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INTERVALS BETWEEN MULTIPLE FRACTIONS PER DAY

Differences between early and late radiation reactions

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Abstract

Assuming the linear quadratic model for dose-response curves enables the proportion of repairable damage to be calculated for any size of dose per fraction. It is given by the beta (dose squared) term, and represents a larger proportion of the total damage for larger doses per fraction, but also for late-reacting than for early-reacting tissues. For example at 2 Gy per fraction, repairable damage could represent nearly half the total damage in late-reacting tissues but only one fifth in early-reacting tissues. Even if repair occurs at the same rate in both tissues, it will obviously take longer for 50% of the damage to fade to an undetectable level (3 or 5%) than for 20% to do so. This means that late reactions require longer intervals than early reactions when multiple fraction per day radiotherapy is planned, even if the half-lives of repair are not different.

Key words: Therapeutic radiology; accelerated fractionation, intervals, early and late reactions.

In radiotherapy with multiple fractions per day (MFD) the potential advantages (3, 10) can be diminished or lost if the intervals between fractions are too short to allow full repair.

The purpose of this note is to show that longer intervals are necessary to limit late reactions than to limit early reactions. This difference is true even if the half-life of repair of sublethal injury is the same in both types of tissue. It is not necessary to postulate a difference in the rates of repair to explain it (8), although if half-lives were longer for late than for early reactions the effect would be enhanced proportionately.

Material and Methods

The concept of 'fading time' enables a distinction to be made between *rate* of repair and *time at which the repair is virtually complete* in practical terms. This time will obviously depend both upon the rate (or half-life) and upon the amount of repairable damage generated by the radiation. 'Fading time' has been defined (4) as the time required for repairable damage (which may represent variable amounts up to 50 or even 70% of the total radiation damage, depending upon dose per fraction and the repair capability of the tissue of interest) to fade to a specified proportion of total damage, such as 3% or 5%. This proportion represents the 'noise' in the biological system, for example the smallest difference between two total doses that can be discerned by careful observations. The choice of this level is obviously arbitrary, and in the present paper a noise level of only 3% is assumed because it should not give over-optimistic answers.

A convenient way of characterising repair capability is to use the ratio α/β of the linear to the quadratic coefficients of the dose-response curve for critical 'tissue-rescuing units' or cells in the tissue (5). This LQ model of dose-response relationship has been discussed fully elsewhere and it has been shown to represent the shape of dose-response curves to a reasonable degree of approximation between about 1 and 7–10 Gy for many tissues (1–3, 7, 11), i.e. over the range of doses per fraction used in clinical radiotherapy. The important point is that early-reacting tissues are characterised by relatively straight dose-response curves with the β term small (α/β=8 to 12 Gy for example) whereas late reactions have more curvy dose-response curves (α/β=2 to 6 Gy) (12). It is assumed that the beta term represents the repairable component of the radiation damage. It can readily be shown that, for a given dose per fraction such as 2 Gy, the repairable component represents 50% of the total damage for a late-

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reacting tissue with $\alpha/\beta=2$ Gy but only 20% of the damage for an early-reacting tissue with $\alpha/\beta=10$ Gy:

$$\frac{\text{Effect}}{\alpha} = \text{total dose} \times \left(1+\frac{d}{(\alpha/\beta)}\right) \quad (1)$$

The concept of fading time says that this 50% will fade down to 3% of the total ultimate damage in a longer time than the 20% will for the same half-life of repair. This is the simple principle.

The amounts of incomplete repair calculated by the present LQ model are identical with those calculated from the Incomplete Repair model of THAMES (9), as explained previously (4). In the present work however, only two fractions or two fractions per day are assumed. Interactions between the pairs on successive days are assumed to be negligible. Calculations for three or more fractions per day will require further interactions between the fractions to be considered and these will be presented elsewhere [B. D. Michael (pers. comm. 1985)].

The value of $T_{\frac{1}{2}}=1.5$ h is chosen here because it has some historical and clinical justification [6] and also because it is towards the upper end of the range discussed recently by THAMES (8). It should not therefore suggest misleadingly short intervals. The results however, can all be scaled in direct proportion to the value of $T_{\frac{1}{2}}$ which is assumed.

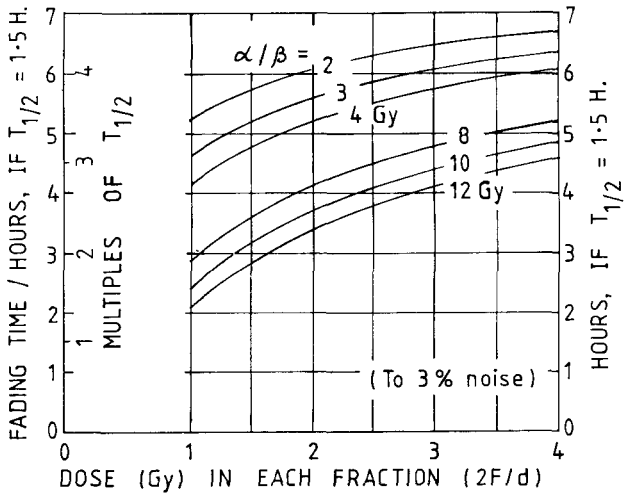

Figure. Results of calculations for two fractions only, or for two fractions per day assuming complete repair overnight. The fading time is the time required for the percentage of repairable damage, calculated from the LQ model, to fade from that percentage to 3%, at which it is assumed to be no longer detectable. The half-time of repair is assumed constant throughout at 1.5 h. The values are examples only, to show the trends, and may be different in practice. These calculations do not apply to three or more fractions per day nor to multiple fractions at equal spacings, although the trends are probably similar.

Results

The Figure shows the results of calculations assuming $T_{\frac{1}{2}}=1.5$ h, for a pair of doses, or for pairs given daily with sufficient interval overnight for all repair damage to be complete before the next pair of fractions. More than 2F/d are not represented by the Figure. The late-reacting tissues are represented by the curves for $\alpha/\beta=2$, 3 and 4 Gy and the early-reacting tissues by those for 8, 10 and 12 Gy.

It is clear that longer fading times are computed for the late-reacting tissues, by about $1\frac{1}{2}$ to 3 h (assuming $T_{\frac{1}{2}}=1.5$ h). There is some variation over the doses per fraction of practical interest, 1–3 Gy. A progressive increase of fading time with increase of dose per fraction can be seen, but it is not as large as the effect of the repair parameter (α/β).

Discussion

The main practical application concerns the question 'What interval must be left between fractions when MFD are used?' The present result cannot provide definitive practical answers because 1) we do not know that 3% is a realistic 'noise' level, 2) we do not know that $T_{\frac{1}{2}}=1.5$ h is a correct assumption for both types of tissue, and 3) we have assumed that the shoulder on the dose-response curve can be represented by the LQ model with the beta component quantifying repairable damage. However, *relative* values and trends are shown which are useful to consider.

First, let us examine the consequences of giving two fractions per day of 1.6 Gy each fraction. The appropriate intervals from the Figure would be about 3–4 h for early damage, but 5–6 h for late damage. This is perhaps the most important point. It is emphasized that the fading times in the Figure are only examples for comparison of trends and that different actual values might apply in practice.

The second example concerns 2 Gy fractions given at 2F/day. For this form of accelerated fractionation, intervals of about 4 h may suffice for acute reactions, but the late reactions would be more severe than expected if intervals of less than 5–6 h were used. Longer intervals are expected if larger doses per fraction are used, in accordance with a larger proportion of repairable damage in the beta (dose-squared) term.

By the same token, slightly shorter intervals might be considered if very small doses per fraction, of say 1.1 Gy, were to be used, but only about $\frac{1}{2}$ h shorter. This shortening in principle amounts to very little shortening in practice.

There could therefore be the following danger in setting up a hyperfractionated schedule. If the total doses were chosen on the basis of acute (e.g. mucosal) reactions, these tissues may undergo sufficient 'repair' in intervals of about 4 h (Figure) for longer intervals to appear unnecessary, *even if dose-seeking tests were made with varying*

intervals. Nevertheless, the *late* reactions would still require longer intervals of 5–6 h (or some reduction in total dose), but this would not become obvious until months or years later when excessive late reactions would be seen.

It appears that THAMES' (8) practical warning that 'dose fractions should be separated by 6 h or more to permit repair to approach completion in late-responding tissues' is indeed important, even if half-lives are not found to be longer for late-reacting tissues.

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