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# Radiation tolerance of the spinal cord: doctrine, dogmas, data

## ABSTRACT

*Radiation damage to the spinal cord is one of the most feared complications in the treatment of cancer with radiation therapy. There is no uniformly accepted definition of the term "tolerance" and this fact reflects differences in the clinical acceptability of the types of treatment related morbidity. Having in mind this fact, to say a dose to the spinal cord of 45 Gy in 23-25 fraction represents cord tolerance, is true only insofar as most radiotherapists accept its use and very few will tolerate in practice a higher dose. Many studies have attempted to define the risk factors associated with chronic progressive radiation myelopathy with differing conclusions. In the present paper the following main factors are discussed in detail: total dose, dose per fraction, length (volume) of the spinal cord irradiated segment of spinal cord and reirradiation of the cord to control the malignant disease. A number of conclusions are obtained regarding the relative influence of these risk factors, particularly for the range of doses usually given incidentally to the spinal cord in the treatment of tumors in the region of the cord. It is obvious that the sample size in the clinical studies is not adequate to define the multiple risk factors of chronic progressive radiation myelopathy. In fact, the sample size required, may be so large that the exact risks may never be completely defined. It is unfortunate that the standard of practice for limiting incidental dose to the spinal cord is determined more by litigation than by clinical judgment. Tumorcidal dose should never be compromised for the purpose of limiting, where such limiting forces even greater probability of compromising the tumorcidal dose.*

**Key words:** Spinal cord; Radiation tolerance; Risk factors; Radiation damage; Radiation complications

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## INTRODUCTION

Radiation damage to the spinal cord is one of the most feared complications in the treatment of cancer using radiation therapy. Its medical and legal consequences often make radiation oncologists compromise with the treatment of malignancy to ensure that the spinal cord dose remains at a "safe" level. According to Schultheiss (1) the currently accepted practice regarding radiation doses delivered incidentally to the spinal cord is rather the evidence of the radiation oncologists' "intolerance" to radiation myelopathy than of the spinal cord's "intolerance" to radiation. Finally, publications and personal opinions have generated a mythology that

has moved the discussion of spinal cord response away from scientific dialogue.

### Radiation myelitis - a feared complication

The term "radiation myelitis" refers exclusively to the syndrome of chronic progressive radiation myelopathy as defined by Reagan et al. (2). This syndrome usually begins about 9 to 15 months (according to some authors - up to 3 years (3) after the end of irradiation with paresthesias, other sensory disturbances and sometimes with later development of bowel and bladder disfunction. Over the next 1 to 6 months it steadily progresses, until multiple spinal cord tracts are involved.

According to Reagan et al. (2) there are four clinical syndromes of radiation myelopathy: 1) an acute transient radiation myelopathy distinguished by the presence of Lhermitte's sign - the most common myelopathy associated with no other abnormalities on neurologic examination, 2) an acutely developing paraplegia or quadriplegia, presumably secondary to an infraction of the spinal cord because of radiation damage to the blood vessels, 3) a lower motor - neuron disease in the upper or lower extremities, presum-

ably the result of selective anterior horn-cell damage, 4) a chronic progressive radiation myelopathy, the only syndrome for which pathologic findings have been described. While the second and the third syndromes are exceedingly rare, the last syndrome is the one most concerning the radiation oncologist. It is progressive and permanent and often leads to fatal complications such as infection or pulmonary embolus. Some patients stabilize after partial neurologic loss, as in the Brown-Sequard syndrome. These permanent signs are caused by presumed vascular damage and damage of oligodendrocytes, resulting in white matter necrosis and demyelination.

In radiotherapy, the term "tolerance" is variously used to describe a safe dose, an acceptable dose, a dose yielding 5%, 50% or some other frequency of response. The fact that there is no uniformly accepted definition reflects differences in the clinical acceptability of the types of treatment related morbidity. As Schultheiss points out (1), the term "tolerance" in statistics has an unequivocal definition: the tolerance dose is that above which an individual will exhibit a response and does not apply to the entire population at risk. The dose response

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function reflects the distribution of tolerance dose over the population at risk. A single tolerance dose for a population is meaningful only when the incidence of injury is 0% below this dose and goes to 100% at the tolerance dose. That is, the dose response is a steep function. Having in mind this fact, the statement that a dose to the spinal cord of 45 Gy in 23-25 fraction represents cord tolerance, is true only insofar as most radiotherapists accept its use and very few will tolerate in practice a higher dose.

The following main factors associated with the risk of chronic progressive radiation myelopathy are discussed: total dose, dose per fraction, length (volume) of the spinal cord irradiated, segment of spinal cord and reirradiation of the cord to control the malignant disease.

Many studies have been aimed to define these risk factors, with differing conclusion (4-10). The relative influence of these factors remains, however, undefined, particularly for the range of doses usually given incidentally to the spinal cord in the treatment of tumors in the region of the cord.

#### Total dose to the spinal cord

The basic recommendation in textbooks (11-18) and in protocol designs is that opposed lateral treatment fields of head and neck cancer must be limited to 45 Gy to exclude the spinal cord from further direct irradiation. It is well known that the spinal cord continues to receive additional dose during the standard treatment though it is shielded by blocks, but there are no recommended limitations on this additional "scatter" dose in relevant literature. Therefore, the actual dose to the cord from all phases of treatment is typically not well documented. Clinical studies do not explicitly state whether or not the scatter dose is included in the total doses reported (4,7,19,20). It is established that in addition to the 45 Gy given before reduction of the initial fields, an average of 6.2 Gy is given to the cord due to scatter and transmitted dose from blocked fields (off-cord laterals) (21). The total dose from the standard plan is 52 Gy on the average and a similar dose is probably delivered to thousands of head and neck cancer patients annually when treated to 70 Gy in the standard manner described above. There are many published reports that indicate how far 45 Gy at 1.8-2.0 Gy per fraction is from the dose sensitive region of the dose response curve.

In suggesting "that the fractions of less than 200 Gy the risk of permanent neurologic damage is very low" Marcus and Million (19) have returned to the idea of making conclusions on data rather than beliefs. They reported the incidence of cervical spinal cord injury to be 0.18% for 1112 patients receiving doses of 30 Gy or higher from treatment of head and neck cancers. None of the patients with cord doses of  $\leq 50$  Gy (not including scatter and transmission dose) developed radiation myelitis. The same referred to the 75 patients with cord doses of  $>50$  Gy.

Wong et al. (20) stated that not a single inci-

dence of myelitis occurred following an equivalent dose of 50 Gy in 1.8-2.0 Gy daily fractions to the cord. Mc Cunniff and Liang (7) studied 144 patients with head and neck cancer who received 56-65 Gy to the cord from opposed lateral treatment fields. One patient who received 60 Gy at 2 Gy per fraction developed myelitis. Cohen and Greditor (22) used data from 96 patients to estimate a risk of 5% for a dose of 4934 Gy in 25 fractions.

These clinical data strongly suggest that the dose of 50 Gy given in 1.8-2.0 Gy fractions is associated with a  $<1\%$  risk level. This opinion has been expressed by others too (1,9,10,17,21).

Based on these and other series using larger doses per fractions, the incidence for myelopathy at 45 Gy in fractions of 1.8-2.0 Gy is most likely below 0.2% and is certainly less than the 5% quoted in major textbooks. The best estimate of the conventionally fractionated dose causing a 5% incidence is 57-61 Gy (1,6,7,23) and for 50% incidence, the dose is probably in the 68-73 Gy range (5,8,24). Unfortunately, according to most of the authors, the published clinical data are inadequate for valid statistical dose-response analysis (10,24).

#### Dose per fraction

An increased incidence of myelopathy with high doses per fraction has been appreciated for over 20 years. According to Marcus and Million (19), of the 403 patients who received at least 4000 cGy (279 of them greater than 4500 cGy) to the cord at fractions greater than 180 cGy per day, none developed myelitis. None of the 233 patients, irradiated twice-a-day developed myelitis. Sixty-one received a dose greater than 240 cGy a day to the cervical spinal cord and 173 received between 200 and 240 cGy to the cord.

Recent experimental and clinical data strongly suggest that reducing the cord dose per fraction below 2 Gy dose, not significantly alter the absolute dose response (15,25). Thus, if an individual's tolerance is exceeded by 2 Gy fractions, giving the same dose in 1.5-1.8 Gy fractions probably would not be beneficial for such an individual. Moreover, using an isoeffect formula to extrapolate from a conventionally fractionated cord dose to an equivalent hyperfractionated cord dose is currently unwise.

#### Length (volume) of the spinal cord irradiated

Clinical evidence in some studies suggests that there may be an effect of volume or length of spinal cord irradiated on the incidence of radiation myelopathy (4,22,26,27). Other clinical studies have not substantiated this impression (8,19,28).

The tolerance dose for the spinal cord was estimated by Emami et al. (29) to be 50 Gy for a 10 cm cord length, with a 5% chance of a complication occurring in 5 years. The 5% figure was perhaps an overestimate of the actual complication, as indicated by recent clinical data.

The volume effects may be related to the

vascular supply, collateral circulation and/or ability to reestablish damaged vasculature by revascularization from field edges being affected by volume.

Vascular damage has been demonstrated in many reports to be very important in the radiation response of the spinal cord (30-34). The release of cytokines and mediators of inflammation may be affected by volume, with large volumes causing the release of larger quantities of potentially damaging substances. Cytokines and mediators of inflammation have been shown to be released in the spinal cord after the irradiation (32,35).

Reanalysis of a published data did not conclusively demonstrate a volume-dependent change in the slope of dose-response curves and it must be considered an open question as to whether one exists (22,27). Parallel or nearly parallel dose-response curves for the spinal cord end-points imply that a volume effect estimated at the 50% probability of injury would also hold at low probabilities of injury typical of the clinic (27).

#### Segment of spinal cord irradiated

Most of the clinical studies discuss mainly the relative tolerance of the cervical and thoracic levels of the spinal cord. The dogma is that the thoracic cord is more sensitive than the cervical cord. This is attributed to the "poor vascular supply" (36) as evidenced by fewer radical arteries, a narrowing of the ventral artery, and fewer central arteries. Answering to this concept Gillan (37) states explicitly that "The blood supply to the thoracic cord is entirely adequate .... and it is relatively as good as for any other cord segment". Furthermore, the distribution of radiation lesions in the spinal cord is more typical of venous lesions in the spinal cord than the arterial ones (38).

Clearly, there is no objective basis for believing that the thoracic cord is more radiosensitive than the cervical cord. The radiotherapy literature certainly does not corroborate the dogma.

#### Retreatment of the cord to control disease

There are cases where retreating the cord is indicated to control disease. The limited treatment to cumulative doses of 80-90 Gy in 1.8-2.0 Gy fractions does not inevitably produce myelopathy, although the risk is certainly not negligible. Tan and Khor (39) report three myelopathies in 22 patients retreated for nasopharyngeal recurrence. The cord doses for two of the myelopathies were approximately 80 Gy, conventionally fractionated, given in approximately equal courses separated by 8 months in one case and 4.5 years in the other.

In conclusion on the basis of the limited treatment data we may conclude that retreatments in less than 2 years may carry the increased risk since the spinal cord damage is most likely to be expressed during this period. Further clinical data could be forthcoming from

Marcus and Million (19) if any of their 1100 patients are retreated.

## DISCUSSION

After Ahlboms article (40) was published in 1941, there followed several publications attempting to define radiation tolerance of the spinal cord. Many studies have attempted to define the risk factors, with differing conclusions.

According to some authors the rare myelopathies that do occur at low doses ( $\leq 45$  Gy) are due to three reasons: extrinsic factors reduce some individuals' radiation tolerance, tens of thousands of patients are irradiated annually at these doses, and the true doses were higher than the estimated ones. There are several possible reasons for the recommended lower doses in the earlier clinical studies: treatment with much higher doses per fraction, the possibility of mistakes in the dosimetry, the use of multiple overlapping fields, the lack of good simulators, treatment with orthovoltage beams which may produce a higher risk of myelitis because of the higher relative biological effectiveness. The limitation of most clinical studies are that they have used a physical dose rather than a biological dose. It may be important to convert the entire physical dose distribution to a biological one corrected for fractionation (41) using the linear-quadratic formula, rather than just the maximum cord dose to a point (4,20). This must be the subject of future studies.

The probable origin of the belief in a difference in sensitivities of the cervical and thoracic levels is the effect of the one-field per day technique used until the mid 1970s. In the thorax, this results in a significantly higher biological dose, but for the cervical cord (treated with lateral fields) there is no such increase.

It is unfortunate that the standard of practice for limiting incidental dose to the spinal cord is determined more by litigation than by clinical judgment. Tumorcidal dose should never be compromised for the purpose of limiting, where such limiting forces even greater probability of compromising the tumorcidal dose. Fifty Gy in 2 Gy fractions has been recommended by many credible experts as an acceptable spinal cord dose (81,19,21) and this recommendation is probably conservative.

It is obvious that the sample size in the clinical studies is not adequate to define the multiple risk factors of chronic progressive radiation myelopathy. In fact, the sample size required may be so large that the exact risks may never be completely defined.

## CONCLUSION

The results of many clinical studies demonstrate that some standard head and neck treatment schemes which have been widely used for many years routinely involve spinal cord doses between 50 and 55 Gy.

It does appear that for fractions of less than

200 cGy given once a day or 120 cGy given twice a day, and a total dose of 5500 cGy or less, the risk of permanent neurologic damage is  $<1\%$ . The best estimate of the conventionally fractionated dose causing a 5% incidence is 57-61 Gy and for 50% incidence, the dose is probably in the 68-73 Gy range.

Recent experimental and clinical data strongly suggest that reducing the cord dose per fraction below 2 Gy does not significantly alter the absolute dose response.

Reanalysis of published data did not conclusively demonstrate a volume-dependent change in the slope of dose-response curves and it must be considered an open question.

There is no objective basis for believing that the thoracic cord is more radiosensitive than the cervical one. The perceived difference in cervical and thoracic cord sensitivities was probably due to the unappreciated difference in the biological dose.

Retreatments in less than 2 years may carry increased risk since the spinal cord dosage is most likely to be expressed during this period.

Higher doses could be given if the clinical situation requires them and the patient is probably informed about the risk and the consequences of myelopathy. It is not by limiting the total spinal cord dose that the incidence of myelopathy should be reduced, but rather by determining what factors in the patients' medical history and physical status make the spinal cord more sensitive than expected. Indeed, given the appropriate clinical situation, an even higher risk may be worth taking if it provides a significantly higher chance of controlling the tumor.

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