

# Radiobiological Evaluation of the Radiation Dose as Used in High-precision Radiotherapy: Effect of Prolonged Delivery Time and Applicability of the Linear-quadratic Model

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## Stereotactic irradiation/IMRT/Intermittent irradiation/Sublethal damage repair/Reoxygenation/LQ model.

Since the dose delivery pattern in high-precision radiotherapy is different from that in conventional radiation, radiobiological assessment of the physical dose used in stereotactic irradiation and intensity-modulated radiotherapy has become necessary. In these treatments, the daily dose is usually given intermittently over a time longer than that used in conventional radiotherapy. During prolonged radiation delivery, sublethal damage repair takes place, leading to the decreased effect of radiation. This phenomenon is almost universally observed *in vitro*. In *in vivo* tumors, however, this decrease in effect can be counterbalanced by rapid reoxygenation, which has been demonstrated in a laboratory study. Studies on reoxygenation in human tumors are warranted to better evaluate the influence of prolonged radiation delivery. Another issue related to radiosurgery and hypofractionated stereotactic radiotherapy is the mathematical model for dose evaluation and conversion. Many clinicians use the linear-quadratic (LQ) model and biologically effective dose (BED) to estimate the effects of various radiation schedules, but it has been suggested that the LQ model is not applicable to high doses per fraction. Recent experimental studies verified the inadequacy of the LQ model in converting hypofractionated doses into single doses. The LQ model overestimates the effect of high fractional doses of radiation. BED is particularly incorrect when it is used for tumor responses *in vivo*, since it does not take reoxygenation into account. For normal tissue responses, improved models have been proposed, but, for *in vivo* tumor responses, the currently available models are not satisfactory, and better ones should be proposed in future studies.

## INTRODUCTION

Newly developed high-precision radiotherapy, i.e., stereotactic irradiation and intensity-modulated radiation therapy (IMRT), is now steadily establishing its role in definitive cancer therapy. Owing to the excellent dose distribution in the target volume and sparing of normal tissues, clinical data showing the advantage of these new treatments are accumulating.<sup>1–6)</sup> While advantages of the new radiation techniques are evident upon physical grounds, a few radiobiological issues remain unresolved regarding the evaluation of radiation doses employed in these treatment modalities.

One of the issues is regarding the prolonged beam delivery time. In conventional radiotherapy, photon delivery in daily treatment is usually completed within 1–2 minutes. In contrast, high-precision radiotherapy takes much longer. Stereotactic irradiation using a linear accelerator generally employs multiple arc or fixed-portal photon beams, and usually a few minutes of beam-off time is necessary in setting respective arcs or ports. Consequently, a markedly longer time, ranging from 5 minutes to 1 hour or even longer, is required for one treatment session. In IMRT, the situation is further complicated, because segments in target volumes receive intermittent irradiation even during one fixed-portal beam delivery. From a radiobiologic point of view, it is questioned whether the radiation dose delivered with such intermissions is equivalent to that administered without breaks, since it is well known that sublethal damage repair (SLDR) occurs when intervals are set between two radiation doses.<sup>7,8)</sup> To date, many studies have been conducted to address this issue, and we review the results in the first part of this article, in addition to summarizing our previous studies on this issue.

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Another issue is regarding the evaluation of different fractionation schedules and conversion of radiation doses using mathematical models. Stereotactic irradiation started with gammaknife treatment, which is usually completed in a single session. However, it is becoming clearer that single-dose radiation is not optimal in the treatment of malignant tumors that contain hypoxic cells.<sup>4)</sup> So, a recent trend in stereotactic irradiation is to use fractionation. Various hypofractionation schedules are currently being tested and used. The number of fractions generally ranges from 2 to 10, and daily doses are mostly between 4 and 20 Gy. To evaluate the treatment outcome, comparison among different fractionation schedules is necessary. For this purpose, many clinicians use linear-quadratic (LQ) formalism. However, it has been questioned whether the LQ model is really applicable to high-dose-per-fraction treatment.<sup>9,10)</sup> Therefore, evaluation of the reliability of LQ formalism in the high-dose range and, if inadequate, the proposal of alternative models are important issues in clinical radiation biology. In the latter part of this article, we review recent work on this issue, including our own studies.

## BIOLOGICAL EFFECTS OF INTERMITTENT RADIATION DELIVERY

### *Summary of our studies*

Regarding this issue, we have conducted four series of laboratory studies. Two were *in vitro* and two were *in vivo* studies. The following is a concise summary of the respective experiments.

### *SLDR during intermittent radiation exposure in cultured cells<sup>11)</sup>*

The effects of fractionated doses delivered at intervals of a few minutes were evaluated in EMT6 mouse mammary sar-

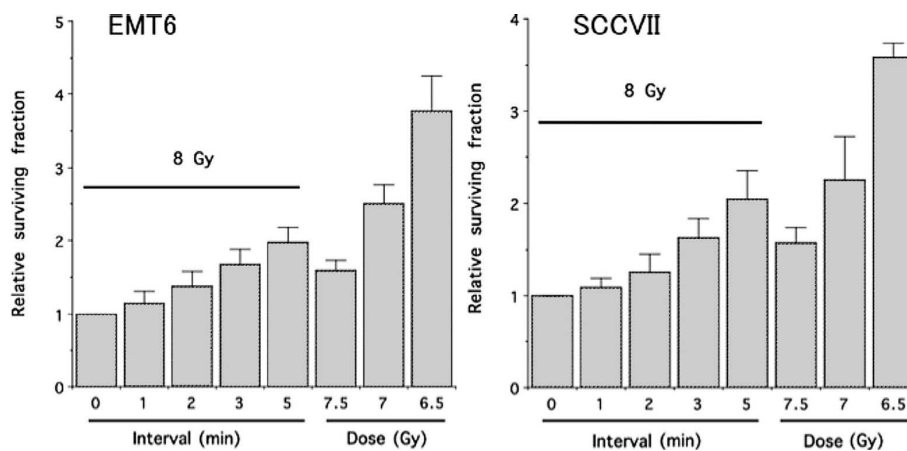
coma and SCCVII mouse squamous cell carcinoma cells. These two cell lines were employed throughout the series of experiments, and their characteristics were described in detail previously.<sup>12,13)</sup> In experiments where 8 Gy was given in 2 fractions, SLDR was observed when the interval was 2 minutes or longer in EMT6 cells and when it was 3 minutes or longer in SCCVII cells. In the next experiment where 8 Gy was given in 5 fractions at intervals of 1 to 5 minutes, significant SLDR was observed when the interval was 2 minutes or longer in both cell lines (Fig. 1). When the interval was 5 minutes, 8 Gy in 5 fractions corresponded to 7.38 Gy in EMT6 cells and 7.29 Gy in SCCVII cells.

Furthermore, the effects of 2 Gy given in 5 or 10 fractions at intervals of 0.5 to 5 minutes were estimated in EMT6 cells using the cytokinesis-block micronucleus assay, which is a sensitive assay to evaluate radiation effects at low doses.<sup>13,14)</sup> In the 5-fraction experiment, the micronucleus frequency decreased significantly as compared to single 2-Gy irradiation when the interval was 2 minutes or longer (Fig. 2). When the interval was 5 minutes, 5 fractions of 0.4 Gy corresponded to a single dose of 1.72 Gy. In the 10-fraction experiment, the micronucleus frequency decreased when the interval was 1 minute or longer. With an interval of 3 minutes each, 10 fractions of 0.2 Gy corresponded to a single dose of 1.76 Gy.

To summarize the *in vitro* study, it was concluded that dose-modifying factors of 1.08 to 1.16 need to be considered when the total irradiation time is 20 to 30 minutes. However, further *in vivo* study is considered necessary to extrapolate this result to clinical situations.

### *Influence of the fraction dose and number and dose rate on the biological effect<sup>15)</sup>*

A total dose of 8 Gy was given to EMT6 and SCCVII



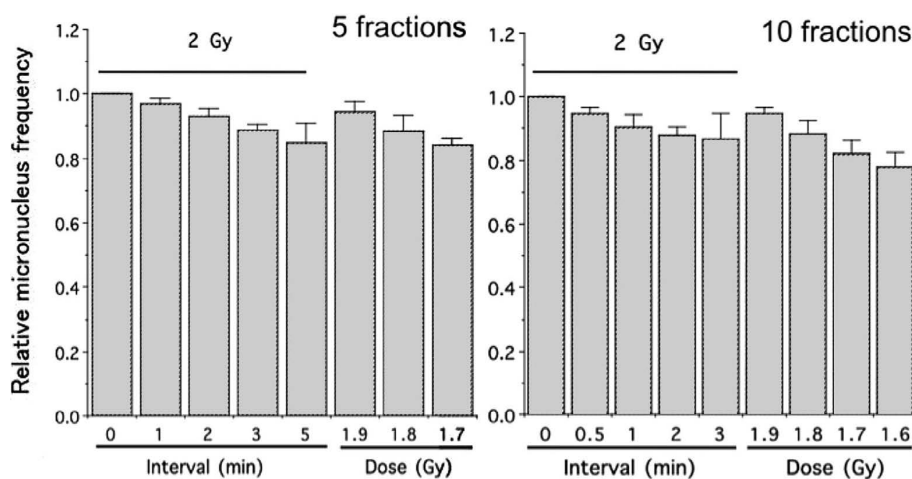
**Fig. 1.** Relative surviving fractions of EMT6 and SCCVII cells after 8 Gy given without a break over 4.5 minutes or in 5 fractions at various intervals. Cell survival after continuous 8-Gy irradiation was regarded as 1. Relative surviving fractions after continuous 6.5-, 7- and 7.5-Gy irradiation are also shown. Bars represent SD. Modified from Reference 11.

cells in 2, 5, 10, 20, and 40 fractions within a fixed period of 15, 30, or 46 minutes, and the effects were compared with continuous 8-Gy irradiation given at a dose rate of 1.55 Gy/minute or at reduced dose rates over 15, 30, or 46 minutes. In all experiments, the relative surviving fractions significantly increased with fractionation and prolonged radiation as compared with the control groups receiving 8 Gy in 5.3 minutes. When the total radiation time was 15 minutes, there were no differences in cell survival among the fractionation schedules, but when the period was 30 or 46 minutes, the radiation effect tended to decrease with an increase in the fraction number up to 20 fractions (Fig. 3). Two-fraction irradiation yielded the greatest effect among the fractionated radiation groups. Continuous low-dose-rate irradiation had a greater effect than 20- or 40-fraction irradiation. Although the implications regarding the clinical application of these results are complicated, this study showed that biological effects could differ with the fraction-

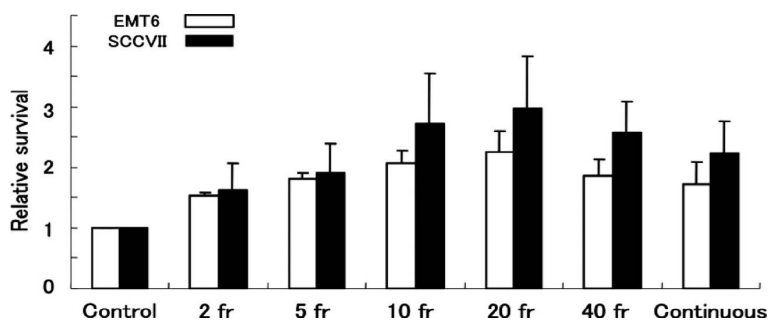
ation schedule even when the total radiation time and dose are identical.

#### *Effects of intermittent irradiation on murine tumors in vivo<sup>16)</sup>*

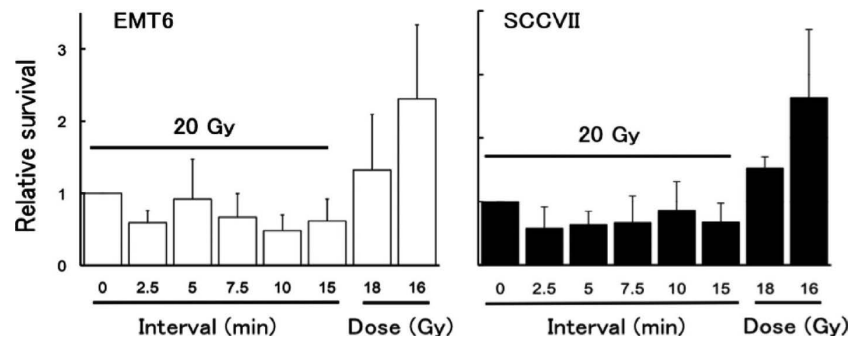
The effect of prolonged radiation delivery was also studied *in vivo*. EMT6 and SCCVII tumors were transplanted into Balb/c and C3H/HeN mice, respectively. When subcutaneous tumors grew to 1 cm in their longest diameter, the mice received 20 Gy in various fractions at 4-hour intervals. Within 24 hours from the first irradiation, the tumors were excised, minced, and enzymatically disaggregated into single cells. Then, cell survival was assessed using a colony assay. Figure 4 shows the results of a 5-fraction experiment; contrary to the *in vitro* data, no decrease in radiation effects was observed, and, by placing 2.5-, 7.5-, 10-, or 15-minute intervals for EMT6 tumors and 2.5-, 5-, 7.5-, or 15-minute intervals for SCCVII tumors, the effect became stronger.



**Fig. 2.** Relative micronucleus frequency in EMT6 cells after 2 Gy given without a break or in 5 or 10 fractions at various intervals. The micronucleus frequency after continuous 2-Gy irradiation was regarded as 1. Bars represent SD. Modified from Reference 11.



**Fig. 3.** Relative surviving fractions of EMT6 and SCCVII cells after 8 Gy given in 2–40 fractions and prolonged continuous irradiation given over 46 min. The control group received a single dose of 8 Gy over 5.3 minutes, while all the other groups received a total dose of 8 Gy over 46 minutes. Cell survival of the control group was regarded as 1. Bars represent SD. Modified from Reference 15. Regarding differences between groups, see Reference 15.

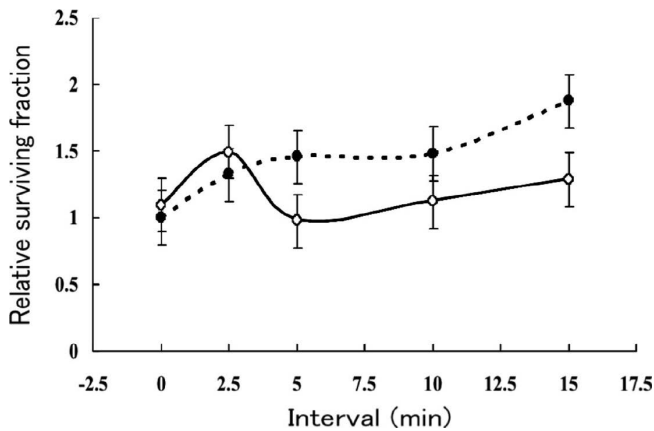


**Fig. 4.** Relative surviving fractions of EMT6 and SCCVII cells irradiated *in vivo* at 16, 18, or 20 Gy without a break or 20 Gy in 5 fractions at various intervals. Cell survival after continuous 20-Gy irradiation was regarded as 1. Bars represent SD. Modified from Reference 16.

Similar results were obtained in 10-fraction experiments. It was speculated that SLDR *in vivo* might be counterbalanced or outweighed by other phenomena such as reoxygenation. Therefore, we subsequently investigated reoxygenation in SCCVII tumors during intervals of several minutes.

#### *Reoxygenation shortly after irradiation and SLDR in vivo in the absence of reoxygenation*<sup>17)</sup>

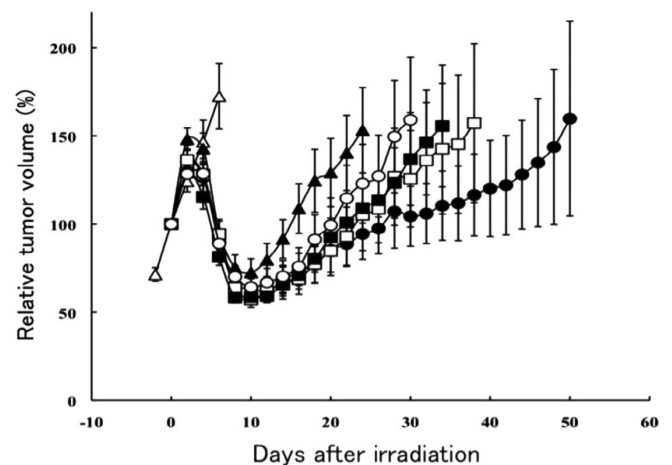
Using 1-cm-diameter SCCVII tumors transplanted into C3H mice, reoxygenation at 0–15 minutes after a 13-Gy dose was investigated; the hypoxic fraction was measured at 0, 2.5, 5, 10, and 15 minutes after 13 Gy using a paired survival curve assay. At given times, the irradiated mice were divided into two, alive and dead groups, and received a second irradiation with 15 Gy. Cell survival in the two groups was compared to assess the hypoxic fraction. As



**Fig. 5.** Relative surviving fractions of SCCVII tumor cells after a priming dose of 13 Gy and a second dose of 15 Gy given at 0- to 15-minute intervals to air-breathing (○) or dead (●) mice. The surviving fraction in the dead group that received the second dose immediately after the priming dose was regarded as 1. The hypoxic fraction is given by the surviving fraction of tumor cells in air-breathing mice divided by that in dead mice at respective time points. Bars represent SE. Modified from Reference 17.

shown in Fig. 5, the hypoxic fraction was 100% at 0 and 2.5 minutes after the end of the first irradiation, but, at 5 minutes, it fell to 67% (95% confidence interval, 41–93%). Thus, reoxygenation was observed at 5 minutes after irradiation. It was suggested that rapid reoxygenation could compensate for SLDR *in vivo*.

To investigate the effect of intermittent irradiation under conditions of restricted reoxygenation, 1-cm-diameter SCCVII tumors in the hind legs of C3H mice were irradiated with the leg fixed using adhesive tape. This procedure was considered to increase the hypoxic fraction and restrict reoxygenation.<sup>18)</sup> Figure 6 compares the growth delay of SCCVII tumors irradiated with 20 Gy, 25 Gy, or 5 fractions of 5 Gy given at 3-, 6-, or 10-minute intervals. The effect of radiation decreased by imposing intervals of 3 to 10 minutes; the effect of 25 Gy given in 5 fractions was between that of 20 Gy and that of 25 Gy delivered continuously. Therefore, it was suggested that the effects of intermittent radiation *in*



**Fig. 6.** Relative volumes of SCCVII tumors after 20 (▲) or 25 (●) Gy given as a single dose, or 5 fractions of 5 Gy given at intervals of 3 (□), 6 (■), or 10 (○) minutes. △: no irradiation. Tumor volumes before irradiation in each group were regarded as 100%. Bars represent SE. Modified from Reference 17.

*in vivo* decrease due to SLDR when reoxygenation is restricted.

#### *Other laboratory studies on the biological effects of intermittent irradiation*

Classically, Elkind and his coworkers<sup>7,8)</sup> were the first to report the SLDR phenomenon. In their experiments, a significant increase in cell survival was observed when intervals of 30 minutes or longer were set between two radiation doses. However, they did not investigate shorter intervals. With the development of radiotherapy techniques, it has become necessary to investigate the influence of radiation interruptions of shorter than 30 minutes.

After the 1990's, Benedict *et al.*<sup>19)</sup> attempted to estimate dose-correction factors for stereotactic radiosurgery using U-87MG cells *in vitro*. In their experiments, the effect of radiation decreased with prolongation of the treatment time, and the correction factor of 0.02 to 0.03 Gy/minute was proposed when a total dose of 6–18 Gy was given. This indicates that when the treatment time prolongs by 30 minutes, 8 Gy would correspond to approximately 7.1 to 7.4 Gy delivered continuously, giving dose-modifying factors of 1.08 to 1.13. These results appear to agree with our own. Mu *et al.*<sup>20)</sup> conducted an *in vitro* study with V79 cells using much more complicated fractionation schedules than those we employed, and compared the surviving fraction ratios between the continuous and prolonged delivery of radiation with those estimated by biological models derived from the LQ model. Their conclusion was that the biological models underestimated the effect of prolonging the fraction time when a total dose of 2 Gy was fractionated. Therefore, estimation of the influence of prolonging the treatment time using biological models alone seems to be insufficient in clinical practice. More recently, Zheng *et al.*<sup>21)</sup> investigated the impact of prolonged fraction delivery times simulating IMRT on two cultured nasopharyngeal carcinoma cell lines. The fraction delivery time was 15, 36, or 50 minutes. The dose-modifying factors for a fraction dose of 2 Gy was 1.05 when the delivery time was 15 minutes, but it increased to 1.11 or 1.18 when the time prolonged to 50 minutes. They emphasized, however, that these results do not necessarily hold *in vivo*. Moiseenko *et al.*<sup>22)</sup> obtained results similar to those of the above-mentioned studies, and suggested that DNA repair underlies the increase in cell survival observed when dose delivery is prolonged, based on measurement of the retention of gammaH2AX, a measure of the lack of DNA damage repair.

Moiseenko *et al.*<sup>23)</sup> investigated the correlation between the magnitude of the loss of effect brought about by prolonged radiation delivery and the  $\alpha/\beta$  ratio in three cell lines. When their results were projected to a 30-fraction treatment, the dose deficit to bring cell survival to the same level was 4.1 Gy in one line, but it was as large as 24.9 and 31.1 Gy in the other two lines. The dose deficit did not relate to the  $\alpha/\beta$  ratio of the three cell lines. On the other hand, Zheng *et*

*al.*<sup>24)</sup> also investigated the issue in two hepatocellular carcinoma cell lines, and a significant decrease in cell survival due to prolonged fraction delivery was observed in one line with an  $\alpha/\beta$  ratio of 3.1 Gy but not in another with an  $\alpha/\beta$  ratio of 7.4 Gy. Therefore, the relationship with the  $\alpha/\beta$  ratio remains unclear and requires further investigation.

All these results indicate that SLDR certainly takes place when radiation delivery is prolonged or given intermittently in daily stereotactic irradiation and IMRT settings. However, it should be noted that these results were obtained using *in vitro* single cells. Until recently, there have been no *in vivo* studies except for our own ones, but another study has now been published. The results of a study by Wang *et al.*<sup>25)</sup> agree with our own; when C57BL mice bearing Lewis lung cancer were irradiated under conditions of limited reoxygenation, intermittent radiation delivery led to a significant reduction in the biological effects. However, more *in vivo* investigations appear to be warranted in the near future. Our study suggests that SLDR *in vivo* can be counterbalanced by reoxygenation. In tumors that reoxygenate rapidly, therefore, the adverse effects of prolonging the radiation delivery time may be none or negligible. However, little is known about the reoxygenation of tumors in humans, so this issue is also an important topic to be investigated in the future to elucidate the effect of intermittent or prolonged radiation delivery in clinical practice.

### **APPLICABILITY OF THE LQ MODEL TO HIGH-DOSE-PER-FRACTION RADIOTHERAPY**

#### *Current controversy*

To evaluate the effect of fractionated irradiation and compare different fractionation schedules, LQ formalism ( $n_2d_2/n_1d_1 = (1 + d_1/[\alpha/\beta])/(1 + d_2/[\alpha/\beta])$ , where  $d_1$  and  $d_2$  are fractional doses and  $n_1$  and  $n_2$  are fraction numbers) and the biologically effective dose (BED) derived from the LQ model ( $BED = D(1 + d/[\alpha/\beta])$ , where  $D$  is the total dose and  $d$  is the fractional dose) are often used because of their convenience and simplicity.<sup>10,26)</sup> While LQ formalism is useful for conversion between relatively low radiation doses as used in conventional radiotherapy, it has been suggested that it is not applicable to higher daily doses or smaller fraction numbers.<sup>9,10)</sup> However, many clinicians have used LQ formalism to convert hypofractionated doses to single doses in their publications,<sup>27,28)</sup> and many have used BED to evaluate the doses of stereotactic irradiation.<sup>29,30)</sup> To further complicate the issue, some investigators, in contrast, claim that the LQ model is applicable to stereotactic irradiation.<sup>31,32)</sup> The support for the latter group is somewhat limited in that the existing clinical data do not significantly deviate from those expected from LQ model calculations, and their data do not necessarily indicate that the LQ model fits best to the high-dose data. Since clinical data usually contain many errors, experimental evaluation of the reliability of the LQ

model in single-fraction and hypofractionated radiation schedules appears to be important and desirable.

#### *Cell survival data for the reliability of the LQ model at high doses per fraction*

The theoretical basis behind the LQ model not being applicable with high doses per fraction is that dose-survival curves for cultured cells cannot be fitted well by the LQ model in high-dose ranges. This has been pointed out for a long time; in the pioneering work of Puck and Markus<sup>33)</sup> who established the colony formation assay, the high-dose region of the dose-survival curve was apparently straight in HeLa cells. Therefore, the LQ model, with which the cell survival curve continues to bend downwards at high doses, does not seem to fit the actual curves at high doses. Joiner and Bentzen<sup>10)</sup> stated in their book chapter that extrapolations by the LQ model beyond 5–6 Gy per fraction are likely to lack clinically useful precision. More recently, Garcia *et al.*<sup>34)</sup> investigated the compatibility of the LQ model regarding dose-survival curves of 4 cell lines in broad dose ranges. In the 4 lines, the LQ model did not fit the curves at very high dose ranges that were > 7.5, 9.5, 11.5, or 13 Gy depending on the cell line. Therefore, the inadequacy of the LQ model at high doses was clearly demonstrated.

In a previous study, our group investigated the reliability of LQ formalism in converting hypofractionated doses (in 2 to 5 fractions) to single doses in single cells and spheroids in culture.<sup>35)</sup> The results showed that LQ formalism is inadequate in doing so; the equivalent single doses for the hypofractionated doses calculated by LQ formalism were apparently lower than the equivalent single doses actually measured. LQ formalism underestimated the effect of fractionated irradiation. The magnitudes of errors were 6–19% for 2- or 3-fraction schedules in cultured V79 and EMT6 single cells, and 18–30% for 2- to 5-fraction schedules in V79 spheroids. Since the reoxygenation of hypoxic tumor cells takes place in *in vivo* tumors between respective fractions,<sup>17,36,37)</sup> the compatibility of LQ formalism to single and hypofractionated radiation regimens was also investigated using murine tumors in the subsequent study.

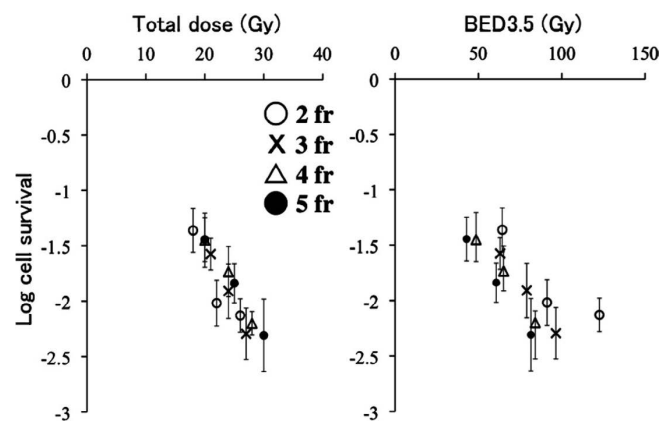
Using EMT6 tumors, the applicability of LQ formalism for converting hypofractionated doses (in 2 to 5 fractions) to single doses was evaluated,<sup>38)</sup> as in the previous *in vitro* study. Again, the use of LQ formalism produced large errors; the equivalent single doses for the hypofractionated doses calculated from LQ formalism were much lower than the equivalent single doses actually measured. The magnitudes of errors were larger than those seen in the *in vitro* study; they were 21% to 31% for 2- or 3-fraction schedules and 27% to 42% for 4- or 5-fraction schedules. The possible larger discrepancy in *in vivo* tumors as compared to *in vitro* single cells and spheroids was considered to be largely due to the reoxygenation of hypoxic tumor cells during intervals between fractions in the hypofractionated groups. This study

clearly showed that LQ formalism is inadequate for high-dose-per-fraction radiotherapy, especially in *in vivo* tumors.

To further evaluate the appropriateness of the BED concept in hypofractionated irradiation, we compared 2- to 5-fraction irradiation schedules simultaneously in the EMT6 tumors in Balb/mice.<sup>38)</sup> Total doses of 18–30 Gy were given in 2 to 5 fractions to the tumor-bearing mice at 4-hour intervals, and tumor cell survival was assessed employing an *in vivo*–*in vitro* colony assay, as in the previous experiment. Tumor cell survival was plotted against the total dose and BED3.5. In the *in vitro* cell survival determination conducted along with the *in vivo* experiment, the  $\alpha/\beta$  ratio of the cell line was 3.5 Gy, so BED3.5 was adopted as a substitute for “BED10” often used clinically to represent the tumor response. Figure 7 shows tumor cell survival plotted against the total dose and BED3.5. Respective dose-response curves almost overlapped when cell survival was plotted against actual radiation doses. However, the curves tended to shift downwards by increasing the fraction number when cell survival was plotted against BED3.5. Thus, it seems that BED is inadequate for use in this dose-per-fraction range, especially for tumors. The total dose reflected the actual effect (tumor cell survival) more accurately than BED in this experiment. The calculated BED tended to become larger than expected from the actual effects when the fraction number decreased. Thus, BED tends to overestimate the actual biologically effective dose with increasing radiation doses.

#### *Normal tissue response data for the reliability of the LQ model at high doses per fraction*

The reliability of the LQ model can also be evaluated based on normal tissue data. In classic radiobiology studies, raw data for various normal tissue responses from animal and human studies were presented as a series of dose-response curves.<sup>39–42)</sup> Measured responses were plotted



**Fig. 7.** Surviving fractions of EMT6 cells *in vivo* after 2-fraction (○), 3-fraction (×), 4-fraction (△), or 5-fraction (●) irradiation plotted against the total radiation dose and BED3.5. Bars represent SE. Modified from Reference 38.

against total radiation doses for each schedule. From horizontal cuts, isoeffect doses could be read off, and these isoeffect doses could then be plotted as a log dose against the log number of fractions or log fraction size. Since the isoeffect curves are concave downwards, it is difficult to determine any particular slope for the curves. Instead, the isoeffect curves can be plotted as the reciprocal total dose as a function of the dose per fraction.<sup>42)</sup> This reciprocal total dose or  $F_e$  plot was elaborated to estimate the  $\alpha/\beta$  ratio of normal tissues.<sup>39)</sup> When the normal tissue response data fall in a straight line on this  $F_e$  plot, the LQ model is considered to be appropriate. The isoeffect curves for most normal tissues were linear in the dose range of 1–8 Gy,<sup>43)</sup> suggesting that the LQ model is adequate in this range of dose per fraction. Brenner<sup>32)</sup> found that the isoeffect curves for the rat spinal cord response, mouse skin reaction, and murine intestinal damage could be visually fitted with straight lines in the dose range between 0 and 25 Gy, and insisted that the LQ model is applicable throughout this dose range. However, statistical validation of the linearity was not performed. Later, Astrahan<sup>44)</sup> analyzed the data for various normal tissues in more detail, and found that the LQ formula closely fitted the curve for the late reaction of the mouse spinal cord for fractions up to about 10 Gy. However, the data for cervical vascular damage did not fit the LQ model but fitted the LQ-L (linear-quadratic-linear) model, which is stated later. Fowler *et al.*<sup>31)</sup> suggested that for certain epithelial tissues, the LQ model may be applicable up to 23 Gy per fraction.

These observations are somewhat contradictory and confusing, but the discrepancy may be, in part, explained by the  $\alpha/\beta$  ratio for the normal tissue responses. The applicability of the LQ model may not simply depend on the absolute dose per fraction; for a tissue with a large  $\alpha/\beta$  ratio, its applicability may be extended to a higher dose region. This is the case with epithelial tissues which usually have an  $\alpha/\beta$  ratio of around 10 Gy. Since the  $\alpha/\beta$  ratio represents the dose at which cell killing from linear ( $\alpha$ ) and quadratic ( $\beta$ ) components of the LQ formula is equal, the LQ model holds around the dose level of the  $\alpha/\beta$  ratio. However, with the increase in the dose, the  $\beta$  cell kill component dominates in the LQ model, from which actual data have been shown to deviate. From these considerations, it may be said that the model is applicable up to a radiation dose approximately two-fold the  $\alpha/\beta$  ratio.

Recently, Borst *et al.*<sup>45)</sup> analyzed radiation pneumonitis data in patients undergoing stereotactic body radiotherapy. Various fractionation schedules were employed ranging from 35 Gy in 4 fractions to 60 Gy in 8 fractions. They tried to correlate the mean lung dose with the occurrence of radiation pneumonitis. They found that the data were best fitted by the LQ model with an  $\alpha/\beta$  ratio of 3 Gy. Although the prescribed dose per fraction was 7.5 to 12 Gy, the mean lung dose per fraction is usually much lower, so it may not be

surprising that the LQ model fitted their mean lung dose data.

#### *Other alternatives to the LQ model*

Since it is becoming clearer that LQ formalism is not adequate for stereotactic irradiation, other models have been proposed one after another. These include the universal survival curve model,<sup>46)</sup> linear-quadratic-linear (LQL) model<sup>47)</sup> (or modified LQ model<sup>48)</sup>, and generalized LQ (gLQ) model.<sup>49)</sup> The universal survival curve model hybridizes the LQ model for low doses and the classic multi-target model ( $S = 1 - (1 - e^{-D/D_0})^n$ , where S is the surviving fraction, D is the dose,  $D_0$  is a parameter that determines the final slope of the survival curve, and n is the y-intercept of the asymptote)<sup>50)</sup> for high doses beyond a single transition dose ( $D_T$ ). Hence the concept is relatively simple. The LQL model derived from a mechanism-based lethal-potentially lethal model<sup>51)</sup> has a mechanistic basis. Although the equations for the LQL model are more complex, cell survival curves extend nearly linearly in a high-dose range, as compared to the LQ model.<sup>47)</sup> Therefore, the applicability of the universal survival curve model and LQL model to a high-dose region may be similar. The most recently proposed gLQ model takes SLDR and the conversion of sublethal damage to lethal damage during irradiation into account; the model is designed to cover any dose delivery patterns. All of these newer models seem to fit better than the LQ model in the high-dose range. We are now evaluating how these models fit experimental data. In the near future, it is desirable for an optimal model to be established for clinical use in high-dose-per-fraction radiotherapy. However, it should be noted that these models are generally applicable to the normal tissue response, especially late damage, and not to tumors, since none of these models takes the reoxygenation phenomenon, as well as cell cycle effects, host immune effects, and effects on vascular/stromal elements, into account. When the overall treatment time becomes longer than that used in stereotactic irradiation, a factor deriving from repopulation should also be considered.<sup>52,53)</sup> In future studies, models that incorporate these factors as well as reoxygenation should be developed in order to use the models for *in vivo* tumor responses to stereotactic irradiation and more conventional radiotherapy.

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