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Development of Program for Relative Biological Effectiveness (RBE) Analysis of Particle Beam Therapy

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Relative biological effectiveness (RBE) of particle beam needs to be evaluated at particle beam therapy centers before the clinical application of the particle beam. However, since RBE analysis is implemented manually, it is useful to have a tool that can easily and effectively handle the data of experiments to generate cell survival curve and to analyze RBE simultaneously. In this work, the development of a program for RBE analysis of particle beam therapy was presented. This RBE analysis program was developed to include two parts; fitting the cell survival curves to linear-quadratic model and calculating the RBE values at a certain endpoint using fitting results. This program was also developed to simultaneously compare and analyze the template results that stored experiment data with photon and particle beam irradiations. The results of the cell survival curve obtained by each irradiation can be analyzed by the user on a desired data after reading the template stored in the easy-to-use excel file. The analysis results include the cell survival curves with error range, which are appeared in the screen and the α and β parameters of linear-quadratic model with 95% confidence intervals, RBE values, and R^2 values to evaluate goodness-of-fit of survival curves to model, which are stored in a text cvs file. This software can generate cell survival curve, fit to model, and calculate RBE all at once with raw experiment data, so it helps users to save time for data handling and to reduce the possibility of making error on analysis. As a coming plan, we will create a user-friendly graphical user interface to present the results more intuitively.

Keywords: Relative biological effectiveness, Particle beam therapy, Software tool

Introduction

Most of the radiation therapy uses high-energy X-rays, but the use and introduction of particle beam radiation therapy using proton or carbon ion has been rapidly increasing in recent years. In the case of particle beam therapy, it is possible to concentrate the radiation dose to the tumor to be treated with greater biological effects compared to X-ray. Thus, this physical and biological superiority of particle beam can maximize the therapeutic effect without causing severe side effects.[1,2]

To compare biological effectiveness of different radiation types, the concept of the relative biological effectiveness (RBE) is introduced. The RBE is the ratio of the dose of test beam required to obtain the same level of biological effect compared to the reference radiation, X-ray. 250 kVp X-rays is the common reference radiation to determine RBE value; however, in clinical situation, ^{60}Co or megavoltage X-ray can be used for RBE of particle beam.[3-5] The concept of RBE is simple, but it is complicated in clinical application, because the RBE depends on the particle type, linear energy transfer (LET), dose, fraction size, type of cell, method of measurement, and endpoint.[6-8] Generic RBE of 1.1 has been implemented for proton treatment planning,[5,6] and RBE prediction models have been applied to for heavy ion treatment planning since the RBE changes rapidly with LET of heavy ion compared to proton.[9,10] Hence, particle beam therapy centers need to evaluate biological dose with RBE measurement via *in vitro* or *in vivo* experiments before the clinical application of the particle beam.

In general, the response of cells to radiation is measured as a function of radiation dose using clonogenic or colorimetric assay which is widely-used, accepted standard method to measure the radiosensitivity of cells. These results are expressed as cell survival curves, and the shape of the curve depends on the type of radiation. RBE is calculated based on the cell survival curves obtained at same measurement conditions.[11,12]

Generating and fitting the cell survival curves are usually performed with a graphing and fitting software, and RBE is manually calculated with excel or calculator after obtaining the dose values at a certain endpoint from those fitted curves. In this regard, it is useful to have a tool that can easily and effectively handle the data of experiments to generate cell survival curve and to analyze RBE together. Therefore, the development of a program for RBE analysis of particle beam therapy was presented in this work. Performance of this program was investigated and fitting result was compared with those obtained from commercial software.

Materials and Methods

RBE analysis program was built with MATLAB code. The RBE analysis program was made to include two parts. First part is fitting the cell survival curves to a model. Second part is calculating the RBE values at a certain endpoint using fitting results.

1. Curve fitting

To run a program with minimum time required to process data for users, a template needs to be prepared, in which users simply fill the experiment data. The linear quadratic equation (1) is a model chosen for describing the survival curve in this program.

$$SF(Surviving\ Fraction) = exp^{[-\alpha(Dose)-\beta(Dose)^2]} \quad (1)$$

With the survival curve, the error range of data is presented as standard deviation for one set of experiment data or standard error for triplicate of experiment. Also, the R^2, the coefficient of determination that is widely used to measure the goodness-of-fit, was evaluated.

2. RBE calculation

RBE for the same biological endpoint is defined as the equation (2).

$$RBE = \frac{Dose\ from\ photon}{Dose\ from\ particle\ beam} \quad (2)$$

The fitting results of equation (1) for photon and particle beams were used to calculate the dose values for each beam at a defined surviving fraction, and then RBE was calculated.

Results and Discussion

1. System configuration

1) Input

As shown in Fig. 1, which demonstrates the procedure of RBE analysis, after cell experiments, users input the acquired experiment data of photon and proton irradiation into the excel-format template created by MATLAB, in which surviving fractions are calculated automatically. Then, users read the template file in MATLAB code and then select data by date of experiment (D1, D2, or D3) when they want to analyze data individually, since the worksheets in the template were divided according to experiment date with the name of D1, D2, and D3. If users want to analyze the triplicate experiment data all together, they can select total date (DT).

2) Output

The selected data file is fitted to survival curve using equation (1), and α and β parameters is obtained using nonlinear least squares regression analysis in MATLAB and expressed with 95% confidence intervals. As the endpoint for the RBE calculation, SF values of 90%, 50%, 37%, and 10% and SF values at 2 Gy, 4 Gy, and 6 Gy are designated. In the result file, these RBE values are expressed in RBE_90, RBE_50, RBE_37, RBE_10, RBE_SF2, RBE_SF4, and RBE_SF6.

The analysis results include the cell survival curves with error range, which are appeared in the screen and α and β parameters with 95% confidence intervals, the RBE values, and R^2 values to evaluate goodness-of-fit of survival curves to model, which are stored in a text cvs file. The cell survival experiments by clonogenic assay for several cell lines were performed at our institution using 6 MV X-ray and 230 MeV proton beam. The cell survival curve fitting and the analysis results with one of our experiment data are shown in Fig. 2 and Fig. 3, respectively.

The main advantage of this program is the ability to simultaneously compare and analyze the template results that stored experiment data. The results of the cell survival curve obtained by each irradiation can be analyzed by the user on a desired data after reading the template stored in the easy-to-use excel file. The copyright of this program was registered with Korea Copyright Commission (No. C-2016-030683).

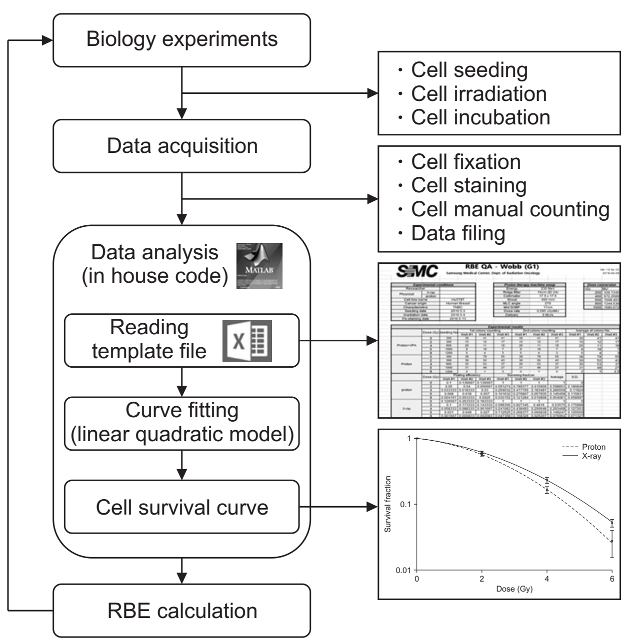

Fig. 1. The process of RBE analysis.

2. Program performance evaluation

In order to assess the performance of this program, we ran this program with three different case data of experiments performed at our institution. The analysis of all cases was successfully performed with this RBE analysis program. The fitting coefficients of linear

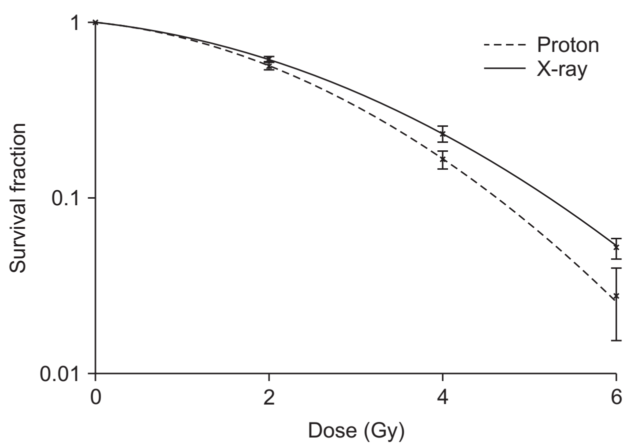

Fig. 2. The example of cell survival curve using RBE analysis program.

```
RBE MCF-7.xlsx
Selected Day = D1

Proton_α = 0.125
 Proton α interval range = 0.111  Proton α interval range = 0.140

Proton_β = 0.081
 Proton β interval range =  0.075  Proton β interval range =  0.086

Proton α/β = 1.553
-----------------------------------------------------------------------------
Photon_α = 0.124
 Photon α interval range = 0.100  Photon α interval range = 0.147

Photon_β = 0.061
 Photon β  interval range = 0.053  Photon β  interval range = 0.068

Photon α/β = 2.046
-----------------------------------------------------------------------------
**RBE_OutPut**
RBE_90 = 1.000
RBE_50 = 1.136
RBE_37 = 1.107
RBE_10 = 1.130

RBE_SF2 = 0.952
RBE_SF4 = 1.053
RBE_SF6 = 1.091

Goodness of fit(R-squared)
Proton_R^2 = 1.0000
Photon_R^2 = 1.0000
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Fig. 3. The example of analysis results obtained with RBE analysis program.

Table 1. Fitting coefficients (α and β) for the linear-quadratic model and goodness-of-fit (R^2) from RBE analysis program (N) and commercial graphing software (E) for example cases.

Cases	SF = exp (−αD −βD²)				Goodness-of-fit	
	α (95% confidence intervals)		β (95% confidence intervals)		R^2	
	N	E	N	E	N	E
Case 1 (X-ray)	0.124 (0.100~0.147)	0.124 (0.114~0.134)	0.061 (0.053~0.068)	0.061 (0.057~0.064)	1.000	1.000
Case 1 (Proton)	0.125 (0.111~0.140)	0.125 (0.111~0.140)	0.081 (0.075~0.086)	0.081 (0.075~0.086)	1.000	1.000
Case 2 (X-ray)	0.470 (0.355~0.584)	0.470 (0.272~0.667)	0.057 (0.010~0.105)	0.057 (−0.025~0.140)	0.9999	0.9948
Case 2 (Proton)	0.905 (0.862~0.949)	0.905 (0.712~1.097)	−0.008 (−0.026~0.010)	−0.008 (−0.089~0.073)	0.9999	0.9986
Case 3 (X-ray)	0.066 (−0.149~0.280)	0.066 (−0.032~0.163)	0.029 (−0.023~0.080)	0.029 (0.005~0.052)	0.9987	0.9439
Case 3 (Proton)	0.122 (0.017~0.227)	0.122 (−0.0163~0.260)	0.037 (0.008~0.065)	0.037 (0~0.074)	0.9989	0.9496

quadratic equations and the goodness-of-fit for each curve for example cases are given in Table 1. The values of R^2 were close to 1.0, demonstrating that survival curves fit the linear quadratic model well. Also, we fitted those cases with commercial graphing software, GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA) and compared α and β parameters and R^2 values which were obtained by our RBE analysis program and Prism 5 software. Those fitting results from two independent programs were comparable as shown in Table 1.

Conclusion

We have presented a new program developed for RBE analysis of particle beam. We have also validated that the cell survival curve could be fitted well with linear quadratic model using the goodness-of-fit and the comparison with commercial graphing software. This new software can generate cell survival curve, fit to model, and calculate RBE all at once with raw experiment data, so it helps users to save time for data handling and to reduce the possibility of making error on analysis. As a coming plan, we will create a user-friendly graphical user interface to present the results more intuitively.

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Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

All relevant data are within the paper and its supporting information files.

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