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Isoeffect calculations based on linear quadratic equations for head and neck cancers

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background The linear quadratic model has led to various methods for the calculation of isoeffect relationships in radiotherapy. In this model, the tissue sensitive parameters α and β usually appear as a ratio, α/β. These parameters are used to describe the response of normal tissues to radiation insult. Different radiation induced biological end points in specific tissues and organs are associated with the characteristics of the α/β ratio. The linear quadratic model has been used clinically to address questions relating to changes in fractions in treatment schedules.

Aim The process of treating cancer with ionizing radiation is complex and subject to dosimetric errors which may potentially result in early or late complications. Our objective was to correct such errors through the application of the incomplete repair linear quadratic model.

Materials/Methods Repair mechanisms are affected if, owing to dosimetric error, excess dose is delivered in single or multiple fractions. Corrections for such errors were simulated, for different clinical situations, in order to avoid late fibrosis in head and neck cancers.

Results NSD, CRE, and TDF approach could not predict, onset of proliferation, overall treatment time, late and early complications, but linear quadratic model calculations predicts isoeffective schedules successfully with above parameters.

Conclusions In head and neck cancers, a number of parameters influence the results of treatment. Isoeffect calculations show the risk factors responsible for fibrosis and spinal cord damage and therefore may be used to calculate dose reductions for all remaining fractions, rather than applying shielding.

Key words **LQ-linear quadratic model • biological effective dose • fibrosis • head and neck cancers**

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BACKGROUND

The linear quadratic model has led to various methods for the calculation of isoeffect relationships in radiotherapy. In this model, the tissue sensitive parameters α and β usually appear as a ratio, α/β. These parameters are used to describe the response of normal tissues to radiation insult. Different radiation induced biological end points in specific tissues and organs are associated with the characteristics of the α/β ratio. The linear quadratic model has been used clinically to address questions relating to changes in fractions in treatment schedules. The linear quadratic model can be used to calculate the biologically effective dose, which makes two schedules equivalent to a particular biological end point. When multiple fractions are given each day, the repair processes arising from one radiation dose may not be complete as the half time for repair is relatively long, in comparison to the time interval between fractions. Incomplete repair tends to reduce the isoeffective dose and corrections must be made for the consequent loss of tolerance. In this article, isoeffect calculations are made based on the BED concept.

AIM

The aim of this present study is to calculate Biological Effective Dose in order to predict late fibrosis in head and neck cancers, taking into account re-population corrections for normal cell proliferation in different clinical situations.

INTRODUCTION

The linear quadratic model describes a wide range of fractionation schedules that are iso-effective [1]. To apply this method we must first have a particular desired end point. The validity of the linear quadratic approach to fractionation depends principally on its ability to predict isoeffective schedules successfully [2]. There is an implicit assumption, that the isoeffect, has a direct relationship with a certain level of cell survival. Generally, the fraction of surviving cells associated with an isoeffect is unknown and it is customary to work in terms tissue effect levels, which we denote as E.

$$\text{Effect (E)} = -\log_e S = D(\alpha + \beta d) \quad (1)$$

Dividing both sides of this equation by α, we obtain

$$\frac{E}{\alpha} = D\left[1 + \frac{d}{\frac{\alpha}{\beta}}\right] \quad (2)$$

= Extrapolated Response Dose (ERD)

where
S – surviving fraction,
α – coefficient of linear term (which determines the initial slope of the survival curve (Gy^{-1}),
β – coefficient of quadratic term (which determines the shape of the shoulder of the survival curve (Gy^{-2}),
D – total dose delivered (Gy).

In order to account for the loss of dose due to repopulation, Orton [3] introduced a correction to ERD, termed the BED equation as follows,

$$BED = D\,[1+d/(\alpha/\beta)] - K(T-T_o) \quad (3)$$

Where K is the dose required per day to counteract proliferation, T is the overall treatment time and T_o is the onset time for proliferation.

BED is a measure of the effect [4] of a course of fractionated or continuous irradiation and has units of dose, usually expressed in grays.

The TE formulation is conceptually similar and has also been used in published literature [5]. In this case, we divide E by β rather than α to get.

$$\text{Total Effect} = E/\beta = D(\alpha/\beta + d) \quad (4)$$

The units of Total Effect are $gray^2$, making the results less convenient than BED.

But note the simple conversion of Total Effect which is the product of α/β and BED (5).

MATERIALS AND METHODS

When multiple fractions per day are used [6], the repair of damage caused by one radiation dose may not be complete before the next fraction is given, especially if the half time for repair $T_{1/2}$ is long in relation to the time interval between fractions [7]. Incomplete repair tends to reduce the isoeffective dose and corrections must be made for the consequent loss of tolerance. This can be executed by the use of an incomplete repair model [8,9]. The amount of un-repaired damage is expressed by the function H_m which is dependent upon the number of equally spaced fractions (m). To represent the time interval between fractions,

for the purpose of isoeffect calculations, an extra term is added to the basic BED formula [9].

For fractionated radiotherapy

$$BED = D\ [1+d/(\alpha/\beta)+H_m \cdot d/(\alpha/\beta)] \quad (6)$$

where
d – dose per fraction,
D – total dose.

For continuous low dose rate radiotherapy

As the dose rate is reduced below the range used in external beam radiotherapy, the duration of irradiation becomes longer, and the induction of damage is counteracted by repair, leading to an increase in the isoeffective dose [10]. The BED formula for continuous irradiation incorporates the factor (g) to allow for incomplete repair [11].

$$BED = D\ [1+ D \cdot g/(\alpha/\beta)] \quad (7)$$

where
D is the total dose = dose rate X time.

Change of fraction size during treatment

Consider the situation when fraction size is changed without changing the overall duration of treatment time [12]. The formula required to calculate the biological effective dose is:

$$BED = D\ [1+ d/(\alpha/\beta)] - K(T-T_o) \quad (8)$$

where
D = total dose in n fractions of size d.

Assuming the conditions for a change of fraction size in BED calculations:
a) select a value for α/β for a specific tissue value,
b) select the reference tolerance dose Dref,
c) select a fraction size for the reference treatment (dref),
d) calculate for the reference treatment: BED ref = Dref [1+ dref/(α/β)],
e) for the new fraction dose, d, calculate the total dose.

$$D = BED_{ref}/[1+d/(\alpha/\beta)] \quad (9)$$

For the first part of the treatment, calculate the partial BED value (PE_1) from d_1 and D_1. The partial tolerance remaining for the second part of the treatment is:

Table 1. LQ variables.

Variable	Value
α/β	3–3.5Gy [17]
K	0.78Gy [21]
T_o	28 days [19]

$$PE_2 = BED_{ref} - PE_1 \quad (10)$$

For the new fractional dose, d_2, the, remaining total dose is given by:

$$D_2 = PE_2/[1+ d_2/(\alpha/\beta)] \quad (11)$$

The same procedure can be adopted for more than two fraction sizes during treatment [11].

BED values were evaluated using equation [5] for the following values of LQ model variables [3] (Table 1).

Results

A number of clinical reports and clinical reviews have shown a significant relationship between overall treatment time and Hendry normal tissue complication rate [13]. In order to reduce late complications, when doses in radiotherapy are changed by mistake, it is generally considered as an over dosage. In such cases. corrections must be made to alter the dose without changing the over all treatment time. The following are some example calculations, which illustrate the application of linear quadratic equations for Head and Neck Cancer.

Example calculations

Example 1

The planned treatment was for 70Gy in 35 fractions but, owing to dosimetric error, the first 6 fractions were given as 4Gy/fraction, rather than 2Gy/fraction. The accumulated dose is thus 24Gy in 6 fraction (OTT – 47days).

Treatment will be continued using 2Gy/fraction

Question:
How many fractions of 2Gy should be given in order to maintain an equal probability of late fibrosis?

Assumptions;
α/β = 3.5Gy Orton [3].

Solution:
1. BED = 70×(1+2/3.5) –0.76(47–28) = 95.56 Gy
2. PE_1 = 24×(1+4/3.5) = 51.4Gy PE for first 6 fr
3. PE_2 = BED-PE_1 = 44.16 D_2 at 2Gy/fr
4. D_2 = 44.16/1.57 = 28.12Gy for 2Gy/fr 28.12/2 = 14 fractions

Example 2

Planned treatment was for 50Gy in 25 fractions but, owing to dosimetric error, 6 fractions were given at a dose rate of 3Gy/fr instead of 2Gy/fr

Question:
How many fractions of 2Gy should be given in order to maintain an equal probability of late fibrosis?

1. BED = 50×(1+2/3.5) –0.76(33–28) = 74.77Gy
2. PE_1 = 18×(1=3/3.5) = 33.43Gy
3. PE_2 = BED-PE_1 = 41.34Gy
4. PE_2 = D×(1+2/3.5) = 41.34Gy
5. D_2 = 41.34/1.57 =26.33Gy

For 2Gy/fr 26.33/2 = 13 fractions

Example 3

Cancer of the oral tongue, stage T_2 (3.5cm). The planned treatment is in two parts:
I. External beam 50Gy in 25 fr followed by
II. Interstitial implant delivering 30Gy in 3 days.

Question:
If the total treatment were to be given in 2Gy/fr what would be the total biologically equivalent dose for late fibrosis?

Assumptions:
α/β=3.5Gy

$T_{1/2}$ =1.0hr

g.factor (3day) =0.04

1. PE_1 =50×(1+2/3.5) – 0.76(37–28) = 71.73Gy External beam
2. PE_2 =30×(1+(30×0.04/3.5) = 40.28Gy Brachytherapy
3. BED = 71.73+40.28 = 112.01Gy
4. BED $D\times\left(1+\frac{2}{3.5}\right)$= 112.01Gy
5. D = 112.01/1.57 = 71Gy in 2 Gy/fr.

Note: Owing to the smaller volumes and different dose distributions for interstitial irradiation, the calculated BED may be too high for an external beam irradiation. It is therefore recommended to reduce the dose for all fractions.

Example 4

The planned treatment is 4 fractions of 5Gy (2fr/week). After the first fraction, by mistake, a further single dose of 12Gy was given.

Question:
How much dose has been given for the 3 remaining fractions?

$\frac{\alpha}{\beta}$ =3Gy

for late complications [14].

1.BED $=20\times\left(1+\frac{5}{3}\right)= 53.3$Gy

2.PE_1 = BED $=12\times\left(1+\frac{12}{3}\right)= 60$Gy

3.PE_2 BED $=20\times\left(1+\frac{5}{3}\right)= 60–53.3=6.7$Gy

4.PE_2 $=D2\times\left(1+\frac{D2}{3}\times3\right)= 60–53.3=6.7$Gy

$6.7 = D_2+(D_2)^2/9$

$0.111(D_2)^2+D_2–6.7$

According to the quadratic equation =

$D=\frac{-b+\sqrt{b2-4ac}}{2a}$

a=0.111; b=1; c=–6.7

D_2=4Gy d_2=3Gy

Spinal cord tolerance calculations:

$\frac{\alpha}{\beta}$ =2Gy – for spinal cord damage [15]

BED*reference* $= 50\left(1+\frac{2}{2}\right)= 100$

BED*planned* $= 20\left(1+\frac{5}{2}\right)= 70$

$$\frac{BED_{planned}}{BED_{reference}} = 0.7$$

Spinal cord tolerance below 30%

$$100 = D_{max} = 1 + \frac{5}{2}$$

$$= 100/3.5 = 28.52 = 28Gy$$

A maximum of 5Gy should be given in the remaining 3 fractions.

Discussion

Deviations from the predictions of the incomplete repair LQ model have become apparent under more extreme conditions, such as reduced spinal cord tolerance in the CHART regime (3 fr/day continuous over 12 days). Most of the deviations that have so far been observed from the LQ model may have arisen from the incorrect choice of two basic parameters α/β and $T_{1/2.}$ The results of these calculations must only be taken as a guide to clinical practice. The linear quadratic approach to fractionation overcomes some of the deficiencies of the NSD and TDF concepts [16]. The validity of the equations is limited to more or less standard conditions. Deviations from the predictions of the incomplete-repair linear quadratic model have become apparent under more extreme conditions. As experience grows, applications for this method of calculation will become more evident.

Conclusions

Using these calculations only as a guide, the linear quadratic approach to fractionation overcomes some of the potential deficiencies of the TDF approach, but cannot be claimed to be universally correct. In reality it would be surprising if such simple equations satisfactorily described all the possible effects of changing dose prescriptions in radiotherapy. Neither the TDF nor the LQ based approach may be put in to clinical use directly without first cross checking retrospective clinical data. The solutions obtained through these calculations should be considered as rough estimates only. When no clinical experience is available, upon which to base a decision, it may be necessary to resort to such a mathematical model.

References:

1. Thames HD, Withers HR, Peters LJ, Fletcher GH: Changes in early and late radiation responses with altered dose fraction: implications for dose – survival relationships. Int J Radiat Oncl Biol Phy, 1982; 8: 219–26
2. Barendsen GW: Dose fractionation, dose rate and iso-effect relation for normal tissue responses. Int J Radiat Oncol Biol Phys, 1982; 8: 1981–97
3. Orton CG: Recent developments in time – dose modeling. Aus Phy Eng Med, 1991; 14(2): 57–64
4. Flower JF: The linear quadratic formula and progress in fractionated radiotherapy. Br J Radiol, 1989; 62: 679–94
5. Jones B, Dale RG: The reduction in tumor control with increasing over all time mathematical considerations. Br J Radiol, 1996; 69: 830–8
6. Wilthers HR, Thames HD, Peters LJ: A new isoeffect curve for change in dose per fraction. Radiother Oncol, 1983; 1: 187–91
7. Dale RG, Fowler JF, Jones B: A new incomplete – repair model based on a reciprocal time pattern of sublethal damage repair, Acta Oncol, 1999: 38: 919–29
8. Thames HD, Henry JH: Fractionation in radiotherapy. London: Taylor and Francis, 1987: 148–63
9. Nilsson P, Thames HD, Joiner MC: A generalized formulation of the incomplete repair model for cell survival and tissue response to fractionated low dose rate irradiation, Int J Radiat Onc Biol Phy, 1990; 57: 127–42
10. Flower JF: How worth while are short schedules in radiotherapy? A series of exploratory calculations. Radiother Oncol, 1990; 19: 165–81
11. Joiner MC: The linear – quadratic approach to fractionation. In: Steel GG, ed. Basic clinical radiobiology. London: Edward Arnold, 1993; 55–64
12. Barendsen GW: Dose fractionation, dose rate, and isoeffect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys, 1981; 8: 1981–97
13. Bentzen SM, Hendry JH: Variability in the radio sensitivity of normal tissues. Int J Radiat Oncol Biol Phys, 1993; 64(4): 393–405
14. Wong CS, Dyk JV, Hill RP: Myelopathy and hyper fractionated accelerated radiotherapy: a radiobiological interpretations. Recent Results in Cancer Research, 1993: 36: 44–9
15. Jones B, Tan LT, Dale RG: Derivation of the optimum dose per fraction from the linear quadratic model. Br J Radiol, 1995; 68: 894–902
16. Bates TD, Peters LJ: Danger of the clinical use of the NSD formula for small fraction numbers. Br J Radiol, 1975; 48; 773