THE EFFECT OF ALTERED FRACTIONATION SCHEDULE ON THE SPINAL CORD RESPONSE: RADIOBIOLOGICAL CONSIDERATIONS

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ABSTRACT

Increased fractionation spares late reacting normal tissues more than acute reacting normal tissues. A linear quadratic model is valid from large dose per fraction down to dose per fraction of 2 Gy. Experimental studies on animals and clinical studies on the spinal cord tolerance have shown incidences of myelopathy at doses lower than 50 Gy. The α/β value of the linear quadratic model have been lower for low doses per fraction, indicating a sparing effect of altered fractionation for spinal cord myelitis. Animal data, clinical and radiobiological explanations suggest limitation of the radiobiological models. Further data suggest that one must not assume the spinal cord to have a greater tolerance at doses per fraction below the conventional dose per fraction of 2 Gy.

INTRODUCTION

In fractionated radiotherapy, the total dose required to induce a certain effect on the tissue, generally increases when the size of the dose per fraction decreases; this is due to recovery of sublethal damage during interval between irradiation.

There is evidence that late reacting normal tissue benefit relatively more from smaller fractions than rapidly proliferating tissues. From the studies of normal tissue which have been reported so far, it can be concluded that the dose fractionation response is described accurately by the Linear Quadratic (LQ) model over the radiation dose range from large single doses down to dose per fraction of about 2 Gy.

Below 2 Gy per fraction, the limited data from literature have been controversial and cast some doubt on the validity as well as the applicability of the LQ model. For late normal tissue damage the reported values for α/β are quite small, indicating a large capacity for repairing sublethal damage.

The introduction of altered fractionation schedules in clinical radiotherapy is an example of how contributions from radiobiological research and clinical observations can lead to the development of novel treatment strategies. The observations that tissues with different turnover kinetics respond differently to changes in dose fractionation and protection of radiotherapy form the basis of attempting to improve outcome by altering radiotherapy schedules.

The two basic approaches that offer the prospects of some improvement in the therapeutic ratio between tumour control and late complications are:

a. Accelerated fractionation, for which the overall time of treatment is signifycantly reduced, while the dose per fraction and the total dose are slightly reduced compared with the conventional schedule.
b. Hyperfractionation, by using a dose per fraction smaller than that employed in a conventional schedule without changing the overall treatment time, which results in an increased total dose. Although the rationale is different, it is necessary to deliver several treatments per day with both strategies.

Information on the rate of repair in various tissues is, therefore, essential for se-

lecting an appropriate interval between radiation doses in specific situations. In order to accommodate such a requirement in a clinical department the interval between fractions has been reduced from the conventional 24 hrs to no more than 3-6 hrs, depending on the type of treatment schedule employed.

These logistic constraints may jeopardise the potential benefit of altered fractionation schedules if they compromise the normal tissue tolerance with a larger extent than they affect tumour control probability because of incomplete repair between fractions.

Radiation myelopathy is one of the devastating complications of clinical radiotherapy. The spinal cord is, therefore, one of the major dose limiting organs in clinical radiotherapy. Indeed, a number of patients have recently been reported to have developed radiation myelopathy following hyperfractionated accelerated radiotherapy (Dische and Saunders [5], Dische [6], Jeremic et al. [8]). In view of the current interest in hyperfractionation and accelerated fractionation, and increasing application of the LQ model to clinical radiotherapy, further data are clearly desirable. This review presents the experimental, radiobiological and clinical aspects of radiation myelopathy for altered fractionation schedules.

Linear Quadratic model for multiple daily fractionation

Dale [4] has further applied the LQ equation to fractionated radiotherapy when there is incomplete normal tissue recovery between fractions, and possible implication for treatment involving multiple fractions a day. He derived a general equation for RE for fractions of dose d, each fraction given after a time interval of x hr:

$$Re = 1 + (\beta/\alpha)\,(d/n)\,[\{n(1-k^2) - 2k\,(1-k^n)\}\,/\,(1-k)^2],$$

where $k = \exp(-\mu x) = e^{(-\mu x)}$

Thames [13] has proposed an incomplete repair model for multiple fractions a day as:

$$TE = (\alpha/\beta + d + d * h_m) * D,$$

where h_m is the incomplete repair factor, the values of h_m for two and three fractions a day having been tabulated.

Supe [12] has derived RE equations for 2 and 3 fractions per day as

$$RE_2 = 1 + d(\beta/\alpha)\,(1 + e^{(-\mu x)}),$$

$$RE_3 = 1 + d(\beta/\alpha)\,(d/3)\,(3+4\,e^{(-\mu x)} + 2\,e^{(-2\mu x)}).$$

Ang [2] has commented on the lack of evidence for increased tolerance of rat spinal cord with decreasing fraction doses below 2 Gy. Rats were irradiated with 18 MV photons for the cervical spinal cord. To assess the effect of small radiation doses, on the spinal cord, four fraction sizes of 1.3 Gy,1.5 Gy, 1.8Gy and 2 Gy were investigated. A constant top up dose of 15 Gy was given. The overall treatment time was kept between 6 to 8 weeks. The percentage of animals in each dose group that developed white matter necrosis was used for constructing dose response curves from which the ED_{50} values were calculated by probit analysis. The isoeffect doses as a function of dose per fraction, as predicated by Ellis type isoeffect formula as well as Linear Quadratic (LQ) model and results of Ang's study, are summarized in *Table 1*.

Table 1. ED_{50} at different fraction sizes.

Dose per fraction (Gy/fr.)	2	1.8	1.5	1.3
Ang	70	62.2	68.8	<75
Prediction by formula $DN^{0.43}$	76	83	95	105
Prediction by LQ model (α/β) 1.7Gy	72	76	84	89

Both the Ellis type formula and the LQ model predict a continuously increasing tolerance dose with decreasing fraction size. A consequence of the present finding would be a cautious use of alpha/beta ratios for predicting isoeffect doses at fraction size smaller than those which experimental and clinical data can predict.

Van der Schueren et al. [15] has showed the influence of reducing the dose per fraction from 2 Gy down to 1 Gy on the radiation response of the rat cervical spinal cord. The radiation treatments were carried out with 18 MV photons. A constant top up dose of 15 Gy was delivered, the total treatment time being 4-6 weeks. The end-point of the experiments was foreleg paralysis due to demyelination and white matter necrosis. The ED_{50} values were calculated by a probit analysis. Experimental ED_{50} values along with predictions of the LQ model are shown in *Table 2*.

Table 2. ED_{50} (Gy) for rat cervical spinal cord.

(Dose per fraction (Gy/fr.))	2	1.8	1.5	1.3	1.0
Exp.data	140	124.4	137.6	<150	159.1
Estimations LQ model (α/β = 1.7 Gy)	-	148.5	162.4	173.3	192.5

Small but probably significant rise in tolerance was suggested, when the dose per fraction was decreased from 2 Gy to 1 Gy. This rise would now be still much less than that predicted by the LQ model, based on the experimental data obtained from fraction sizes larger than 2 Gy. The repair of sublethal radiation damage in the rat spinal cord in hyperfractionation experiments is incomplete for the dose per fraction between 2 Gy and 1 Gy.

Lavey et al. [9] has undertaken a study to determine the extent to which hyperfractionation may spare the spinal cord as well as increase the latent period for the development of transverse myelitis. The spinal cord of mice was irradiated with a conventionally fractionated regimen of 2 Gy once daily or a hyperfractionated regimen of 1.2 Gy twice daily separated by 8 hrs. A top up dose of 15 Gy was given.

Overall, the spinal cord was not spared by hyperfractionation to the extent predicted by the Ellis or LQ model. The threshold dose was higher in the hyperfractionated than in the conventionally fractionated group. The latent period and ED_{50} did not significantly differ between the two regimens.

The continuation of the process of sublethal damage repair in the spinal cord beyond 8 hrs after irradiation may have influenced these results. The slow component of SLD repair should be considered in the design of hyperfractionated or accelerated radiation therapy schedules for clinical use.

Data from the mouse and the rat as well as human clinical trials do not support the use of hyperfractionated radiation schedules with short interfraction intervals aimed at delivering higher doses to the spinal cord than would otherwise be considered safe with conventional fractionation. Additional work is required to confirm the suggestion that hyperfractionation significantly increases the threshold dose for the induction of radiation myelitis.

Niewald et al. [10] has examined in rats whether the radiation tolerance of the spinal cord is enhanced by using hyperfractionated radiotherapy compared with a conventional schedule. Cervical spinal cords of 276 healthy rats were irradiated over 6 weeks hyperfractionally with single doses, varying from 0.75-2.5 Gy up to total doses ranging from 45-150 Gy (66 fra-

ctions) and conventionally with single doses of 1.5-4.0 Gy up to total doses of 45-120 Gy (30 fractions). The rats were examined neurologically and were sacrificed when paralysis of the hind leg occurred. After fixation the spinal cord was removed and examined histologically. Dose effect relationship and latency from the beginning of radiotherapy to the onset of paralysis were computed and analysed using a multivariate logistic regression model. The model fitted the data excellently *(Table 3).*

Table 3. Rate of myelopathy for conventional fractionation and hyperfractionation.

Dose (Gy)	Rate of myelopathy	
	Conventional fractionation	Hyperfractionation
45.0	0.00	0.00
52.5	0.00	-
60.0	0.18	0.11
67.5	0.00	-
75.0	0.82	0.22
82.5	0.75	0.10
90.0	1.00	0.40
97.5	1.00	0.20
105.0	-	1.00
120.0	-	1.00
135.0	-	1.00
150.0	-	1.00

There were highly significant results both for the dose level and for the treatment regimen. A latency analysis showed earlier and more intense acute side effects after hyperfractionation, but radiomyelopathy occurred markedly later.

These results show that, compared with conventional fractionation, a distinctly higher dose of 28% could be applied using hyperfractionated radiotherapy at the 50% level of damage; at the 5% level of damage a 39% higher dose could be applied. This finding fits well with that of the literature. For experimental purposes these values seem suitable. The sparing effect of hyperfractionation on the spinal cord as predicted by radiobiologists was confirmed. Thus it seems possible to escalate tumour doses using hyperfractionation without an enhanced risk to late responding tissues.

Dependence of LQ model parameters on dose per fraction

Ang et al. [3] investigated the possible dependency of the kinetics of repair of the sublethal damage in the rat spinal cord on the fraction size. A wide range of doses per fraction (1.5-17.5 Gy) was given, with interfraction interval varying from 0.5 to 24 hrs. A direct method for the analysis of quantal response and an incomplete repair model for survival after fractionated exposures with shorter intervals were used to interpret the data *(Table 4).* There appeared to be no signifycant effect of fraction size on the rate of repair.

Table 4. Effect of fraction size on repair kinetics.

Dose/fr (Gy)	α/β (Gy)	$T_{1/2}$ (hr)
1.7 – 5.1	2.7	1.6
6.2 – 12	2.0	1.6
11.5 – 17.5	2.7	1.9

Another feature in the analysis of results is that the alpha/beta determined from the complete repair data (1.7 Gy) is considerably smaller than that estimated from the incomplete repair data (4.3 Gy).

Wong [18] has described results of a series of experiments which were designed to assess the radiation response of the spinal cord at fraction sizes down to 0.55 Gy given once daily. All irradiation were carried out with 100 kV X rays. For the cervical spinal cord, alpha/beta values were evaluated for three dose per fraction ranges as shown in *Table 5.*

Table 5. Alpha/beta values for different dose per fractions.

Dose / fr (Gy)	α/β (Gy)
25.0 – 1.98	2.41
10.0 – 1.64	3.41
1.60 – 0.55	0.48

The LQ model based on the large dose per fraction data underestimates the sparing effects of small doses per fraction, provided sufficient time is allowed between each fraction for repair of the sublethal damage.

Wong [17] has commented on the response of the rat spinal cord to very small doses per fraction. The rat spinal cord was irradiated with a top up dose of three daily doses of 10.25 Gy, followed by graded single doses or fractionated doses. The endpoint was forelimb paralysis secondary to white matter necrosis confirmed histologically. Alpha/beta values were evaluated for two dose per fraction ranges *(Table 6)*. The study provided no evidence for of an increase in the radiosensitivity of the rat spinal cord below 1 Gy down to 0.4 Gy per fraction.

Table 6. Alpha/beta values for different dose per fraction.

Dose / fr (Gy)	α/β (Gy)
1.79 – 25.0	2.46
0.41 – 1.78	1.50

Thames [14] has commented on whether incomplete repair explains the apparent failure of the basic LQ model to predict spinal cord and kidney responses to low fraction doses. His findings are given in *Table 7*.

Table 7. Repair capacity and kinetics after multiple day experiments.

	Spinal cord
10 alpha (Gy^{-1})	0.70
100 beta (Gy^{-2})	2.60
Alpha / Beta (Gy)	2.7
$T_{1/2}$ (hr)	1.64

For the spinal cord, the data could be interpreted by assuming that the repair process with a half time of 1.7 hrs was incomplete. This half time is negligibly different from the estimate obtained from repair kinetics experiments with a larger dose per fraction. The clinical implications could be that multiple fractions per day treatment would benefit from the use of the largest feasible interfraction interval when late reactions are dose limiting.

The sparing effects of hyperfractionation on the spinal cord, as predicted by radiobiologists, could be confirmed by this experiment. Thus it seems possible to escalate tumour doses using hyperfractionation without an enhanced risk to the spinal cord but with higher probability of tumour cure.

Radiobiological explanation for spinal cord myelitis in clinical radiotherapy

Jeremic [8] has investigated whether the thoracic spinal cord dose of 50.4 Gy given via 1.2 Gy per fraction, two fractions per day, carries a risk of developing radiation myelitis in studies using hyperfractionated radiation therapy with and without concurrent chemotherapy. Three hundred patients with stage III non-small cell lung cancer (NSCLC) were treated on in two consecutive phase II studies, 158 patients received 50.4 Gy to a portion of their spinal cord and survived >1 year after the beginning of the therapy. The interfraction interval varied from 4.5 to 6.0 hrs Therefore the influence of potentially contributing factors on the occurrence of radiation myelitis, such as interfraction interval or those unproven yet such as cord length or administration of concurrent chemotherapy, could not be determined. Given the continuing interest in HFX RT and encouraging results obtained in studies on lung cancer, further investigation is needed to get more information about the risk of developing thoracic radiation myelitis with this cord dose.

Dische [5] has published an interim report upon late morbidity for continuous, hyperfractionated accelerated radiotherapy (CHART). 206 patients of advanced head and neck cancer received either a total dose of 50.4 Gy at dose per fraction of 1.4 Gy, or 54 Gy at dose per fraction of 1.5 Gy (3 fr/day with 6 hrs interval). Employing the alpha/beta ratio of 2.5, a dose increment of 1.5 Gy and a total dose of 42 Gy, the LQ equation gives a result of 64.2 alpha damage units, and this can be compared with 72 alpha damage units for 40 Gy given in 2 Gy increments.

With a small dose increment and a limited total dose of radiation in the CHART regime there seemed to be a good reserve of tolerance in the spinal cord. It is of relevance that there are uncertainties as to the existence of further sparing below a dose per fraction of 2 Gy.

In general, the impression that late damage with smaller fractions is lower than that after conventional radiotherapy is sustained. Two patients who developed myelitis presented with advanced tumours which responded well. A modification to avoid myelitis is essential as is also the pursuits of CHART as part of the effort to improve tumour control by modification of the programming of radiotherapy.

Radiobiological explanation for spinal cord myelitis in clinical radiotherapy

Guttenberger [7] has introduced a new incomplete repair model by assuming that repair is complete during long intervals, e.g. overnight intervals of 12-24 hrs. The model was used to assess the risk of myelopathy resulting from continuous hyperfractionated accelerated radiotherapy (CHART) in the light of recent experimental data on the rat spinal cord. Computer simulations were carried out using alpha/beta of 2 Gy. Model calculations employing an incomplete repair model and bi-exponential repair kinetics showed that the CHART treatments might result in a higher myelopathy risk than an equal dose given in conventional 2 Gy fractions if the parameters obtained from the animal data hold. From computer simulations a myelopathy risk of approximately 0.3-1.2% is predicted for the currently employed maximum CHART dose to the spinal cord, i.e. 42 Gy.

The CHART experience is not compatible with the new experimental data. Incomplete repair is unlikely to be the sole reason for the unexpected toxicity of CHART. However the compounding effect of incomplete repair could be minimised by rearranging the modified CHART schedule which would result in an increase of the tolerance dose by approximately 10%.

Wong [16] has offered a radiobiological interpretation of meylopathy in hyperfractionated accelerated radiotherapy. From 1975 to 1982, 32 patients with a diagnosis of anaplastic carcinoma of the thy-

roid were entered into a protocol of hyperfractionated accelerated radiotherapy. The tumour dose was 35-40 Gy at 1 Gy per fraction given 4 times a day at 3 hr intervals. Two patients developed radiation myelopathy at 8 and 13 months, total spinal cord doses being 39.9 and 48.3 Gy, respectively. The risk of spinal cord damage was much higher than expected.

The spinal cord doses for patients with myelopathy were 5 Gy + 35Gy/ 35 fr/ 11 days, gap 21 days, 5 Gy + 45 Gy/ 45 fr/ 16 days, gap of 13 days. Neurological symptoms indicated that the two patients had myelopathy. The neurological symptoms and signs were consistent with the anatomic level of the spinal cord irradiated.

The spinal cord doses of the two patients were recalculated using the incomplete repair model described by Thames [14]. Dose equivalent in alpha damage units was calculated using an alpha/beta ratio of 2,3 and 4 Gy and repair half time of 1.5, 2 and 3 hr. As a consequence of the shortened interfraction interval, the incomplete repair model seems to increase the radiation effects in terms of alpha damage units by 7% using a repair half time of 1.5 hr and as much as 35% with the repair half time of 3 hr. When the accepted spinal cord tolerance, i.e., 50 Gy in 2 Gy daily fractions, was compared with the two cases in terms of alpha damage units, even corrected for the lack of incomplete repair, case 1 in fact received a dose well below what is generally accepted to be the tolerance dose for the spinal cord, and case 2 received a cord dose approaching the cord tolerance using the repair half time of 1.5 hr and 2 hr, respectively. When the repair half time of 3 hr was used in the calculations the cord dose exceeded the cord tolerance. This repair time is much greater than the values obtained from the spinal cord.

In the continuous hyperfractionated accelerated radiotherapy (CHART) regime at the Mount Vernon Hospital, Middlesex, England, there have been four cases of radiation myelopathy with doses of 46.0, 45.2, 48.3 and 46.6 Gy. All 6 patients developed radiation myelopathy at the spinal cord doses which were considered to be well within the spinal cord tolerance. There was no apparent explanation for the spinal cord damage seen. These cases, therefore, raise serious concerns about the underlying radiobiological model upon which these altered fractionation schemes are based.

To conclude, observations of 6 myelopathy cases in patients treated with hyperfractionated accelerated radiotherapy and recent animal data both suggest limitations of the LQ or IR model and indicate that these models should be used with caution to predict spinal cord tolerance doses for altered fractionation regimens in clinical radiotherapy.

CONCLUSION

Currently accepted practice regarding radiation doses delivered incidentally to the spinal cord is evidence of more radiation oncologists' intolerance of radiation myelopathy than of the spinal cord's intolerance to radiation. Furthermore, excessive dependence upon published or personal anecdotes has generated a myth that has moved the discussion of the spinal cord response away from scientific dialogue towards catechisms.

We must be cautious in the interpretation of clinical reports where there is a low incidence of complication of treatment, for there is always a possibility of technical error, complicating factor and unusual sensitivity. Radiation myelopathy is, however, a most serious occurrence following radiotherapy and even a low incidence associated with a new regime must be carefully considered.

The rare myelopathies that occur at low doses (<=45 Gy) are seen for three reasons:

a. Extrinsic factors reduce some individual's radiation tolerance,
c. Tens of thousands of patients are irradiated annually at these doses, and
c. The true dose was larger than that estimated.

The clinical observations have also underscored the importance of obtaining radiobiological data in clinically relevant dose fractionation schemes to confirm or refute predictions from biological models. The ultimate test for the validity of a biolo-

gical model are, however, clinical observations.

However, the final model is the patient undergoing radiotherapy and this experience underlines the need for a very careful observation of patients entered into clinical trials of methods to improve the effectiveness of treatment. Normal tissue effects must be observed with the same meticulous care given to tumour control. It is most important that promising methods for improvement of tumour control must be abandoned because of such problems.

Knowledge gained from the laboratory and the clinic must be applied to the preventional morbidity and advance in management.

Recent evidence has indicated that the isoeffect dose for the spinal cord may be overestimated for fraction sizes as small as 1 or 2 Gy, when calculated for the Linear-Quadratic (LQ) model fitted to the data obtained from fractions larger than 2 Gy. Reasons for this are unknown, but possible interpretations include exhaustion of repair capacity and incomplete repair in experiments designed to study the response to these small doses [1].

Furthermore, further data suggest otherwise, in view of the devasting effect of radiation myelopathy, that one must not assume the spinal cord to have a greater tolerance at fraction sizes below 1.8 to 2 Gy.

Further experimental data are desirable to confirm the validity of the LQ model at small doses per fraction and to characterize the repair kinetics at small doses per fraction.

At present, in clinical protocols of multiple daily fractions, it is essential to space the fractions interfraction interval as (as long as) possible. In view of the devasting effect of radiation myelopathy, repair of sublethal damage in the spinal cord or central nervous system cannot be regarded to be complete even after an interfraction interval of 8 hr. The repair kinetics in the spinal cord is slower than previously anticipated. Therefore there is no rationale to use interfraction intervals <6hr.

The appearance of radiation myelitis in patients receiving accelerated radiotherapy has led to further laboratory experiments, particularly those with a view to determining the half time of repair in neural tissues. Experiments suggest that there may be a component of repair in nervous tissues which may exceed 4 hours. Such a component must be expected to increase the risk of radiation injury when two or more fractions are given each day. When the half time of repair exceeds 4 hr, even an extension of the interval between treatments to 8 hr, will still leave a considerable element of non-repaired damage, and if all treatments are given as in CHART over a continuous 12 day period, there will also be an accumulation of non-repaired damage at the end of each treatment day.

The evidence now available suggests that in accelerated treatment, sparing of late damage in the spinal cord with the use of hyperfractionation does not occur and that when equal doses are given, it is increased. Mathematical models based upon the analysis of laboratory and clinical data are extremely important in advancing our knowledge.

It is unfortunate that the standard practice for listing incidental doses to the spinal cord is determined more by litigation than by clinical judgement. Tumouricidal doses should never be compromised for the purpose of limiting the cord dose to 45 Gy.

Limiting the cord dose to 45 Gy in a hyperfractionation schedule leads to even greater likelihood of compromising the tumour dose. Many credible experts have recommended 50 Gy in 2 Gy fractions as an acceptable spinal cord dose and this recommendation is probably conservative.

Even higher doses could be given if the clinical situation requires them and the patient is properly informed of the risk and the consequences of myelopathy. It is not by limiting the spinal cord dose that the incidence of myelopathy should be reduced, but rather by determining what factors in the patient's medical history and physical status make the spinal cord more sensitive than expected. By controlling excessive risk factors, myelopathies can be kept to a minimum and the tumour dose can be prescribed to suit the disease.

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