

The use of the LQ model in determining the equivalence of different radiation scenarios and its use in a semi-empirical model for the prediction of disease free survival probability and the controversy over hypofractionation.

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1.0 Introduction.

There have been numerous mathematical models describing the interaction between radiation and cells. Although they differ in detail, the main assumption in these theories is that cells are lethally damaged by radiation through breaks in the DNA molecule that lead to cell death at mitosis although in some cases cell death may occur before this (apoptosis). Most of the damage inflicted on DNA by radiation is correctly repaired but some double-strand breaks (DSB's) are either unrepairable or they are incorrectly repaired so that they prove lethal to the cell survival. Some of these lethal breaks are produced by a single photon track that causes an unrepairable double-strand break (DSB) – “one track action”. Other lethal lesions are caused by incorrectly repaired near pairs of DSB's resulting from the passage of pairs of photons within the timescale that it takes to repair DNA damage. In these cases, the individual DSB's may not have been lethal on their own but when occurring within the repair time scale, the dual DSB's are lethal. The main output from these mathematical models is a prediction of the fraction of cells that survive irradiation. Although the various theories differ in detail from one another, there is a good degree of consistency in the prediction of the survival fraction from the various models. One of the simplest of these models is the so-called linear-quadratic model (LQ model) that has the practical advantage that it results in a simple analytic expression for survival fraction that can easily be manipulated to study the impact of different radiation scenarios and also can be used in the prediction of disease free survival probability. This theory comes in varying degrees of complexity depending on the various physical processes that are included in the model. The processes most commonly included are cell repair and cell repopulation but redistribution and reoxygenation have been included too (see, for example, Brenner et al (1995)). However, each process involves additional parameters about which not too much is known and it is the simplest model including only cell repair that is most widely used and which seems to account for most of the dominant features of the cell survival characteristics. This basic form of the LQ model gives

$$S_f = e^{-\alpha D(t) - \beta G(t) D(t)^2} \quad (1)$$

where S_f is the cell survival fraction and $D(t)$ is the total dose of radiation given up to some time t . α and β are two constants for a particular cell type. The term involving α represents the lethal cell damage from one-track action and is directly proportional to the total radiation dose $D(t)$. This is the linear term and it is not dependent on the history of the dose. The second quadratic term involving β can be thought of as the contribution to lethal cell damage from pairs of photon transits. The individual DSB's would not be lethal and so if the two DSB's occur at different times, they may be repairable. This involves a repair time constant and the effect is represented by the

$G(t)$ term. The basic LQ model is derived from a pair of ordinary differential equations from which $G(t)$ takes on the form known as the Lea-Catcheside function

$$G(t, \tau) = \frac{2}{D(t)^2} \int_0^t dt' R(t') \int_0^{t'} dt'' R(t'') e^{-\left(\frac{t'-t''}{\tau}\right)} \quad (2)$$

where τ is the cell repair time constant, $R(t)$ is the dose rate (Gy's per second) and $D(t)$ is the total dose as before.

Particular forms of $G(t)$ as a function of the dose rate history $R(t)$ will be considered in section 2 but the function has the general characteristics that $G(t) \rightarrow 1$ as $t/\tau \rightarrow 0$ (i.e. no repairs) and $G(t) \rightarrow 0$ as the timescale for delivering the radiation becomes large compared the repair time constant, τ (i.e. all potentially lethal DSB pairs are repaired).

2.0 The cell survival fraction for different radiation scenarios.

The forms of the function $G(t)$ for common radiation scenarios have been published many times and it is sufficient for present purposes simply to reiterate these solutions.

2.1 External beam radiotherapy.

With normal ebrt, the duration of delivering a fraction is measured in seconds whereas the repair time constant is typically of the order of an hour. Under these circumstances, $G(t)$ is effectively unity and the dose is referred to as an 'acute' dose. Moreover, if successive fractions are given at daily intervals, there is no interaction between the fractions so that after n fractions of dose d , the overall survival fraction is simply the product of the survival fraction from each of the fractions, namely

$$S_f = e^{-\alpha nd - \beta nd^2} = e^{-(\alpha + \beta d)D} \quad (3)$$

where $D = nd$ is the total dose.

2.2 Brachytherapy.

In the case of brachytherapy with slowly decaying radioactive seeds like ^{125}I and ^{103}Pd , the dose delivered $D(t)$ and the dose rate $R(t)$ as functions of time are given by

$$D(t) = D_\infty \left(1 - e^{-\frac{t}{T_d}} \right) \quad \text{and} \quad R(t) = \frac{D_\infty}{T_d} e^{-\frac{t}{T_d}}$$

where D_∞ is the total dose delivered by the seeds and T_d is the decay time constant related to the half-life by $T_d = T_{1/2} / \log_e 2 = 1.4427 T_{1/2}$. The half-life of ^{125}I is about 60 days and, for ^{103}Pd , it is about 16 days. Thus, for ^{125}I , $T_d = 87$ days and, for ^{103}Pd , $T_d = 23$ days.

The repair time constant for cells is much less than the seed decay time constant and, under these circumstances, it can be shown that for large times

$$G(t) \rightarrow \frac{\tau}{T_d} \quad \text{as} \quad \frac{t}{T_d} \rightarrow \infty$$

The survival fraction for brachytherapy thus becomes

$$S_f = e^{-\alpha D_\infty - \beta \frac{\tau}{T_d} D_\infty^2} \quad (4)$$

The second term is much less than the first term but it is not always so small as to be completely negligible at high values of the overall dose D_∞ .

2.3 Ebrt and brachytherapy.

Except for very low risk patients when there is a high probability that the cancer is prostate confined, it is now common to use permanent seed low dose rate brachytherapy in conjunction with external beam radiotherapy. Typically, about a third of the total dose is provided by the ebrt with the remaining two thirds from the permanent seeds. Some clinics like the Radiotherapy Clinics of Georgia insert the seeds first and then follow this with the ebrt about three weeks later. Others – like the Seattle Prostate Institute – carry out the ebrt first. In the literature, there has been some discussion about the relative merits of the two approaches but the reality is that there is little difference between the two in so far as the impact on the cell survival fraction is concerned. For simplicity, therefore, we will consider the case when the ebrt is given first followed by the low dose rate brachytherapy. Under these circumstances, the cell survival fraction is given simply by the product of equations (1) and (2)

$$S_f = e^{-\alpha(nd+D_s) - \beta \left(nd^2 + \frac{\tau}{T_d} D_s^2 \right)} \quad (5)$$

where n is the number of acute doses d of ebrt and D_s is the total dose delivered by the permanent seeds.

3.0 The relationship between cell survival fraction and disease free survival probability and its use in the determination of α and β .

One of the techniques for the determination of parameters α and β is to use clinical data on disease free survival probability. In order to do this, it is necessary to be able to relate this clinical survival data to the cell survival fraction in the LQ model. Munro and Gilbert (1961) proposed a relationship for what they referred to as the tumour control probability but which we will refer to as the disease free probability. It was based on the notion that the distribution of clonogens (i.e stem cells from which new tumours can develop) in tumours after irradiation was Poisson distributed and that the probability of there being zero clonogens in a particular tumour - and thus disease free - was given by

$$\text{Disease free probability, } P_\infty = e^{-N}$$

where N is the average number of clonogens in irradiated tumours. If N_0 is the average number of clonogens in tumours before irradiation then

$$P_\infty = e^{-N_0 S_f} \quad (6)$$

where, in the present case, the cell survival fraction, S_f , is taken to be given by the appropriate LQ expression for a particular radiation scenario.

It is important to stress that equation (6) is the long-term probability of being disease free and, for a particular time, it might be more appropriate to replace it with

$$\text{Disease free probability at time } t, P(t) = e^{-N_0 F(t) S_f} \quad (7)$$

This is the form given by Zaider et al (2001) in a statistical analysis of disease free probability results obtained from ebrt data from the Memorial Sloan Kettering Cancer Centre. The function $F(t)$ is zero at $t=0$ and tends to 1 as $t \rightarrow \infty$. However, in addition to time, this function may also depend on other things like the initial patient conditions and the radiation scenario but this is impossible to establish at the moment. From the data produced by Zaider et al (2001), it seems that the function does not have a glaring dependence of these clinical parameters and it will be assumed to be a function only of time for the moment. An entirely empirical approach will be adopted here by choosing

$$F(T) = 1 - e^{-\frac{t}{T_c}}$$

which is a simple function that has the required limiting behaviour. The time constant T_c seems to have a value of about three years from the Zaider et al data and this will be the value used in later analysis.

Brenner and Hall (1999) fitted clinical disease free probability data effectively to equation (6). They used three-year disease free probability data from ebrt and from brachytherapy results. In the case of brachytherapy, they ignored the small quadratic term in equation (4) and so were able to obtain a value of α . From the ebrt data, equation (3) shows that they could obtain $(\alpha + d\beta)$ and hence both α and β could finally be evaluated from the combination of the brachytherapy and ebrt results. In addition to α and β , their fitting procedure also yielded average of the number of clonogens N_0 present in tumours at the end of the radiation treatment. Although Brenner and Hall do not specifically give their estimates of N_0 , it will be shown later that they are in the range of 10's to 100's. On the face of it, this seems a very low number because according to Steel (2002), the number of clonogenic cells in a tumour before irradiation is in the order of 10^6 or more. Wang et al (2003) later suggested that the procedure adopted by Brenner and Hall was in error because of the neglect of cell repopulation. In the case of prostate cancer, this is normally ignored in the LQ model because the cell doubling time from repopulation reflected in the rate of rise of PSA seems to be in the order of a year and, even for brachytherapy, this is long compared to the treatment time and so may be ignored. However, Wang et al used a doubling time of 42 days based on data of Haustermans and Fowler (2000) and, under these circumstances, the neglect of repopulation in analysing the brachytherapy data leads to errors in the estimates of α and β . In addition, the values of the clonogen numbers N_0 produced in Wang et al's fitting procedure was in the order of 10^6 which they argued was more realistic. It is not the purpose of this present paper to get immersed in the controversy over the values of α and β because the authors of these papers have published a number of notes dealing with the various points of difference – Fowler et al (2003a), Wang et al (2003a) and Carlson et al (2003). Because of the uncertainties

over the interpretation of the clinical disease free probability data, it seems unwise to adopt a very rigid view on the accuracy of the values of α and β and, for the moment, it is sufficient to note the differences in the values of α and β obtained by Brenner and Hall and Wang et al – see table 1.

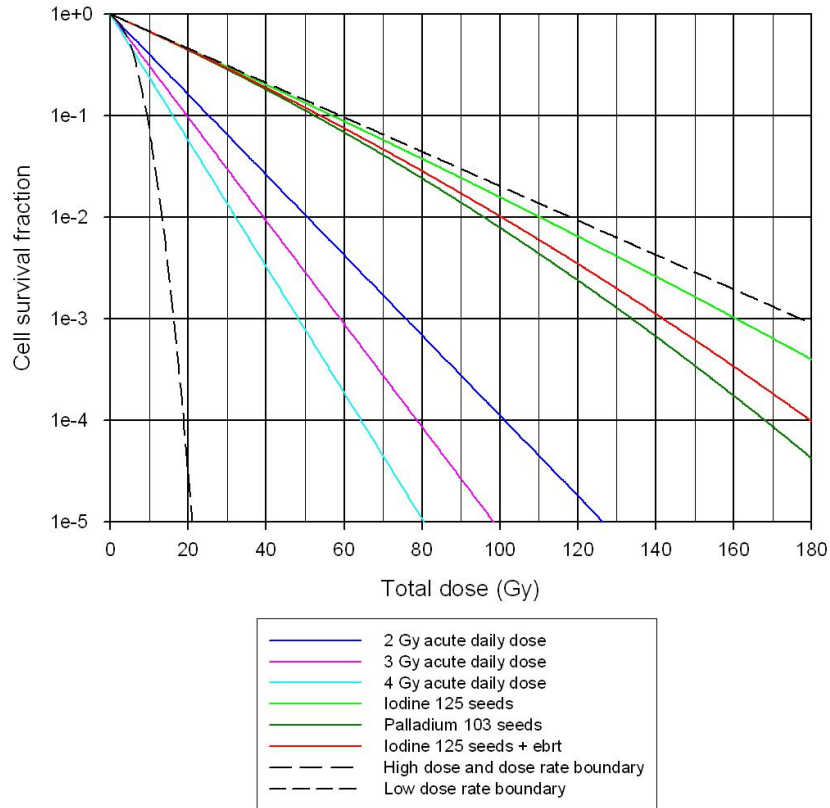
	$\alpha \text{ Gy}^{-1}$	$\beta \text{ Gy}^{-2}$	$\alpha/\beta \text{ Gy}$	τ hours	N_0
Brenner & Hall (1999)	0.036	0.024	1.5	2	Order(100)
Wang et al (2003)	0.15	0.05	3.0	0.25	Order(10^6)

The critical point about these two sets of values lies in the values of the α/β ratio. They are both less than the current best estimate of the ratio for late-responding rectal complications and so hypofractionated protocols (i.e. increase fractions with a reduced total dose) could be adopted which would improve tumour control without increasing late side-effects. This will be discussed further in section 6.0.

4.0 Survival fractions for different radiation protocols and the sensitivity of results to the α/β ratio.

Using equations (3), (4) and (5), the cell survival fractions can be calculated for a number of different radiation protocols. Figure (1) shows the results of such calculations using the Brenner and Hall constants. For radiation delivered in acute doses, three examples are shown of 2 Gy per day (this is the most common dose used), 3 Gy and 4 Gy per day. For brachytherapy with Iodine seeds combined with external beam radiotherapy, it has been assumed that the ratio of the dose delivered by the ebrt is one third of the total dose delivered by the seeds. It is also assumed that the ebrt is delivered in 30 fractions. This ratio is similar to that used by the Radiotherapy Clinics of Georgia where a total dose of about 165 Gy is generally given. For brachytherapy alone, a total dose of about 150 Gy is typical for Iodine seeds and 120 Gy for Palladium seeds.

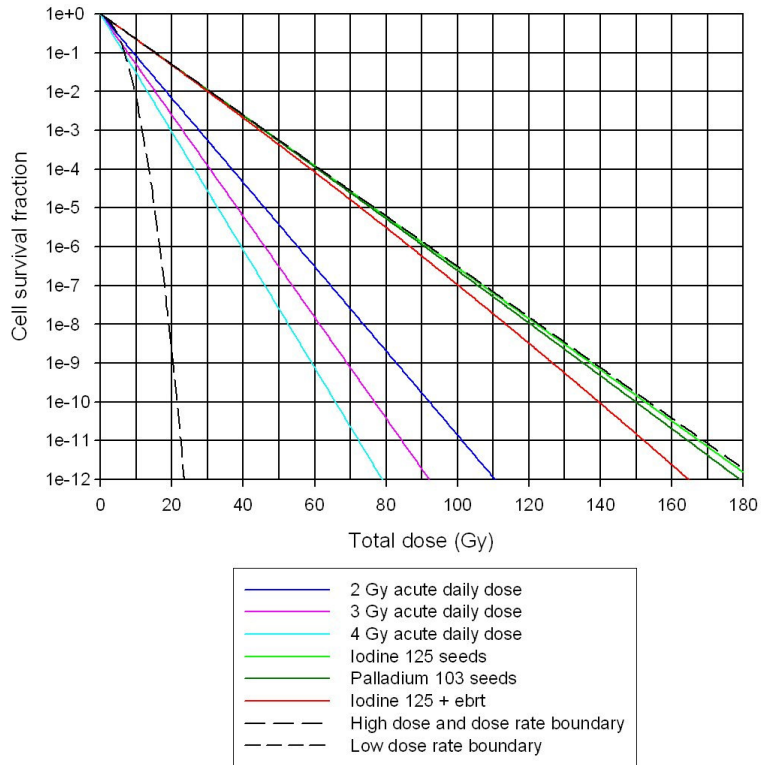
These results show fairly obvious trends. All the low dose rate seed data are close to the low dose rate boundary because the cell repair time constant is so much less than the half-life of the seeds. By contrast, the acute dose scenarios show a significant influence of dose rate as would be expected for a low α/β ratio of 1.5. It should also be noted that, for practical overall fractionated doses in the region of 70Gy for 2 Gy fractions and the doses referred to above for the brachytherapy, the cell survival fractions are in the region of 10^{-3} . For brachytherapy with ebrt of 165 Gy total dose, the survival fraction is smaller at around 10^{-4} . How this translates into disease free survival probability will be discussed in section 4.



Cell survival fractions for various radiation scenarios.
 Brenner and Hall constants. $\alpha=0.039 \text{ Gy}^{-1}$; $\beta=0.026 \text{ Gy}^{-2}$; $\tau= 2 \text{ hours}$.

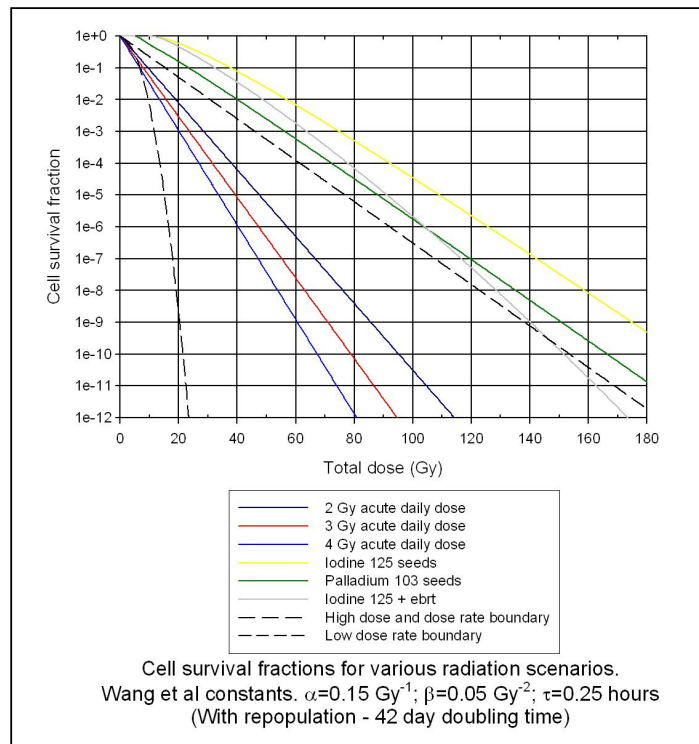
Figure 1.

Figure(2) shows the same set of calculations but now using the Wang et al constants. For the moment, the effects of repopulation have been ignored in these results. The cell survival fractions are smaller by orders of magnitude than those shown in figure (1) and, because of the even smaller repair time constant of 15 minutes, all the brachytherapy data is very close to the low dose rate boundary and there is little to distinguish between Iodine and Palladium seeds. Once again, the 165 Gy combination of brachytherapy with ebrt gives the smallest survival fraction of around 10^{-12} whereas fractionated 70Gy in 2 Gy doses gives a survival fraction of about 10^{-8} . However, Wang et al derived their constants on the basis that repopulation played a significant role in the survival fraction and figure (3) shows the results when repopulation is included with a repopulation time constant of 62 days. The effect of repopulation on the fractionated acute dose results is not particularly significant because the overall treatment time is still less than the repopulation time constant but, in the case of the brachytherapy results, there is a significant effect and the cell survival rates are higher and now lie above the low dose rate boundary. Also, there is now a bigger distinction between the Iodine and Palladium cell survival rates. Once again, the brachytherapy plus ebrt results for 165Gy produce the lowest cell survival rates compared with other typical treatment regimes.



Cell survival fractions for various radiation scenarios.
 Wang et al constants. $\alpha=0.15 \text{ Gy}^{-1}$; $\beta=0.05 \text{ Gy}^{-2}$; $\tau=0.25$ hours.
 (No repopulation)

Figure 2



Cell survival fractions for various radiation scenarios.
 Wang et al constants. $\alpha=0.15 \text{ Gy}^{-1}$; $\beta=0.05 \text{ Gy}^{-2}$; $\tau=0.25$ hours
 (With repopulation - 42 day doubling time)

Figure 3

5.0 A semi-empirical expression for the probability of disease free survival.

Following equation (6), we will assume that the relationships between cell survival fraction and disease free survival probability is

$$P(t) = e^{N_0 S_f \left(1 - e^{-\frac{t}{T_c}}\right)}$$

The final link now is to tie the initial number of clonogens to the initial prognostic patient parameters. The simplest assumption is to assume that the clonogen number is proportional to the PSA level (Brenner et al (1999) whence

$$P(t) = e^{-\lambda P_{SA} \left(1 - e^{-\frac{t}{T_c}}\right) S_f} \quad (8)$$

where λ is a constant and P_{SA} is the PSA level¹. Other factors like the Gleason score might impact on clonogen numbers but it is a qualitative parameter and there is no obvious way that the stage of the cancer can be fed into the survival probability estimate. To determine the constant λ , we will adopt the simple expedient of fitting the expression to the data collected by Fowler et al (2003) for the 70Gy point which gives a five year disease free survival probability of 63.2%.

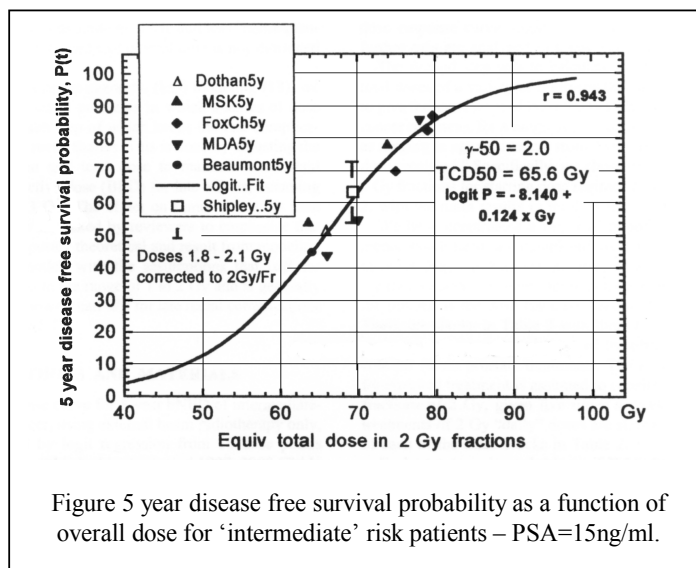


Figure 5 year disease free survival probability as a function of overall dose for 'intermediate' risk patients – PSA=15ng/ml.

The table shows the value of λ using Brenner and Hall's constants and also Wang et al's constants.

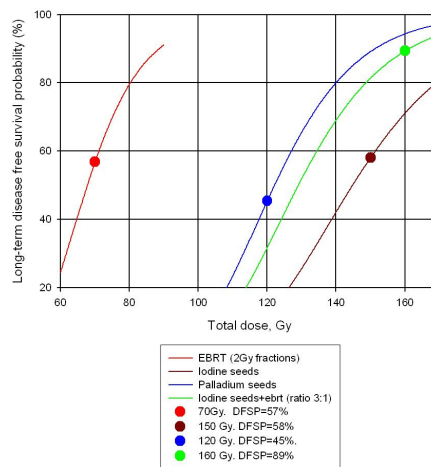
70Gy in 2Gy fractions	Survival fraction	λ based on P(5yrs)=63.2%
Brenner & Hall (1999)	1.71×10^{-3}	22
Wang et al (2003)	2.51×10^{-8}	1501967

¹ Healthy prostate tissue produces a PSA level of about one tenth of the prostate volume in cubic centimetres so that some allowance for this could be made by assuming that $N_0 \sim (P_{SA} - 0.1V_p)$ where V_p is the prostate volume in ccs. However, in view of other uncertainties in the expression, this would not improve the accuracy of the expression in any significant way.

There is a huge difference in the values of λ which is linked to the number of clonogens N_0 . Wang et al were critical of the Brenner and Hall's values of α and β because they implied very low clonogen numbers down in the order of tens. However, the significance of this has been disputed by Fowler et al (2003a) and, in any case, it is not the purpose of this paper to get into the details of this dispute but rather to show the sensitivity of the predictions of disease free survival and the iso-effective doses to the differing values of α and β .

We are now in a position to look at some predictions of disease free survival for a variety of radiation treatments. It is important at this stage to emphasise that the precise values of these predictions are less important than the prediction of the relative effects of one treatment to another.

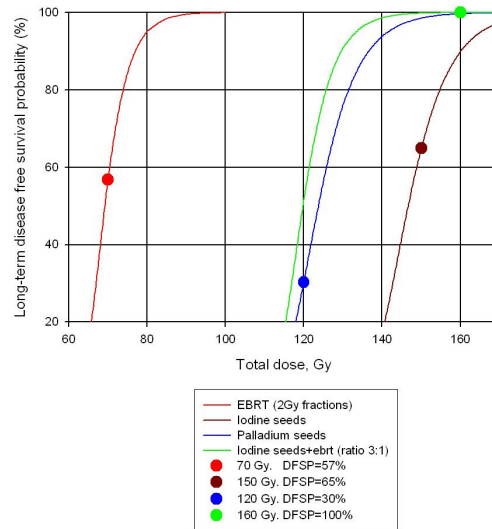
Firstly, figure (6) shows the long-term disease free survival probability for 'intermediate' risk patients (PSA=15ng/ml) with external beam radiotherapy delivered in 2 Gy fractions, brachytherapy with Iodine seeds, brachytherapy with Palladium seeds and Iodine seeds with additional ebrt amounting to one third of the seed dose. The results in this figure have been calculated using the Brenner and Hall values of α and β . Also shown by the circular symbols are the survival probabilities for doses that are used typically for these various radiation protocols.



Long-term disease free survival probability as a function of total dose for a range of radiation protocols. (Brenner and Hall α and β values)

Figure 6

Figure (7) are the same set of calculations as shown in figure (6) but now with the Wang values of α and β and including repopulation.



Long-term disease free survival probability as a function of total dose for a range of radiation protocols. (Wang α and β values with repopulation)

Figure 7

It is important to emphasise that the results have been matched so that the survival probability for ebrt at 70Gy are the same. In broad terms, the results are similar to one another and demonstrate that the typical dose used in brachytherapy with Iodine seeds combined with ebrt leads to the highest disease free survival probability. It is also clear that the sensitivity of disease free survival to dose at the dose levels used in the other therapies is significant. In fact, the results using the Wang constants seem excessively steep and not in accord with clinical data. In this respect, the results using the Brenner and Hall constants seem more realistic. If the Brenner and Hall data is assumed the more realistic, it is nevertheless clear that in the case of ebrt, for example, raising the dose from 70 to around 80 Gy results in a significant improvement of around 20% in disease free survival probability. Doses as high as this are now achievable with conformal and intensity modulated radiotherapy without a significant worsening of side effects.

As far as seed implants without ebrt are concerned, it would seem that this therapy is most suitable for low risk patients for whom there is a high probability that the disease is organ confined. The merits of brachytherapy alone as compared with ebrt for higher risk patients seem controversial and involves issues outside the scope of this note.

The lowest survival fractions and highest disease free survival probabilities are achieved with combined brachytherapy and ebrt. Although treatment of this sort has been widely available in the USA for a number of years, it is still not widely practiced in the UK and it clearly has attractions. The only point to note here is that the issue of side effects is not clear because Brandeis et al (2000) reported that patients treated with external beam radiotherapy in combination with brachytherapy recorded higher levels of acute side effects than those experienced by brachytherapy only patients.

In conclusion, it is important to stress that equation (12) is a semi-empirical expression containing many uncertainties. Nevertheless, it has the advantage over an entirely empirical nomogram like the one developed by the Memorial Sloan Kettering Cancer Center (Kattan et al (2000)) because it has some scientific foundation in its development and so is a better framework into which clinical data can be fitted.

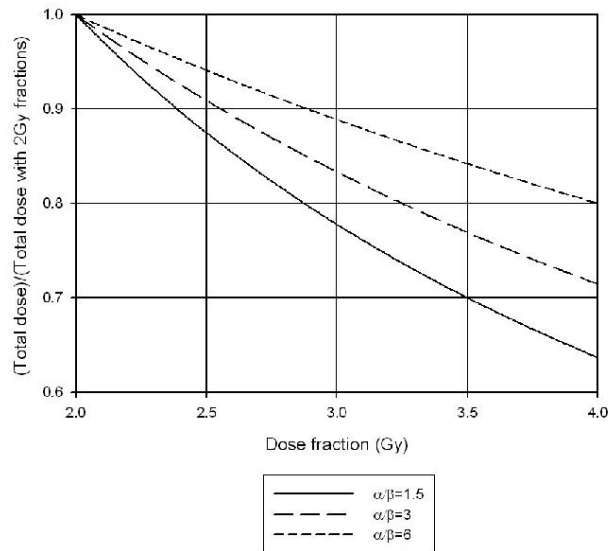
6.0 Iso-effective dose relationships for fractionated ebrt and their sensitivity to the α/β ratio – the case for hypofractionation.

In this present section, attention is going to focus solely on external beam radiotherapy as the form of treatment.

If we compare two ebrt fractionated schemes and ignore repopulation effects², equation (3) shows that for equal cell survival fractions,

$$\frac{D_2}{D_1} = \frac{1 + \frac{\beta}{\alpha} d_1}{1 + \frac{\beta}{\alpha} d_2}$$

The importance of this relationship is that it is a function only of the α/β ratio and not on the values of α and β individually. If we take our reference daily acute dose as 2 Gy, figure (8) shows the overall iso-effective dose ratio for three values of the α/β ratio of 1.5, 3 and 6. The value of the α/β ratio of 6 has been included because this is thought to be about the ratio for late-responding rectal complications – see Brenner (2004)



Iso-effect total dose ratio as a function of the dose fraction.

Figure 8

² The treatment period for ebrt is short compared with the repopulation time scales so that this is not a serious omission.

As has been cogently discussed by Fowler et al (2003), a value of the α/β ratio of 1.5 leads to the conclusion that a hypofractionated scheme is possible in which the late-responding rectal damage could be kept at the same level as is currently achieved with 2Gy schemes but achieving a better long-term disease free survival probability and, in their paper, they give numerous examples of such possible schemes. However, a slightly different approach will be adopted here. To adopt a cautious approach, probable bounds will be set on the α/β ratio are so that we can see what is the ‘best’ and ‘worst case’ scenarios of a particular hypofractionated scheme. Two schemes will be considered, namely, 3Gy and 4Gy fractions. The table below shows the dose ratios

	$\alpha/\beta=1.5$ dose ratio	$\alpha/\beta=3$ dose ratio	$\alpha/\beta=6$ dose ratio
3 Gray	0.778	0.833	0.889
4 Gray	0.636	0.714	0.800

For the prostate, the upper and lower bounds on the α/β will be taken to be 3 Gy and 1.5 Gy respectively corresponding to the Brenner et al value and the Wang et al value. For late rectal complications, they will be taken to be 6 Gy and 3 Gy respectively. The lower bound for rectal complications has been set equal to the upper prostate bound because the spread of estimates of α/β for late rectal complications does not generally drop below about 4 so setting this lower bound ratio at 3 Gy seems to be a reasonable ‘worst’ case scenario.

6.1 The 4 Gray fractionated scheme.

We consider first the ‘best-case’ scenario. If we keep the probability of late rectal complications the same as the ‘standard’ 70 Gy in 2 Gy treatment, the equivalent 4 Gy fraction dose is $0.8 \times 70 = 56$ Gy. This dose would be delivered in 14 treatment days. However, the 2 Gy fraction equivalent dose as far as the prostate is concerned is $56/0.636 = 88$ Gy. Using the Brenner values of $\alpha=0.039 \text{ Gy}^{-1}$ and $\beta=0.026 \text{ Gy}^{-2}$ in equation (8), this gives a disease free survival probability for a PSA=15 (‘intermediate’ risk) of $89.6\%^3$ which is a very significant increase above the ‘standard’ treatment value of 56.8% .

In the worst-case scenario with $\alpha/\beta=3$ for both the prostate and late rectal complications, 56 Gy in 4 Gy fractions would amount to a 2 Gy fraction dose of 78.4 Gy. It is difficult to estimate the increase in late developing rectal bleeding that might accompany such an increase. With 3-D CRT, rectal bleeding occurs in only about 1% of patients with the 70Gy in 2Gy fraction treatment and, from data on dose escalation, it seems that this might double with an equivalent dose of 78 Gy. However, it would be accompanied by an improvement in disease free survival and, using the Wang et al constants in equation (8) with a PSA=15, the probability rises to 93.4% - which is higher than the estimate for $\alpha/\beta = 1.5$ using the Brenner constants.⁴

³ The accuracy of predicting of disease free survival does not justify quoting results to one decimal place but they are given just as part of the exercise.

⁴ The steepness of the Wang sensitivity to dose has already been remarked upon.

An alternative way of assessing the worst-case scenario is to use the entirely empirical nomogram developed by Kattan (2000) at the Memorial Sloan Kettering Cancer Centre. If we choose a PSA=15, Gleason 3+4 and T-staging of either T1c or T2a, we obtain 5 year disease free survival estimates of 64% and 55% respectively for 70 Gy in 2Gy fractions. Doing the same exercise for 78 Gy, the figures become 82% and 69% respectively. These improvements are less than those predicted by equation (8) but they confirm the order of improvements that are possible.

Before discussing these results, the 3Gy fractionated scheme will be considered.

6.2 The 3 Gray fractionated scheme.

For the 'best' case scenario, the equivalent 70Gy in 2Gy fractions for $\alpha/\beta=6$ is $70 \times 0.889=62.2$ Gy. Rounding this up so that it is divisible by 3 gives 63 Gys – i.e. 21 treatment days. The equivalent 2Gy fraction dose to the prostate with $\alpha/\beta=1.5$ is $63/0.778=81$ Gy. From equation () with a PSA=15 and the Brenner constants gives a disease free survival probability for this case of 81.2%.

The 'worst' case scenario is that the 63 Gy in 3Gy fractions would amount to $63/0.833=75.6$ Gy. Even with 3D-CRT, this is not likely to lead to a noticeable effect on late rectal bleeding but would still result in an improvement in disease free survival. Using the Wang constants and a PSA=15, the disease free survival probability is given as 87% - once again higher than the Brenner estimate.

Repeating the exercise as before using the MSKCC nomogram for 75.6 Gy, we obtain 5 year disease free survival probabilities of 67% and 80% for T2a and T1c respectively with PSA=15 and Gleason=3+4.

6.3 Discussion.

The object of the above rather messy analysis was to try and put bounds on the consequences of two hypofractionated schemes. It seems that whichever way you look at it within the present framework, there is no obvious evidence of a serious downside of risk to these hypofractionated schemes and yet there is potential for a significant improvement in disease free survival which, in terms of the large numbers of men treated by ebrt, would amount to thousands of years of life expectancy. It would also save money for both patients and hospitals and be a generally more convenient protocol.

If one wanted to adopt the most cautious approach, 63Gy in 3Gy fractions would be a scheme with the least apparent 'jump' from present practice and it is only one fraction more than the fractionated trial reported by Livsey et al (2003) at the Christie Hospital NHS trust. One could argue that, provided the risks were properly explained, patients should at least have the hypofractionation options made available to them. As a personal observation, I think the ability of patients to balance risks and quality of life issues is under-estimated by clinicians.

7.0 Concluding remarks.

This paper discusses the use of the LQ model to predict the cell survival fractions for different radiation protocols including ebrt combined with brachytherapy. The controversy over the values of the α/β ratio is discussed and it is shown that irrespective of the precise values of this ratio, it seems that the combined use of brachytherapy with external beam radiotherapy at overall dose levels of around 165 Gy in the case of Iodine seeds leads to survival probabilities that are higher than are achieved with conventional 70Gy (with 2 Gy fractions) external beam radiotherapy as is the normal practice in the UK. However, if hypofractionated ebrt schemes are considered, significant improvements in disease free survival probability can be achieved without apparently large downside risks of late rectal complications. If one adds hormone therapies to these hypofractionated schemes then the disease free survival would be improved further and would make ebrt a significantly better options than is currently the case.

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