

RADIOBIOLOGICAL CONSIDERATIONS OF RE-IRRADIATION TOLERANCE OF THE SPINAL CORD

Sanjay S. Supe¹, K.M. Ganesh², J. Velmurugan³, B.S. Rana⁴, B.N. Sankar⁵

¹ Dept. of Radiation Physics, K.M.I.O., Bangalore

² M.S. Ramaiah Medical College Hospital, Bangalore

³ Dept. of Radiotherapy, K.M.C., Manipal

⁴ Manipal Goa Cancer Hospital, Goa

⁵ Dept. of Physics, Anna University, Chennai

Received May 10th, 2001; received in a revised form January 3rd 2002; accepted February 12th 2002

ABSTRACT

Re-irradiation tolerance of the spinal cord depends upon the volume of the spinal cord irradiated, the total dose, the dose per fractional, the elapsed time between the treatments and the region of the spinal cord involved. Clinical data on the retreatment tolerance of the spinal cord are sparse and inconclusive. Radiobiological laboratory evidence has indicated the presence of long term recovery of the spinal cord damage. Fractionation sensitivity during reirradiation is comparable with the first session of radiation treatment. After an initial dose of 45 Gy, 50% recovery has been reported by Schultheiss and Stephens for an elapsed period of two years for re-irradiation considerations.

INTRODUCTION

The spinal cord is a major dose limiting organ in radiotherapy. Injury to it results in a devastating functional deficit manifested one to several years after treatment. Recently, knowledge of radiobiology as applied to dose fractionation schedules has provided useful guidelines so that a radiation oncologist can now limit the spinal cord dose to levels which practically eliminate the occurrence of this complication.

As the survival rates of patients with various tumours increase, radiation oncologists are more frequently faced with the problem of treatment of late recurrences or second tumours situated within or close to a previously treated site. A rationale for treatment decision under such conditions is even more complex than under the original conditions and requires knowledge of the kinetics of the decay of occult injury from the previous treatment.

The radiation oncologist contemplating the retreatment of a site such as the neck or thorax within which the spinal cord has previously been irradiated is faced with serious medical and legal considerations. Past treatment history such as the volume

of spinal cord irradiated, the total dose, the dose per fraction, the length of the elapsed time since radiation exposure and the spinal cord region should help in the decision making process.

To change the conservative treatment attitudes and practices, what is necessary in clinical radiotherapy is laboratory and clinical evidence. Decisions whether to re-irradiate the spinal cord are often based on anecdotal reports in the literature, and on the legal consequences of treatment decisions resulting in myelopathy.

If treatment to the spinal cord is too conservative, a less than optimum tumour dose and diminished probability of local tumour control may result. Thus the question is primarily, if a higher tumour dose is worth the increased risk of myelopathy in clinical situations. Since radiation myelopathy is the most catastrophic late consequence of radiotherapy, clinicians usually err on the side of conservatism when the spinal cord is within the treatment volume.

Clinical data on the retreatment tolerances of the spinal cord are sparse, being generally limited to case reports. Whether the human spinal cord has the ability for long term recovery of radiation injury is also unclear. To date, deci-

sions regarding retreatment tolerance of the spinal cord have largely been made empirically.

In the experimental literature, there is now accumulating evidence to support the presence of time-dependent long-term recovery of radiation damage to the spinal cord, with the rat spinal cord being the most common animal model studied. Early data using split doses and more recent data using fractionated doses have revealed a significant long term recovery of the radiation damage in the rat, mouse, guinea pig and monkey spinal cord.

This review describes the experimental, radiobiological and clinical considerations of re-irradiation tolerance of the spinal cord.

Radiobiological Evidence

Ruifrok et al [6] performed experiments to investigate whether the fractionation sensitivity in the rat spinal cord is changed during radiation treatment. All rats received the first irradiation dose of 15 Gy. A second course of irradiation was given either on day one (control) or 6 months after the first dose with a single dose or fractionated treatments, with fraction sizes of 3, 4 and 6 Gy. The latent time for the development of paresis, ED₅₀ values and alpha/beta values for various dose schedules are given in table I. Following irradiation 6 months after the first dose, the latent times are shortened by about 1-2 months compared with latency after control treatments. ED₅₀ values were also higher for re-irradiation after 6 month interval. There was no significant difference in the alpha/beta value. After a six month interval, the long term recovery from the first treatment was about 45%.

Ruifrok et al [5] investigated the dose dependence and time course of long term recovery in the cervical spinal cord of rats. The single dose ED₅₀ for white matter mediated paresis was about 21 Gy in 3 week old as well as adult rats, although latency to paresis development increased from about 90 days in 3-week-old rats to about 250 days in adult rats. The main long term recovery was seen during the first month after the initial radiation treatment after 3 weeks.

This is in contrast to the long term recovery in adult rats, in which the main recovery took place between 2 and 6 months after the first irradiation. Calculations according to the incomplete repair (IR) model showed that the extra dose given to the cervical spinal cord after a 1-6 months interval, a 3-week-old rat recovers a maximum of about 20% of the total biological effect resulting in paresis.

In adult rats the extra dose that can be given to the cervical spinal cord after a 6- month interval represents about 40% of the total biological effect. These studies show that the time course, as well as the extent of long-term recovery from radiation treatment, not only depend on tissue and species, but also on age.

Wong et al [12] performed experiments to assess the re-irradiation fractionation sensitivity of the rat cervical spinal cord. Initially animals were given three daily fractions of 9 Gy, representing 75% of tolerance at the ED₅₀ level. After an interval of 20 weeks, they were re-irradiated with graded doses of X-rays in single, 2, 5, 10 and 20 daily fractions or a single retreatment top up of 12.5 Gy (equivalent) to 80% of retreatment tolerance, followed by doses in 1, 2, 4, 10 and 20 daily fractions.

The latent periods for forelimb paralysis ranged from 189 to 245 days from the day of the initial treatment, or 49 to 105 days from the day of re-treatment. For animals retreated with an initial top-up dose followed by smaller fractions, the latent times were similar, ranging from 188 to 233 days from the day of the initial treatment.

The direct fit of the LQ model gave similar alpha/beta values of 3.07 Gy and 3.34 Gy for the retreatment experiments without and with top-up doses. The fractionation sensitivity during retreatment compares well with that of previously non-irradiated animals, alpha/beta value of 2.41 Gy for fraction sizes down to 2 Gy/fraction. Following both initial fractionation schedules, the retreatment ED₅₀ values were both 58% of ERD, i.e. 42% of the initial damage was recovered by 20 weeks. The previous radiation damage to a level of 75% tolerance dose does not change the capacity for repair of damage when the spinal cord is re-irradiated with fractionated X-ray dose after 20 weeks.

Wong [11] investigated the influence of the level of the initial radiation damage on the long-term recovery and re-irradiation tolerance in the rat spinal cord. Rats were initially irradiated with 0, 10, 20, 30, 36 daily fractions of 2.15 Gy. After an interval of 20 weeks, retreatment with graded single doses of X-rays was given.

Latent times to paralysis were inversely proportional to the level of the initial injury and retreatment doses. The retreatment ED₅₀ were 19.0, 17.0, 15.7, 14.0 and 11.8 Gy. Using the ERD concept, alpha/beta of 3.0 Gy, the retreatment ED₅₀ in percentage ERD were 81, 70, 58 and 42% after the initial doses of 25, 50, 75 and 90% ERD, respectively.

The level of the initial injury appeared to influence the proportion of the residual injury. For an initial injury of 25% and 90% ERD, the residual injury was 74% and 65% of the initial damage. For an initial injury of 50% and 75%, the residual injury decreased to 59% and 57%, respectively. It is concluded that there was a significant long term recovery in the rat spinal cord, and the level of the initial radiation damage influenced both the retreatment tolerance and the time of expression of injury.

Ang et al [1] designed a study to assess the tolerance of the cervical spinal cord of Rhesus monkeys to reirradiation. Control animals received a single course of treatment to a total dose of 70.4 Gy, 77.0 Gy or 83.6 Gy in daily fractions of 2.2 Gy. Twelve asymptomatic animals that received 70.4 Gy were irradiated two years later to cumulative doses of 83.6, 92.4 or 101.2 Gy. Another group of 15 animals received 44 Gy and 2 years later were reirradiated to cumulative doses of 83.6, 92.4, 101.2 or 110 Gy. The clinical endpoint was myeloparesis. The ED₅₀ values of the single course irradiation was 76.1 +/- 1.9 Gy, while the extrapolated ED₅₀ for retreatment after 44 Gy was \geq 110 Gy.

Substantial recovery of occult injuries induced by initial 44 Gy had occurred within two years. The difference between the type of lesions observed after a single vascular injury may recover less efficiently or at a slower rate than white matter damage.

Mason et al [4] assessed various factors affecting the tolerance of the spinal cord

to irradiation using a guinea pig model of lumbar myelopathy. A 3cm section of the lumbar spinal cord of guinea pigs was irradiated with fractionated doses of 4.5 Gy given as 5 fractions per week. Guinea pigs were primed with 9 x 4.5 Gy in 7 days, which constitutes 60% of the ED₅₀ for a continuous course of treatment. After 28 or 40 weeks, animals were retreated with 6-14 fractions of 4.5 Gy. Twenty-eight or 40 weeks after 9 x 4.5 Gy only about 8% of the initial injury was remembered.

The amount of the residual injury was dependent on the initial damage in proportion to the tolerance doses. The spinal cord shows a greater capacity for long-term recovery than it is generally appreciated and re-treatment doses clinically prescribed may be lower than necessary.

Lavey et al [3] designed an experiment to assess the influence of the fraction size and time interval between fractions on the tolerance of the spinal cord to high cumulative doses of radiation and the influence of the long term recovery process on the tolerance of the spinal cord to reirradiation. The spinal cord of mice was irradiated using a conventionally fractionated regimen of 2.2 Gy once daily, a prolonged fractionated regimen of 1.2 Gy once daily, a hyperfractionated regimen of 1.2 Gy twice daily, and a single dose of 12 Gy followed 0 - 190 days later by a second dose of 5 - 20 Gy. Mice in the multi fractionated regimen group were given a single 15 Gy top up dose 24 hrs after receiving a cumulative fractionated dose of 24 - 70 Gy. The residual from a simple 12 Gy radiation dose was 17% after 190 days, leaving the retreatment ED₅₀ only 10% below the ED₅₀ of the previously non-irradiated spinal cord.

Wong and Hao [10] aimed to assess the influence of the level of initial injury on the long-term recovery kinetics of radiation damage in the central nervous system using a rat spinal cord model. The adult spinal cord was initially given two or three daily fractions of 3 Gy or three daily fractions of 10.25 Gy. On day 4 of week 6, 8, 12, 20, 28, 40, 52 animals were re-irradiated with graded single doses of X-rays. The endpoint was forelimb paralysis caused by white matter necrosis.

The latent time to paralysis increased with increasing time interval between the initial treatment and re-irradiation, but decreased with increasing the size of initial injury. No significant increase in tolerance was observed for retreatment given within 8 weeks of initial treatment.

A significant long-term recovery was observed thereafter and it increased with increased time interval to retreatment. The retreatment tolerance and radiation damage recovered at different intervals were influenced by the initial dose.

Using a direct analysis the recovery kinetics could be well described by introducing a time function consisting of a linear and quadratic time component dependent on the initial dose in the LQ model.

Clinical Evidence

Tan and Khor [8] have reported a series of retreatment cases with the spinal cord in both treatments. Their treatment for the carcinoma of the nasopharynx was 5500 r through two lateral and an anterior facial field to the post nasal space, given over a 6-7 week period as five treatments per week. The spinal cord received about 4000 r. In 22 cases, a second full course was given within a few months to 4 years after the first treatment. Three cases of radiation myelopathy occurred, two of which are reported in detail. The intervals between treatments for the two reported cases were 8 and 52 months. The survival data of the non-myelopathy cases were not reported.

To assess the latent time, survival and dose fractionation factors associated with permanent radiation myelopathy following single and multiple courses of radiotherapy to the spinal cord, a retrospective analysis was undertaken of all patients who were registered at the Princess Margaret Hospital between 1955 and 1985 and who developed permanent radiation myelopathy [9]. Twenty-four patients developed permanent myelopathy after one course of radiation and 11 patients following retreatment.

Latent times for myelopathy following a single course of treatment (18.5 months) were significantly longer than those after re-irradiation (11.4 months). There was not

a single incident of myelopathy in patients who received fractionated radiotherapy given once daily to an ERD of 100 Gy₂ (equivalent to 50 Gy in 25 daily fraction).

Four patients who developed myelopathy after an ERD of < 100 Gy₂ were all treated according to accelerated fractionation protocols. Patients who were re-irradiated received significantly higher doses (ERD 148 Gy₂) than those who had a single course of treatment (ERD 121 Gy₂).

The risk of myelopathy with conventional fractionation is extremely small: multiple fractions per day reduce the spinal cord tolerance, the latent time to myelopathy decreases following re-treatment, and there is a possible long-term recovery of radiation damage in the human spinal cord.

CONCLUSION

In summary, recovery from initial damage has been well proven. The amount of recovery seems to be influenced by different factors, mainly the initial damage expressed as the percentage of the cord tolerance. The interval between the first treatment and retreatment is probably also important.

The real total tolerance of the spinal cord may be about 130% of the tolerance dose for the first treatment as estimated by Kogel [2]. Although the general phenomenon of repair is surely present in humans as compared to animals, some controversies remain in terms of transforming the experimental animal data to the clinic. First, the histological pattern of radiation myelitis in guinea pigs differs from that in humans. Second, the repair kinetics is probably different, and it is questionable how long it takes to achieve maximum repair and retolerance in humans.

Schultheiss and Stephens [7] in their review of permanent radiation myelopathy, conclude: "Because of the life span, latency and dose response difference, only general guidelines for clinical application can be offered from the rodent data. These data indicate that substantial recovery of spinal cord tolerance is achieved during a sufficiently long interval after initial radiation therapy. In general, a higher retreatment dose can be given following lower initial doses and longer intervals between

treatments. From the sparse clinical and primate data, it appears that at least 50%

recovery of 45 Gy would be obtained 2 years after treatment".

Tab. 1 : Latent time for development of paresis ED₅₀

Treatment	ED ₅₀ (Gy)			Functional parameters	
	One day interval	6 month interval		One day interval	6 month interval
15 Gy + S D	16.2	18.5	10 α (Gy ⁻¹)	0.47	0.29
15 Gy + 6 Gy/fr	36.8	43.2	100 β (Gy ⁻²)	2.1	1.5
15Gy + 4 Gy/fr	47.2	65.1	α/β (Gy)	2.3	1.9
15 Gy + 3 Gy/fr	56.6	...			
2 fr/day	42.0	54.9			

REFERENCES

1. Ang KK, Price RE, Stephens LC, Jiang GL, Feng Y, Schulthesis TE and Peters LJ: The tolerance of primate spinal cord to reirradiation. *Int J Rad Oncol Biol Phys* 1993;25:459-64.
2. Kogel AJVD: Retreatment tolerance of the spinal cord. *Int J Rad Oncol Biol Phys* 1993;26:15-7.
3. Lavey RS, Taylor JMG, Tward JD, Li LT, Nguyen AA, Chon Y, McBride WH: The extent, time course and fraction size dependence of mouse spinal cord recovery from radiation injury. *Int J Rad Oncol Biol Phys* 1994;30:609-17.
4. Mason KA, Withers HR, Chiang CS: Late effects of radiation on the lumbar spinal cord of guinea pigs: Retreatment tolerance. *Int J Rad Oncol Biol Phys* 1993;26:641-8.
5. Ruifrok ACC, Kleiboer BJ and Kogel AJVD: Reirradiation tolerance of the im-mature rat spinal cord. *Radiother Oncol* 1992;25:249-56.
6. Ruifrok ACC, Kleibuer BJ and Kogel AJVD: Fractionation sensitivity of the rat cervical spinal cord during radiation retreatment. *Radiother Oncol* 1992;25:295-300.
7. Schultheiss TE and Stephens LC. Invited review: Permanent radiation myelopathy. *Brit Jr Radiol* 1992;63:737-53.
8. Tan BC and Khor TH: Radiation myelitis in carcinoma of the nasopharynx. *Clin Radiol* 1969;20:329-31.
9. Wong CS, Dyke JV, Milosevic M, Lapierre NJ: Radiation myelopathy following single courses of radiotherapy and retreatment. *Int J Rad Oncol Biol Phys* 1994;30:575-81.
10. Wong CS and Hao Y: Long term recovery kinetics of radiation damage in rat spinal cord. *Int J Rad Oncol Biol Phys* 1997;37:171-9.
11. Wong CS, Poon JK and Hill RP: Reirradiation tolerance in the rat spinal cord: influence of level of initial damage. *Radiother Oncol* 1993;26:132-8.
12. Wong CS, Minkin S, Hill RP: Reirradiation tolerance of the rat spinal cord to fractionated X-ray doses. *Radiother Oncol* 1993;28:197-202.