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Accelerated proliferation correction factors in linear-quadratic and multiple-component models

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Background: Study in design to incorporate accelerated proliferation correction factors into linear-quadratic and multiple-component models. ***Materials and Methods:*** Accelerated proliferation rate correction factor has been incorporated into the linear-quadratic and the multiple component models by applying accelerated exponential cell growth to explain the tumor cell kinetics and estimates proper treatment results. Biological effectiveness and tumor control probability, in terms of BED (LQ model), BRD (MC model), TCP(LQ model) and TCP(MC model), were computed for three conventional and two accelerated hyperfractionated radiation therapy treatment schedules with using a range of accelerated proliferation rate constants to demonstrate the effect of the proliferation process. ***Results:*** The results of the study show that the accelerated proliferation rate reduces the effectiveness of a treatment schedule delivered in a prolonged period of time. ***Conclusion:*** Care should be taken in the selection of a treatment protocol for a patient of head and neck cancer with an account of the cell kinetics of the tumor. **Iran. J. Radiat. Res., 2007; 5 (2): 53-61**

Keywords: *Accelerated proliferation rate, growth fraction, tumor control probability, LQ model, MC model.*

INTRODUCTION

The linear-quadratic (LQ) model [1] was modified to the multiple-component (MC) model [2-4] to address the issues of irradiating tissues that cloud not be explained by the LQ model [5]. The basic equations of the LQ and MC models are unable to explain the issue of proliferation in early reacting tissues and tumors. Proliferation effect in late reacting tissues is hardly a matter of consideration because no excessive proliferation is present in these tissues during radiotherapy treatment, or may have very little influence at the end of the treatment.

The proliferation correction factors applied in these models such as the LQ and the MC models [6-8] were based on the assumption of a constant proliferation rate after its initiation. But, the cells in early reacting normal tissues and tumors divide faster than before, after its initiation, during irradiation to compensate the loss [9]. Hence, the correction factors based on the assumption of a constant proliferation rate may not be able to predict true cell kinetics of early reacting tissues and tumors and may estimate wrong treatment outcome. In this paper, we introduced a proliferation correction factor, in the LQ and the MC models to account for accelerated proliferation rate.

MATERIALS AND METHODS

Assumption of Proliferation Rate

The potential doubling time (T_p) of tumor cells in clinical radiation oncology is the cell cycle time per fraction of proliferating cells, i.e. the ratio of cell cycle time to the growth fraction (GF), hence the T_p is the function of GF. The potential doubling time does not take cell loss into account. It is shown that the increase in GF does not increase for the first 2 or 3 weeks of radiotherapy treatment, but then however, it increases very rapidly as a function of time [6, 7]. To account for accelerated proliferation rate, we have

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assumed that initially, at the time of starting irradiation, there is no excess proliferation rate, i.e. d(GF)/dt=0, and does not start for few days to few weeks depending on the type of irradiating tissue. Once it started at T_d days after initiation of irradiation then it increases with constant rate till it reaches to the maximum rate, i.e. d(GF)/dt=c. After attaining fastest proliferation rate it continue to maintain the same rate, i.e. d(GF)//dt=0. Graphically it is represented in figure 1.

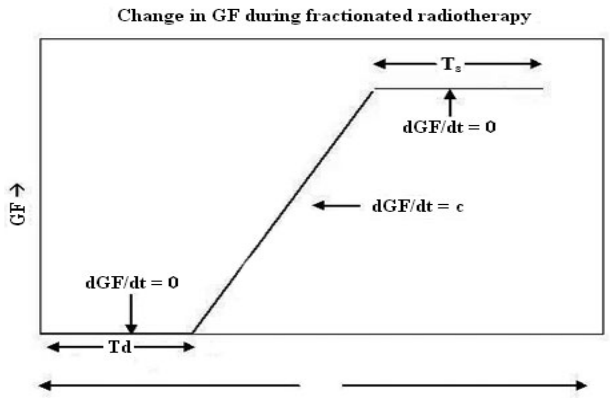

Figure 1. Accelerated proliferation pattern during fractionated radiation therapy.

It is obvious from figure 1 we can write the limits as

$d(GF)/dt = 0$ when $t \leq T_d$

$d(GF)/dt = c$ when $Td < t \leq (T\text{-}T_s)$

and $d(GF)/dt = 0$ when $t \geq T_s$

Where d(GF)/dt is the change in GF per unit time, t is the completed treatment time, T_d is the delay time in starting enhanced proliferation rate, T is the total treatment time, and T_s is the time during which proliferation rate is fastest and remain constant.

Derivation for proliferation correction factor

Since, compensatory proliferation in type-H and type-F tissues starts when radiation induced cell loss, in proliferating compartment, reaches to a significantly low level, and the initiation of the compensatory proliferation depends on the life span of the mature cells, which is the delay time in the onset of excessive proliferation rate. If during the delay period N_d number of fractions were delivered, then the accelerated proliferation rate will start at T_d^{th} day after starting irradiation. This period is known as the delay region (DR). The accelerated proliferation rate will continue for next N_p fractions and reaches to the fastest rate. This period is the accelerated proliferating region (APR). After APR, the proliferation rate becomes constant for remaining period of time, i.e. for N_s number of fractions. This period is known as saturation region (SR). The proliferation rate, T_p, in APR at time t is given by

$$T_p = T_{p0} - c \int_{T_d}^{T_d + t} dt \qquad (1)$$

Where Tp = 2 days if $T_{p0} - c\int dt \leq 2$ and here T_{p0} is the potential doubling time at the time of initiation of accelerated proliferation.

Now the expression of net survival fraction for whole fractionated treatment schedule may be written as

$$S = S_d \times S_p \times S_s \qquad (2)$$

Where S, S_d, S_p & S_s are the survival fractions for a whole treatment schedule, for DR, for APR and for SR, respectively.

In the derivation of proliferation correction factor, we assumed that the proliferating cells divide exponentially, the accelerated proliferation rate is the linear function of time, i.e. λ ($=\ln 2/T_p$) increases linearly with time in APR, and the entire radiation treatment is delivered with equal dose per fraction and equal time interval between the fractions. It is also assumed that in APR, N_p number of fractions are delivered. In the derivation of accelerated proliferation rate correction factor, for the LQ and the MC models, we have used the exponential model and the expression, from equation (j) of Appendix-A, is written by

$$S_p = \exp\left[x \sum \left\{ \ln 2 / \left(Tp - C \int_{T_d}^{T_d + ix} dt \right) \right\} \right] \qquad (3)$$

For simplification let us assume

$$\sum \left\{ \ln 2 / \left(T_p - C \int_{T_d}^{T_d + ix} dt \right) \right\} = \Gamma$$

Now equation (6) may be written as

$$S_p = \exp(\Gamma x) \quad (4)$$

If there is no accelerated proliferation, i.e. C = 0, than equation (4) changes to

$$S_p = \exp[(\ln 2/T_p)T] \quad (5)$$

Where T if the total treatment time in days.

The survival fraction for SR may be written by

$$S_s = \exp[x \ln 2\ (N_s/T_p)] \quad (6)$$

Hence, the expressions of the LQ and the MC models with proliferation correction factors may be written using equations (2), (4) & (6).

2.1. LQ model

The expressions of survival fraction (S), biologically effective dose (BED) and tumor control probability (TCP), with proliferations correction factor, for the LQ model are as follows:

Survival fraction (S)

$$S_{LQ} = \exp[-N(\alpha d + \beta d^2)] \times \exp(\Gamma_p x) \times \exp[x \ln 2(N_s/T_p)]$$

or $$S_{LQ} = \exp[-N(\alpha d + \beta d^2) + \Gamma_p x + x \ln 2\ (N_s/T_p)] \quad (7)$$

where α & β are the tissue specific coefficients of lethal and sublethal damages, respectively.

Log-cell-kill (LCK)

By taking logarithm of equation (7), we may write

$$-\ln(S_{LQ}) = LCK = N(\alpha d + \beta d^2) - \Gamma_p x - x \ln 2\ (N_s/T_p) \quad (8)$$

The term $-\ln(S_{LQ})$ is known as log-cell-kill (LCK).

Biologically effective dose (BED)

By rearranging equation (8), the BED can be written as

$$BED = D\{1 + d/(\alpha/\beta)\} - (1/\alpha)\{\Gamma_p x + x \ln 2\ (N_s/T_p)\} \quad (9)$$

Where $(LCK_{LQ})/\alpha$= BED (Biologically effective dose), α/β ratio is a tissue specific factor and its value depends on the type of tissue, and D=Nd (total dose).

Tumor control probability (TCP)

General expression of tumor control probability (TCP) is

$$TCP = \exp(-\rho v S) \quad (10)$$

Where ρ, v & S are the number of clonogenic cell per unit cm^3 in a tumor (tumor cell density), tumor volume in cm^3 and survival fraction, respectively. Now its expression for LQ model is

$$TCP_{LQ} = \exp[-\rho v \exp\{-N(\alpha d + \beta d^2) + \Gamma_p x + x \ln 2\ (N_s/T_p)\}] \quad (11)$$

2.2. MC model

Similarly, the expressions of different relevant terms of the MC model are

Survival fraction (S)

$$S_{MC} = S_{MC} \times S_p = \exp[-a\,Nd \exp(bd)] \times \exp(\Gamma_p x) \times \exp[x \ln 2\ (N_s/T_p)]$$

or $$S_{MC} = \exp[-a\,D \exp(bd) + \Gamma_p x + x \ln 2\ (N_s/T_p)] \quad (12)$$

Log-cell-kill (LCK)

Expression of LCK we may write as

$$LCK_{MC} = a\,D \exp(bd) - \Gamma_p x - x \ln 2\ (N_s/T_p) \quad (13)$$

Biologically responsive dose (BRD)

Dividing equation (13) by a to both sides and rearranging the equation, we have

$$BRD = D \exp(bd) - (1/a)\{\Gamma_p x + x \ln 2\ (N_s/T_p)\} \quad (14)$$

Where $(LCK_{MC})/\alpha$= BRD (Biologically responsive dose).

Tumor control probability (TCP)

With the use of equations (10) and (12) we may write the expression of TCP for MC model.

$$TCP_{MC} = \exp[-\rho v \exp\{-a\,D \exp(bd) + \Gamma_p x + x \ln 2\ (N_s/T_p)\}] \quad (15)$$

Above described equations have a number of tissue specific parameters, therefore, for the proper use, for any individual patient; one must know the radio-responsiveness of normal tissues and tumor cells, i.e. nature of the cells in terms of radio-sensitivity, acceleration rate of proliferation during treatment, and delay time of the proliferation onset.

RESULTS AND DISCUSSION

To demonstrate the effect of accelerated proliferation rate, the values of BED and TCP_{LQ}, of the LQ model, and BRD and TCP_{MC}, of the MC model, were calculated for routinely used different treatment schedules. For the purpose, we assumed the values of α=0.35 per Gy, and α/β=10 Gy, for early reacting tissues and tumors, of the LQ model; and a=0.35 per Gy, and b=0.08 per Gy, for early reacting tissues and tumors, of the MC model; delay time in start of excessive proliferation for head and neck tumor, T_d=14, 21 and 28 day; the potential doubling time, T_{p0}=20 days, at the time of its initiation that reaches to its fastest rate of 2 days and then after remains constant during remaining part of the treatment, and C=1.5, 1.0, 0.5 & 0.25 per day in APR. Three conventional treatment schedules, 30F×2Gy=60Gy, 35F×2Gy=70Gy and 40F×1.8Gy=72Gy, delivered over a period of 6, 7 and 8 weeks, respectively, with 5 fractions per week, and two multi-fractionation hyperfractionated schedules, the accelerated hyperfractionated (AHF) of 33F×1.4Gy=46.2Gy, and the continuous hyperfractionated accelerated radiation therapy (CHART) of 36F×1.5Gy= 54Gy delivered three fractions per day with an interfraction interval of at least 6 h, in 12 days treating 6 days and 7 days per week, respectively. To compute the TCP, the clonogenic cell density, $\rho=10^6$ and tumor volume of 100 cc were taken.

The values of BED and BRD are calculated using the LQ and MC models, respectively for above described five treatment schedules. The figure 2 shows the plots of BED versus C, for the LQ model, and figure 3 of BRD versus C, for the MC model.

It is clear from these figures that there is no effect of excessive proliferation rate on the out come of AHF and CHART treatment schedules that is because radiation treatment completes well before starting excessive proliferation rate, but CHART is more effective than HF by about 15%. Close inspection of the figures 2 and 3 reveals that for lowest value of C, i.e. C = 0.1 per day, 35F×2Gy and 40F×1.8Gy treatment schedules are more effective than others and are almost isoeffective. For C = 0 per day the effectiveness of 40F×1.8Gy is slightly higher than that of the 35Gy×2Gy treatment schedule. On the other hand, 40F×1.8Gy treatment schedule is least effective at higher values of C compare to other four treatment schemes.

Figures 2 (a, b) and 3 (a, b) show that by increasing the value of C, we find a point

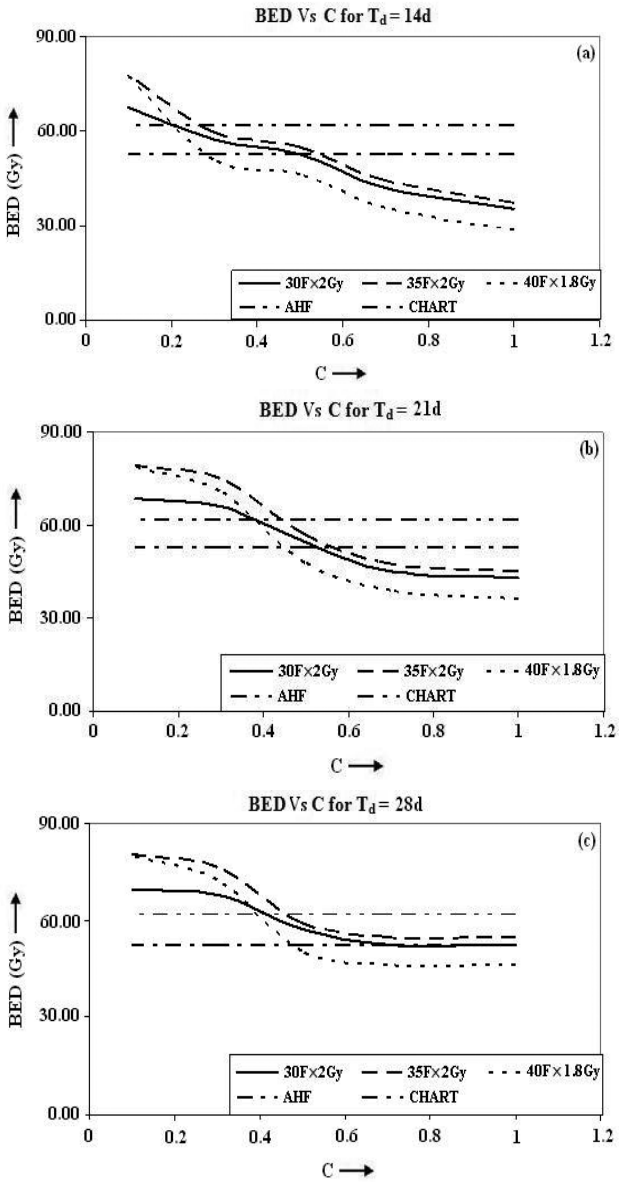

Figure 2. Plots between biologically effective dose (BED) and accelerated proliferation rate constant (C) for conventional and hyperfractionated treatment schedules (a) for proliferation delay time Td = 14 days, (b) for proliferation delay time Td = 21 days, and (c) for proliferation delay time Td = 28 days

where the BED (or BRD) values for 30F×2Gy, 40F×1.8Gy and CHART are almost equal and at this point these three treatment schedules are isoeffective. While in figures 2(c) and 3(c) it's not a single point, but is a triangle of very close three intersection points within ±1.0% variation, hence fairly it can be consider as a single point and intersecting treatment schedules as isoeffective. Similarly we can find other points where two or more treatment schedules are isoeffective. The

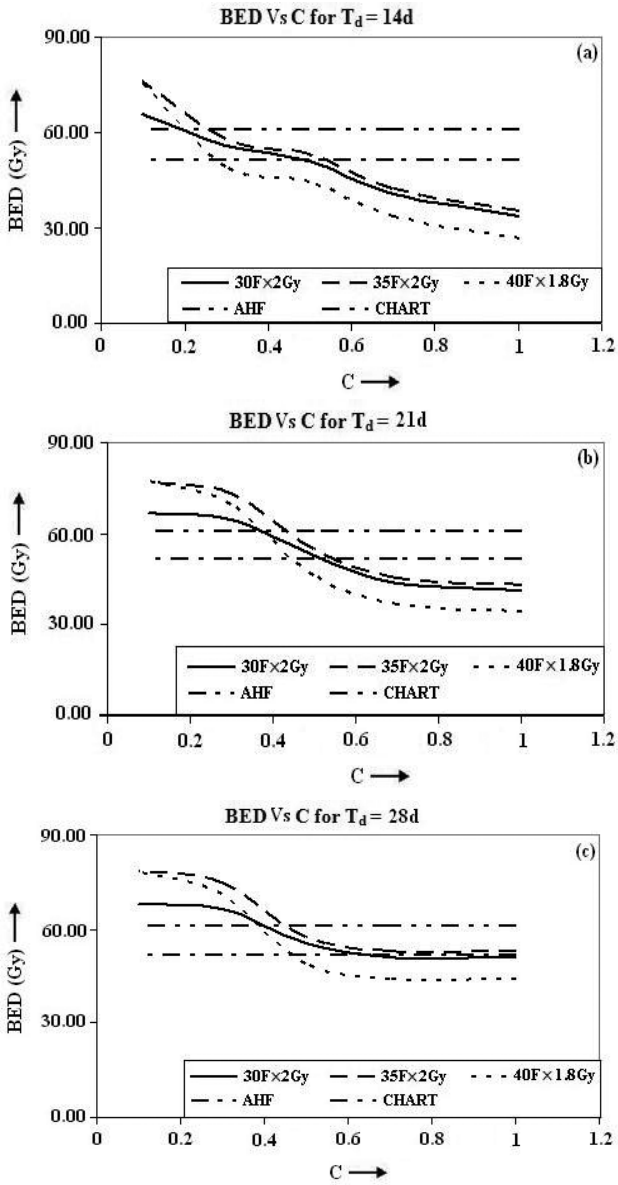

Figure 3. Plots between biologically responsive dose (BRD) and accelerated proliferation rate constant (C) for conventional and hyperfractionated treatment schedules (a) for proliferation delay time T_d = 14 days, (b) for proliferation delay time Td = 21 days, and (c) for proliferation delay time Td = 28 days.

window width between first and last intersection points decreases with increasing the value of T_d. Hence for large values of C and T_d (i.e. T_d=28 days) the treatment protocol of 35F×2Gy becomes more effective than AHF, while it was less effective for large values of C and T_d=14 and 21 days. For large C and T_d=28 days, the LQ model predicts that the treatment schedules of 30F×2Gy and AHF are almost isoeffective, on the other hand the MC model predicts that AHF is slightly more effective than 30F×2Gy. But the variation in the results is less than ±1.0%, hence the predictions of both the models can be considered consistent.

Figures 4 and 5 are the plots of TCP versus C, for the LQ model and the MC model, respectively. From these figures, it can also be seen that there is no proliferation effect on the out come of CHART and AHF, but the TCP, predicted by both the models, is very low for AHF compared to the CHART. Figures 4(a) and 5(a) show that for T_d = 14 days and C=0.1 per day, all three conventional treatment protocols are almost equally effective for 100 cc tumor with clonogenic cell density of 10^6 cells per cc, but TCP decreases very rapidly, for 40F×1.8Gy, with increasing C than two other conventional treatment schedules. The pattern of decrease of TCP curves in figure 5(a) is slightly more rapid than in figure 4(a) for 30F×2Gy and 35F×2Gy treatment schedules. Irrespective of model dependent predictions, the three conventional treatment schedules are equally effective for T_d=21 days and above values and the values of C from 0 to 0.3 per day (figures 4(b), 4(c), 5(b) and 5(c)). For T_d=21 days, both models predicts same results with ± 5.0% maximum variation at some points as shown in figures 4(b) and 5(b). For $T_d \leq 21$ days and C≤0.7 per day, the TCP reaches to its minimum value for three conventional treatment schedules and for both the models (figures 4(a), 4(b), 5(a) and 5(b)). Figures 4(c) and 5(c) reveals that for $T_d \geq 28$ days and C≥0.7 per day for three conventional treatment schedules becomes constant. The predictions of the LQ model, shown in figure 4(c), that the TCP of

30F×2Gy and AHF for $T_d \geq 28$ days and C≥0.7 per day are comparable to each other, while on the other hand the MC model predicts (figure 5(c)) that AHF gives higher TCP by about 7.6% than 30F×2Gy.

The calculated values of BED and BRD for the LQ and the MC models, respectively, are listed in table 1, for the case if there is no excessive proliferation during the treatment period. Corresponding values of TCP are given in table 2 for above described 5 treatment schedules.

The BED and BRD values revealed that 35F×2Gy = 70Gy treatment schedule is hotter approximately by 14% than 30F×2Gy = 60Gy, 37% than AHF, 26% than CHART and approximately 1.1% cooler than 40F×1.8Gy = 72Gy treatment schedules, respectively.

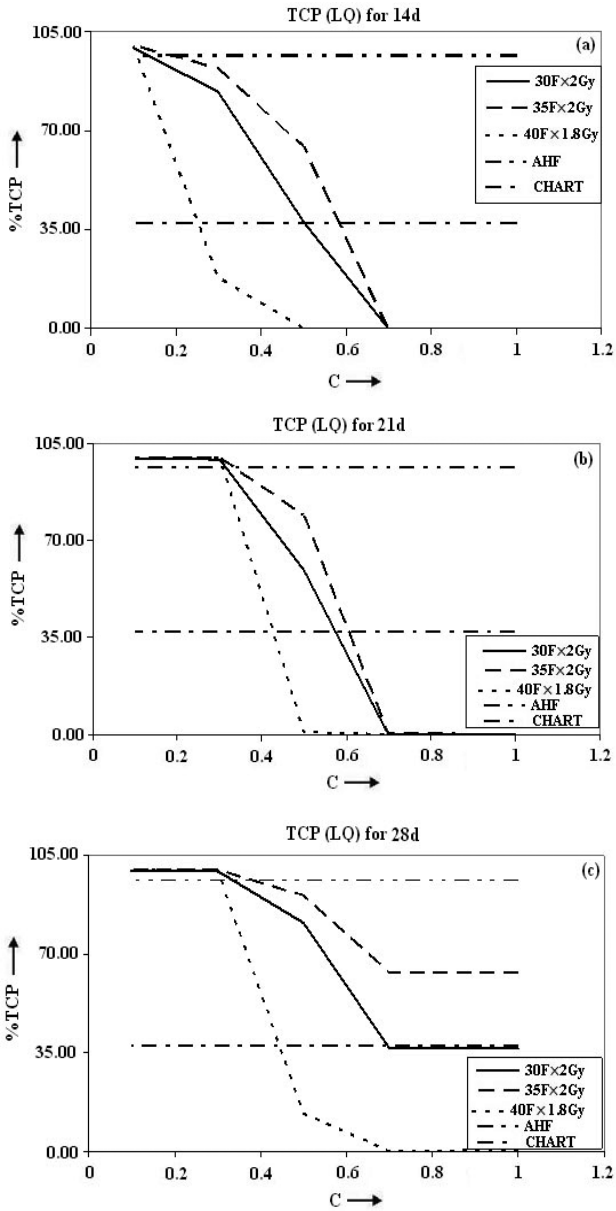

Figure 4. Plots between tumor control probability calculated using LQ model [TCP(LQ)] and accelerated proliferation rate constant (C) for conventional and hyperfractionated treatment schedules (a) for proliferation delay time T_d = 14 days, (b) for proliferation delay time T_d = 21 days, and (c) for proliferation delay time T_d = 28 days.

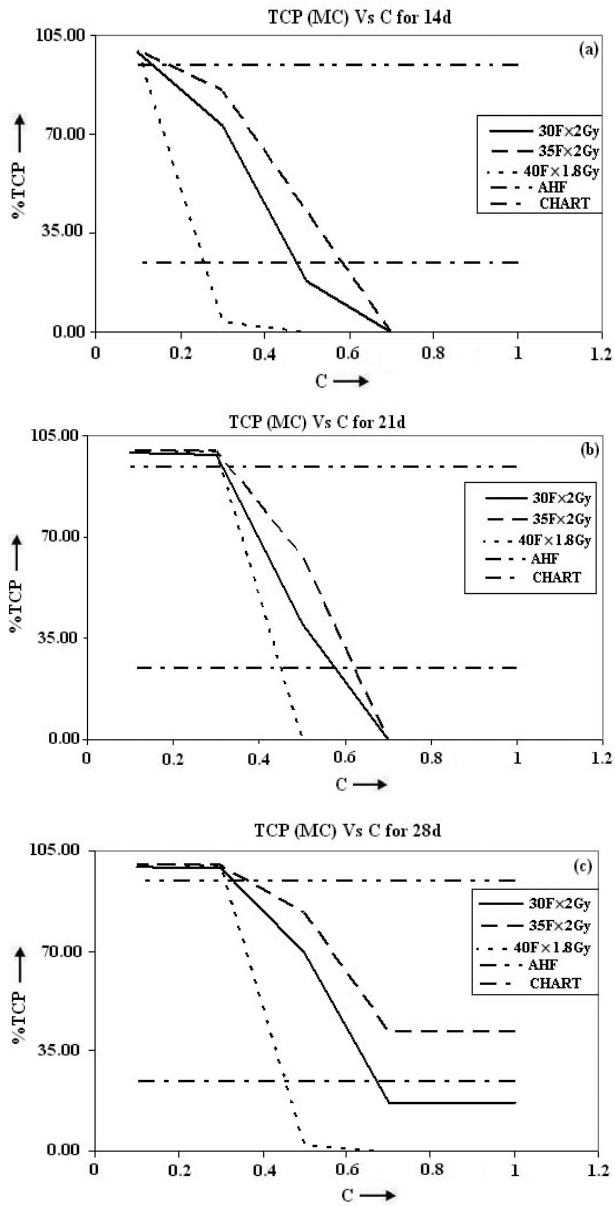

Figure 5. Plots between tumor control probability calculated using MC model [TCP(MC)] and accelerated proliferation rate constant (C) for conventional and hyperfractionated treatment schedules (a) for proliferation delay time T_d = 14 days, (b) for proliferation delay time T_d = 21 days, and (c) for proliferation delay time T_d = 28 days.

From table 2 it is clear that the AHF is far inferior compared to others. The TCP calculated by the LQ model for AHF is about 12.5% higher than that by MC model, but this difference in TCP at this level is meaningless.

To examine the application of these proposed LQ and MC equations for accelerated proliferation rate correction factor, we analyzed the result of a comparative study done by Awwad *et al* [10]. In this study, the accelerated hyperfractionation (AHF) of 33F×1.4Gy= 46.2Gy, delivered three fractions per day with an interfraction interval of at least 6 h, in 12 days, treating 6 days per week, and the conventional fractionation (CF) of 30F×2Gy, delivered 5 fractions per week in 6 weeks, radiotherapy treatment protocols were used to treat postoperative locally advanced head and neck cancer to see the effect of proliferation process. The 3-year locoregional control (LC) rate were 88 ± 4% and 57 ± 9% in AHF and CF arms. According to above assumed parameters, there would not be any effect of accelerated proliferation in the results of AHF arm, so the LC of this arm was used to find out average tumor volume and then it was used in the result of CF result to find out the value of accelerated proliferation rate constant 'C', using both the models. The average tumor volume of 12.95 cc and 9.17 cc were determined by the LQ and the MC model, respectively. Using the LQ model interpretations, the values of C were found 0.576 per day for T_d = 14 days, and 0.595 per day for T_d = 21 days. Similarly with the use of MC model interpretations, it was 0.568 and 0.587 per day for T_d = 14 days and T_d = 21 days, respectively. Both models predict higher values of TCP for T_d = 28 days than the results of AHF and CF arms, hence it can be concluded that excessive accelerated proliferation in head and neck tumors starts in the range of 2 to 3 weeks with fast accelerated proliferation rate, i.e. the value of C in the range of 0.5 to 0.6 per day, and once excessive proliferation starts, the value of T_p reaches to its maximum value of 2 day in 2 to 3 weeks. Therefore it is recommended that for advanced head and neck tumors, the radiotherapy treatment protocol should be of 3 to 4 week total treatment time.

Table 1. BED and BRD for the LQ and the MC model with no excessive proliferation rate.

Treatment Schedule	BED (Gy)	BRD (Gy)	Diff.(Gy) = BED(Gy) - BRD(Gy)
30F × 2Gy=60Gy	72.00	70.41	1.59
35F × 2Gy=70Gy	84.00	82.51	1.49
40F × 1.8Gy=72Gy	84.96	83.15	1.81
AHF	52.67	51.68	0.99
CHART	62.10	60.88	1.22

Table 2. Calculated %TCP for 100 cc tumor volume and $\rho=10^6$ using the LQ and the MC models with no excessive proliferation rate.

Treatment Schedule	%TCP (LQ)	%TCP (MC)	Diff.(%) = %TCP(LQ) - %TCP(MC)
30F× 2Gy=60y	99.89	99.80	0.09
35F × 2Gy=70Gy	100.00	100.00	0.00
40F × 1.8Gy=72Gy	100.00	100.00	0.00
AHF	37.27	24.73	12.54
CHART	96.43	94.59	1.84

CONCLUSION

The results obtained with the LQ and the MC models, with accelerated proliferation rate correction factors, explains the effect of accelerated proliferating tumors of head and neck region. It is important to note here that the assumption of constant proliferation rate may not provide the desired results since it fails to account for tumor cell kinetics during irradiation

From the above results, it is seen that the effect of accelerated proliferation rate reduces the effectiveness of a treatment schedule delivered in a prolonged period of time. Hence care should be taken in the selection of a treatment protocol for a patient of head and neck cancer with an account of the cell kinetics of the tumor.

Appendix- A

In the derivation of proliferation correction factor, we assumed that the proliferating cells divide exponentially, the accelerated proliferation rate is the linear function of time, i.e. $\lambda(=\ln 2/T_p)$ increases linearly with time in APR, and the entire radiation treatment is delivered with equal dose per fraction and equal time interval between the fractions. It is also assumed that in APR, N_p number of fractions is delivered.

To describe the proliferation rate, we have used the exponential model, which is defined by

$$S_{apr} = \exp(\lambda t) \qquad (a)$$

Where S_{apr} is the survival fraction due to proliferation, $\lambda(=\ln 2/T_p)$ is the proliferation rate constant, and t is the time period. In the derivation of proliferation correction factor, it is assumed that proliferation rate is the linear function of time, i.e. λ increases linearly with time. To derive the derivation following steps were taken:

The component of survival fraction, S_{apr}, for first fraction of radiation after initiation of accelerated proliferation and after a time interval of x_1 is

$$S_{apr1} = \exp(\lambda_1 x_1) \qquad (b)$$

Here it is assumed that after first fraction of radiation dose the value of proliferation rate constant is λ_1 during first time interval x_1. It becomes λ_2, after second fraction, during second time interval x_2, which is higher than λ_1.

The survival fraction, due to proliferation, for second fraction after initiation of accelerated proliferation and second time interval will be

$$S_{apr2} = \exp(\lambda_2 x_2) \qquad (c)$$

After second fraction and second time interval, the survival fraction was

$$\begin{aligned} S_{apr12} &= S_{apr1} \times S_{apr2} \\ &= \exp(\lambda_1 x_1) \times \exp(\lambda_2 x_2] \\ &= \exp(\lambda_1 x_1 + \lambda_2 x_2) \end{aligned}$$

By extending the argument for 'N_d' number of fractions, survival fraction is written as

$$S_p = S_{apr1} \times S_{apr2} \times S_{apr3} \times \ldots\ldots\ldots \times S_{aprNd-1}$$

$$= \exp[\lambda_1 x_1 + \lambda_2 x_2 + \ldots\ldots\ldots + \lambda_{Nd-1} x_{Nd}] \qquad (d)$$

If an average interfraction interval between the fractions is $x_1 = x_2 = \ldots\ldots\ldots = x_{Nd-1} = x$, then equation (5) may be written as

The proliferation rate constants can be written as

$$S_p = \exp[(\lambda_1 + \lambda_2 + \lambda_3 + \ldots\ldots\ldots + \lambda_{Nd-1})x] \qquad (e)$$

Substituting the values of above described proliferation rate constants from equations (a), (b), (c) and (d) in equation (5) and rearranging the expression, we have

$$\lambda_1 = \ln 2/(Tp - C\int_{T_d}^{T_d + 0x} dt) \qquad (f)$$

$$\lambda_2 = \ln 2/(Tp - C\int_{T_d}^{T_d + 1x} dt) \qquad (g)$$

$$\lambda_3 = \ln 2/(Tp - C\int_{T_d}^{T_d + 2x} dt) \qquad (h)$$

$$\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots$$

$$\lambda_{Nd-1} = \ln 2/(Tp - C\int_{T_d}^{T_d + (N_d - 1)x} dt) \qquad (i)$$

Where i = 0, 1, 2, 3,……, N_d - 1. Equation (j) is the expression of survival fraction for APR.

$$S_p = \exp[x \sum\{\ln 2/(Tp - C\int_{T_d}^{T_d + ix} dt)\}] \qquad (j)$$

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