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Research Paper

A Semi-Empirical Formula to Describe the RBE-Survival Relationship for Proton Irradiation of V79 Cells

Education

KEYWORDS : RBE, proton, LET, V79, Survival

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ABSTRACT

Abstract: Objectives: The main aim here is to describe the dependence of the relative biological effectiveness (RBE) of proton irradiation of V79 cells on survival. Method: This is done by fitting survival curves of various proton energies to the Linear Quadratic equation, The RBE values at survival levels of 0.2 - 0.9 were calculated using ^{60}Co gamma ray as a reference radiation. Results: An equation with four free parameters is suggested to describe the RBE-vs.-Survival relationship. Conclusion: RBE –vs- Surviving fraction curves were adequately fitted to an exponential plus cubic function with four free parameters. Two of those parameters are LET dependent. The rest nearly constants.

Introduction

The biological effect of proton beams in comparison to a reference radiation is described by the Relative Biological Effectiveness or RBE[Edward L.Alpen 1990]. It is Defined as the ratio of the dose of the reference radiation (Dref) and the respective proton dose (Dp) required to yield the same effect (e.g. cell survival S):

RBE= Dref (S)/ Dp (S)

In general, the RBE of ionizing radiations depends on the dose or dose per fraction, the tissue or cell type, the biological end point (e.g. cell survival , chromosome aberrations or mutation), the reference radiation and energy or linear energy transfer (LET). These dependencies are most obvious for in vitro experiments with cell cultures[Belli et al.1990, Barendson 1994, Fumio Yatagai. 2004. Hooshang et al. 2010, Belli et al 1997]. The RBE of a given radiation quality relative to 60Co gamma rays, is not a unique value but varies to a large extent with dose, and biological system effects. RBE values varies within large limits. The RBE increases with decreasing dose. Their values for late effects are definitely higher compared with those for early effects. This is particularly true at low doses[Wambersie et al.2002].

The most relevant value of RBE for charged particles is that calculated with respect to 2 Gy dose of gamma ray. This is due to the fact that radiotherapy centers currently deliver the X or gamma ray dose described to the patient in fractions of 2 Gy . Nowadays, and because of the observation of new structures in survival curves as a result of the hypersensitivity phenomenon, adaptive response and bystander effect, there is growing interest towards adopting new dose fractionations procedures other than 2 Gy[Joiner et al. 2001], this will result in different survival per dose fraction and hence different RBE values. Consequently, the RBE weighting factor which is usually used in radiation clinical centers has to be modified in order to account for these changes.

A knowledge of the dependence of RBE on survival fraction may add some improvement to the RBE weighting factor in addition better understanding of the damage mechanisms. In this work, published data for the in vitro irradiation of V79 cells by protons of variable energy are used to calculate the RBE at different survival fractions using 60Co gamma ray as a reference radiation.

Method

Multiple survival curves measurements for the irradiation of V79 cells by protons were used in this study. Published survival curves data for clonogenic survival were taken from references[Belli et al 1998, Belli et al. 1989, Folkard et al. 1989, Schettino et al 2001] , Special matlab computer code is written and used to retrieve numerical data from graphical presentations in published works. with estimated errors of not more that 5%.

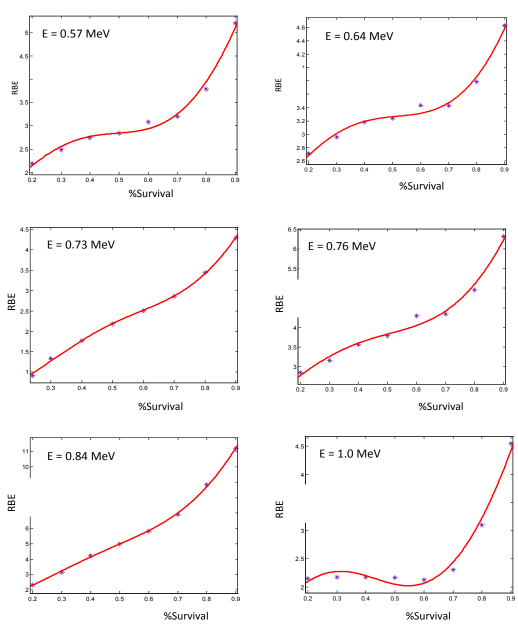
Fourteen survival curves in the energy range (0.57-5.01) MeV were fitted to the Linear Quadratic equation using the curve fitting tool (cftool) facility in MATLAB system. The dose that corresponds to survival values of (0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9) were extracted from each fitted curve. The curves selected are conventional survival curves that show no evidence of a hypersensitivity phenomenon. A 60Co survival curve data for V79 cells[taken from Suzuki 1993] was also fitted to the (LQ) equation and the dose that corresponds to each survival value mentioned above is selected. All the fits were done satisfied the minimum 95% confidence level criteria. This criteria is based on the constrains that the sum of squares due to error(SSE) and the Root Mean Square Error (RMSE) should be very close to zero and the R-square and the Adjusted R-square should be very close to 1. The relative biological effectiveness (RBE) is calculated using the proton dose at a given survival to represent Dp (S) in equation 1 and the corresponding gamma ray dose at the same survival to represent Dref (S) in this equation. The RBE- vs.- survival curves plotted for each proton energy . All the curves were fitted to the equation:

$$RBE = a \times e^{-((S-b)/c)^2} + d \times S^3 \quad (2)$$

Where S is the survival fraction, a, b, c, and d are free parameters.

Results

The LQ model fitting parameters(α and β) for the survival of V79 cells irradiated by different proton energies are presented in table 1, the goodness of fit parameters (SSE, RMSE,R-square and ADJ) are also shown. The α and β parameters for the energies (0.57 0.64 0.76 1.41 and 3.2) MeV obtained in this study are in good agreement with those found by[Belli et al 1997].



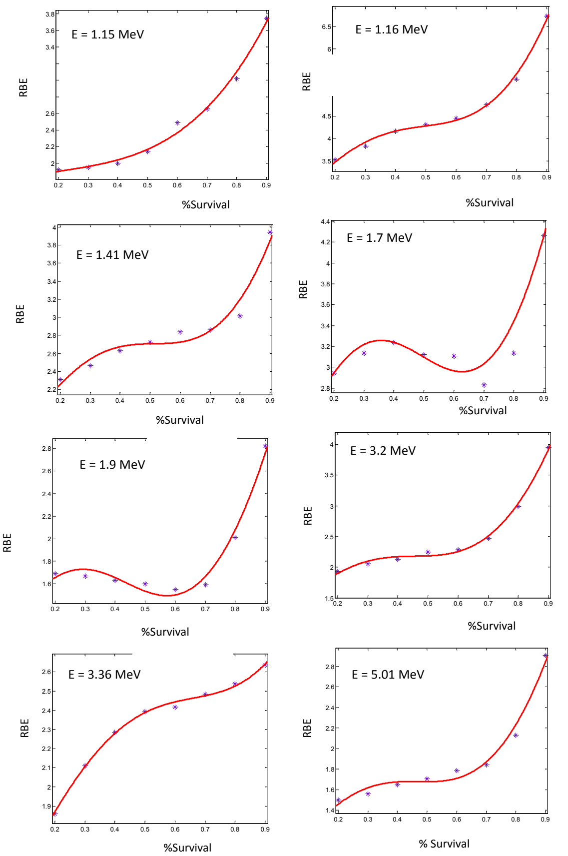


Figure 1. Data points for the Relative Biological Effectiveness (RBE) against Survival for proton Irradiation of V79 cells, * data points, --- fitted equation.

Relative Biological Effectiveness versus survival fitted to equation (2) are shown in figure 1, together with the fitting parameters (a, b, c, and d) and the goodness of fit parameters at the energies specified. These are shown in table 2. The a and d parameters resulted from fitting of equation 2 show a strong dependence on LET as seen in figures 2a and 2d respectively, while the b and c parameters are nearly constant as seen in figures 2b and 2c respectively.

Discussion

The RBE versus Survival curves presented in this study (figure 1) show an increase of RBE with increasing survival but the curves takes different shapes. Equation 2 which is being suggested shows an adequate description of all the data. The equation is a sum of an exponential term which describes the low survival region and a cubic term which describes the high survival region. In the middle region the two terms act jointly. In other words, it can be argued that the cause of damage that leads to low survival fractions is different from that which results in higher survival fractions, and interference between the two processes occur in the middle survival region .

Considering figure 2a. one notices that the 'a' factor which is the coefficient of the exponential term in the predicted equation, varies with LET and this variation can be approximated by three hand drawn straight lines. This means that there are three processes for cell damage that runs linearly with LET. The slope of these lines represents the size of damage associated with each process, The LET- intercept represents the LET value that is required to initiate the particular process. There can be several explanations of such behavior. One is that these processes are associated with three mechanisms for the direct action of ionizing radiations such as single strand breaks (SSB) , double strand breaks (DSB) , protein cross links or base damage in DNA (see Friedland et al. 2003 for DNA damage), Another explanation is that the cells having different responses to radiation during different phases of their cell division

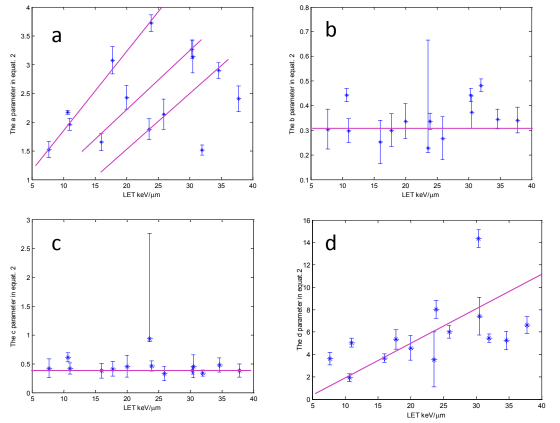


Figure 2. The fitted parameters from predicted equation 2 plotted as a function of LET, the lines are drawn by hand

The linear relation of the 'd' factor which is the coefficient of the cubic term in equation (2) with LET (figure 2d) indicates that there is another mechanism process that varies linearly with LET. Furthermore, it seem that this process follows a unique route. This is because all data points can be approximately described by a single line. The process related to this kind of damage could be the indirect action in which the energy of radiation is absorbed by water molecules and the associated production of free radicals.

The independence of the 'b' and 'c' coefficients on LET means that they are related to biological factors such as cell ability to repair damage irrespective of radiation quality.

A detailed knowledge of the relative biological effectiveness (RBE) for inactivation in irradiated tissue is fundamental for prevention of late radiation effects in normal tissue in general, and for optimizing the treatment in particular.

In clinical practice, the radiation oncologist has to select one RBE value to weight the absorbed dose in order to produce optimum clinical effect as with conventional photon therapy[Wambersie et al 2002]. In conventional therapy treatment of 2 Gy fractions, surrounding normal tissue will receive lower dose which means higher survival fraction. The curves shown in figure 1 indicates that higher survival fractions can have higher RBE values. This suggests that the effect of low proton doses at a given survival fraction on normal tissue is much higher than the effect of gamma ray corresponding to the same survival.

In cases where dose fractionation other than 2 Gy are used, the surviving fraction in tumor tissue will be different, This will lead to different RBE values, and will result in an increase or decrease in the total dose given to the patient depending upon the fractional dose. In cases where the fractional dose is lowered, the results will be higher survival in the tumor region. This will dictate the need for larger total dose to kill the tumor.

Conclusion

The relative biological effectiveness of protons as a function of survival can be described by a single equation with four free parameters. Two of these parameters are LET dependent and the other two are nearly constants. This equation may be useful in clinical practice for prevention of late radiation effects and in prescribing the total dose in radiation therapy. The dependence of the parameters in the predicted equation on LET may play an important role in understanding radiation action mechanism.

Table 1. The LQ model fitting parameters for the inactivation of V79 cells by protons of various energies, The goodness of fit parameters are shown

E(MeV)	α Gy-1	β Gy-2	SSE	RSQ	ADJ	RMSE
0.57	0.5712	2.8e-014	0.002292	0.9972	0.9972	0.01954
0.64	0.6162	0.02118	0.002115	0.997	0.9975	0.02057
0.73	0.5192	-0.04816	0.0004317	0.9992	0.9993	0.007853
0.76	0.7354	0.00013	4.23e-006	1.0	1.0	0.000839
0.84	1.01	-0.09686	0.003526	0.9952	0.9958	0.02245
1.0	0.7688	2.6e-014	0.003888	0.9955	0.9955	0.02357
1.15	0.2658	0.06875	0.001098	0.9987	0.9989	0.01252
1.16	0.7529	0.07867	0.0006358	0.999	0.9992	0.01128
1.41	0.4693	0.03869	0.00033	0.9994	0.9995	0.008157
1.7	0.3851	0.1901	0.001681	0.9973	0.9977	0.01833
1.9	0.1144	0.1073	8.5e-005	0.9999	0.9999	0.003766
3.2	0.3354	0.07871	0.00601	0.9935	0.9936	0.0293
3.36	0.4156	0.03134	0.0003261	0.9994	0.9995	0.008076
5.01	0.3028	0.01691	0.0006616	0.9981	0.9984	0.01286

Table 2. The RBE-vs. Survival fitting parameters from predicted equation, goodness of fit parameters are also given

E(MeV)	a	b	c	d	SSE	RSQ	ADJ	RMSE
0.57	2.404	0.3414	0.3778	6.635	0.06579	0.9894	0.9815	.1283
0.64	2.895	0.3454	0.4783	5.252	0.02777	0.9883	0.9796	0.08332
0.73	1.513	0.4824	0.3361	5.46	0.009473	0.9989	0.9981	0.04866
0.76	3.139	0.373	0.4555	7.422	0.125	0.9853	0.9744	0.1768
0.84	3.266	0.4428	0.3843	14.34	0.03643	0.9994	0.999	0.09544
1.0	2.136	0.2676	0.3298	6.002	0.07979	0.9844	0.9726	0.1412
1.15	1.876	0.2285	0.9383	3.538	0.02746	0.9904	0.9832	0.08286
1.16	3.722	0.3364	0.4577	8.029	0.03228	0.9955	0.9921	0.08984
1.41	2.428	0.3374	0.4551	4.562	0.06551	0.9621	0.9336	0.128
1.7	3.074	0.2998	0.4099	5.354	0.0774	0.9427	0.8998	0.1391
1.9	1.655	0.2519	0.3776	3.67	0.02574	0.9801	0.9651	0.08022
3.2	1.961	0.2985	0.4188	5.03	0.01525	0.9951	0.9951	0.06174
3.36	2.167	0.4427	0.6139	1.919	0.001116	0.9975	0.9956	0.0167
5.01	1.52	0.3045	0.4207	3.62	0.02806	0.9807	0.9663	0.08376

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