International Journal of Cancer Therapy and Oncology
www.ijcto.org

Estimation of linear quadratic (LQ) model parameter alpha/beta (α/β) and biologically effective dose (BED) for acute normal tissue reactions in head and neck malignancies

Mirza Athar Ali[1], Shankar Lal Jakhar[2], Dharam Pal Punia[3], MR Bardia[2], Ajay Sharma[2], HS Kumar[2], Sandeep Jain[4], Neeti Sharma[2], Vinod Agrawal[5], Kamlesh Kumar Harsh[2], Ashok Kumar Kalwar[2], Muntimadugu Babaiah[1], Prabhakar Mariappan[1], N. Madhusudhan[1], Sujana Priya Vuba[1]

[1]Department of Radiation Oncology, American Oncology Institute, Hyderbad, India
[2]ATRCTRI, Bikaner, Rajasthan, India
[3]Mahatma Gandhi University of Medical Sciences & Technology, Jaipur, Rajasthan, India
[4]SMS Medical College, Jaipur, Rajasthan, India
[5]Bhagwan Mahaveer Cancer Institute, Jaipur, Rajasthan, India.

Received April 02, 2016; Revised December 15, 2016; Accepted December 25, 2016; Published Online December 28, 2016

Original Article

Abstract

Purpose: Linear-Quadratic (LQ) model has been widely used for describing radiobiological effectiveness of various fractionation schedules on tumour as well as normal tissues. This study estimates α/β for acute normal tissue reactions using Fe-plot method. **Methods:** 50 cases of locally advanced head and neck squamous cell carcinoma (stage III and IV) treated with external beam radiotherapy were included in this study. Patients were randomly distributed into Hyper-fractionation (HF) arm (1.2 Gy/fraction, twice daily, 6 hours apart) and conventional fractionation (CF) arm (2 Gy/fraction, once daily) with 25 cases in each arm. α/β and BED were calculated for acute normal tissue reactions using Fe-plot method. **Results:** In our study, the estimated values of α/β for RTOG (Radiation Therapy Oncology Group) grade 1, 2 and 3 skin reactions were 11.2 Gy, 10.1 Gy and 9 Gy respectively. Estimated values of α/β for RTOG grade 1, 2 and 3 mucosal reactions were 9.7 Gy, 8.0 Gy and 9.1 Gy respectively. For Hyper-fractionation arm, calculated BED values for grade 1, 2 and 3 skin reactions were 54.45 $Gy_{11.239}$, 66.90 $Gy_{10.114}$ and 73.43$Gy_{9.001}$ respectively and for grade 1, 2 and 3 mucosal reactions were 33.5 $Gy_{9.797}$, 57.8 $Gy_{8.011}$ and 70.8 $Gy_{9.106}$ respectively. For conventional fractionation arm, calculated BED values for grade 1, 2 and 3 skin reactions were 54.09 $Gy_{11.239}$, 66.88 $Gy_{10.114}$ and 73.33 $Gy_{9.001}$ respectively and for grade 1, 2 and 3 mucosal reactions were 33.52 $Gy_{9.797}$, 57.68 $Gy_{8.011}$ and 70.73 $Gy_{9.106}$ respectively. **Conclusion:** LQ model and the concept of BED provide an excellent tool to compare different fractionation schedules in radiotherapy. The estimated values of α/β for acute reacting normal tissues are in good agreement with the available literature.

Keywords: LQ Model, α/β, BED, Fe-plot method

1. Introduction

Management of cancer involves a complex and close integration of biological and physical science in conjunction with sound clinical principles to obtain the best possible therapeutic results. There has been a general evolution in our basic biologic understanding of ionizing radiation and its interaction with living tissues.

Coutard[1] in 1934 established that fractionation of radiation doses improve the results of radiotherapy as

Corresponding author: Mirza Athar Ali; Department of Radiation Oncology, American Oncology Institute, Hyderbad, India.

***Cite this article as**: Ali MA, Jakhar SL, Punia DP, Bardia MR, Sharma A,Kumar HS, Jain S, SharmaN, AgrawaV, Harsh KK, Kalwar AK, Babaiah M, Mariappan P, Madhusudhan N, Vuba SP. Estimation of linear quadratic (LQ) model parameter alpha/beta (α/β) and biologically effective dose (BED) for acute normal tissue reactions in head and neck malignancies. Int J Cancer Ther Oncol. 2016; 4(4):449. **DOI:** 10.14319/ijcto.44.9*

 ISSN 2330-4049

compared to a single dose. Since then, radiation schedules consisting of dose per fraction of 180-200 cGy daily, 5 days per week over several weeks have become conventional in clinical practice. Some of the radiobiologists have suggested that conventional fractionation in radiotherapy may not be most optimal with respect to cellular kinetics and radio-sensitivity of proliferating tumour cells. Some biological experiments suggest that if the inter-fraction interval is reduced to 3-8 hrs and radiation is given 2-3 times per day, the therapeutic ratio can be improved.[2, 3, 4] Since then, variety of dose fractionation schedules have been practiced in radiotherapy with an aim of increasing the radiation effects on malignant cells and at the same time sparing the normal cells as much as possible.

In order to compare various fractionation schedules, several mathematical models such as NSD (nominal standard dose),[5] CRE (cumulative radiation effect)[6] and TDF (time dose fractionation)[7] have been used. These semi-empirical models were in use to assess the dose required to produce tolerable normal tissue reactions. However, such models are only capable of giving reliable results for early reactions of normal tissues but fail to do so for late reactions.

Linear-Quadratic (LQ) model[8, 9] has been widely used for describing radiobiological effectiveness of various fractionation schedules on tumour as well as normal tissues. LQ model has provided a satisfactory mathematical description to the mechanism of radiation induced cell kill. It is now clear that, LQ formulation may be applied to a wider variety of clinical circumstances by careful selection of parameters which are characteristic of a particular tissue response. LQ model was originally proposed by Keller and Rosi in 1972 as a consequence of the micro-dosimetry of radiation induced cellular lesions. The "linear" term results from interaction of radiation that occur along a single ionizing track, while the "quadratic" term results from the interaction of radiation occurring along two different particle tracks. The fact that LQ model could be used to obtain iso-effect relations for normal tissue damage was noted by Douglas and Fowler in 1976.

LQ model is useful in identifying the important difference in the effect of dose fraction size between rapidly proliferating tissues (acute reacting normal tissues and most tumours) and slowly proliferating tissues (late reacting normal tissues).

LQ model is based on the following assumptions:[10]

a) Ionizing radiation produce damage in cell parts which cause effective radiation damage with frequency increasing linearly with the absorbed dose (D), while other radiation induced tissue injury called sub-effective (sub-lethal) lesions can cause the same cellular effects through mutual interaction. These later effects increase with the square of the dose (D^2).
b) The effective radiation damage results from the interaction of sub-effective lesions requiring production close to each other in space and in time in the same cell. In the case of low LET (linear energy transfer) radiation, each of the sub-effective lesions is produced independently i.e. by different electrons passing through the same cell.
c) The sub-effective lesions remain available for interaction during a limited time interval after their production. The decay of their capacity for interaction is assumed to be an exponential function characterized by a half-life of 0.5-2 hrs. This assumption corresponds to the concept of sub-lethal damage introduced by Elkind and Sutton on the basis of cell survival data.[11]
d) The influence of cell proliferation during a treatment regime must be accounted for separately for each type of tissue.
e) Equal reduction of log survival is obtained after each fraction.

LQ model is so called on account of the assumed mathematical form of underlying dose response equation. The main feature of LQ model is that the frequency of biological effect (E) i.e. log cell kill following a radiation dose 'D' is given by:

$$E = \alpha.D + \beta.D^2$$

where, 'α' and 'β' are constants.[12]

The above equation describes two processes each of which may lead to cell death. In the first process, two critical sites within the cells are simultaneously damaged in single radiation event (single hit). Such hits in adjacent targets lead to the death of the cell. In the second process, the targets are damaged in separate radiation events after which the damaged sites may co-operate to produce cell death. When one of the target doublets is damaged by radiation, we call the cell to be sub-lethally damaged. In broad terms, α and β are two measures of the relative importance of the two processes of cell kill and thus the ratio α/β is of prime significance.

'α' is the linear component of cell kill, representing the intrinsic radio-sensitivity of the cells and mathematically defined as log (to the base 'e') of total number of cells killed per Gray of radiation dose in a non-repairable way. Its unit is Gy^{-1}. 'β' is the quadratic component of cell kill, representing the repair capacity of the cells and hence the repairable portion the cell damage, requiring 6 hr or more for complete repair. Its unit is Gy^{-2}.

'E' is the $\log_e$ sum of the non-repairable 'α' term and the partly repairable 'β' term.

 ISSN 2330-4049

For 'n' fractions of dose 'd' per fraction (in Gray):

$$E = n\left(\alpha.d + \beta.d^2\right)$$

Therefore,

$$\frac{E}{a} = nd\left(1 + \frac{d}{\alpha / \beta}\right) \text{--------- Eq. 1}$$

α/β ratio precisely represents the dose at which 'α' component of cell kill is equal to the 'β' component of cell kill (Figure 1).

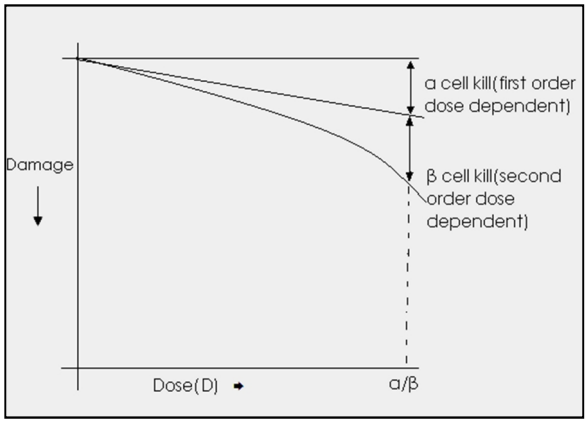

Figure 1: Cell survival curve showing 'α' and 'β' components of cell kill.[9]

Acute epithelial tissue reactions in radiotherapy tend to be characterised by a relatively high α/β ratio, typically in the range of 8-13 Gy with an average of about 10 Gy.[13] Late tissue reactions tend to be characterized by a relatively low α/β ratio typically in the range of 2-6 Gy, but spread of values may extend outside this range.[9] Tumour responses tend to be characterized by a high α/β ratio, typically 6-25 Gy.[14]

Clinical estimates of α/β are usually carried out through Fe-plots between the reciprocal of iso-effect dose and the dose per fraction.[15] To plot such a graph, patients need to be irradiated to different dose fractionation schedules to obtain iso-effects for specific end point tissue effect (tumour control, early or late tissue reactions). Iso-effect doses measured for the schedules under consideration are used to plot a Fe-graph to obtain α/β for a specific end point tissue effect. Estimated values of α/β can thus be used to calculate BED (biologically effective dose) for the respective end point tissue effect and hence, evaluation of biological equivalence of various dose fractionation schedules can be done.

The basic concept of BED was defined by Barendsen[8] in 1982 who first called it extrapolated tolerance dose (ETD), meaning that dose which if given in infinite number of infinitely small fractions (i.e. at very low dose rate) so that all the quadratic damage has been repaired, would cause the same log cell kill as the schedule under consideration.[16] Since it was obvious that this conceptual extrapolation to very small dose per fraction could be applied to any level of damage, not just to the maximum tolerated level or only to normal tissues, it was soon renamed as extrapolated response dose (ERD) and later to a more general term of BED.[16] Because BED is defined in relation to the initial slope of cell survival curve (Figure 2) i.e. the linear component of damage, it is represented as "E/α".

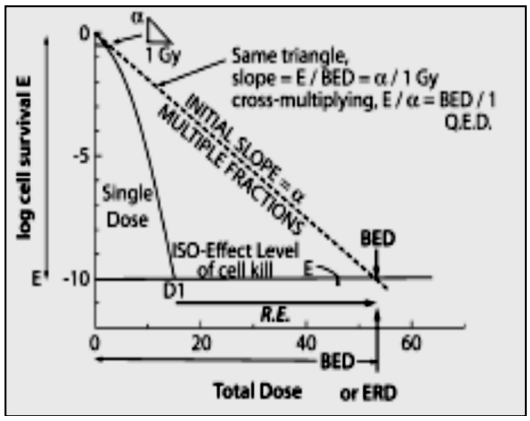

Figure 2: Log Cell Survival Curve.[16]

Therefore, BED = E/α.

The unit of BED is Gy. Since, the definition of BED is the ratio E/α, the individual values of E and α are irrelevant for estimating relative total doses. The ratio E/α is mathematically a link function, signifying biological equivalence between two schedules having equal effect (iso-effect). Values of "α" are particularly vulnerable to variation of tumour size, stage and accuracy of dose, but provided that the ratio E/α does not vary between one prospective population and another, there are no effects on the ratios of doses between schedules, which is what one intends to compare. This is the important reason why BED is robust.

2. Methods and Materials

2.1. Patient selection

A total of 50 cases of locally advanced squamous cell carcinoma of head and neck region (stage III and IV) without any evidence of distant metastasis were included in this study. Patients were randomly distributed into Hyper-fractionation (HF) arm (1.2 Gy/fraction, twice daily, 6 hours apart) and conventional fractionation (CF) arm (2 Gy/fraction, once daily) with 25 cases in each arm.

Criteria for patient selection:

i. Histopathologically proven squamous cell carcinoma of head and neck.
ii. Location of primary: Tongue, tonsil, floor of mouth, palate, buccal mucosa and alveolus where tumour response and normal tissue

acute reactions can be assessed easily by clinical examination.

iii. Locally advanced disease (stage III and IV).
iv. No evidence of distant metastasis at the time of presentation.
v. Previously untreated cases.
vi. Karnofsky performance status (KPS) ≥ 70.
vii. No evidence of second malignancy.
viii. Adequate baseline organ functions and hematological status.
ix. Age limit: 18-70 yrs.
x. No evidence of any dermatological disease or aphthous ulcers at the time of start of radiotherapy.

2.2. Treatment plan

All the 50 cases in this study were treated with external beam radiotherapy by parallel opposite pair technique on Cobalt-60 machine (Theratron 780 C and E).

Conventional fractionation (CF) arm received 2 Gy per fraction, treated once daily, 5 days a week over 6 weeks to a total dose of 60 Gy. Initial treatment fields included the primary tumor with adequate safe margins and primary nodal drainage regions (whole neck) and 44 Gy was delivered through these fields. Subsequently, fields were reduced to spare spinal cord. Primary site with gross nodes (if any) were further irradiated to a total dose of 60 Gy.

Hyper-fractionation (HF) arm received 1.2 Gy per fraction, 2 fractions per day separated by a gap of 6 hrs, 5 days a week over 5-6weeks (39 treatment days) to a total dose of 64.8 Gy. Initial treatment fields included the primary tumor with adequate safe margins and primary nodal drainage regions (whole neck) and 43.2 Gy was delivered through these fields. Subsequently, fields were reduced to spare spinal cord. Primary site with gross nodes (if any) were further irradiated to a total dose of 64.8 Gy.

2.3. Observation and evaluation

During radiotherapy, all the patients were assessed weekly once for development of acute skin and mucosal reactions. Grading of acute skin and mucosal reactions was done using RTOG criteria (Table 1).[17] Doses at which patients developed graded acute skin and mucosal reactions were noted. Using these values, mean iso-effect doses were calculated for specific end point tissue reactions for both CF and HF arms. After 4 weeks of completion of radiotherapy, patients were assessed for treatment response in terms of disease control (tumor regression) using RECIST (Response Evaluation Criteria in Solid Tumors) criteria (Table 2).[18, 19]

Table 1: RTOG criteria for grading of acute skin and mucosal reactions.[17]

Grade	Acute skin reactions	Acute mucosal reactions
0	No reaction	No reaction
I	Erythema	Erythema
II	Dry Desquamation	Patchy mucositis
III	Moist Desquamation	Confluent mucositis
IV	Necrosis	Ulceration / Necrosis

Table 2: Response evaluation criteria in solid tumors.[18,19]

Best response	Change in sums longest diameters
Complete response (CR)	Disappearance; Confirmed at 4 weeks.
Partial response (PR)	30% Decrease; Confirmed at 4 weeks.
Stable disease (SD)	Neither PR nor PD criteria met.
Progressive disease (PD)	20% Increase; No CR, PR or SD documented before increased disease.

2.4. Construction of Fe-plot

A graphical representation of the biological normal tissue response to conventional and hyper-fractionated radiotherapy was performed by taking dose per fraction on x-axis and inverse of iso-effect dose on y-axis (Figure 3). A plot was constructed by marking iso-effect doses for acute skin and mucosal reactions for both hyper-fractionation schedule and conventional fractionation schedule.

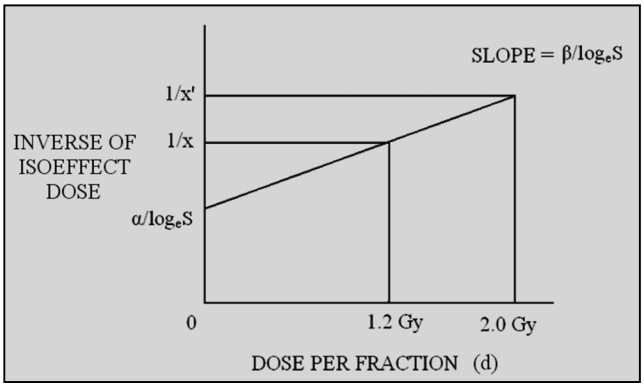

Figure 3: Fe plot – Isoeffect dose curve

2.5. Calculation of LQ parameter α/β

The point at which the extrapolated line joining iso-effect doses for conventional and hyper-fractionated radiotherapy schedule intersects y-axis corresponds to $\alpha/\log_e S$ (I). Slope of the plot corresponds to $\beta/\log_e S$ (II). α/β can be calculated by dividing (II) from (I) which will give numerical value (in Gy) of α/β for acute skin/mucosal reactions.

Calculation of total dose (Dx) for hyper-fractionated schedule, which is biologically iso-effective to the dose given by conventional radiotherapy schedule (Dr).[16]

$$\frac{D_r}{D_x} = \frac{\left(\frac{\alpha}{\beta} + d_x\right)}{\left(\frac{\alpha}{\beta} + dr\right)} ------ Eq.\ 2$$

Where;
Dr: Known total dose (60 Gy) for conventional RT schedule.
Dx: New total dose to be calculated for hyper-fractionated schedule.
dr: Dose per fraction for conventional radiotherapy schedule: 2 Gy.
dx: Dose per fraction for hyper-fractionated radiotherapy schedule: 1.2 Gy.

Considering value of α/β to be 10 Gy[3, 20, 21, 22] for acute skin/mucosal reactions:

$$\frac{60}{D_x} = \frac{(10+1.2)}{(10+2.0)} ------ \text{Eq. } 3$$

Therefore,

Dx = 64.28 Gy.

Approximating this value to obtain an exact multiple of 1.2 Gy, the total dose arrived at was 64.8 Gy.

2.6. Calculation of biological effective dose (BED)

Using α/β values calculated from Fe-plot, BED for acute normal tissue reactions (Gy_{10}) was calculated for both conventional and hyper-fractionated radiotherapy schedule.[9, 23]

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right) ---- \text{Eq. } 4$$

where, 'D' is total dose and 'd' is dose per fraction.

3. Results

Table 3 shows the incidence of acute skin reactions in terms of RTOG grade as a function of treatment duration in weeks.

Table 3: Incidence of acute skin reactions.

Treatment duration (weeks)	Hyper-fractionation Arm (HF)						Conventional fractionation Arm (CF)					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
1st week	25	0	0	0	0	25	25	0	0	0	0	25
2nd week	25	0	0	0	0	25	25	0	0	0	0	25
3rd week	25	0	0	0	0	25	25	0	0	0	0	25
4th week	14	11	0	0	0	25	25	0	0	0	0	25
5th week	0	8	17	0	0	25	0	25	0	0	0	25
6th week	0	0	22	3	0	25	0	0	23	2	0	25
1 month follow up	0	18	7	0	0	25	0	17	8	0	0	25

Table 4 shows the incidence of acute mucosal reactions in terms of RTOG grade as a function of treatment duration in weeks.

Table 4: Incidence of acute mucosal reactions.

Treatment duration (weeks)	Hyper-fractionation Arm (HF)						Conventional fractionation Arm (CF)					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
1st week	25	0	0	0	0	25	25	0	0	0	0	25
2nd week	25	0	0	0	0	25	25	0	0	0	0	25
3rd week	0	25	0	0	0	25	6	19	0	0	0	25
4th week	0	13	12	0	0	25	0	22	3	0	0	25
5th week	0	0	15	10	0	25	0	3	22	0	0	25
6th week	0	0	0	25	0	25	0	0	0	25	0	25
1 Month follow up	0	17	8	0	0	25	0	15	10	0	0	25

Table 5 shows total radiation dose delivered corresponding to the treatment duration in weeks.

Table 5: Total delivered dose (Gy) corresponding to treatment duration.

Arm	1st week	2nd week	3rd week	4th week	5th week	6th week
HF Arm	12 Gy (10 fractions)	24 Gy (20 fractions)	36 Gy (30 fractions)	48 Gy (40 fractions)	60 Gy (50 fractions)	64.8 Gy (54 fractions)
CF Arm	10 Gy (5 fractions)	20 Gy (10 fractions)	30 Gy (15 fractions)	40 Gy (20 fractions)	50 Gy (25 fractions)	60 Gy (30 fractions)

Table 6 shows the mean iso-effect doses of radiation as a function of RTOG grade of acute skin and mucosal reactions.

Table 6: Mean iso-effect dose (Gy) for acute skin and mucosal reactions.

RTOG Grade	Hyper-fractionation arm (HF)		Conventional fractionation arm (CF)	
	SKIN	MUCOSA	SKIN	MUCOSA
Grade 1	49.2 Gy	29.904 Gy	45.92 Gy	27.84 Gy
Grade 2	59.808 Gy	50.304 Gy	55.84 Gy	46.16 Gy
Grade 3	64.8 Gy	62.592 Gy	60 Gy	58 Gy
Grade 4	-	-	-	-

Table 6A: Statistical table.

Acute reactions	Grade	Hyper-fractionation Arm (HF)		Conventional fractionation Arm (CF)		t	p
		Mean	S.D	Mean	S.D		
Skin reactions	Grade 1	49.20	2.42	45.92	1.87	5.357	<0.001
	Grade 2	59.808	3.21	55.84	2.76	4.231	<0.001
	Grade 3	-	-	-	-	-	-
Mucosal reactions	Grade 1	29.904	2.64	27.84	3.21	2.730	<0.05
	Grade 2	50.304	2.99	46.16	3.91	4.391	<0.001
	Grade 3	62.59	2.32	58.0	2.65	6.235	<0.001

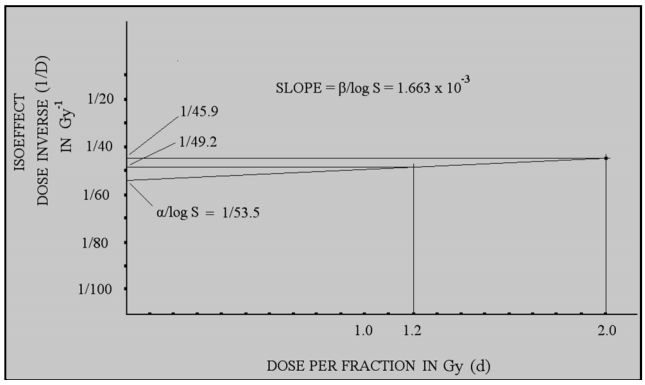

Figure 4: Fe-plot for grade I skin reaction.

Figure 4 shows the Fe-plot drawn for iso-effect doses of grade 1 skin reaction. X-axis shows dose per fraction of the treatment schedule and Y-axis shows inverse of total dose delivered. While HF arm patients developed grade 1 skin reaction at a mean iso-effect dose of 49.2 Gy, CF arm patients developed the same at mean iso-effect dose of 45.9 Gy. Numerical value on y-axis (1/53.5) obtained by extrapolating the line joining the respective isodose points corresponds to $\alpha/\log_e S$ and the slope of the curve (1.663×10^{-3}) corresponds to $\beta/\log_e S$.

Figure 5 shows the Fe-plot drawn for iso-effect doses of grade 2 skin reaction. While HF arm patients developed grade 2 skin reaction at a mean iso-effect dose of 59.8 Gy, CF arm patients developed the same at mean iso-effect dose of 55.8 Gy. Numerical value on y-axis (1/66) obtained by extrapolating the line joining the respective isodose points corresponds to $\alpha/\log_e S$ and the slope of the curve (1.498×10^{-3}) corresponds to $\beta/\log_e S$.

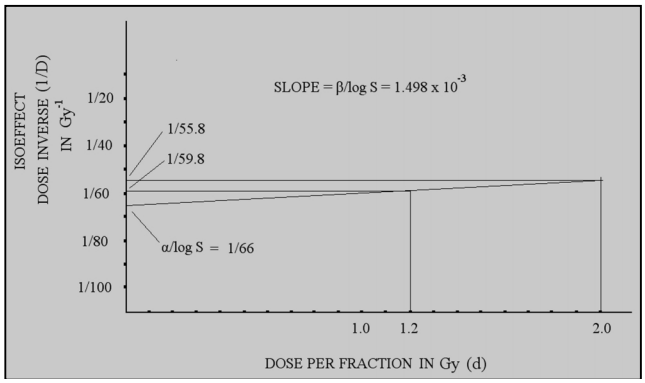

Figure 5: Fe-plot for grade 2 skin reaction.

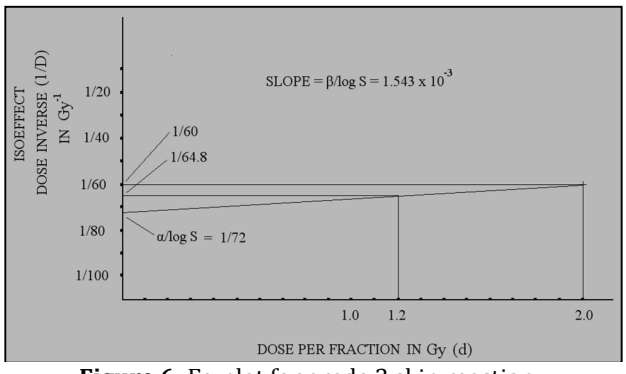

Figure 6: Fe-plot for grade 3 skin reaction.

Figure 6 shows the Fe-plot drawn for iso-effect doses of grade 3 skin reaction. While HF arm patients developed grade 3 skin reaction at a mean iso-effect dose of 64.8 Gy, CF arm patients developed the same at mean iso-effect dose of 60 Gy. Numerical value on y-axis (1/72) obtained by extrapolating the line joining the respective isodose points corresponds to $\alpha/\log_e S$ and the slope of the curve (1.543×10^{-3}) corresponds to $\beta/\log_e S$.

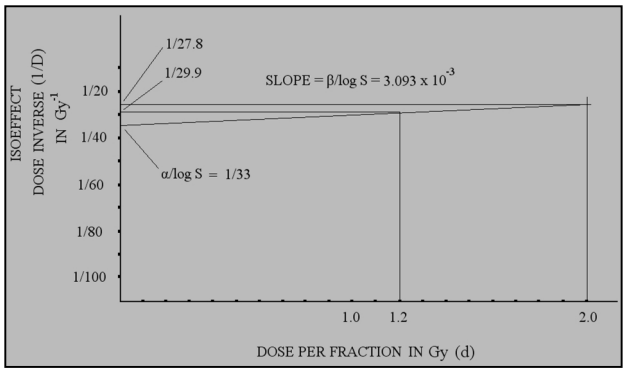

Figure 7: Fe-plot for grade I mucosal reaction.

Figure 7 shows the Fe-plot drawn for iso-effect doses of grade 1 mucosal reaction. While HF arm patients developed grade 1 mucosal reaction at a mean iso-effect dose of 29.9 Gy, CF arm patients developed the same at mean iso-effect dose of 27.8 Gy. Numerical value on y-axis (1/33) obtained by extrapolating the line joining the respective isodose points corresponds to $\alpha/\log_e S$ and the slope of the curve (3.093×10^{-3}) corresponds to $\beta/\log_e S$.

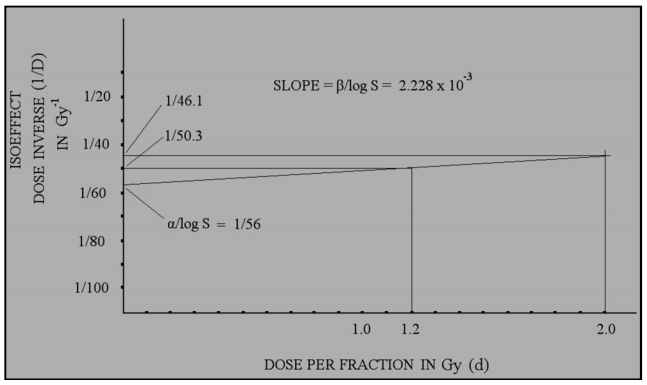

Figure 8: Fe-plot for grade 2 mucosal reaction.

Figure 8 shows the Fe-plot drawn for iso-effect doses of grade 2 mucosal reaction. While HF arm patients developed grade 2 mucosal reaction at a mean iso-effect dose of 50.3 Gy, CF arm patients developed the same at mean iso-effect dose of 46.1 Gy. Numerical value on y-axis (1/56) obtained by extrapolating the line joining the respective isodose points corresponds to $\alpha/\log_e S$ and the slope of the curve (2.228×10^{-3}) corresponds to $\beta/\log_e S$.

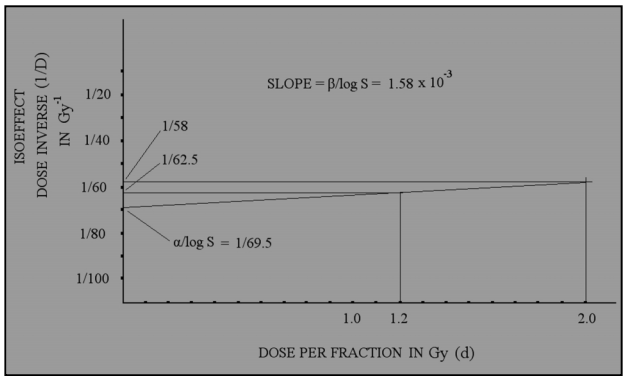

Figure 9: Fe-plot for grade 3 mucosal reaction.

Figure 9 shows the Fe-plot drawn for iso-effect doses of grade 3 mucosal reaction. While HF arm patients developed grade 3 mucosal reaction at a mean iso-effect dose of 62.5 Gy, CF arm patients developed the same at mean iso-effect dose of 58 Gy. Numerical value on y-axis (1/69.5) obtained by extrapolating the line joining the respective isodose points corresponds to $\alpha/\log_e S$ and the slope of the curve (1.58×10^{-3}) corresponds to $\beta/\log_e S$.

3.1. Calculation of LQ model parameter α/β (Table 7)

'Y' intercept of Fe-plot corresponds to $\alpha/\log_e S$.
Slope of the curve corresponds to $\beta/\log_e S$.
Hence, $\alpha/\beta = (\alpha/\log_e S) \div (\beta/\log_e S)$

3.2. Calculation of biological effective dose (BED) (Table 8)

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right) ----\text{Eq. 4}$$

Table 7: Calculated values of α/β for acute skin and mucosal reactions using Fe-plot method.

Acute radiation reactions		'Y' Intercept ($\alpha/\log_e S$)	Slope ($\beta/\log_e S$)	$\alpha/\beta = (\alpha/\log_e S) \div (\beta/\log_e S)$
Skin	Grade 1	1/53.5	1.663×10^{-3}	11.239
	Grade 2	1/66	1.498×10^{-3}	10.114
	Grade 3	1/72	1.543×10^{-3}	9.001
Mucosa	Grade 1	1/33	3.093×10^{-3}	9.797
	Grade 2	1/56	2.228×10^{-3}	8.011
	Grade 3	1/69.5	1.58×10^{-3}	9.106

Table 8: BED calculation: Using α/β values calculated from Fe-plot, BED for acute normal tissue reactions ($Gy_{\alpha/\beta}$) was calculated.

RTOG grade of acute reactions	BED ($Gy_{\alpha/\beta}$)			
	HF Arm (D = iso-effect dose & d = 1.2 Gy)		CF Arm (D = iso-effect dose & d = 2 Gy)	
	SKIN	MUCOSA	SKIN	MUCOSA
Grade 1	54.45 $Gy_{11.239}$	33.566 $Gy_{9.797}$	54.09 $Gy_{11.239}$	33.52 $Gy_{9.797}$
Grade 2	66.90 $Gy_{10.114}$	57.839 $Gy_{8.001}$	66.88 $Gy_{10.114}$	57.68 $Gy_{8.001}$
Grade 3	73.439 $Gy_{9.001}$	70.84 $Gy_{9.106}$	73.33 $Gy_{9.001}$	70.73 $Gy_{9.106}$

Where 'D' is iso-effect dose and 'd' is dose per fraction.

Table 9: Treatment response evaluation for disease control using RECIST criteria.

Disease response	Stage	HF Arm				CF Arm			
		End of treatment	1st Month follow up	3rd Month follow up	6th Month follow up	End of treatment	1st Month follow up	3rd Month follow up	6th Month follow up
Complete response (CR)	III	8	11	11	10	7	9	10	10
	IV	1	5	5	4	1	2	2	2
Partial response (PR)	III	3	1	1	2	7	5	4	4
	IV	8	7	6	6	7	8	7	6
Stable disease (SD)	III	1	0	0	0	0	0	0	0
	IV	3	0	1	1	2	0	1	2
Progressive disease (PD)	III	0	0	0	0	0	0	0	0
	IV	1	1	1	1	1	1	1	1
Total		25	25	25	24*	25	25	25	25

* One patient of HF arm was lost to follow up after 3rd month.

Table 9A: Statistical table.

Disease response	STAGE	End of treatment		1st Month follow up		3rd Month follow up		6th Month follow up	
		χ^2	p	χ^2	p	χ^2	p	χ^2	p
Complete response(CR)	III	0.0952	>0.05	0.3333	>0.05	0.0821	>0.05	0	-
	IV	0	-	1.495	>0.05	1.495	>0.05	0.7576	>0.05
Partial response (PR)	III	2.00	>0.05	3.0303	>0.05	2.00	>0.05	0.7576	>0.05
	IV	0.0952	>0.05	0.0952	>0.05	0.104	>0.05	0	-
Stable disease (SD)	III	1.0204	>0.05	0	-	0	-	0	-
	IV	0.2222	>0.05	0	-	0	-	0.3546	>0.05
Progressive disease (PD)	III	0	-	0	-	0	-	0	-
	IV	0	-	0	-	0	-	0	-

4. Discussion

This study showed the estimated values of α/β for grade 1, 2 and 3 skin reactions to be 11.2 Gy, 10.1 Gy and 9 Gy respectively. Fowler *et al.*[24] in 1974 estimated value of α/β for skin desquamation to be 9.4 Gy (6.1 Gy - 14.3 Gy). Douglas *et al.*[25] in 1976 estimated value of α/β for skin desquamation to be 11.7 Gy (9.1 Gy - 15.4 Gy). Joiner *et al.*[26] in 1986 estimated value of α/β for skin desquamation to be 10.5 Gy (8.5 Gy - 12.5 Gy). Bentzen *et al.*[27] in 1988 estimated α/β for skin erythema to be 12.3 Gy (2 Gy – 23 Gy). Turesson *et al.*[28] in 1989 estimated α/β for skin desquamation to be 11.2 Gy (8.5 Gy – 17.6 Gy). They estimated value of α/β for skin erythema to be 8.8 Gy (6.9 Gy – 11.6 Gy). In this study, the estimated values of α/β for grade 1, 2 and 3 mucosal reactions were 9.7 Gy, 8.0 Gy and 9.1 Gy respectively. Rezvani *et al.*[29] in 1991 estimated α/β for acute mucosal reactions to be 15 Gy (0 – 45.2 Gy).

Estimated values of α/β were used to calculate biologically effective dose (BED) for acute skin and mucosal reactions for both HF and CF arms. For HF arm, estimated values of BED for grade 1, 2 and 3 skin reactions were 54.45 $Gy_{11.239}$, 66.90 $Gy_{10.114}$ and 73.43$Gy_{9.001}$ respectively and for grade 1, 2 and 3 mucosal reactions were 33.5 $Gy_{9.797}$, 57.8 $Gy_{8.011}$ and 70.8 $Gy_{9.106}$ respectively. For CF arm, estimated values of BED for grade 1, 2 and 3 skin reactions were 54.09 $Gy_{11.239}$, 66.88 $Gy_{10.114}$ and 73.33 $Gy_{9.001}$ respectively and for grade 1, 2 and 3 mucosal reactions were 33.52 $Gy_{9.797}$, 57.68 $Gy_{8.011}$ and 70.73 $Gy_{9.106}$ respectively. An EORTC study[30]

which studied hyper-fractionated schedule of 1.15 Gy per fraction, twice a day to a total dose of 80.5 Gy in 42 days, measured the value of BED for acute skin and mucosal reactions to be 79.45 Gy_{10}. An RTOG study[31] which studied hyper-fractionated schedule of 1.2 Gy per fraction, twice a day to a total dose of 81.6 Gy in 42 days, measured the value of BED for acute skin and mucosal reactions to be 81.09 Gy_{10}. Results of EORTC and RTOG studies show higher BED values from that of our study because the planned total dose in these studies were greater than that was planned in our study.

The importance of the estimated values of BED for specific end point tissue reaction lies in its utility in comparing different fractionated radiotherapy schedules. BED values obtained in our study show that the hyper-fractionated radiotherapy schedule using 1.2 Gy per fraction, 2 fractions per day for a total dose of 64.8 Gy is biologically equivalent to the conventional fractionated radiotherapy schedule of 2 Gy per fraction, 1 fraction a day to a total dose of 60 Gy in terms of acute skin and mucosal reactions. However, reactions appeared early in hyper-fractionated schedule.

Evaluation of treatment response in terms of disease control using RECIST criteria showed that 36% of HF arm and 32% of CF arm patients had complete response, 44% of HF arm and 56% of CF arm patients had partial response, 16% of HF arm and 8% of CF arm patients had stable disease and 4% of HF arm and 4% of CF arm patients had progressive disease. Statistical evaluation showed that hyper-fractionated and conventional fractionated radiotherapy used in our study are biologically equivalent in terms of disease control as well.

5. Conclusion

LQ model and the concept of BED provide an excellent tool to compare different fractionation schedules in radiotherapy and form the basis of selection of a particular fractionation schedule in order to achieve a better therapeutic ratio. Ample amount of work has been done in the field of radio-biology to estimate the values of LQ model parameter α/β for specific tissue reactions, however further efforts in this direction will certainly be solicited towards the ultimate goal of higher tumour control probability and low normal tissue complication probability.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Coutard H. Principle of x-ray therapy for cancer. Lancet. 1934; 2:1-8.
2. Douglas BG, Worth AJ. Superfractionation in glioblastoma multiforme-results of a phase II study. Int J Radiat Oncol Biol Phys. 1982; 8(10):1787-94.
3. Douglas BG. Preliminary results using super-fractionation in the treatment of glioblastoma multiforme. J Can Assoc Radiol. 1977; 28:106-10.
4. Simpson WJ, Platts ME. Fractionation study in the treatment of glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 1976; 1:639–44.
5. Ellis F. The relationship of biological effect to dose-time-fractionation factors in radiotherapy. W: Ebert M and Howard A. Current Topics in Radiation Research. 1968; 4:357-397.
6. Kirk J, Gray WM, Watson ER. Cumulative radiation effect. Part 1: Fractionated treatment regimens. Clin Radiol. 1971; 22:145-53.
7. Orton CG, Ellis F. A simplification in the use of NSD concept in practical radiotherapy. Br J Radiol. 1973; 46(547):529-37.
8. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys. 8(11):1981-97.
9. Perez CA, Brady LW, Halperin EC, *et al*. Principles and Practice of radiation oncology. 4th Ed. 2004; 1:28-32.
10. Astrahan M. Some implications of linear-quadratic-linear radiation dose-response with regard to hypofractionation. Medical Physics. 2008; 35(9):4161-4172.
11. Ellis F. Dose, time and fractionation: A clinical hypothesis. Clinical Radiology. 1969; 20(1):1-7.
12. Fowler JF. The first James Kirk memorial lecture. What next in fractionated radiotherapy? Br J Cancer Suppl. 1984; 6:285-300.
13. Williams MW, Denekamp J, Fowler JF. A review of alpha/beta ratios for experimental tumors: implications for clinical studies of altered fractionation. Int J Radiat Oncol Biol Phys. 1985; 11(1):87-96.
14. Maciejewski B, Preuss-Bayer, Trott KR. The influence of the number of fractions and overall treatment time on the local control of cancer of the larynx. Int J Radiat Oncol Biol Phys. 1983; 9:321.
15. Douglas BG, Fowler JF. The effect of multiple small doses of x-rays on skin reactions in the mouse and a basic interpretation. Radiat Res. 1976; 66(2):401-26.
16. Levitt SH, Purdy JA, Perez CA, *et al.* Technical basis of radiotherapy. 2007; 1:10-11.
17. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995; 31(5):1341-6.

 ISSN 2330-4049

18. Padhani AR, Ollivier L. RECIST criteria: Implications for diagnostic radiologists. Br J Radiol. 2001; 74(887):983-6.
19. Patrick T, Sussane GA, Elizabeth AE et al. New guidelines to evaluate the response to treatment in solid tumors. Journal of National Cancer Institute. 2000; 92:3.
20. Saunders MI, Rojas AM. Management of cancer of head and neck – a cocktail with your PORT. N Engl J Med. 2004; 6:350(19):1997-9.
21. Seiwert TY, Cohen EE. State of the art management of locally advanced head & neck cancers. British J. Cancer. 2005; 92(8):1341-8.
22. Seiwert TY, Vokes EE. Head and neck cancer. The cancer handbook. 2nd Ed. (Alison.M.R) Chichester, UK, Wiley, in press.
23. Fowler JF. The linear quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989; 62(740);679-94.
24. Fowler JF, Denekamp J, Delapeyre C, *et al*. Skin reactions in mice after multifraction x-irradiation. Int J Radiat Biol Relat Stud Phys Chem Med. 1974; 25(3):213-23.
25. Douglas BG, Fowler JF. The effect of multiple small doses of x-rays on skin reactions in the mouse and basic interpretation. Radiat Res. 1976; 66(2):401-26.
26. Joiner MC, Denekamp J, Maughan RL. The use of "top-up" experiments to investigate the effect of very small doses per fraction in mouse skin. Int J Radiat Biol. 1986; 49:565-80.
27. Bentzen SM, Juul-Christensen J, Overgaard J. Some methodological problems in estimating radiobiological parameters from clinical data: alpha/beta ratios and electron RBE for cutaneous reactions in patients treated with postmastectomy radiotherapy. Acta Oncol. 1988; 27:105-16.
28. Turesson I, Thames HD. Repair capacity and kinetics of human skin during fractionated radiotherapy: erythema, desquamation and telangiectasia after 3 and 5 years follow up. Radiother Oncol. 1989; 15(2):169-88.
29. Rezvani M, Alcock CJ, Fowler JF, *et al.* Normal tissue reactions in the British Institute of Radiology study of 3 fractions per week versus 5 fractions per week in the treatment of carcinoma of the laryngo-pharynx by radiotherapy. Br J Radiol. 1991;64(768):1122-33.
30. Horiot JC, Le Fur R, N'Guyen T *et al.* Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol. 1992 ;25(4):231-41.
31. Fu KK, Pajak TF, Trotti A, *et al.* A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys. 2000 ;48(1):7-16.

 ISSN 2330-4049