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FRACTIONATED RADIATION THERAPY AFTER STRANDQVIST

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Abstract

Models for predicting the total dose required to produce tolerable normal-tissue damage in radiation therapy are becoming less empirical, more realistic, and more specific for different tissue reactions. The progression is described from the 'cube root law', through STRANDQVIST'S well known graph to NSD, TDF and CRE and more recently to biologically based time factors and linear-quadratic dose-response curves. New applications of the recent approach are reviewed together with their implications for non-standard fractionation in radiation therapy. It is concluded that accelerated fractionation is an important method to be investigated, as well as hyperfractionation; and that more data are required about the proliferation rates of clonogenic cells in human tumours.

The most often quoted reference in discussions about fractionated doses in radiation therapy is that of STRANDQVIST (18). The discussions always concern the adjustment in total dose that has to be made when the dose is delivered in more or fewer fractions of smaller or larger size, respectively, and in different overall times. All that we can say with confidence is that the normal tissue tolerance will not be exceeded if we follow certain empirical rules relating the total dose to number and size of fractions and to overall time of the treatment. It is of course hoped that the dose given will be sufficient to cure the tumour, but knowledge about this aspect is less well developed than about normal tissue reactions. Such relationships have evolved gradually from being completely empirical to recent approaches based more firmly on known biologic factors. This biologic basis has emerged strongly in the last 2 or 3 years. These factors will be discussed here.

There has been a progression from the completely empirical 'cube root law', through STRANDQVIST'S slope of 0.22 on his famous plot of log total dose against log overall time (and number of fractions because all treatments were then given at 6 per week), to NSD, TDF and CRE which have separate time and fraction number exponents, and to the better approximations for normal tissues which are now available. In this progression, the workers at the Sahlgrenska Sjukhuset have maintained a leading position in providing good clinical and experimental data relating to the tolerance of normal tissues, especially for the relationship between late and early normal-tissue reactions (26). Their findings are broadly confirmed by results from other centres.

Today the interest in non-standard fractionation in radiation therapy is even greater than it has been at some times in the past. Improved clinical results in radiation therapy are being sought by hyperfractionation (a larger number of smaller fractions than usual); by accelerated fractionation (dose fractions of conventional size given at, say, 2 per day, so that the overall time would be halved); or by continuous low dose rate irradiation as in interstitial implants. There is still a hankering after hypofractionation (a few large fractions) because that would spare patients' travelling time and departments' working time. Indeed one of the major questions is whether 2 or 3 fractions per week are always bad, or whether they can sometimes give as good results as conven-

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tional daily fractionation for less trouble and expense. Current clinical trials are investigating all these approaches and a brief review of the radiation biologic background is now given.

The separation of dose-per-fraction and overall time factors

Twenty years ago FOWLER et coll. (11) were concerned in some experiments on skin reactions in pigs which went some way to separating the effect of size or number of fractions from that of overall time. It was clear that in ordinary radiation therapy the effect of overall time was smaller than that of the repair between successive fractions (which depended on size and number of fractions) but that it was not negligible.

These proportions were formalized by ELLIS (6) from clinical data and intuition in the NSD formula:

$$\text{Total dose} = \text{NSD} \times N^{0.24} \times T^{0.11} \qquad (1)$$

where N was the number of fractions and T was the overall time. Thus a clear separation was specified between the effects of overall time and number of fractions. This concept has been tidied up algebraically as CRE (13) and as TDF (14). The exponent 0.24 of fraction number was obtained simply from STRANDQVIST'S slope of 0.22 by allowing for 5 instead of 6 treatments per week. The exponent 0.11 of overall time was obtained equally simply from the difference between STRANDQVIST'S 0.22 and the exponent (slope on a log-log plot) of 0.33 from the older cube root law. ELLIS (6) assumed negligible proliferation in tumours, an assumption which is no longer acceptable.

The effect of overall time

Any single exponent of overall time gives completely the wrong shape of correction for total iso-effective dose as a function of overall time, because it implies more recovery early and less later. It is now known that proliferation does not affect the total dose required to produce a given biologic reaction until 2 to 4 weeks after the start of fractionated irradiation in rapidly proliferating tissues such as skin or mucosa. The total dose required then rises rapidly as compensatory proliferation begins. Fig. 1 illustrates this for mouse skin (4). The 2 week delay time, before the rise of total dose occurs, reflects the transit time of cells from the basal through the keratinizing layers of mouse skin. It is not a coincidence that this is about the time at which desquamation begins to be apparent.

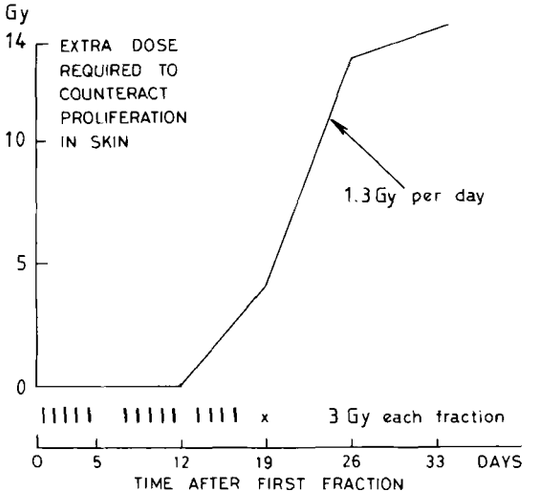

Fig. 1. The extra dose required to counteract proliferation in mouse skin does not become significant until about 2 weeks after the start of 'daily' fractionation. From DENEKAMP (4).

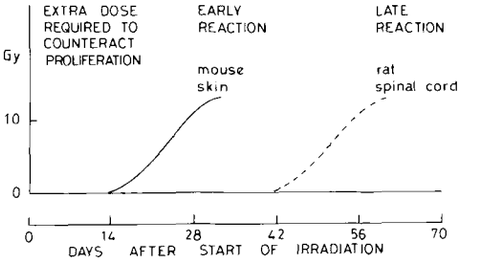

Fig. 2. The extra dose required to counteract proliferation does not become significant until much later for the late-reacting tissues such as spinal cord, beyond the 6 week overall time of irradiation.

It follows that for reactions which appear late, because of a slower turnover time in the tissue at risk, proliferation only causes the iso-effect dose to rise after much longer overall times, usually many weeks. This would of course be after the end of the usual 5 to 7 weeks overall time in radiation therapy, as illustrated in Fig. 2.

Thus 2 important conclusions follow: (1) Prolonging the overall time, in the normal radiation therapy range, has little sparing effect on late reactions but a large sparing effect on early reactions. This is a basic principle of radiobiologic cell kinetics and is one factor that accounts for the lack of prediction of late damage by the early reactions. (2) The shape of

Table 1

Extra dose required to compensate for proliferation (Gy)

Overall time (weeks)	Skin (rats)	Spinal cord (rats)	Kidney (mice)
0–1	0	0	0
1–2	0	0	0
2–3	3	0	0
3–4	10	0	0
4–5	10	0	
5–6	10	0	2.5
6–7	10	0	

TURESSON & NOTTER (27) have shown that in human skin proliferation begins 4 weeks after the start of fractionated irradiation.

the curve relating the extra dose (due to proliferation) to the overall time of irradiation should be a sigmoid as in Figs 1 and 2. None of the previous mathematical models have allowed for this correctly. Both NSD and CRE imply a large initial sparing, decreasing exponentially with time. Even the COHEN (3) model, which could accommodate a realistic sigmoid shape, has so far assumed a single time factor starting without delay. These wrong time factors did not lead to major clinical disasters because they are rather small over the 6 weeks of irradiation, corresponding to only about one third of the total increase of dose as the number of 'daily' fractions increases. For example the $T^{0.11}$ factor in NSD predicts only an 8 per cent increase in dose if the overall time is doubled. This is a rough average approximating to no increase in the first 4 weeks of clinical radiation therapy followed by a large increase in the final 2 weeks.

Table 1 lists the times at which significant proliferation has been observed to begin in animals, from experiments in which overall time was deliberately varied. It is from data such as these that true time factors for use in radiation therapy will ultimately be derived. Recently TURESSON & NOTTER (27) have provided evidence that this proliferation in human skin begins at 4 weeks.

It can be concluded that prolongation of irradiation is bad because: (1) it allows tumours to proliferate and (2) it does not spare late injury to normal tissues.

Nevertheless, overall times cannot be cut too short because prolongation: (1) allows reoxygenation to sensitize hypoxic tumours and (2) spares acute injury to rapidly proliferating normal tissues.

Dose–response curves

In a multifraction irradiation with the overall time shorter than the times listed in Table 1, we can be sure that proliferation is not affecting the total dose. Then, provided sufficient intervals are allowed to ensure complete repair of Elkind-type sublethal injury (i.e. 3–6 h), it is legitimate to analyse the results of multifraction experiments in terms of the shape of a dose–response curve. This is simply done, independently of any particular dose–response formula, by plotting 1/n of the full effect against the dose per fraction which gives the chosen endpoint when n fractions are used (10).

The shape of the resulting dose–response curve can be analysed in a number of ways; the formulae that should be considered include: (a) the linear quadratic model (LQ), (b) the multi-target two-component model (TC), (c) repair–misrepair models (RMR) (22).

Before we need to choose one model, there are some considerations which are independent of which model we might choose. It is dose–response curves, not cell-survival curves, that are obtainable from an analysis of multifraction isoeffect doses (7). Important differences have been found between the apparent shapes of the dose–response curves for early and for late reactions. The late reactions correspond to a more rapidly bending dose–response curve, so that the iso-effective total doses vary more steeply with dose-per-fraction for late than for early radiation damage.

Clinical data

There are several clinical results which indicate the more rapid increase of late reactions with increasing dose per fraction than of early reactions (2, 16, 26). The formulae for NSD (or TDF) and CRE seem to work reasonably well for acute reactions (if the overall times are as short as 4 weeks), but clearly not for late reactions, in a direction which is not in dispute. When the early reactions were matched, late reactions were worse after large doses per fraction than after small doses per fraction. This was particularly marked if large doses per fraction of 6 to 7.5 Gy were used. A smaller effect in the same direction was seen after 3.6 Gy per fraction.

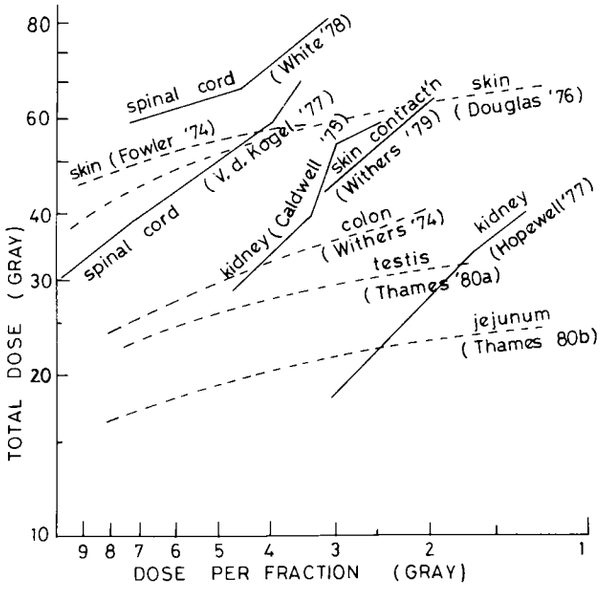

Fig. 3. The increase of total isoeffect dose as a function of decreasing doses per fraction, i.e. increasing number of fractions, for various normal-tissue reactions. The late reactions (—) show a steeper variation than the early reactions (– – –). From WITHERS et coll. (30).

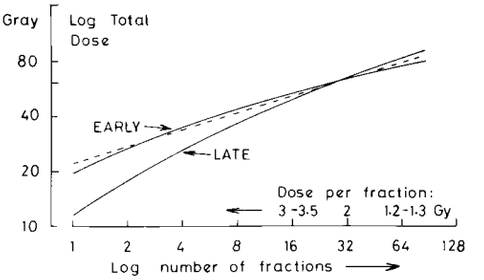

Fig. 4. The increase of total dose as a function of increasing number of fractions, or decreasing dose per fraction, for early as compared with late reactions in radiation therapy (schematic). The dotted line of slope 0.24 represents the NSD, TDF or CRE factor, which does not differ greatly from the true curve for early reactions in skin or mucosa over a limited range.

Animal experimental data

Fig. 3 shows curves of total dose versus fraction size or number, for many published animal experiments (30). It is obvious that the dotted lines (early effects) are less steep than the full lines (late effects).

Fig. 4 shows schematically the importance of this difference between late and early damage on a Strandqvist-type plot. A 30×2 Gy schedule is taken as the normalization schedule. Some obvious consequences apply:

(1) *A smaller number of larger fractions* would cause worse late damage if the early reactions are matched, as reported by SINGH (16).

(2) If late reactions are matched instead, the total dose must be reduced more than NSD or CRE would suggest, so that early reactions would be less severe, as indeed reported by BATES & PETERS (2). One then worries whether the tumour control would also be lower.

There is a region of clinical doubt—and hot debate—for more modest doses per fraction up to 3.5 or 4 Gy. In principle they should of course give worse late reactions for equal early reactions. In practice the difference from conventional fractionation may be too small to detect in clinical trials with realistic numbers of patients.

Indeed, if the overall time is shortened when a smaller than usual number of larger fractions are used, the shortening may provide some advantage in tumour control which would enable lower total doses to give tumour control so that worse late reactions could be avoided after all. The similar results obtained by HENK & JAMES (12) for 30 F/42 d and 10 F/22 d might be explained on this basis.

(3) If a *larger number of smaller fractions* is considered (Fig. 4, right part), then late injury should be spared if equal early reactions are achieved. This is one of the rationales for hyperfractionation. Alternatively, the total dose could be increased more than NSD or CRE would suggest to yield equal late damage but to cause more damage to early-reacting tissues, both tumours and normal tissues. This is the other potential advantage of hyperfractionation.

The prolongation of treatment is undesirable, because of rapid proliferation in some tumours (15, 17, 23, 24), so that the use of multiple fractions per day (MFD) becomes necessary in order to use hyperfractionation.

Effect of dose per fraction

Where proliferation differences can be neglected (i.e. short overall times or equal overall times in the schedules compared), the increase of total fractionated dose with fraction number defines the shape of the relevant dose–reponse curve. Fig. 5 shows the essential difference in shape between the dose–response curves for late and early reactions. The late reactions have a more curvy dose–response curve than the early reactions, which are straighter and are also steeper at very low doses per fraction. This

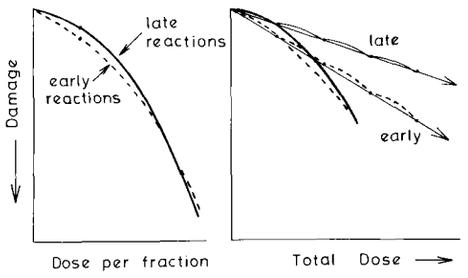

Fig. 5. The difference in shape between dose–response curves for early or late reactions, matched at 2 Gy per fraction. Smaller doses per fraction would require a larger increase of total dose for late than for early reactions.

Table 2

Ratio of linear to quadratic terms from multifraction animal experiments

	α/β (Gy)
Early reactions	
Skin	9–12
Jejunum	6–10
Colon	10–11
Testis	12–13
Callus	9–10
Late reactions	
Spinal cord	1.7–4.9
Kidney	1.0–3.5
Lung	2.4–6.3
Bladder	3.1–7

conclusion is unavoidable, whatever model is used for further analysis (8).

The use of the linear quadratic formula can be justified:

$$\text{Effect} = E = n(\alpha d + \beta d^2) \qquad (2)$$

where n is the number of fractions of size d each. Only two parameters, α and β, are required to describe the shape of this curve over the range of doses per fraction used in radiation therapy.

The ratio α/β has the dimensions of dose and gives the value of dose per fraction at which the linear (probably non-repairable) α-component of damage is equal to the dose-squared (repairable) β-component of damage:

$$\alpha d = \beta d^2 \quad \text{when} \quad d = \alpha/\beta \qquad (3)$$

A 'curvy' dose–response curve will obviously have a small value of α/β whilst a rather straight curve will have a large value of α/β. Thus the differences between early and late reactions shown in Figs 3 or 5 are well supported by the non-overlapping ranges of α/β values shown in Table 2, obtained from animal experiments. α/β is the same as BARENDSEN'S (1) ratio a_1/a_2 (Gy) and the inverse of THAMES' preferred ratio β/α (Gy^{-1}) which, as he points out, is larger if more repair is present.

α/β can be readily determined by plotting reciprocal total dose against dose per fraction (5), if isoeffect doses are known for several fractionation schedules (minimum of two schedules).

Table 3 shows that preliminary values for tumour α/β values are all high, like other fast proliferating tissues or even higher (28).

Applications

There are three applications of the linear quadratic model in fractionated radiation therapy. These applications should be tested out, using existing and future data. If they continue to be appropriate, then the model could be cautiously introduced in place of NSD, CRE, etc. The difference now known between early and late reactions already requires that NSD and CRE should be replaced, especially for late reactions.

Flexure dose. The dose per fraction at which the dose–response curve just begins to bend away from the straight initial region was called the 'flexure' dose by WITHERS (29). This is the dose per fraction down to which radiation therapy might have to go in order to gain the utmost sparing of late damage. A value of 0.1 α/β is a reasonable approximation to flexure dose (9, 25). The doses per fraction corresponding to 0.1 α/β would be as low as 0.2 to 0.6 Gy per fraction. There would however be no further sparing of acute reactions (including tumours) when doses per fraction lower than 0.8 to 1.5 Gy were used.

To estimate changes in total dose as size and number of fractions are changed. This estimate was the main purpose of NSD, CRE, etc. It should now be possible to do it better as follows. First, any change in overall time must be allowed for separately, as outlined in Table 1.

Then, from the linear quadratic model, the ratio of total doses in two schedules is simply:

$$\frac{\text{Total dose 2}}{\text{Total dose 1}} = \frac{n_2 d_2}{n_1 d_1} = \frac{1 + d_1 \cdot \beta/\alpha}{1 + d_2 \cdot \beta/\alpha} \qquad (4)$$

Table 3

Ratios of α/β for experimental mouse tumours. From WILLIAMS *et coll. (28), which contains full references*

Tumours	Assay	Clamped or miso	α/β (Gy)	Experimenters
C_3H mouse mammary carcinoma	Cure	Clamp	9–19	SUIT et coll. (1966–1977)
Mammary carcinoma and fibrosarcoma	Growth delay	Miso	16–32	DENEKAMP et coll. (1976–1979)
C_3H mammary carcinoma and carcinoma MT	Cure	Miso	12–26	FOWLER & SHELDON (1976–1978)
Adenocarcinoma, 284 and AT 17	Growth delay	Clamp	9–20	TROTT & KUMMERMEHR (1980–1982)

$$= \frac{\alpha/\beta + d_1}{\alpha/\beta + d_2} \qquad (5)$$

where d_1 and d_2 are the respective doses per fraction. Some examples are worked out in the Appendix and in the reviews by FOWLER (8) and BARENDSEN (1).

A conscious choice of α/β or β/a must be made for each tissue considered. Sometimes $\alpha/\beta=10$ Gy has been assumed for early reaction and $\alpha/\beta=3$ Gy for late reactions but rigidity must be avoided until more clinical data are available. It appears reasonable to assume $\alpha/\beta=2$ Gy for kidney or spinal cord damage but $\alpha/\beta=4$ Gy for pneumonitis. Similarly, $\alpha/\beta=8$ Gy might be assumed for other normal tissues and $\alpha/\beta=15$ Gy perhaps for tumours, although they are likely to be very variable (Table 3).

Acceleration versus hyperfractionation. The third application is important for radiotherapeutic strategy, especially in the selection of non-standard fractionation schedules. It was pointed out above that, to avoid prolongation, *hyperfractionation* requires the use of multiple fractions per day. If this logistical inconvenience can be overcome, there is another use for MFD: in *accelerated fractionation*, i.e. a conventional number and size of fractions given in a shorter overall time (19).

Whether it would be better to use hyperfractionation or accelerated fractionation, if one is considering a change to 2 fractions per day, can be calculated from data like those in Fig. 4, and by assuming various proliferation rates in the tumour. THAMES et coll. (20) have calculated that if the clonogenic cells in a tumour double in less than 5 days, then acceleration would give better results than hyperfractionation, in terms of tumour control compared with late complications. Values for α/β or 10 and 3 Gy respectively were assumed. A similar time of 5 days was found if 3 fractions per day were considered instead. Are there human tumours with cell number doubling times as short as this? The values of STEEL (17) suggest that there are (Table 4).

Such calculations emphasize the need for more information about the proliferation rates of cells in human tumours during treatment. Clearly we cannot be complacent about overall times as long as 6 weeks, or gaps in treatment, or delays in starting treatment. This is a challenge for the next decade.

Table 4

Proliferation factors in human tumours. From STEEL *(17)*

Type of tumour	No.	Volume doubling time (days)		Cell number doubling time (days)	Cell loss factor (per cent)
		Median	Range		
Colorectal carcinoma	56	90	60–170	3.1	96
Squamous cell carcinoma, head and neck	27	45	33–150	6.8	85
Undifferentiated bronchial carcinoma	55	90	40–160	2.5	97
Malignant melanoma	8	52	20–150	14	73
Sarcomas	101	39	16–78	23	40
Lymphomas	11	22	15–70	16	29
Childhood tumours	4	20		3.6	82

Conclusions

It is an interesting consequence of the smaller α/β values for late-reacting tissues that continuous low dose rate irradiations, obtained from interstitial implants, can give a notable shortening of overall time, from 6 weeks to about 1 week, with the same advantage as hyperfractionation in sparing late reactions.

Models for estimating total doses required to give equal effects when different fractionation schedules are used have evolved to the stage of using reasonable dose–response curves to represent the biologic effect of each fraction, plus a separate time factor.

ACKNOWLEDGEMENTS

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Appendix

Some sample calculations

(1) *To calculate the total dose $n_2 d_2$ which should give the same biologic effect as the known schedule $n_1 d_1$ given in the same overall time.* From eq. (5):

$$\frac{\text{Total dose 2}}{\text{Total dose 1}} = \frac{n_2 d_2}{n_1 d_1} = \frac{\alpha/\beta + d_1}{\alpha/\beta + d_2} \tag{5}$$

Let us use 32×2 Gy as the standard known treatment and calculate the new total dose and number of fractions if the dose per fraction is reduced to $n_2 = 1.2$ Gy.

(a) *For equal early damage, assume $\alpha/\beta = 10$ Gy.*

$$\frac{n_2 d_2}{n_1 d_1} = \frac{10+2}{10+1.2} = \frac{12}{11.2} = 1.071$$

Therefore the total dose should be increased by 7.1 per cent, to 68.54 Gy which requires 57.12 fractions.

(b) *For equal late damage assume $\alpha/\beta = 3$ Gy.*

$$\frac{n_2 d_2}{n_1 d_1} = \frac{3+2}{3+1.2} = \frac{5}{4.2} = 1.190$$

Therefore the total dose should be increased by 19%, to 76.16 Gy which would require 63.5 fractions. It should be noted that the acute reactions will now be more severe. However, if the increase of only 7.1 per cent were used as in (a), the late reactions would be less severe than in the standard schedule.

It is assumed that the effect of each dose fraction is identical in a given schedule, i.e. that there is neither failure of repair nor increase of radiation sensitivity as the schedule proceeds. This is a more severe limitation for acute than for late damage because reassortment is less likely to occur in the slowly reacting tissues.

It is also assumed that proliferation is either negligible or is equal in both schedules. Ideally, a certain equivalent dose should be subtracted from the total dose of the standard schedule to allow for proliferation, and another equivalent dose should be added to the new schedule after the calculation above. Data for these subtractions and additions will come from results like those in Table 1 but for human patients.

(2) *To calculate the dose per fraction d_2 which should be used to obtain the same biologic effect as the known schedule $n_1 d_1$ if the number of fractions is changed to n_2.*

$$\text{Effect of schedule 1} = E_1 = n_1 d_1 (\alpha + b d_1).$$

As an example let us carry out the calculation for equal *late* effects, i.e. assume $\alpha/\beta = 3$ Gy. Then

$$\text{Effect}_1 = n_1 d_1 \alpha_3 (1 + d_1 (\beta/\alpha)),$$

where α_3 is shorthand for indicating that a value of 3 Gy has been assumed for α/β.

Now if the standard schedule consists of $n_1 = 32$ and $d_1 = 2$ Gy,

$$\begin{aligned} \text{Effect}_1 &= 64\alpha_3(1+2/3) \\ E_1 &= 64 \times 1.667 \times \alpha_3 \quad \text{'damage units'} \\ E_1 &= 106.7 \quad \text{'}\alpha_3 \text{ damage units'} \end{aligned}$$

This amount of damage should be made equal in any new schedule. In the present calculation, assume that the number of fractions is being changed from $n_1 = 32$ to $n_2 = 20$ fractions. We want to compute the dose per fraction d_2 to use with the 20-fraction schedule. For equal late effects:

$$E_2 = 106.7\alpha_3 = n_2 d_2 \alpha_3 (1 + d_2(\beta/\alpha)),$$

still using the $\alpha/\beta = 3$ Gy value appropriate for late effects. Therefore

$$106.7\alpha_3 = 20 d_2 \alpha_3 (1 + d_2/3).$$

It is clear that α_3 can be cancelled from both sides. The equation can then be solved as a standard quadratic equation for d_2:

$$106.7 = 20 d_2 + (20/3) d_2^2$$

Dividing both sides by (20/3) and rearranging:

$$d_2^2 + \frac{20 \times 3}{20} \cdot d_2 - \frac{3 \times 106.7}{20} = 0$$

i.e.

$$d_2^2 + 3d_2 - 16.0 = 0$$

Hence

$$d_2 = \frac{-3 \pm \sqrt{3^2 + 4 \times 16}}{2}$$

$$d_2 = \frac{-3 \pm 8.544}{2}$$

Taking the positive root:

$$d_2 = 2.77 \text{ Gy}$$

A check calculation of $E_2 = 20 \times 2.77 \times \alpha_3 (1 + 2.77/3)$ yields the result 106.7 α_3 damage units which is correct. Thus the schedule 20×2.77 Gy should give the same

incidence of late complications as 32×2 Gy given in the same overall time, assuming α/β=3 Gy.

It should be noted that effect in α_3 damage units can be compared with or added to other α_3 damage units as long as α/β=3 Gy has been assumed for all the schedules compared. They cannot be compared with α_{10} damage units for example, which would be obtained if the calculations were repeated for equal early effects assuming α/β=10 Gy. Effects in α_{10} damage units however could be compared with each other for various schedules, provided that α/β=10 Gy was assumed for all of them.

For different overall times, the data in Table 1 should be considered, together with any data about human normal tissues that have emerged since the time of writing this. Overall time is expected to have little effect for late damage unless schedules are exceptionally prolonged. Overall time will however have a large effect on early damage for overall times longer than 4 weeks.

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