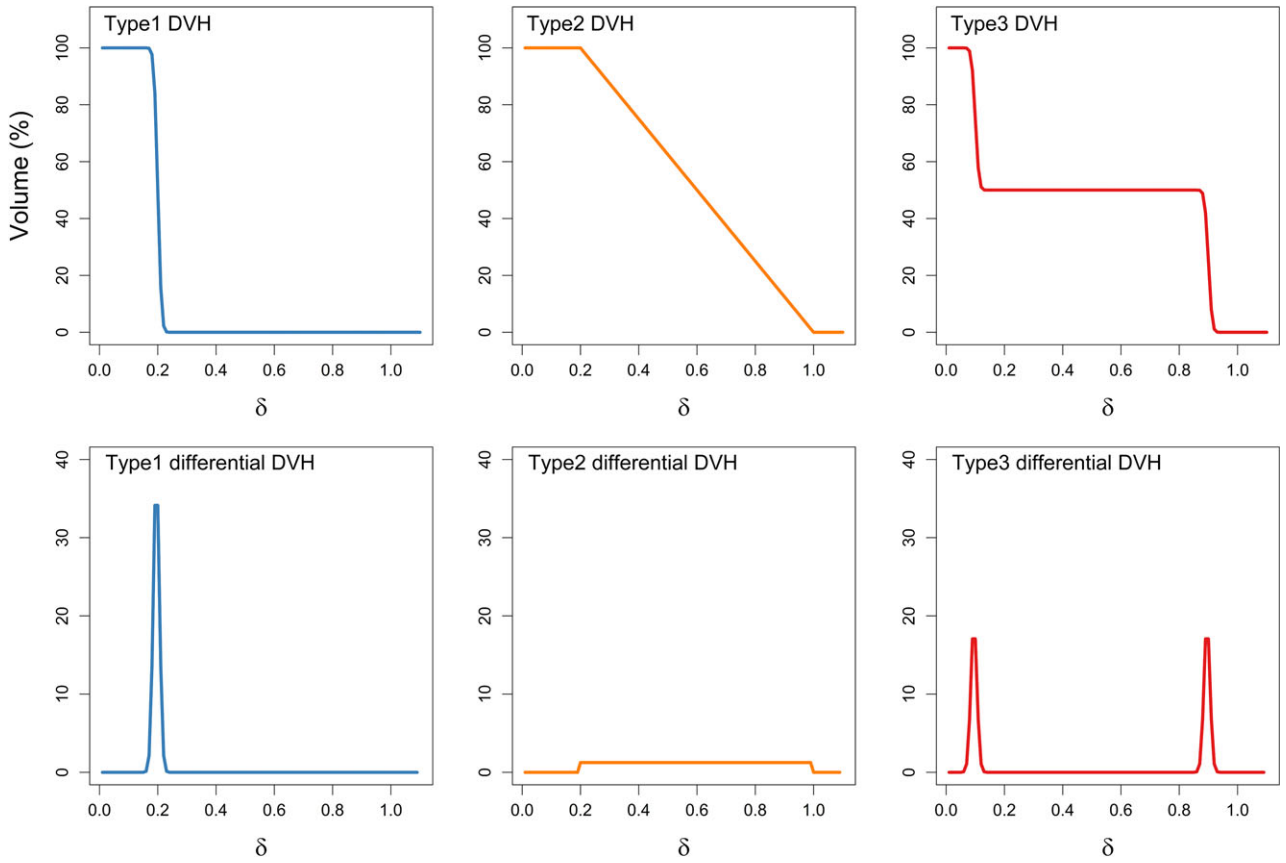

Fig. 2. Artificial dose–volume histograms (top) and differential dose–volume histograms (bottom) of organ at risks for Type 1 (left), Type 2 (center) and Type 3 (right).

Table 2. Derived irradiation regimens for organs at risk for prostate cancer radiotherapy planning (bladder and rectum) in three risk groups

	LQ-R		USC-R	
Risk group	ASF	IBED	ASF	IBED
Bladder				
High	12.442/1	12.442/1	18.710/2	21.685/3
Intermediate	14.935/1	14.935/1	26.188/3	28.901/4
Low	15.007/1	15.007/1	26.399/3	29.112/4
Rectum				
High	12.442/1	12.442/1	21.685/3	21.685/3
Intermediate	14.935/1	14.935/1	28.901/4	28.901/4
Low	15.007/1	15.007/1	29.112/4	29.112/4
				total dose (Gy) /# fractions

ASF = average surviving fraction, IBED = integral biologically effective dose, LQ-R = linear–quadratic model with tumor repopulation, USC-R = universal survival curve with tumor repopulation.

Table 3. Derived irradiation regimens for organs at risk for lung cancer radiotherapy planning: spinal cord, trachea, esophagus, bronchus, aorta, pulmonary artery and lung

	LQ-R		USC-R	
OARs	ASF	IBED	ASF	IBED
SC	23.266/1	23.266/1	45.700/6	45.700/6
Trachea	23.266/1	30.671/2	47.476/7	49.253/8
Esophagus	23.266/1	23.266/1	47.476/7	47.476/7
Bronchus	23.266/1	70.574/31	49.253/8	70.574/31
Aorta	59.726/16	70.000/30	59.726/16	70.000/30
PA	23.266/1	75.733/41	49.253/8	75.733/41
Lung	23.266/1	73.269/36	49.253/8	73.269/36
				total dose (Gy)/ # fractions

SC = spinal cord, PA = pulmonary artery, OAR = organ at risk, ASF = average surviving fraction, IBED = integral biologically effective dose, LQ-R = linear–quadratic model with tumor repopulation, USC-R = universal survival curve with tumor repopulation.

Table 4. Derived irradiation regimens for organs at risk with simulated dose–volume histograms (Type 1, 2 and 3) for high α/β (=10) ratio (top) and low α/β (=0.6) ratio (bottom) cancer

	LQ-R		USC-R	
	ASF	IBED	ASF	IBED
High α/β				
Type 1[a]	23.266/1	23.266/1	42.147/4	49.253/8
Type 2[b]	23.266/1	78.907/48	43.924/5	78.907/48
Type 3[c]	23.266/1	81.853/55	40.371/3	81.853/55
Low α/β				
Type 1[a]	12.448/1	12.448/1	21.702/3	18.727/2
Type 2[b]	12.448/1	12.448/1	24.678/4	21.702/3
Type 3[c]	12.448/1	12.448/1	24.678/4	15.751/1
				total dose (Gy)/ # fractions

ASF = average surviving fraction, IBED = integral biologically effective dose, LQ-R = linear–quadratic model with tumor repopulation, USC-R = universal survival curve with tumor repopulation.
[a]An organ at risk, which is irradiated with a low dose to a small proportion of its volume.
[b]An organ at risk, which is irradiated with a range of doses over its volume.
[c]An organ at risk, which is irradiated with a low dose to half its volume and with a high dose to the remaining volume.

In Type 2, the derived irradiation regimens for low α/β ratio cancer are almost the same. On the other hand, for high α/β cancer, the optimal number of fractions with IBED is much greater than that with ASF based on both the LQ-R and the USC-R. In Type 3, for high α/β cancer, the optimal number of fractions is small with ASF based on the LQ-R and the USC-R, whereas the number is large with IBED.

We investigated the influence of the doubling time for the tumor for three artificial DVHs and the results are shown in Fig. 3. The results suggest that the number of fractions derived by IBED are high compared to that by ASF both with the LQ-R and the USC-R. All of the DVH types suggested that the optimal number of fractions by ASF is smaller than that by IBED.

DISCUSSION

In this study, we compared ASF with IBED based on the LQ-R or the USC-R in the irradiation regimens for several cancers. We also constructed three OAR dose distributions that are common in real cases [14]. Our results suggest that hypofractionated radiotherapy is better with ASF or IBED for low α/β ratio cancer (prostate) in all risk groups. On the other hand, for high α/β ratio cancer (lung), ASF indicates that adopting hypofractionated radiotherapy is better, while IBED indicates that hyperfractionated radiotherapy is better in several DVHs for OARs. The differences between ASF and IBED occurred only for high α/β ratio cancers. This was also apparent in the results for artificial DVHs of OARs (Type 2 and Type 3) where the irradiation was distributed non-uniformly. For the case of non-uniform distribution, palpable differences between ASF and IBED were observed only for high α/β ratio cancers. The shape of the DVH for OARs has a positional relationship between the tumor and the OARs. For the case of uniform distribution, the optimal irradiation scheme is only affected by the δ and α/β for the tumor and the OAR [12]. Recent advances in radiation technology such as intensity-modulated radiotherapy and image-guided radiotherapy allow us to radiate with high accuracy to the tumor while reducing the irradiated volume on OARs (i.e. relatively low δ_i) [15]. In other words, these enable us to reduce the effects on the OARs and increase the effect on the tumor.

For a realistic estimation of the effects of irradiation, we need to take care not to apply the LQ model in the high-dose range. Although the LQ model is a convenient model for calculating a dose effect, it is constructed based on clinical outcomes of *in vitro* cell survival data. It requires the parameters α and β, which illustrate the effects on the linear and quadratic terms, respectively. This model estimates the effects well in the low-dose range, but overestimates the effects in the high-dose range. The curve of the effects in the high-dose range is linear, and thus the LQ model estimates excessive effects due to the quadratic term [16, 17]. The USC, another model for calculating dose effect, lessens the quadratic effect in the high-dose range by using an alternative linear curve to describe more realistic effects of radiation [8]. The USC is a hybrid model of the LQ model in the low-dose range and the multi-target model in the high-dose range. The high-dose range means the radiation to the tumor or to the OAR exceeds the transition dose of $D_{t,1}$ or $D_{t,0}$. By correcting the quadratic curve in the high-dose range to be linear, the USC estimates more realistically the actual state of the tissues. The results based on the LQ-R often show single-fractionation rather than hypofractionated radiotherapy, but the results are not practical in general. As mentioned, when the optimal irradiation dose based on the LQ-R is in the high-dose range, the use of the USC-R is better for optimizing the regimen. We set the transition dose from low to high at 6 Gy. Thus, the results above 6 Gy per fraction with the LQ-R are overestimated compared with the USC-R.

Radiotherapy for low α/β ratio cancers such as prostate and breast cancer suggests hypofractionated irradiation because of their beneficial clinical outcomes [18–21]. On the other hand, some reports claim that high α/β ratio cancers also should be treated with hypofractionated radiotherapy [22–24]. In addition, hypofractionated radiotherapy for various cancers (e.g. malignant glioma, hepatoma, bile duct cancer, and cerebral arteriovenous malfunction) can provide the same or more beneficial results compared with conventional radiotherapy [25–30].

Our results show that the optimal number of fractions with the IBED model is greater than that with the ASF model for high α/β cancers. In addition, the regimens with the IBED model indicate extreme hyperfractionated radiotherapy in some OARs. We must pay careful attention when using the IBED model in the clinic, because we may irradiate an excessive number of fractions, which may lead to a prolonged treatment time. On the contrary, the results with the ASF model are consistently within the range of clinical practice, even if calculated for various DVHs of OARs. Thus, the ASF model demonstrates robustness in deriving irradiation

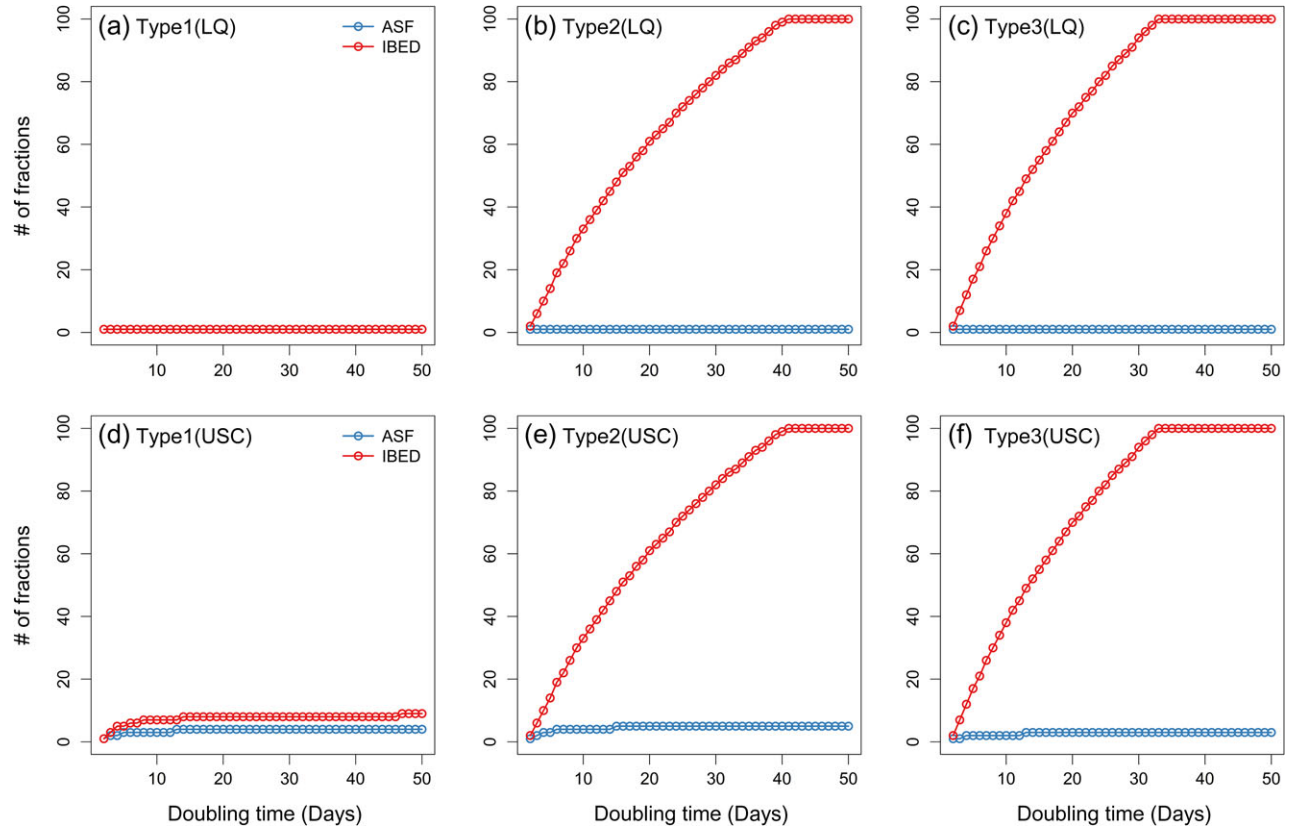

Fig. 3. Derived irradiation regimens with doubling time effects for Type 1, Type 2 and Type 3 DVHs. (a), (b) and (c) describe the number of fractions with the LQ-R with the Type 1, Type 2 and Type 3 DVH, respectively. (d), (e) and (f) describe the number of fractions with the USC-R with the Type 1, Type 2 and Type 3 DVH, respectively.

schemes for a wide range of DVHs of OARs compared with the IBED model.

The present study shows that the derived radiation regimens with ASF suggest the plan in the range of clinical use, whereas IBED sometimes recommends extreme hyperfractionated radiotherapy for high α/β ratio cancers. The differences are caused by non-uniform DVHs for OARs. On the other hand, the results derived with ASF are consistently within the range of clinical use in our simulations. The use of ASF for deriving the radiation scheme thus seems to be better for both high and low α/β ratio cancers. Of course, we need further study on the optimal solutions for other cancer types in radiotherapy and on any adverse effects, but we regard the present outcome as a feasible solution for a model-based approach for radiotherapy.

FUNDING

This work was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 16K12397.

REFERENCES

1. Fowler JF. 21 years of biologically effective dose. *Br J Radiol* 2010;83:554–68.
2. Clark BG, Souhami L, Pla C et al. The integral biologically effective dose to predict brain stem toxicity of hypofractionated stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* 1998;40:667–75.
3. Unkelbach J, Craft D, Salari E et al. The dependence of optimal fractionation schemes on the spatial dose distribution. *Phys Med Biol* 2013;58:159–67.
4. Saberian F, Ghate A, Kim M. Optimal fractionation in radiotherapy with multiple normal tissues. *Math Med Biol* 2016;33:211–52.
5. O'Donoghue JA. Implications of nonuniform tumor doses for radioimmunotherapy. *J Nucl Med* 1999;40:1337–41.
6. Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Med Phys* 1997;24:103–10.
7. Moonen L, Bartelink H. Fractionation in radiotherapy. *Cancer Treat Rev* 1994;20:365–78.
8. Park C, Papiez L, Zhang S et al. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;70:847–52.
9. Andisheh B, Edgren M, Belkić D et al. A comparative analysis of radiobiological models for cell surviving fractions at high doses. *Technol Cancer Res Treat* 2013;12:183–92.
10. Mizuta M, Date H, Takao S et al. Graphical representation of the effects on tumor and OAR for determining the appropriate fractionation regimen in radiation therapy planning. *Med Phys* 2012;39:6791–5.

11. Sugano Y, Mizuta M, Takao S et al. Optimization of the fractionated irradiation scheme considering physical doses to tumor and organ at risk based on dose–volume histograms. *Med Phys* 2015;42:6203–10.
12. Mizuta M, Takao S, Date H et al. A mathematical study to select fractionation regimen based on physical dose distribution and the linear–quadratic model. *Int J Radiat Oncol Biol Phys* 2012;84:829–33.
13. Miralbell R, Roberts SA, Zubizarreta E et al. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: α/β = 1.4 (0.9–2.2) Gy. *Int J Radiat Oncol Biol Phys* 2012;82:e17–24.
14. Robertson SP, Quon H, Kiess AP et al. A data-mining framework for large scale analysis of dose–outcome relationships in a database of irradiated head and neck cancer patients. *Med Phys* 2015;42:4329–37.
15. Tomé WA, Meeks SL, McNutt TR et al. Optically guided intensity modulated radiotherapy. *Radiother Oncol* 2001;61:33–44.
16. Kirkpatrick JP, Meyer JJ, Marks LB. The linear–quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. *Semin Radiat Oncol* 2008;18:240–3.
17. Miyakawa A, Shibamoto Y, Otsuka S et al. Applicability of the linear–quadratic model to single and fractionated radiotherapy schedules: an experimental study. *J Radiat Res* 2014;55:451–4.
18. De Bari B, Arcangeli S, Ciardo D et al. Extreme hypofractionation for early prostate cancer: biology meets technology. *Cancer Treat Rev* 2016;50:48–60.
19. Di Franco R, Borzillo V, Ravo V et al. Rectal/urinary toxicity after hypofractionated vs conventional radiotherapy in low/intermediate risk localized prostate cancer: systematic review and meta analysis. *Oncotarget* 2017;8:17383–95.
20. Valle LF, Agarwal S, Bickel KE et al. Hypofractionated whole breast radiotherapy in breast conservation for early-stage breast cancer: a systematic review and meta-analysis of randomized trials. *Breast Cancer Res Treat* 2017;162:409–17.
21. Zhou Z-R, Mei X, Chen X-X et al. Systematic review and meta-analysis comparing hypofractionated with conventional fraction radiotherapy in treatment of early breast cancer. *Surg Oncol* 2015;24:200–11.
22. Ma L-H, Li G, Zhang H-W et al. Hypofractionated stereotactic radiotherapy with or without whole-brain radiotherapy for patients with newly diagnosed brain metastases from non-small cell lung cancer. *J Neurosurg* 2012;117:49–56.
23. Lartigau E, Mirabel X, Prevost B et al. Extracranial stereotactic radiotherapy: preliminary results with the CyberKnife. *Onkologie* 2009;32:209–15.
24. Laine AM, Pompos A, Timmerman R et al. The role of hypofractionated radiation therapy with photons, protons, and heavy ions for treating extracranial lesions. *Front Oncol* 2015;5:302.
25. Khan L, Soliman H, Sahgal A et al. External beam radiation dose escalation for high grade glioma. *Cochrane Database Syst Rev* 2016;8:CD011475.
26. Amelio D, Lorentini S, Schwarz M et al. Intensity-modulated radiation therapy in newly diagnosed glioblastoma: a systematic review on clinical and technical issues. *Radiother Oncol* 2010;97:361–9.
27. Huang B-S, Tsang N-M, Lin S-M et al. High-dose hypofractionated X-ray radiotherapy for hepatocellular carcinoma: tumor responses and toxicities. *Oncol Lett* 2016;6:1514–20.
28. Greco C, Catalano G, Di Grazia A et al. Radiotherapy of liver malignancies. From whole liver irradiation to stereotactic hypofractionated radiotherapy. *Tumori* 2004;90:73–9.
29. Hong T-S, Wo J-Y, Yeap BY. Multi-institutional phase ii study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 2016;34:460–8.
30. Jones J, Jang S, Getch CC et al. Advances in the radiosurgical treatment of large inoperable arteriovenous malformations. *Neurosurg Focus* 2007;23:E7.