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A model for calculating tumour control probability in radiotherapy including the effects of inhomogeneous distributions of dose and clonogenic cell density

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Abstract. Most calculations of the biological effect of radiation on tumours assume that the clonogenic cell density is uniform even if account is taken of non-uniform dose distribution. In practice tumours will almost certainly have a non-uniform clonogenic cell density. This paper extends one particular model of tumour control probability (TCP) to incorporate a variable clonogenic cell density while at the same time assuming a constant 2 Gy fraction size and a uniform radiosensitivity throughout the treatment. Since there are virtually no *in vivo* data on the variation of density we consider some model situations. One clear conclusion is that a large reduction in clonogenic cell density at the edges of a tumour would permit only a very modest decrease in dose if the TCP is not to be reduced. In general the effect on TCP is a complicated function of the variation in both dose and clonogenic cell density. We give the equations which enable both to be included.

1. Introduction

Much effort in radiotherapy is currently being devoted to optimizing physical dose distributions to enable the dose to the tumour to be raised without at the same time increasing the probability of damaging normal tissues. This is generally referred to as 'conformal' radiotherapy (Tait and Nahum 1990, Webb 1993). A crucial element in this endeavour is the ability to estimate the effect that a given change in tumour dose will have on the probability of local tumour control. This change may not be a matter of just raising the target dose but also of altering the distribution of this dose. In particular, some optimization techniques (Brahme 1988, Mohan *et al* 1992, Webb 1991, 1992) result in much less homogenous dose distributions than are the norm in conventional external-beam radiotherapy. Some workers now even include tumour control probability (TCP) prediction in the cost function to be optimized in 3D treatment planning (Mohan *et al* 1992).

In this paper we develop further a TCP model first described by Nahum and Tait (1992) to incorporate the effect of distributions in the dose to the tumour and also the density of clonogenic cells. The latter factor has not, to our knowledge, been modelled in the literature except for work by Brahme and Ågren (1987). Not much is known about the distribution of clonogenic cells *in vivo* in particular patients and in the paper we show how to predict the TCP for specimen conditions. Our TCP model differs from those of Brahme (1984) and Goitein (1987) in that it is very largely based on parameters involved in basic radiobiological experiments on cell survival.

We are well aware of the large number of factors that will influence TCP in a real tumour, such as oxygenation status, tumour doubling time, fractionation pattern and so on. We make

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no claim to be able to model these, but concentrate here on the effect of clonogenic cell density.

2. Theory

2.1. TCP with uniform clonogenic cell density and uniform dose

Nahum and Tait (1992) have derived the TCP with a model based on the survival of clonogenic cells. When the dose D is considered to be uniform across the tumour, then the number N_s of surviving clonogenic cells from a starting number N_0 after irradiation is given by

$$N_s = N_0 \exp(-\alpha D) \tag{1}$$

where α is the familiar term from the linear–quadratic model of cell survival (Deacon *et al* 1984); the β term can be ignored for 2 Gy fractions. There would have been no difficulty in principle in including the β term in equation (1) but we have chosen to limit the studies with our model to the most common type of fractionation scheme.

The TCP then follows as

$$\text{TCP} = \exp(-N_s). \tag{2}$$

based on the assumption of no single surviving clonogenic cells. If the dose dependence of the TCP is plotted for a fixed value of α (the very steep curve in figure 1) it is found that the dose response curve is far too steep to match clinically observed data. For this reason Nahum and Tait (1992) incorporated a distribution of α values among a representative cohort of patients.

For K groups of patients, each with a separate α_i value, the TCP_{α_i} is given by equation (2) above. The overall mean TCP is then

$$\text{TCP} = \sum_{i=1}^{K} g_i \text{TCP}_{\alpha_i} \tag{3}$$

where a fraction g_i of patients have $\alpha = \alpha_i$ and $\sum g_i = 1$. In the case of a Gaussian distribution,

$$g_i \propto \exp[-(\alpha_i - \alpha_m)^2/2\sigma_\alpha^2] \tag{4}$$

where α_m and σ_α are the mean and standard deviation of the values of α respectively.

An alternative way to evaluate this overall TCP is as follows:

$$\text{TCP} = (1/K) \sum_{i=1}^{K} \exp(-N_s(i)) \tag{5}$$

where

$$N_s(i) = N_0 \exp(-\alpha_i D) \tag{6}$$

and N_0 is the initial number of clonogenic cells (taken to be $\rho_c V_t$) where $\rho_c = 10^7$ cm^{-3} is the uniform density of clonogenic cells in the tumour, V_t is the tumour volume in cm^3 and

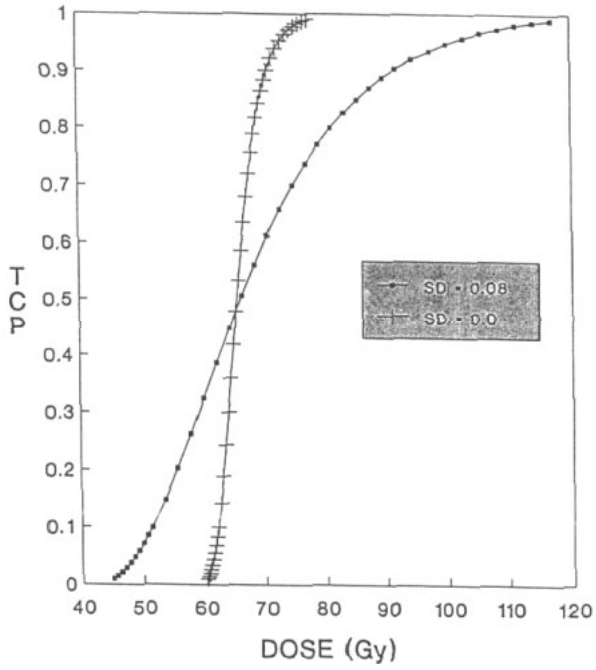

Figure 1. The variation of TCP with dose when α is constant (steeply rising curve) and randomized (curve with data points marked by filled squares). The mean value of α was 0.35 and the standard deviation of α is shown in the shaded box. For a tumour whose volume is 320 cm^3 this gives a TCP of 0.479 with a uniform dose of 64 Gy.

D is the uniform dose to the tumour. For each value of K, α is randomized. K should be a large number such as 10^3 or 10^4. Nahum and Tait (1992) evaluated the TCP by the first method and we subsequently verified that both methods gave the same result.

For example the less steep curve in figure 1 shows the TCP when α is set to 0.35 and is randomized with a Gaussian distribution with a standard deviation of 0.08. The 0.35 value is taken from Deacon *et al* (1984) for human bladder tumours. The 0.08 value for the standard deviation was arrived at by gradually increasing the parameter until the slope of the curve became consistent with the clinical dose-effect data for megavoltage photon radiation observed by Batterman *et al* (1981). Mohan *et al* (1992) have discussed an alternative approach to modelling the reduced slope for a real patient population based on Goitein's work (1987). It should be noted that for a target volume of 320 cm^3, which is an average derived from our own clinical data for bladder tumours, the predicted TCP at 64 Gy is about 0.48, which is consistent with that observed clinically.

Combining equations (5) and (6) we have

$$\text{TCP} = (1/K)\sum_{i=1}^{K}\exp[-\rho V_t \exp(-\alpha_i D)]. \tag{7}$$

This generates the characteristically sigmoidal curve for TCP as a function of dose (figure 1). This figure shows the very steep curve for $\sigma_\alpha = 0$ and the less steep one for $\sigma_\alpha = 0.08$.

If the density of clonogenic cells is constant throughout the tumour, one might ask the question whether, for a given amount of energy available for deposition, it is best to

deposit this energy uniformly or in some non-uniform distribution. In the appendix we show that if the clonogenic cell density is constant throughout the tumour then a uniform dose distribution produces the highest TCP for a fixed energy deposition. Brahme (1984) also arrived at this conclusion by showing that the TCP was a maximum for zero standard deviation of dose in the tumour volume.

2.2. *TCP with non-uniform clonogenic cell density and non-uniform dose*

Now suppose that *both* the dose distribution *and* the distribution of clonogenic cell density are non-uniform. We assume the tumour is divided into sufficiently small volume elements, labelled by the subscript j, that within each element the dose D_j can be considered locally uniform. Let there be M such elements of volume. Suppose also that the clonogenic cell density is non-uniform and takes the value ρ_j in the jth volume element. The TCP in this non-uniform situation is calculated as follows:

The total number $N_{s,tot}$ of surviving clonogenic cells is

$$N_{s,tot}(i) = \sum_{j=1}^{M} N_{0,j} \exp(-\alpha_i D_j) \tag{8}$$

where $N_{0,j} = \rho_j V_t f_j$ is the initial number of clonogenic cells in the jth element and f_j is the fractional volume of the jth element. By analogy with equation (5) the TCP is

$$\text{TCP} = (1/K) \sum_{i=1}^{K} \exp(-N_{s,tot}(i)). \tag{9}$$

Putting these two equations together we have

$$\text{TCP} = (1/K) \sum_{i=1}^{K} \Pi_{j=1}^{M} \exp[-\rho_j V_t f_j \exp(-\alpha_i D_j)]. \tag{10}$$

In order to understand how the TCP will depend on the distribution of dose and clonogenic cell density, we have coded equation (10) and used a computer to predict the TCP for various distributions of ρ_j and D_j.

2.3. *The simple case of constant local TCP*

It is illustrative to consider how the dose must vary with clonogenic cell density when we require that the TCP remains *constant* for each volume element. In this case it is straightforward to show that the change in dose at position r, $\Delta D(r)$, is related to the clonogenic cell density at the centre of the tumour, where ρ is assumed to have the uniform value ρ_0, and to the density at r, $\rho(r)$, by

$$\Delta D(r) = (1/\alpha) \ln[\rho_0/\rho(r)]. \tag{11}$$

Figure 2 shows a hypothetical tumour with a region at the edge where the clonogenic cell density falls off gradually, and the corresponding ratio $D(r)/D_0$ of the dose at r to the dose at the centre which satisfies equation (11). In the figure the lowest value of $\rho(r)/\rho_0$ is 0.01, corresponding to a dose of 51 Gy for a central dose of 64 Gy. This emphasizes

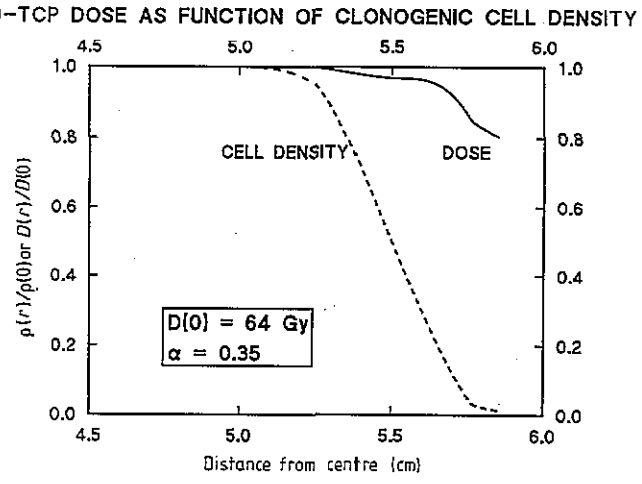

Figure 2. The variation of dose in order to keep the TCP per unit volume constant as the clonogenic cell density decreases at the edge of a tumour; $\alpha = 0.35$ and $D_0 = 64$ Gy in equation (11).

how dose may be safely reduced by only a few Gy for a corresponding decrease in $\rho(r)$ of several orders of magnitude.

This result gives support to the general rule in radiotherapy that only small inhomogeneities in dose can be tolerated. Thus it is absolutely vital that adequate margins are employed at the edge of the tumour. This is particularly so in conformal therapy, as by definition there will be a larger surface of the target volume close to the edge of the high-dose volume (HDV) than with the conventional box-shaped HDVs. Thus the chances are higher that a shift in patient position could bring some region of the target volume outside the HDV. Further, it emphasizes that the clonogen density in the periphery must be extremely low if boost therapy, where a significantly lower dose is given outside the central boost region, is to be successful (Brahme and Ågren 1987).

2.4. Spherically symmetric clonogenic cell density and dose

We have modelled a spherically symmetric situation, representing the case of a spherical tumour of volume V_t with a radial dose distribution $D(r)$ and a radial distribution of clonogenic tumour cells $\rho(r)$. Equation (10) becomes

$$\text{TCP} = (1/K)\sum_{i=1}^{K}\Pi_{j=1}^{M}\exp[-\rho_{r_j}V_t f_{r_j}\exp(-\alpha_i D_{r_j})] \tag{12}$$

where r_j is now the radius of the jth spherical shell or annulus, f_{r_j} is the fraction of the volume within this shell and D_{r_j} is the dose in this shell. The volume is considered to be made up of M such concentric annuli. This allows us to model the effect of variations of clonogenic cell density and dose between the centre and the outside of a tumour such as may occur in stereotactic radiotherapy of an approximately spherical brain tumour.

To gain some insight into the relative importance of knowing the clonogenic cell density and of striving to obtain a high uniform dose in the tumour, we coded equation (12) to study simultaneously 400 different spherically symmetric dose distributions with each specification

of the clonogenic cell density radial distribution (see equations (13)–(15) below). These were

$$\begin{aligned} D(r) &= D_0 \qquad \text{for } r \leqslant p \\ D(r) &= D_0 - (D_0 - D_R)[(r-p)/(R-p)] \qquad \text{for } r \geqslant p \end{aligned} \tag{13}$$

where R is the outer radius of the tumour and the two parameters p and D_R specify the distribution (figure 3). D_0 is the maximum dose. The variables p and D_R have been allowed to take values from almost zero to their maximum values of R and D_0 respectively. Because of the non-linear dependence of the TCP on p and D_R, the values for p and D_R were non-uniformly spaced, in order to compute more values where the TCP was changing rapidly, via the following simple scheme with p/R and D_R/D_0 running from near zero to unity, the subscript n labelling the sample points:

$$(p/R)_n = 1 + (1/8000) - n^3/8000 \qquad n = 1, 2, \ldots, 20 \tag{14}$$

$$(D_R/D_0)_n = 1 + (1/8000) - n^3/8000 \qquad n = 1, 2, \ldots, 20 \tag{15}$$

Two models of the clonogenic cell density (figure 3) were considered, parameterized by p and ρ_R:

(i) first model:

$$\begin{aligned} \rho(r) &= \rho_0 \qquad \text{for } r \leqslant p \\ \rho(r) &= \rho_R \qquad \text{for } r \geqslant p \end{aligned} \tag{16}$$

where ρ_0 is the largest clonogenic cell density (taken to be 10^7 cm^{-3});

(ii) second model:

$$\begin{aligned} \rho(r) &= \rho_0 \qquad \text{for } r \leqslant p \\ \rho(r) &= \rho_0 - (\rho_0 - \rho_R)[(r-p)/(R-p)] \qquad \text{for } r \geqslant p \end{aligned} \tag{17}$$

where ρ_0 is the largest clonogenic cell density (taken to be 10^7 cm^{-3}).

The first model is a sudden change of clonogenic cell density at radius p. The second model is a more slowly varying linear function.

For each model and for each value ρ_R, a 3D plot of the TCP$(p/R, D_R/D_0)$ was formed (see, e.g. figure 4).

3. Results

3.1. First model of clonogenic cell density variation

Figure 4 shows the variation of TCP for the 400 radial distributions with $D_0 = 64$ Gy and the first model for clonogenic cell variation with $\rho_R = 10^{-1}\rho_0$, $\alpha = 0.35 \pm r^* \times 0.08$ (r^* is a random number from a Gaussian distribution), and tumour volume $V_t = 320$ cm^3. Note that the vertical axis in figure 4 is a plot of the *ratio* of the TCP $(p/R, D_R/D_0)$ to the value TCP $(p/R = 1, D_R/D_0 = 1)$. Hence the quantity plotted can increase above unity if the dose distribution and clonogenic cell density distribution are such that TCP values above that for uniform dose and cell density arise. This will occur, for example, when the clonogenic cell density is very small (i.e. orders of magnitude smaller that ρ_0) in parts of the tumour, even if the dose in these regions is lower than D_0. The value at $p/R = 1$, $D_R/D_0 = 1$ represents the TCP with uniform dose and clonogenic cells, of course. This value was 0.479 (as in figure 1). We observed the following features common to plots of this type:

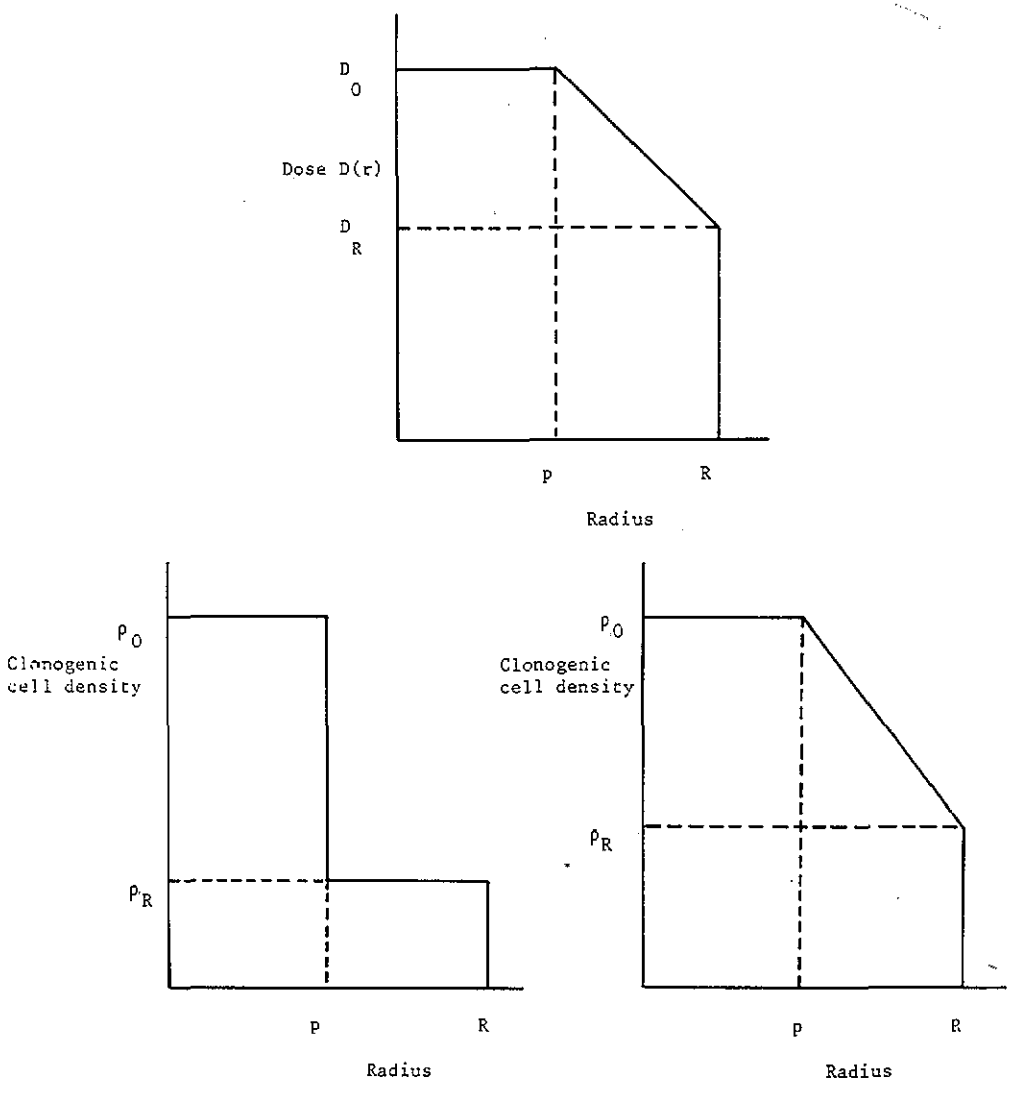

Figure 3. How the radial distribution of clonogenic cells and dose is parameterized. The upper part of the figure shows how the radial dose function is specified. The dose is constant, D_0, from the centre to radius p and then decreases linearly to dose D_R at the outer radius R of the tumour. The lower left part of the figure shows the radial variation of the clonogenic cell density in the first model. The value is a constant, ρ_0, from the centre to radius p and then falls to a constant value ρ_R between radius p and the outer radius R. The lower right part of the figure shows the radial variation of the clonogenic cell density in the second model. The value is a constant, ρ_0, from the centre to radius p and then decreases linearly to ρ_R between radius p and the outer radius R.

(i) Along the $D_R/D_0 = 1$ axis (dose constant), the variation in TCP is entirely due to the reduction in clonogenic cell density with falling p. The value to which the TCP ratio rises depends on the value of ρ_R. The smaller this value, the larger becomes the TCP ratio. Table 1 shows the ratio of the TCP ($p/R \simeq 0, D_R/D_0 = 1$)/TCP ($p/R = 1, D_R/D_0 = 1$) as a function of ρ_R. The smaller ρ_R is, the larger this ratio becomes reflecting the fact

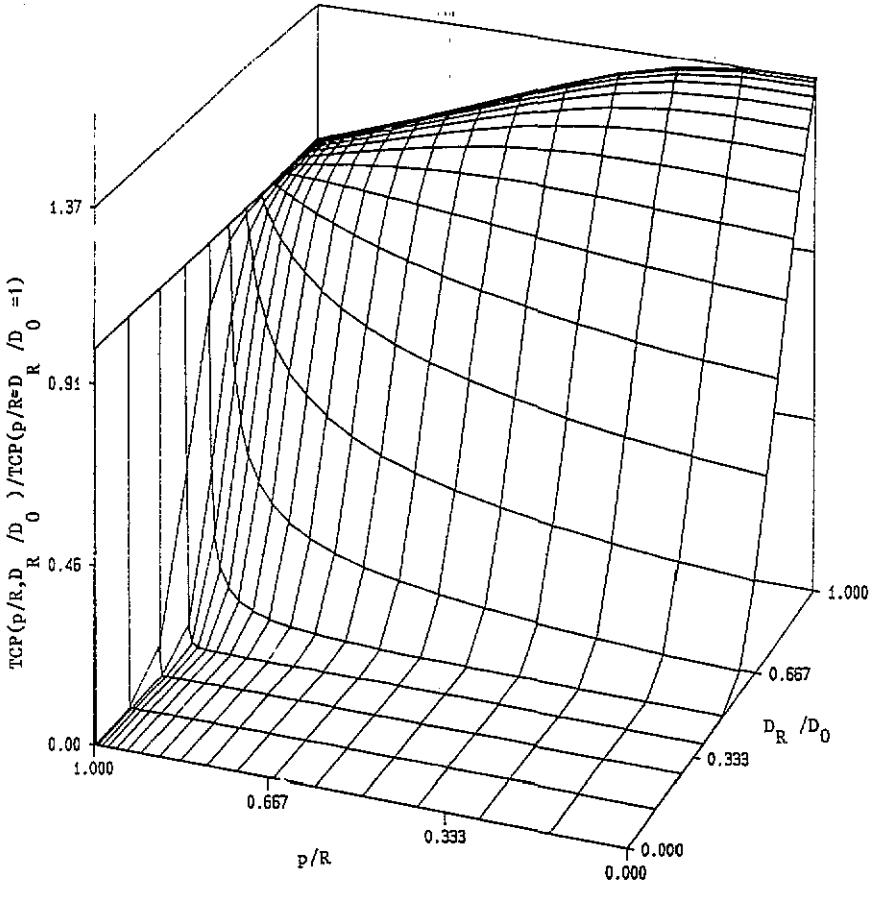

Figure 4. The variation of TCP for the 400 radial distributions with $D_0 = 64$ Gy and the first model for clonogenic cell variation with $\rho_R = 10^{-1}\rho_0$, $\alpha = 0.35 \pm r^* \times 0.08$ where r^* is a random number from a Gaussian distribution. The tumour volume $V_t = 320$ cm^3. The value plotted on the vertical axis is the ratio TCP $(p/R, D_R/D_0)$/TCP $(p/R = D_R/D_0 = 1)$, i.e. TCP $(p/R = D_R/D_0 = 1) = 0.479$ is the TCP which would result from a uniform irradiation of all the volume to dose D_0 with uniform clonogenic cell density ρ_0.

that there are fewer cells to kill. For the lowest value of ρ_R considered ($10^{-7}\rho_0$) the ratio of TCP $(p/R \simeq 0, D_R/D_0 = 1)$/TCP $(p/R = 1, D_R/D_0 = 1)$ rises to 2.08 indicating that TCP $(p/R \simeq 0, D_R/D_0 = 1) = 2.08 \times$ TCP $(p/R = 1, D_R/D_0 = 1) = 0.479$ which is 1.0.

(ii) The TCP is constant of course along the $p/R = 1$ axis (dose and clonogenic cell density are the same everywhere in the tumour).

(iii) There is a D_R/D_0 line along which the TCP is approximately constant as p changes. Figure 5 explains why this occurs. In the left diagram the dose and cell density profiles are shown for some particular p and in the right diagram for a smaller value of p. These are any two values of p along that D_R/D_0 line for which the TCP is roughly constant. Consider the two regions labelled A and B. In region A the dose is lower for the right part of the figure than for the left part and the cell density the same for both parts of the figure. Hence the TCP for this region alone is lower. However in region B, although the dose is lower

Table 1. Variation of two characteristic parameters in the 3D TCP plot with ρ_R/ρ_0.

ρ_R/ρ_0	TCP $(p/R = 0, D_R/D_0 = 1)$/ TCP $(p/R = D_R/D_0 = 1)$	D_R/D_0 value of line of approximately constant TCP
1	1.0	1.0
0.1	1.37	0.83
0.01	1.69	0.73
0.001	1.90	0.58
0.0001	2.00	0.49
0.000 01	2.05	0.39
0.000 000 1	2.08	0.21

in the right part than in the left part, the cell density is also reduced and the TCP for this region alone is higher. The two effects cancel out giving approximately the same TCP for the whole tumour volume in the two cases. The D_R/D_0 location of this line depends again on the vaue of ρ_R which 'controls' the effect. The line moves to lower D_R/D_0 values as ρ_R is reduced (see table 1).

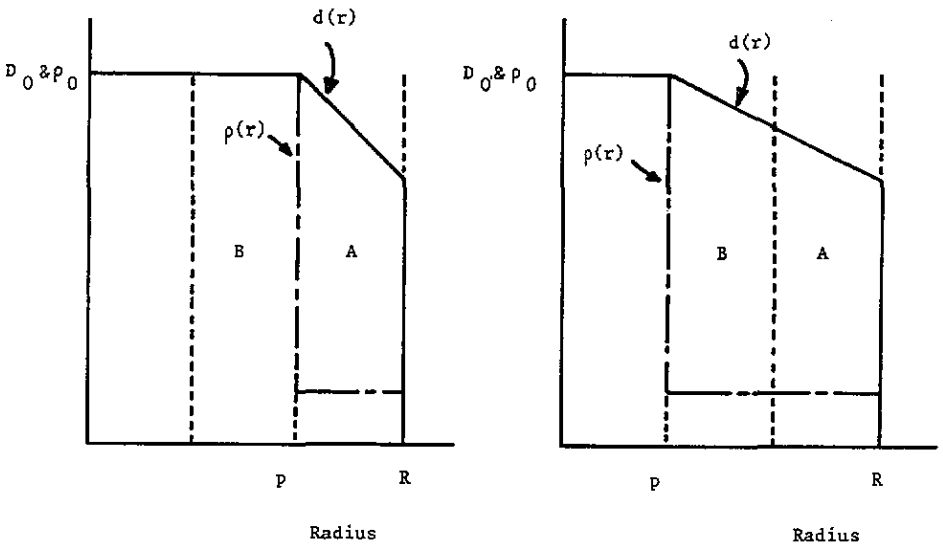

Figure 5. The explanation for the line of constant TCP in the plot of TCP $(p/R, D_R/D_0)$ (see text for details). The full lines represent the dose variation; the chain lines represent the variation of the clonogenic cell density (first model). The broken lines simply delineate two annular regions A and B. The two parts of the figure illustrate two particular values of p, the right-hand one lower than the left-hand one.

3.2. Second model of clonogenic cell density variation

Figure 6 shows the variation of TCP for the 400 radial distributions with $D_0 = 64$ Gy and the second model for clonogenic cell variation, with $\rho_R = 10^{-7}\rho_0$, $\alpha = 0.35 \pm r^* \times 0.08$ (r^* is a random number from a Gaussian distribution), and a tumour volume $V_t = 320$ cm^3.

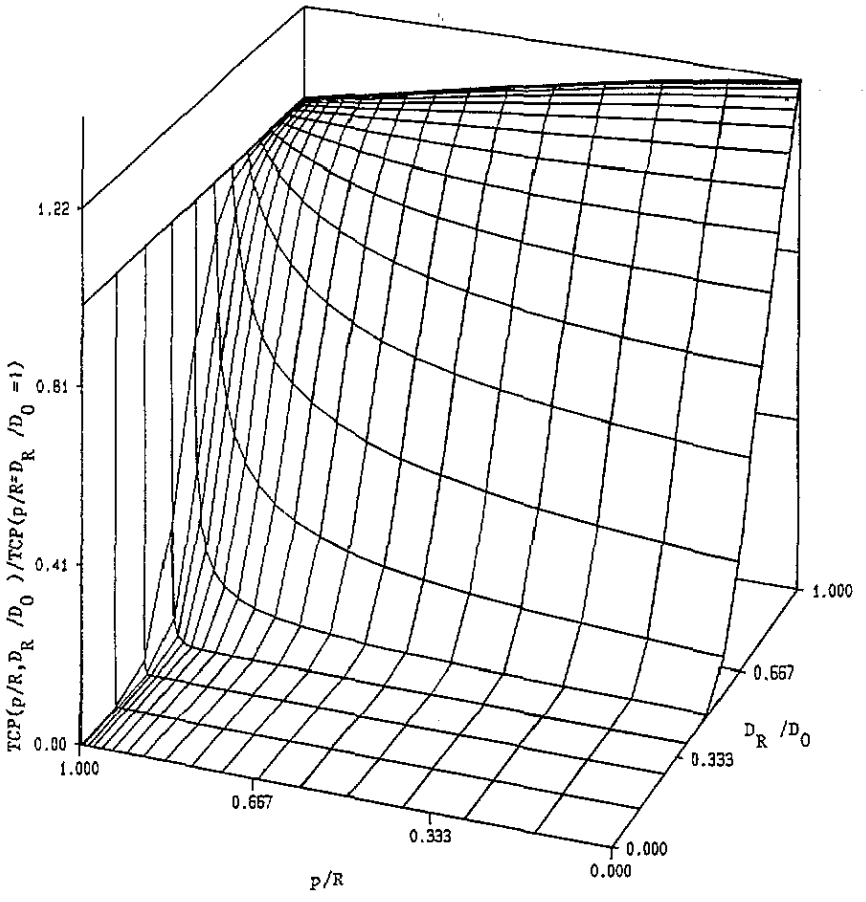

Figure 6. The variation of TCP for the 400 radial distributions with $D_0 = 64$ Gy and the second model for clonogenic cell variation, with $\rho_R = 10^{-7}\rho_0$ and $\alpha = 0.35 \pm r^* \times 0.08$ where r^* is a random number from a Gaussian distribution. The tumour volume $V_t = 320$ cm^3. The value plotted on the vertical axis is the ratio TCP $(p/R, D_R/D_0)$/TCP $(p/R = D_R/D_0 = 1)$, i.e. TCP $(p/R = D_R/D_0 = 1) = 0.479$ is the TCP which would result from a uniform irradiation of all the volume to dose D_0 with uniform clonogenic cell density ρ_0.

The value at $p/R = D_R/D_0 = 1$ is still 0.479 of course. We may observe the following features common to plots of this type:

(i) Along the $D_R/D_0 = 1$ axis, the variation in TCP ratio is entirely due to the reduction in clonogenic cell density with falling p. The value to which the TCP ratio rises depends on the value of ρ_R. The larger this value, the larger the TCP ratio becomes. However even for the very low value of ρ_R illustrated the TCP does not rise substantially above the value for uniform clonogenic cells (shown at $p/R = D_R/D_0 = 1$).

(ii) Again there is a D_R/D_0 line along which the TCP is approximately constant as p changes.

4. Discussion

The importance of avoiding low-dose regions in the tumour is clearly illustrated by the rapid fall-off to zero of the TCP when lower doses arise. However if the low-dose regions also correspond to regions where there is a decrease in clonogenic cell density then the TCP will not necessarily be reduced. In fact under some circumstances it could be increased. The actual value of the TCP depends on the trade-off between the variations in these two quantities. Equation (12) allows these trade-offs to be investigated.

To emphasize the trade-off, without considering the complexity of non-uniform dose and clonogenic cell density variations, imagine two targets of the same fixed volume V_t and the same radiosensitivity. Equations (1) and (2) show that the TCP depends only on the initial number of cells $N_0 = \rho_c V_t$ and on the dose D. Suppose the clonogenic cell densities in targets 1 and 2 are ρ_1 and ρ_2 respectively and the doses are D_1 and D_2 respectively. Then the two values of the TCP are

$$\text{TCP}_1 = \exp[-\rho_1 V_t \exp(-\alpha D_1)] \tag{18}$$

and

$$\text{TCP}_2 = \exp[-\rho_2 V_t \exp(-\alpha D_2)] \tag{19}$$

from which

$$\text{TCP}_2/\text{TCP}_1 = \exp\{V_t[\rho_1 \exp(-\alpha D_1) - \rho_2 \exp(-\alpha D_2)]\}. \tag{20}$$

To obtain $\text{TCP}_2 \geqslant \text{TCP}_1$ requires $\rho_1 \exp(-\alpha D_1) \geqslant \rho_2 \exp(-\alpha D_2)$. Now suppose that the dose in the second target is actually lower than that in the first, i.e. $D_2 \leqslant D_1$, the TCP in the second target can still be greater than that in the first if

$$\rho_2/\rho_1 \leqslant \exp[\alpha(D_2 - D_1)] \tag{21}$$

i.e. the smaller dose to the second region gives a higher TCP because there are fewer cells to kill.

The same 'balance' arises (only in a more complex way) in the numerical cases studied where both the dose and clonogenic cell density are non-uniform.

From equation (10) we may derive the variation of dose which, for varying clonogenic cell density, keeps the TCP constant. If the clonogenic cell density were lower than the often used 'default' value of 10^7 cm^{-3}, the dose could be reduced, keeping the TCP constant, and this may be beneficial if it also means that nearby radiosensitive organs at risk receive a lower dose with correspondingly decreased normal tissue complication probability.

For the moment imagine α is kept constant. We need

$$\Pi_{j=1}^{M} \exp[-\rho_j V_t f_j \exp(-\alpha D_j)] = C \tag{22}$$

where C is a constant. From this we have

$$\log C = -\sum_{j=1}^{M} \rho_j V_t f_j \exp(-\alpha D_j). \tag{23}$$

This is the most general equation describing how the dose D_j should vary in relation to variations in clonogenic cell density ρ_j so that the TCP stays constant. Note that this does

not give D_j in terms of ρ_j *at a point* because the overall TCP is the product over a large number of small volumes. However if we invoke a relation between the clonogenic cell density at each point in space, such as is given by equation (17), then equation (23) can be 'solved' for the free parameter (D_R in equation (13)). We have

$$\sum_{r=0}^{R} \frac{\rho(r)}{\rho_0} f_{r_j} \exp \alpha(D_0 - D(r)) = 1 \tag{24}$$

with $D(r)$ and $\rho(r)$ specified by equations (13) and (17) respectively. For any particular ρ_R specification, the free parameter D_R follows from equation (24).

We have studied the way D_R must vary to maintain a constant TCP for a variety of values of ρ_R characterizing the variation in clonogenic cell density, when both the dose and clonogenic cell density ramp down to these values from radius p via equations (13)–(17). As the value of ρ_R falls, clearly we expect D_R to fall correspondingly. We shall not present 3D plots showing a wide variety of cases to avoid confusion but simply state some sample results which illustrate a very important observation.

Firstly we recall that if there is no variation in dose or clonogenic cell density and these take the constant values 64 Gy and 10^7 cm^{-3} respectively, the TCP was found to be TCP $(p/R = 1, D_R/D_0 = 1) = 0.479$. If the clonogenic cell density now varies, parameterized by $p/R \simeq 0$ and $\rho_R/\rho_0 = 1/8000$ and *if the dose is considered constant* $D_R = D_0 = 64$ Gy, the TCP is 1.221 times the value TCP $(p/R = 1, D_R/D_0 = 1) = 0.479$.

If, instead, equation (24) is solved to give the value of D_R which would give the same TCP for this variation in clonogenic cell density across the spherical target as the value which would arise if the clonogenic cell density and dose were constant (i.e. the value TCP = 0.479), it turns out that $D_R = 57.82$ Gy. Thus we see that even when the clonogenic cell density varies by nearly four orders of magnitude across the target, the dose only varies by some 6 Gy (cf figure 2). This is a consequence of the exponential behaviour in the fundamental equations (1) and (2).

There are very few, if any, real data on the variation of clonogenic cell density across tumours. Establishing these data could be very important for stereotactic radiotherapy for brain tumours, for example. If the clonogenic cell density falls off towards the periphery of such a tumour it may not be necessary to irradiate this volume to such a high dose.

Furthermore, in the types of plan now being produced by conformal therapy techniques, particularly in the pelvis (see, e.g., Mohan *et al* 1992), the dose distributions in the target region are sometimes deliberately non-uniform in order to achieve the maximal normal tissue sparing. In such cases the value of the TCP will critically depend on the assumptions made about clonogenic cell density.

Acknowledgments

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Appendix

We present here proof that for a tumour with a uniform clonogenic cell density, a uniform dose distribution produces the highest tumour control probability.

Suppose

(i) the clonogenic cell density is a uniform ρ,
(ii) the dose response curve has a fixed value of α,
(iii) the tumour has volume v and is divided into N compartments of equal mass; let N be odd for convenience,
(iv) the integral dose is kept constant at a value D.

The mean dose is then (D/N). Suppose the dose in each compartment differs from the previous one by δ. The dose in the ith compartment is then

$$d_i = (D/N) - ([N-1]/2)\delta + \delta(i-1) \qquad \text{for } i = 1, 2, \ldots, N \tag{A1}$$

i.e.

$$d_i = (D/N) + \delta[(2i - N - 1)/2] \qquad \text{for } i = 1, 2, \ldots, N \tag{A2}$$

The tumour control probability is

$$T = \exp\left(-\gamma \sum_i \exp(-\alpha d_i)\right) \tag{A3}$$

where $\gamma = \rho v$.
So

$$T = \exp\left(-\gamma \sum_i \exp[[-\alpha\{(D/N) + \delta[(2i - N - 1)/2]\}]]\right). \tag{A4}$$

Taking the log of both sides

$$\log T = -\gamma \exp(-\alpha D/N) \sum_i \exp\{-\alpha\delta[(2i - N - 1)/2]\}. \tag{A5}$$

Differentiating and setting $\mathrm{d}T/\mathrm{d}\delta = 0$ we have

$$(1/T)\,\mathrm{d}T/\mathrm{d}\delta = -\gamma \exp(-\alpha D/N) \sum_i (-\alpha)[(2i - N - 1)/2] \exp\{-\alpha\delta[(2i - N - 1)/2]\} = 0. \tag{A6}$$

Since T cannot be zero we have

$$\sum_i [(2i - N - 1)/2] \exp\{-\alpha\delta[(2i - N - 1)/2]\} = 0. \tag{A7}$$

This is satisfied by $\delta = 0$ since then the left-hand side becomes

$$\sum_i^N [(2i - N - 1)/2] \tag{A8}$$

which is zero by definition.

Hence the best distribution of dose is that in which the dose to all the compartments is the same (QED).

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