

Short communications

Optimal radiotherapy of tumour cells following exponential-quadratic survival curves and exponential repopulation kinetics

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A previous paper (Wheldon and Kirk, 1976) presented the mathematical derivation of optimal treatment schedules in radiotherapy, assuming a single-hit multi-target radiation survival curve (see Elkind and Whitmore, 1967) and exponential repopulation kinetics for tumour cells, and utilizing the Cumulative Radiation Effect (CRE) representation of radiation damage to normal connective tissue (Kirk *et al.*, 1971).

Recently, attention has been focused on cell survival curves which, contrary to the multi-target model, have non-zero initial slopes (Alper, 1975). Some evidence favours an exponential-quadratic survival curve with non-zero initial slope and continuously steepening slope as radiation dose increases (Neary, 1965; Sinclair, 1969; Kellerer and Rossi, 1971; Chadwick and Leenhouts, 1973; Douglas and Fowler, 1975). This form, the exponential-quadratic form, though not dependent essentially on any theory, can be derived from a molecular theory of radiation damage which emphasizes the role of radiation-induced single-strand and double-strand breaks in chromosomal DNA (Chadwick and Leenhouts, 1973).

The present paper presents an analytical derivation of optimal treatment schedules for the radiotherapy of tumour cells following the exponential-quadratic form of survival curve, other assumptions being as before (Wheldon and Kirk, 1976).

With exponential-quadratic survival and exponential repopulation by surviving cells, the fraction of cells (σ) surviving N treatments, each of d rad, administered with inter-treatment times of t days, is:

$$\sigma = \text{Exp} \{N(\lambda t - \alpha d - \beta d^2)\} \dots\dots\dots(1)$$

where α and β are the survival curve parameters and λ is the exponential repopulation constant for surviving cells. If the number of treatments is limited by the radiation tolerance of normal connective tissue, and this is assessed on the CRE system (Kirk *et al.*, 1971), the maximum number of treatments is

$$N_{\max} = \left(\frac{d}{R_t^{\max}} \right)^{-1/a} t^{b/a} \dots\dots\dots(2)$$

where $\alpha=0.65$, $\beta=0.11$ and R_t^{\max} is the numerical value of the CRE for connective tissue tolerance.

Substituting N_{\max} in (2) for N in (1) we obtain σ_t , the final surviving fraction when the treatment schedule is terminated. This is:

$$\sigma_t = \text{Exp} \left\{ \left(R_t^{\max} \right)^{1/a} \left(\lambda \cdot d^{-1/a} \cdot t^{1+b/a} - \alpha d^{1-1/a} \cdot t^{b/a} - \beta \cdot d^{2-1/a} \cdot t^{b/a} \right) \right\} \dots\dots(3)$$

To obtain the optimal dose per treatment (d^*) and the optimal interval between successive treatments (t^*) we must simultaneously solve the equations

$$\frac{\partial}{\partial d} (\sigma_t) \Big|_{d=d^*} = 0 \dots\dots\dots(4)$$

$$\frac{\partial}{\partial t} (\sigma_t) \Big|_{t=t^*} = 0 \dots\dots\dots(5)$$

choosing only physically meaningful solutions yielding a minimum for σ_t .

We obtain:

$$d^* = \frac{\alpha \{1 - (a+b)\}}{\beta \{2(a+b) - 1\}} \dots\dots\dots(6)$$

and

$$t^* = \frac{b \{ \alpha d^{*a} + \beta (d^*)^2 \}}{\lambda (a+b)} \dots\dots\dots(7)$$

Substituting $\alpha=0.65$ and $\beta=0.11$ and setting $\tau = \frac{0.69}{\lambda}$

where τ is tumour doubling time (in days) we find

$$d^* = 0.46 \frac{\alpha}{\beta} \text{ rad} \dots\dots\dots(8)$$

$$t^* = 0.14 \frac{\alpha^2}{\beta} \tau \text{ days} \dots\dots\dots(9)$$

from which optimum treatment schedules can easily be calculated.

For illustrative purposes we have calculated optimal schedules for hypothetical tumour cell populations with survival curve parameters $\alpha=2.0 \times 10^{-3} \text{ rad}^{-1}$ and $\beta=4.0 \times 10^{-6} \text{ rad}^{-2}$, and a range of doubling times. The parameter values chosen are close to those reported for a

TABLE I
COMPARISON OF OPTIMAL AND CONVENTIONAL SCHEDULES

Doubling time (τ days)	Optimal dose (d^* rad)	Optimal interval (t^* days)	Treatment number (N_{\max})	Optimal surviving fraction	Conventional surviving fraction
1	230.8	0.14	17.28	5×10^{-5}	5.4×10^1
10	230.8	1.41	25.51	4×10^{-7}	4×10^{-7}
30	230.8	4.23	30.72	3×10^{-8}	1×10^{-7}
70	230.8	9.86	35.46	1×10^{-9}	7×10^{-8}
100	230.8	14.09	37.66	4×10^{-10}	6×10^{-8}
150	230.8	21.13	40.34	8×10^{-11}	6×10^{-8}

Survival parameters: $\alpha=2.0 \times 10^{-3} \text{ rad}^{-1}$, $\beta=4.0 \times 10^{-6} \text{ rad}^{-2}$.
Conventional schedule: $d=200 \text{ rad}$, $t=1 \text{ day}$, $N_{\max}=30$.

"typical" line of mammalian cells (Chinese hamster ovary cells) growing in culture (Chadwick *et al.*, 1976).

Table I gives the optimal schedule parameters and schedule effect on tumour cells for this case. The CRE value (R_0^{\max}) is 1825 radiation effect units (REU), a value close to tolerance of normal connective tissue, and attained on completion of a more conventional schedule consisting of 30 treatments, administered daily, each of 200 rad. The effects of the conventional schedule on the tumour cell populations of different doubling times are also given for comparison.

While no great stress should be placed on the numerical details, it is of interest that (for this cell line) optimal scheduling appears to be advantageous for very fast and very slowly growing tumours, but differs little from conventional therapy for doubling times in the region of ten days. It should be appreciated, of course, that many tumours may follow Gompertzian rather than exponential growth kinetics, the growth rate accelerating as the tumour size is reduced by treatment.

This suggests a non-uniform treatment schedule, the inter-fraction time reducing progressively as treatment proceeds. Analysis of this case is currently in progress.

The present analysis permits deduction of theoretically optimal schedules where an exponential-quadratic function constitutes a better fit to the available data than the more conventional multi-target function. Where the two functions provide equally good fits to the available data it is to be expected that the same optimal schedules would be predicted in each case, provided the theoretical optimum falls within a region of the survival curve for which experimental data are available.

The possibility arises, of course, that one or other of the alternative representations leads to the prediction of an optimum dose which lies outside the experimentally documented region of the survival curve (*i.e.* involves extrapolation of the mathematical representation into experimentally uncharted areas), in which case experimental investigation of the region concerned would be necessary in order to verify that the representation remained valid.

It is of interest to note that the optimal dose obtained (231 rad) for the "typical" cell line considered here is in a well-documented region of the survival curve and could have been equally well deduced from a multi-target representation with parameter values $n=1.6$ and $D_0=225$ rad. The equivalence of optimum schedules derived from the two representations need not hold for cells with more unusual parameter values, in which case a decision as to which representation is appropriate becomes necessary.

As with the multi-target analysis (Wheldon and Kirk, 1976), the analysis fails for the case of a purely exponential

"shoulder-less" survival curve, the optimum dose predicted by equation (6) increasing without limit as the quadratic parameter tends towards zero. The exponential curve is indeed a special case which requires separate consideration and will be treated in a forthcoming publication.

We must emphasize, as before, that the parameter values quoted pertain to *hypothetical* tumour cells *in vivo* and that the numerical calculations presented are intended as illustrations of the method and not as recommendations for departures from conventional practice in clinical radiotherapy. More realistic models, incorporating non-exponential tumour growth, non-uniform scheduling, and the optimal therapy of mixtures of oxic and hypoxic tumour cells, will be presented in future papers.

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