SLD Repair Impact On Treatment Effectiveness of Proton Therapy with Various Cell Specific Parameters

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INTRODUCTION

At present, most of the model-based studies of proton biological effectiveness have focused on acute irradiation and neglect the reduction of the biological effectiveness due to sub-lethal damage (SLD) repair during the delivery of radiation.
Nevertheless, the dose-rate dependence may become more important as advanced treatment techniques, such as hypofractionation and respiratory gating, come into clinical practice, as these techniques sometimes require long treatment times [1-3].

AIM

1. Extend the dose protraction factor in linear quadratic (LQ) model to evaluate the biological dose in general clinical proton beam delivery (e.g. multi-field irradiation, scanning beam delivery)
2. Evaluate the biological dose decrease caused by the repair effect systematically with possible ranges of cell specific parameters of both $(\alpha/\beta)_x$ and $T_{1/2}$.

METHOD

- The dose protraction factor in the LQ model, *G*, was extended for the arbitrary number of different LET proton irradiations delivered sequentially with arbitrary time lags, referring to the theory of dual radiation action[4]. The dependence of RBE on LET was included by employing the model by McNamara et al[5]. For the case of *M*-field plan with dose delivery time per field *T* and inter-field time lag τ, the equation reduces to:

$$D_{\mathrm{bio}} = \left[\frac{1}{2}\left\{\sqrt{\left(\frac{\alpha}{\beta}\right)_x^2 + \frac{4}{\beta_x}\left(\sum_{m=1}^{M}\alpha_m D_m + G\left(\sum_{m=1}^{M}\sqrt{\beta_m}D_m\right)^2\right)} - \frac{1}{2}\left(\frac{\alpha}{\beta}\right)_x\right\}\right] \times D_{\mathrm{phys}}$$

$$G = \frac{2}{\left(\sum_{m=1}^{M}\sqrt{\beta_m}D_m\right)^2}\left\{\frac{\lambda T + e^{-\lambda T} - 1}{\lambda^2 T^2}\sum_{m=1}^{M}\beta_m D_m^2 - \frac{(1-e^{-\lambda T})(1-e^{\lambda T})}{\lambda^2 T^2}\sum_{m=2}^{M}\sum_{l=1}^{m-1}\sqrt{\beta_l\beta_m}D_l D_m e^{-\lambda(m-l)(T+\tau)}\right\}$$

where α_m, β_m are $\mathrm{LET_d}$ dependent LQ parameters of *m*-th field and λ is the repair constant ($\lambda = \ln 2/T_{1/2}$) [6].

- The continuous irradiation of spread out Bragg peak (SOBP) in water phantom was simulated with four sets of cell specific parameters ($(\alpha/\beta)_x$ [Gy], $T_{1/2}$ [min]) = (1.5, 20), (1.5, 80), (10, 20), (10, 80)). The simulation with variable cell specific parameters were also carried out.

- Clinical cases of lung tumor was examined with the cell specific parameters obtained from literature. A three-field beam arrangement was used. $D_{99\%}^{\mathrm{bio}}$ and biological dose homogeneity coefficient (HC ≡ $(D_{5\%}^{\mathrm{bio}} - D_{95\%}^{\mathrm{bio}})/D_{99\%}^{\mathrm{bio}}$) were calculated using the dose rate structures with the total irradiation time of 0-60 min.

RESULTS

Systematic evaluation with varying $(\alpha/\beta)_x$ and $T_{1/2}$

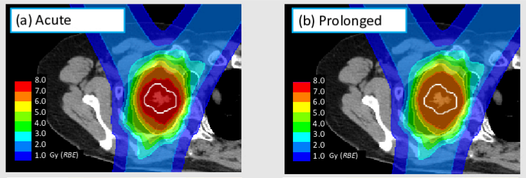
- In Fig 1, biological dose distributions with representative cell specific parameters are shown for irradiation time ranging from 0 to 90 min. Average dose within SOBP was set as 2 Gy. The magnitudes of biological dose decrease compared to acute irradiation at the center of SOBP at T_{irr} = 5, 10, 20, 30, 60, and 90 min were 1.74, 3.37, 6.29, 8.83, 14.7, and 18.7% with $(\alpha/\beta)_x$ = 1.5 Gy and $T_{1/2}$ = 20 min, respectively, while less than 2% for all T_{irr} with $(\alpha/\beta)_x$ = 10 Gy and $T_{1/2}$ = 80 min.

- Fig. 2 shows the representative plot of the value of relative biological dose decrease in terms of various biological parameters of $(\alpha/\beta)_x$ and $T_{1/2}$. It was largely dependent on cell specific parameters. For example, fixed value of $T_{1/2}$ = 30 min gives an relative dose decrease from 2.3% to 6.8% with an $(\alpha/\beta)_x$ range of 1–15 Gy.

Clinical cases

- Fig 3 shows the repair effect in the clinical case of lung tumor. The high dose region found in the CTV undergoing acute irradiation diminished with prolonged irradiation; with the current set of parameters, the relative dose decrease was higher than 7% in most of the CTV region.

- The variation of $D_{99\%}^{\mathrm{bio}}$ and HC are shown in Fig 4 (a) and (b), respectively. While $D_{99\%}^{\mathrm{bio}}$ gradually decreased with increasing irradiation time, HC did not largely changed.



$(\alpha/\beta)_x$ = 1.5 Gy, $T_{1/2}$ = 20 min — $(\alpha/\beta)_x$ = 10 Gy, $T_{1/2}$ = 80 min

Figure 1. Biological dose distribution with water phantom. Black solid curves and broken curves correspond to the biological dose with acute and prolonged irradiation, respectively.

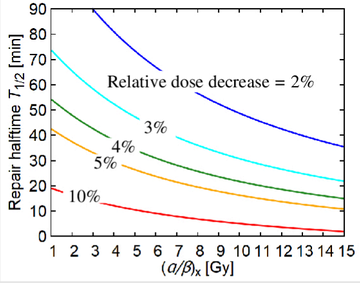


Figure 2. The contour map of relative dose decrease at the center of SOBP with the dose of about 2 Gy and $\mathrm{LET_d}$ of 2.31 keV/μm. As the dose delivery structure, single continuous irradiation of 30 min was taken. The values of relative dose decrease corresponding with each curve are indicated on the each curve.

Figure 3. The dose and $\mathrm{LET_d}$ distribution calculated for the lung case with $(\alpha/\beta)_x$ = 3.9 Gy [7] and $T_{1/2}$ = 32.4 min [8] : (a) acute irradiation, (b)prolonged irradiation. (c) relative dose decrease calculated from (a) and (b). (d) $\mathrm{LET_d}$ distribution in this plan. The clinical target volume (CTV) is delineated by the white line and located at the center of each image.

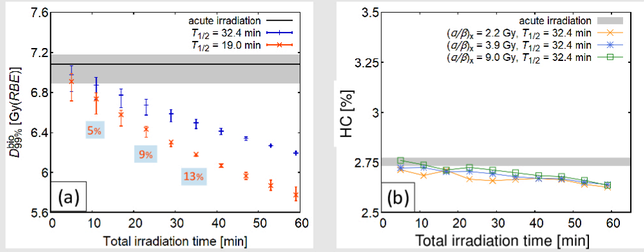


Figure 4. The variation of $D_{99\%}^{\mathrm{bio}}$ (a) and HC (b) in CTV for lung case with various irradiation time. The gray band shows the calculated value with acute irradiation, including $(\alpha/\beta)_x$ uncertainty. In (a), error bars for plots correspond with the uncertainty of $(\alpha/\beta)_x$. Since the results of three $(\alpha/\beta)_x$ were sometimes reversed for (b)., three datapoints were plotted without error bars but with independent lines.

CONCLUSIONS

In this research, we explored the impact of SLD repair on prolonged proton irradiation with various cell-specific parameters ($(\alpha/\beta)_x$ and $T_{1/2}$). Our calculation using the LQ model with extended dose protraction factor suggested that the large variation of the repair effect occurs with the possible ranges of the cell-specific parameters. This result elucidates the importance of considering these parameters in the evaluation of the repair effect. The calculation of HC revealed that the repair effect did not distort the dose homogeneity, thus, a loss of biological effectiveness can be compensated by merely rescaling the prescribed dose. This simplifies the replanning procedure in adaptive treatment strategy. Although the determination of an absolute value for the compensation still suffers from the uncertainty of cell-specific parameters, we believe that the results of our study suggest the possibility of biologically adapted replanning that recovers the expected biological dose.

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