Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2011 April 1; 79(5): 1302–1309. doi:10.1016/j.ijrobp.2010.10.052.

Spinal Cord Tolerance in the Age of Spinal Radiosurgery: Lessons from Pre-clinical Studies

Paul M. Medin, PhD and
Department of Radiation Oncology, UT Southwestern Medical Center, Dallas, TX, USA

Thomas P. Boike, MD
Department of Radiation Oncology, UT Southwestern Medical Center, Dallas, TX, USA

Abstract

Clinical implementation of spinal radiosurgery has increased rapidly in recent years but little is known regarding human spinal cord tolerance to single-fraction irradiation. In contrast, preclinical studies in single-fraction spinal cord tolerance have been ongoing since the 1970's. The influences of field length, dose rate, inhomogeneous dose distributions and reirradiation have all been investigated. This review summarizes literature regarding single-fraction spinal cord tolerance in pre-clinical models with an emphasis on practical clinical significance. The outcomes of studies that incorporate uniform irradiation are surprisingly consistent among multiple small and large animal models. Extensive investigation of inhomogeneous dose distributions in the rat has demonstrated a significant dose-volume effect while preliminary results from one pig study are contradictory. Pre-clinical spinal cord dose-volume studies indicate that dose distribution is more critical than the volume irradiated suggesting that neither dose volume histogram analysis nor absolute volume constraints are effective in predicting complications. Reirradiation data is sparse, but results from guinea pig, rat and pig studies are consistent with the hypothesis that the spinal cord possesses a large capacity for repair. The mechanisms behind the phenomena observed in spinal cord studies are not readily explained and the ability of dose response models to predict outcomes is variable underscoring the need for further investigation. Animal studies provide insight into the phenomena and mechanisms of radiosensitivity but the true significance of animal studies can only be discovered through clinical trials.

Keywords

spinal cord; radiation tolerance; preclinical; radiosurgery; animal

Introduction

Investigators of single-fraction spinal cord tolerance in the 1970's and 1980's could not have predicted that their work would become directly clinically relevant but pioneering efforts in spinal radiosurgery at the University of Arizona(1) followed by the development of image-

Corresponding author: Paul Medin, PhD, Department of Radiation Oncology, UT Southwestern Medical Center at Dallas, 5801 Forest Park Rd, Dallas, Tx 75390-9183, Paul.medin@utsouthwestern.edu, Ph: (214) 645-8591, Fax: (214) 645-2885.

Conflicts of Interest Notification
Paul Medin teaches radiosurgery courses sponsored by BrainLAB AG.

guidance and dose-shaping technologies caused a renewed interest in the single-fraction irradiation paradigm for management of tumors in and around the spine. Clinical implementation of spinal radiosurgery has increased rapidly in recent years; the entire spinal radiosurgery experience reported in the literature prior to 2003 included approximately 50 patients (2–5) but today one group alone has treated well over 1000 lesions(6). The recent opening of a prospective phase II/III study of image-guided radiosurgery/SBRT for localized spine metastases by the Radiation Therapy Oncology Group (RTOG 0631) has launched a new era in the investigation of spinal radiosurgery.

While the image-guidance technology that enables spinal radiosurgery has matured to the extent that patient positioning can be verified in near real-time, understanding of normal tissue tolerance lags behind. Normal tissue response to high-dose, single-fraction irradiation is poorly understood for most organs but the spinal cord is considered the dose limiting organ at risk in spinal radiosurgery and is the focus of this review. Clinical dose-response information regarding single-fraction spinal cord irradiation with uniform dose distributions beyond a dose of 8 Gy is sparse. Macbeth et. al.(7) reported a group of 114 patients that received a single 10 Gy spinal cord dose with no myelopathy. Only four clinical cases of myelopathy(8–10) have been reported (as of September 2010) following varied doses from single-fraction spinal radiosurgery making it difficult to draw firm conclusions regarding spinal cord tolerance. Conclusions drawn by leading authors are: a) the partial volume tolerance of the human spinal cord is at least 10 Gy to 10% of the spinal cord volume defined as 6 mm above and below the radiosurgery target(8), b) use caution when treating over 1.0 cm^3 of spinal cord to doses greater than 8 Gy or higher dose equivalent(9), and c) a maximum point dose of 10 Gy to the thecal sac is safe(11).

In contrast to the paucity of clinical data on single-fraction spinal cord tolerance, a wealth of data is available from animal models. Rats, guinea pigs, mice, and pigs have been used to establish general dose response curves and to investigate irradiation conditions that modify response. Many variables have been shown to modify spinal cord tolerance including: a) dose rate, b) irradiated length, c) irradiated lateral cross-section, d) irradiated region, e) dose to adjacent spinal cord, f) previous irradiation, and g) age. As the number of patients receiving spinal radiosurgery grows and dose escalation is considered, a review of the parameters that are known to affect spinal cord response is increasingly important. While human spinal cord tolerance can only be determined through clinical trials, animal studies serve as a guide to parameters of interest that should be considered during the design of clinical trials or when prescribing spinal radiosurgery.

Limitations of Animal Models

Animal models have long been used to study the phenomena and mechanisms of spinal cord tolerance because the complex responses of the central nervous system to irradiation necessitate biological models. Every animal model needs to be evaluated for its relevance to human biology and an understanding of the limitations of animal studies is crucial to the interpretation of their results.

Individual designs vary among the many studies cited in this review but generalized limitations are noted in the following: a) enrollment, b) followup period, c) comorbidity, d) previous therapies, e) neurologic assessment, f) anesthesia. Preclinical studies are designed to minimize the number of animals involved while maintaining the reliability of results. Dose-response curves are commonly derived from 4–7 dose groups with 4–5 subjects per group, thus, conclusions are drawn for a population from the response of 16–30 animals. The reader is always compelled to consider the margin of error in any study usually reported as a 95% confidence interval or as standard error. Animal studies frequently include a

followup period that is either shorter than the possible latency of the morbidity or life expectancy of the corresponding human population. Exceptions exist but most spinal cord tolerance studies include a followup period of twelve months or less while latency for human myelopathy has been described with a bimodal distribution peaking at approximately 9 and 26 months(12). Two distinct pathologies with differing latencies have also been noted in the rat, white matter necrosis usually occurs in less than 8 months while vascular injury can lead to paralysis between 8–18 months(13). The authors of a pig study with 70–110 week followup reported that the latency for myelopathy was 7.5–16 weeks but two pigs experienced late myelopathy at 64.5 and 75 weeks post-irradiation(14). The only lesion found in late-responding pigs was an 80% occlusion of the main ventral artery. In contrast, only a single phase of latencies has been observed for rhesus monkeys(12). Although long-term followup is desirable for clinically-oriented studies, few investigators are afforded the resources to complete it. In contrast to the majority of patients who receive spinal radiosurgery, preclinical spinal cord tolerance studies are performed in young healthy animals without comorbidity or previous therapies. The effects of comorbidity and previous therapies on spinal cord tolerance are unknown but have been questioned in human spinal radiosurgery literature(9). The assessment of neurologic response in animals is limited compared to humans. Although methods have been reported to assess sensory deficits in animals, practical challenges and the associated pitfalls limit their reliability. Radiation dose-response studies are typically limited to assessment of motor neurologic changes as determined by observation of gait. Gait change has been reported to correlate perfectly with the presence of histologic change in one pig study(15) but a study in rats reported a deviation between gait response and histologic response(16). One must always consider that subtle changes in neurologic status that are detectable in humans may be undetected in animals. Finally, all animal studies are performed under anesthesia but anesthesia is unusual for humans receiving spinal radiosurgery. The effects of anesthesia and oxygen concentration on spinal cord tolerance have not been studied widely but van der Kogel(17) reported a decrease of 2–2.5 Gy in ED_{50} values for rats receiving single dose irradiation with 1% halothane/99% O_2 versus intraperitoneal injection of sodium pentobarbital (60 mg/kg). Fortunately, the anesthesia effect noted by van der Kogel results in reduced ED_{50} values so results from such studies can be expected to be skewed in the direction of safety.

Dose-Response to Uniform Irradiation

This review summarizes literature regarding single-fraction spinal cord tolerance in pre-clinical models with an emphasis on practical clinical significance. An understanding of spinal cord tolerance characteristics resulting from uniform irradiation is necessary prior to the review of conditions that modify radiation response. A summary of spinal cord tolerance studies that have been performed under conditions of uniform irradiation to lengths ≥ 16 mm is presented in Table 1. The outcomes of studies that incorporate uniform irradiation are surprisingly consistent among multiple small and large animal models. The dose-response curves for rats, guinea pigs, mice and pigs are all very steep and have similar ED_{50}'s clustered around 20 Gy. Prior to the development of image-guided spinal radiosurgery, single-fraction spinal cord doses greater than 10 Gy were rarely reported and the probability of myelopathy was extremely low.

Dose-Rate Effect

The dose-rate effect is well-established in radiobiology and has been demonstrated in the spinal cord by multiple studies. Scalliet, et. al.(18), investigated the effect of continuous ^{60}Co irradiation delivered to a 2 cm long segment of the rat cervical spinal cord. The dose leading to paralysis in 50% of animals (ED_{50}) was 21.3, 27.2, 36.5 and >45 Gy for dose rates of 107.6, 14.7, 3.9, and 2.0 Gy/hr. Pop, et al., irradiated a 1.0–1.5 cm segment of

the thoraco-lumbar (T12-L2) spine of rats using interstitial ^{192}Ir at dose rates of 180, 14.85, 6.6, 3.82, 2.46, 1.44, 1.35, 0.80, 0.74 Gy/hr (at maximum dose points) and found resulting ED_{50}'s of 26.0, 32.9, 37.8, 47.0, 64.8, 75.5, 82.2, 112.5 and 121.4 Gy (19–21). The studies by Scalliet and Pop clearly demonstrate a dose-rate effect but would appear to have significantly different ED_{50}'s for comparable dose rates. These studies should be compared with the understanding that ^{60}Co produces a uniform dose across the spinal cord while ^{192}Ir irradiation results in a steep dose gradient and this most likely affected the resulting ED_{50}'s. A large body of data, including multiple species and irradiation modalities, indicate that the dose-rate effect in spinal cord occurs in a range of dose rates that is lower than used in modern spinal radiosurgery. The ED_{50} for rats and mice appears to plateau between dose rates of 15 and 107 Gy/hr and becomes insensitive to further increases. The ED_{50} for pigs is consistent with rats at dose rates between 12–18 Gy/hr and preliminary data from an ongoing study by Medin et. al.(22), indicate that the ED_{50} for pigs is consistent with rodents at higher dose rates of 240–440 Gy/hr. The dose-rate effect phenomenon provides insight into the kinetics of normal tissue repair and must be understood to interpret the relationship between various preclinical studies and their relevance to human therapy. The dose-rate effect may not be a critical factor in clinical spinal radiosurgery; realization of a significant increase in spinal cord tolerance would require treatment times on the order of two hours and the corresponding influence on tumor control probability is unknown. The absence of a dose-rate effect in rats at high dose rates of 600–900 Gy/hr is of clinical interest considering the recent introduction of linear accelerators that are capable of producing dose rates in excess of 800 Gy/hr.

Dose-Volume Effects

Dose-volume effects are of great significance in radiation therapy and have been summarized for many organs by the Quantitative Analysis of Normal Tissue Effect in the Clinic (QUANTEC) collaboration(23). A substantial effort has been made to characterize dose-volume effects in the spinal cord and additional studies are ongoing(10,24). Rats and pigs have been used to study lateral and longitudinal dose-volume effects for single-fraction irradiation and both irradiated length and lateral cross-section have been shown to influence spinal cord tolerance in rats.

Longitudinal Dose-Volume Effects

Longitudinally Homogeneous Dose Distribution—Three studies performed to investigate the influence of irradiated length on spinal cord tolerance are summarized in Table 2. In all three studies, various lengths of the cervical spinal cord were uniformly irradiated and the resulting ED_{50}'s were determined. Irradiated length had a profound affect on spinal cord tolerance for lengths less than 16 mm with ED_{50} increasing fourfold as length was decreased to 2 mm. In contrast, there was no data to suggest that increasing length from 25 mm to 100 mm results in decreased tolerance. A decrease in tolerance for lengths greater than 100 mm has been reported in dogs (40 mm versus 200 mm length) using fractionated irradiation(25) but this study is beyond the scope of this review. The "length effect" may not play a role in clinical radiosurgery for spinal metastases because spinal cord lengths greater than 16 mm are commonly irradiated; however, the "length effect" may become important for other indications such as hemangioblastoma(26).

Longitudinally Inhomogeneous Dose Distributions—Spinal cord tolerance to longitudinally inhomogeneous dose distributions was investigated by Bijl, et. al.(27,28) who irradiated the cervical spinal cords of rats with a 150 MeV proton beam. A series of experiments, referred to as "split dose" and "bath and shower," were designed to evaluate the influence of the dose to adjacent spinal cord on the tolerance of a short segment

irradiated to a high dose. In the "split dose" experiment, two 4 mm long segments were irradiated uniformly to a high dose with either 8 mm or 12 mm separation (center to center) between them. The dose to the spinal cord between the segments was less than 5% of D_{max}. Resulting ED_{50}'s (Table 3) from the 4 mm split fields were compared to single contiguous field lengths of 4 mm and 8 mm. The split fields were more similar in sensitivity to a single 4 mm field than to an 8 mm field.

Two experimental designs, symmetric and asymmetric, were used in the "bath and shower" experiments. For the symmetric "bath and shower" study, a uniform dose (the "bath") was delivered to a 20 mm segment followed by irradiation of a 2–8 mm segment (the "shower") centered within the bath region. For the asymmetric study, a uniform dose (the "bath") was delivered to a 12 mm segment followed by irradiation of a 2–4 mm segment (the "shower") located within either the cranial or caudal end of the bath region. The shower dose was delivered between 11–19 minutes after the bath dose. Results from the bath and shower experiments are shown in Table 4.

The "bath and shower" experiments demonstrated conclusively that the spatial distribution of dose within the spinal cord is an important factor in modulating toxicity. The extent of the modulation was dependent on the length of the high-dose "shower" segment, and on the location and magnitude of the dose to surrounding spinal cord. A "bath" dose as low as 4 Gy to adjacent spinal cord reduced the tolerance of a 2 mm single segment by as much as 26.6 Gy while the same "bath" dose had almost no effect on an 8 mm irradiated segment. The 18 Gy "bath" dose resulted in a more dramatic reduction of 57 Gy in ED_{50} for the single 2 mm field. The asymmetric "bath and shower" experiments demonstrated that the repair mechanisms that result in toxicity modulation are not sensitive to direction along the spinal cord. Results from the "bath and shower" experiments suggest that clinicians should consider minimizing the dose to spinal cord superior and inferior to the treated lesion. In practice, this is achieved by limiting the number of non-coplanar fields.

The biologic mechanisms behind the longitudinal dose-volume effects are still not fully explained. White matter necrosis, characterized by demyelination, loss of axons, focal necrosis and liquefactive necrosis, is the primary cause of early paralysis for doses ≥20 Gy(29,30). Data from the "length effect" studies suggests that migration of remyelinating cells from the unirradiated field edges is at least partially responsible for restoring the damaged glial cell population(29,31). Chari et. al.(32), demonstrated that migrating oligodendrocyte progenitor (OP) cells were able to repopulate a 7 mm length of rat thoracic spinal cord irradiated to 40 Gy; however, the role of the OP cells in the development of white matter necrosis in unclear. Data from the "split field" and "bath and shower" studies indicate that cell migration cannot be the sole mechanism involved in radiation repair.

Philippens, et. al.(16) investigated repair kinetics in the "bath and shower" study design by increasing the time interval between the "bath" and "shower" doses from 8 minutes to 24 hours. A "bath" dose of 4 Gy was delivered to a 2 cm segment in the cervical spinal cord of rats followed by a "shower" dose to a 4.6 mm segment centered within the "bath" volume. Animals were followed for 210 days or until the development of paralysis; spinal cords were subsequently examined for white matter necrosis and demyelination. Results are shown in Table 5. The spinal cords of a subset of rats without neurologic deficits had demyelination leading to slightly different ED_{50} values for paralysis and histological demyelination. ED_{50} values for the "shower" dose increased from 36.8 to 47.9 Gy as the time interval between the "bath" and "shower" increased from 8 minutes to 24 hours. The influence of the "bath" dose lasted at least 12 hours but became insignificant by 24 hours. The mechanism responsible for the disappearance of the "bath and shower" effect is unknown but the authors note that the underlying molecular events are probably different than those

responsible for the repair of radiation damage derived from low-dose and fractionated treatments(16).

Lateral Dose-Volume Effects

Lateral volume effects have been investigated by van Luijk, et. al.(33), who used a 150 MeV proton beam to irradiate 50% of the lateral cross-section of the cervical spinal cord in rats. The irradiation method resulted in an extremely steep dose gradient (100% to <10% isodose) across the spinal cord with the 50% isodose line bisecting the spinal cord. A 20 mm field length was used to avoid confounding the results with the "length effect." An ED_{50} (95% confidence interval) of 30 Gy (26.3–31.3) was observed for paralysis compared to an ED_{50} of 20.4 Gy (19.6–21.1) for full cross-section irradiation. A more extensive followup study affirmed the lateral volume effect and demonstrated that the lateral white matter is much more radiosensitive than the central part of the white matter(34). Medin, et. al.(15), have investigated lateral volume effects in the cervical spinal cord of pigs using a 6 MV image-guided linear accelerator to produce a steep lateral gradient across the spinal cord. The dose gradient produced in the pig study is also 95% to 10% isodose across the spinal cord with the 50% isodose line bisecting the cord (similar to van Luijk, et. al. (33)) but the diameter of the pig cervical spinal cord is about three times that of a rat (spinal cord diameter is 8–11 mm for a pig versus 3.5 mm for a rat). Longer fields (≈50 mm) are also used in this study to avoid the "length effect." An ED_{50} (95% CI) of 20.0 Gy (18.3–21.7) for maximum spinal cord dose was observed for neurologic response in the lateral spinal cord irradiation cohort. Preliminary data for uniform irradiation of a 50 mm spinal cord length in this pig study indicates that the resulting ED_{50} will be between 18–20 Gy. The reason for the lack of a demonstrable spinal cord sparing effect in pigs irradiated with steep lateral dose gradients is not clear but the physical size of the spinal cord and/or the steepness of the dose gradient appear to be factors in the repair mechanism. A better understanding of dose-volume effects in the spinal cord is critical because spinal radiosurgery treatment plans, and subsequently prescriptions, are often made based on dose volume histograms (DVH). A large body of data from preclinical studies suggests that the spatial distribution of absorbed dose within the spinal cord is probably more relevant to spinal cord tolerance than the irradiated volume; therefore, the DVH alone is not an appropriate tool for the evaluation of spinal radiosurgery treatment plans for the avoidance of radiation myelopathy. For example, Bijl et. al.(29), observed no response when a dose ≤ 36 Gy was delivered to the full cross section of a 4 mm long spinal cord segment; however, a dose of 35 Gy to the lateral edge of the spinal cord resulted in 100% response when a 20 mm segment was irradiated(33). These two irradiation scenarios can produce similar or very different DVH's depending on the length of spinal cord contoured. Preliminary results from a dose-volume effect study in pigs confirm the observation that the DVH alone is not a reliable tool to assess the probability of radiation myelopathy(22). In the pig study, neurologic deficits begin to occur at approximately 18 Gy when either the entire cross-section or just the lateral edge of the spinal cord is irradiated. Philippens, et. al.(35), and van Luijk, et. al.(36), evaluated many dose-response models with data from dose-volume studies (lateral and longitudinal) in the rat spinal cord and found none of the models applied produced acceptable goodness of fit. In contrast, Philippens, et. al.(37), reported that multiple models produced acceptable goodness of fit when an alternate dose distribution was created in rat spinal cords.

Lateral/Longitudinal Combination Dose-Volume Effects

Philippens, et. al.,(37) investigated regional differences in radiosensitivity by applying nonuniform dose distributions to the thoraco-lumbar spinal cord of rats using an ^{192}Ir high-dose-rate afterloader. One uniform and two nonuniform distributions were created by stepping the source through one, two or six catheters placed around the spine. For the nonuniform distributions, catheters were inserted lateral to the spinous process so a steep

dose gradient resulted in the dorsal/ventral direction. A dose gradient was also present in the rostral/caudal direction due to the nature of the delivery technique. A 2 cm length of spinal cord was targeted including levels T12-L2. Uniform irradiation resulted in an ED_{50} (95% CI) of 22.1 (21.0–23.2) Gy. For nonuniform irradiation, thoracic dorsal and lateral white matter regions were found to have comparable sensitivity with maximum dose ED_{50}'s close to 33 Gy while the lumbar dorsal and ventral nerve roots were much more sensitive with ED_{50}'s of 25.9 (25.3–26.4) Gy and 24.1 (23.6–24.6) Gy, respectively.

Regional Variation of Tolerance

Dose modulation techniques are commonly used in spinal radiosurgery with the goal of minimizing dose to the spinal cord, but resulting dose distributions are heterogeneous within the target and organs at risk. Bijl et. al.(34) investigated the regional differences in radiosensitivity between the central and lateral spinal cord in a rat model. A 2 cm segment of either the central or lateral portion of the spinal cord was irradiated using the plateau portion of a 150 MeV proton beam. Two different dose distributions were created for irradiation of the lateral spinal cord by changing the steepness of the lateral dose gradient (20–80% isodose lines) to either 0.8mm (tight) or 1.1mm (wide). A third dose distribution was created in which only the central spinal cord was irradiated. Resulting ED_{50}s were 33.4, 28.9 and 71.9 Gy for the lateral "tight," lateral "wide," and central distributions, respectively. In comparison, the ED_{50} for rats that received uniform irradiation to a 2 cm segment was 20.4 Gy. All partial distributions resulted in an increase of the tolerance but the increase for the central spinal cord irradiation was surprisingly dramatic. Histologic analysis revealed that paralysis was due to white matter necrosis and no gray matter lesions were observed. Differences in white matter response are probably due to anatomic and physiologic differences within the spinal cord architecture. The mechanisms behind the central/lateral sensitivity differences in the white matter are not understood but the authors note that the results cannot be explained by simple dose/volume differences, as the amount of white matter irradiated in the central beam was greater than that in almost all lateral beam experiments. Regional differences such as blood flow or the migratory capacity of oligodendrocyte progenitor cells may play a role in this phenomenon(34).

Variations in radiosensitivity between the cervical, thoracic and lumbar regions have been suggested in human spinal cord literature but never established by objective data analysis(12). No single study has been performed in animals to investigate variation in spinal cord tolerance between regions; however, all three regions have been studied independently in rats. Multiple groups have reported the single-fraction ED_{50} tolerance of the rat cervical spinal cord is very close to 21 Gy when irradiated uniformly(18,29,31). Philippens, et. al.(37), reported an ED_{50} of 22.1 Gy for uniform irradiation of the thoraco-lumbar spinal cord using a high dose rate brachytherapy source. van der Kogel compared the tolerance of the cervical versus lumbo-sacral spine and found resulting ED_{50}s of 19.5 and 19.0 Gy, respectively (17,38). Clinical practice, defined by the Radiation Therapy Oncology Group 0631 protocol, is consistent with animal data in that prescribed dose is not dependent on vertebral level.

Re-irradiation

Data regarding single-fraction spinal cord tolerance following previous irradiation is sparse. Ruifrok, et. al.(39) performed split-dose studies in the cervical spines of 3 week old rats. Animals were irradiated by one of two schedules: A) initial dose of 12 Gy followed by reirradiation at 1, 3 or 6 months; or B) initial dose of 14.9 Gy followed by reirradiation at 1 day, 14 days, 1 month, 3 months, or 6 months. Over a followup period of 200 days, it was observed that the ED_{50} increased most quickly in the first month after irradiation and then

continued to make slight but insignificant gains up to 6 months. Reirradiation tolerance never fully recovered after 6 months with an ED_{50} of approximately 17 Gy compared with 21 Gy for unirradiated spinal cord. A companion study in adult (18 week old) rats demonstrated that the period of significant recovery occurred between 2–6 months and the maximum extent of recovery was greater than for the 3 week old rats. Knowles investigated reirradiation tolerance using a guinea pig model. One day old guinea pigs received a single 10 Gy dose followed one year later by another single dose. The ED_{50} for paralysis for retreated animals (19.5 Gy) was only slightly lower than animals treated de novo (20.5 Gy) at one year of age(40).

The most comprehensive study of the extent and kinetics of recovery from irradiation injury was performed in rhesus monkeys(41). The cervical/upper thoracic spinal cord was given 44 Gy in daily 2.2 Gy fractions and then re-irradiated to doses of 57.2 Gy (2.2 Gy fractions) after one year or two year intervals, or 66 Gy (2.2 Gy fractions) after two or three year intervals. Animals were observed for 2–2.5 years after re-irradiation to assess the early and late effects of their radiation treatment. Fitting observed myeloparesis data with a model assuming all dose-response curves (single course and reirradiation) were parallel, resulted in recovery estimates of 33.6 Gy (76%), 37.6 Gy (85%), and 44.6 Gy (101%) of the initial dose after 1, 2, and 3 years, respectively. Using a model with more conservative assumptions resulted in an overall recovery equivalent of 26.8 Gy (61%)(41). Although this study design did not include single-fraction irradiation, it showed that the primate spinal cord has a significant capacity for repair.

A current study by Medin, et. al.(22), is investigating the dose-related incidence of motor neurologic deficit in pigs that receive 30 Gy in ten fractions followed one year later by singe-fraction radiosurgery to their cervical spinal cords. Preliminary results suggest that within a one-year followup period, the reirradiated pigs are not at significantly higher risk of developing motor deficits than pigs that receive radiosurgery alone.

Age Effect

The response of the spinal cord to singe-fraction irradiation has been shown to be dependent on age in pig, rat, and guinea pig models. The cervical spines of mature (37–42.5 weeks) and immature (15.5–23 weeks) pigs were irradiated to investigate differences in the ED_{50} for paralysis(14). In an observation period up to 110 weeks post-irradiation, it was demonstrated that the doses which paralyzed mature pigs only resulted in transient neurological changes in immature pigs. The ED_{50} (±SE) for paralysis in mature pigs was 27.02±0.36 Gy while the ED_{50} (±SE) for transient neurologic changes in immature pigs was 26.09±0.37 Gy. A study in rats aged 1–18 weeks showed that the ED_{50} (95% CI) was significantly reduced to 19.5 Gy (18.7, 20.3) in one week old animals but remains constant at 21.4 Gy (21.0, 21.7) after the age of two weeks(42). Knowles irradiated the lumbar spinal cords of guinea pigs aged 1 day, 30 days and 1 year and the resulting ED_{50}'s were 14.75, 19.5 and 20.5, respectively(40). The two rodent studies suggest that dose tolerance becomes constant after a certain age for a given species but only two timepoints have been studied in a large animal. Based on the studies presented, age is a factor in determining radiation response but the nature and significance of the age effect is unclear and may vary among species.

Conclusions

Animal models are sometimes dismissed as irrelevant to human therapy but, in the proper context, phenomena and mechanisms discovered through animal data should be very useful in the design of clinical trials. Many spinal cord tolerance phenomena have been cited but

the following points stand out to the present authors: a) spinal cord tolerance to single-fraction, uniform irradiation has been demonstrated to be consistent across four animal species, b) nonuniform irradiation has been shown to modify dose response in a rat model but this result has not been confirmed in a larger animal, c) the spatial distribution of dose is probably more relevant to tolerance than irradiated volume or dose-volume histogram analysis, and d) the ability of dose-response models to accurately predict the outcomes of animal spinal cord tolerance studies varies with the dose distribution irradiated.

The correlation between human and animal spinal cord tolerance has never been rigorously tested but current protocol guidelines(43) accepted in clinical spinal radiosurgery are consistent with lessons learned from preclinical studies. Most notably, the probability of myelopathy approaches zero at spinal cord doses currently accepted for humans(43). Increased reliance on preclinical data will be necessary if dose escalation is to continue, thus, a thorough understanding of the data is crucial. Increasing evidence suggests a local control advantage with increasing dose(44,45) and/or a pattern of failure for tumors in the epidural space(46) where dose must be compromised to meet spinal cord dose constraints.

This review is intended to increase the reader's awareness of spinal cord tolerance phenomenon demonstrated in preclinical models. Many caveats regarding the interpretation of animal studies are provided yet none of them address the fundamental question of the similarity between animal and human spinal cord tolerance; this question could only be answered through clinical trials.

Acknowledgments

Paul Medin's research is funded by the National Institute of Neurological Disorders and Stroke, R01 NS049517.

References

1. Hamilton AJ, Lulu BA, Fosmire H, et al. Preliminary clinical experience with linear accelerator-based spinal stereotactic radiosurgery. Neurosurgery. 1995; 36:311–319. [PubMed: 7731511]
2. Takacs II, Hamilton AJ, Lulu B, et al. Frame based stereotactic spinal radiosurgery: experience from the first 19 patients treated. Stereotactic and Functional Neurosurgery. 1999; 73:69. [PubMed: 10853102]
3. Murphy MJ, Chang S, Gibbs I, et al. Image-Guided Radiosurgery in the Treatment of Spinal Metastases. Neurosurgical Focus. 2001:11.
4. Ryu SI, Chang SD, Kim DH, et al. Image-guided hypo-fractionated stereotactic radiosurgery to spinal lesions. Neurosurgery. 2001; 49:838–846. [PubMed: 11564244]
5. Yin FF, Ryu S, Ajlouni M, et al. A technique of intensity-modulated radiosurgery (IMRS) for spinal tumors. Medical Physics. 2002; 29:2815–2822. [PubMed: 12512715]
6. Gerszten, P. Number of Spinal Radiosurgery Patients Treated. Medin, P., editor. Dallas: 2009.
7. Macbeth FR, Wheldon TE, Girling DJ, et al. Radiation myelopathy: estimates of risk in 1048 patients in three randomized trials of palliative radiotherapy for non-small cell lung cancer. The Medical Research Council Lung Cancer Working Party. Clin Oncol (R Coll Radiol). 1996; 8:176–181. [PubMed: 8814372]
8. Ryu S, Jin JY, Jin R, et al. Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery. Cancer. 2007; 109:628–636. [PubMed: 17167762]
9. Gibbs IC, Patil C, Gerszten PC, et al. Delayed radiation-induced myelopathy after spinal radiosurgery. Neurosurgery. 2009; 64:A67–A72. [PubMed: 19165076]
10. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. Int J Radiat Oncol Biol Phys. 2010; 76:S42–49. [PubMed: 20171517]
11. Sahgal A, Ma L, Gibbs I, et al. Spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys. 2010; 77:548–553. [PubMed: 19765914]

12. Schultheiss TE, Stephens LC. Invited review: permanent radiation myelopathy. British Journal of Radiology. 1992; 65:737–753. [PubMed: 1393407]
13. van der Kogel, A., editor. The cellular basis of radiation-induced damage to the central nervous system. Edinburgh: Churchill Livingstone; 1983.
14. van den Aardweg GJ, Hopewell JW, Whitehouse EM, et al. A new model of radiation-induced myelopathy: a comparison of the response of mature and immature pigs. Int J Radiat Oncol Biol Phys. 1994; 29:763–770. [PubMed: 8040022]
15. Medin P, Foster R, Van der Kogel A, et al. Spinal Cord Tolerance to Single-Fraction Partial-Volume Irradiation: A Swine Model. Int J Rad Onc Biol Phys. 2010 In Press.
16. Philippens ME, Pop LA, Visser AG, et al. Bath and shower effect in spinal cord: the effect of time interval. Int J Radiat Oncol Biol Phys. 2009; 73:514–522. [PubMed: 19046823]
17. Van der Kogel, A. Late Effects of Radiation On The Spinal Cord. Amsterdam: University of Amsterdam; 1979. p. 160Vol PhD
18. Scalliet P, Landuyt W, Van der Schueren E. Repair kinetics as a determining factor for late tolerance of central nervous system to low dose rate irradiation. Radiotherapy and Oncology. 1989; 14:345–353. [PubMed: 2727321]
19. Pop LA, van der Plas M, Skwarchuk MW, et al. High dose rate (HDR) and low dose rate (LDR) interstitial irradiation (IRT) of the rat spinal cord. Radiotherapy and Oncology. 1997; 42:59–67. [PubMed: 9132828]
20. Pop LA, van der Plas M, Ruifrok AC, et al. Tolerance of rat spinal cord to continuous interstitial irradiation. Int J Radiat Oncol Biol Phys. 1998; 40:681–689. [PubMed: 9486620]
21. Pop LA, Millar WT, van der Plas M, et al. Radiation tolerance of rat spinal cord to pulsed dose rate (PDR-) brachytherapy: the impact of differences in temporal dose distribution. Radiother Oncol. 2000; 55:301–315. [PubMed: 10869745]
22. Medin, P.; Foster, R.; van der Kogel, AJ., et al. Lateral Dose Volume Effects and Reirradiation Tolerance of the Porcine Spinal Cord. 51st Annual Meeting of The American Society for Therapeutic Radiology and Oncology; Chicago: Int J Rad Oncol Biol Phys; 2009. p. S100-101.
23. Various. Qualitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC). Int J Rad Onc Biol Phys. 2010; 76:S1–S160.
24. van der Kogel AJ. Dose-volume effects in the spinal cord. Radiother Oncol. 1993; 29:105–109. [PubMed: 8310135]
25. Powers BE, Thames HD, Gillette SM, et al. Volume effects in the irradiated canine spinal cord: do they exist when the probability of injury is low? Radiother Oncol. 1998; 46:297–306. [PubMed: 9572623]
26. Daly, MGI.; Choi, C.; Moss, J.; Lieberson, R.; Chang, S.; Adler, J.; Soltys, S. Tolerance of the spinal cord to stereotactic radiosurgery: insights from hemangioblastomas. 51st Annual Meeting of The American Society for Therapeutic Radiology and Oncology; Chicago: Int J Rad Onc Biol Phys; 2009. p. S101
27. Bijl HP, van Luijk P, Coppes RP, et al. Unexpected changes of rat cervical spinal cord tolerance caused by inhomogeneous dose distributions. Int J Radiat Oncol Biol Phys. 2003; 57:274–281. [PubMed: 12909243]
28. Bijl HP, van Luijk P, Coppes RP, et al. Influence of adjacent low-dose fields on tolerance to high doses of protons in rat cervical spinal cord. Int J Radiat Oncol Biol Phys. 2006; 64:1204–1210. [PubMed: 16504760]
29. Bijl HP, van Luijk P, Coppes RP, et al. Dose-volume effects in the rat cervical spinal cord after proton irradiation. Int J Radiat Oncol Biol Phys. 2002; 52:205–211. [PubMed: 11777640]
30. van der kogel, A. Central nervous system radiation injury in small animal models. In: Gutin, PHLS.; Sheline, GE., editors. Radiation injury in the central nervous system. New York: Raven Press; 1991. p. 91-111.
31. Hopewell JW, Morris AD, Dixon-Brown A. The influence of field size on the late tolerance of the rat spinal cord to single doses of X rays. Br J Radiol. 1987; 60:1099–1108. [PubMed: 3690151]
32. Chari DM, Blakemore WF. Efficient recolonisation of progenitor-depleted areas of the CNS by adult oligodendrocyte progenitor cells. Glia. 2002; 37:307–313. [PubMed: 11870870]

33. van Luijk P, Bijl HP, Coppes RP, et al. Techniques for precision irradiation of the lateral half of the rat cervical spinal cord using 150 MeV protons [corrected]. Phys Med Biol. 2001; 46:2857–2871. [PubMed: 11720351]
34. Bijl HP, van Luijk P, Coppes RP, et al. Regional differences in radiosensitivity across the rat cervical spinal cord. Int J Radiat Oncol Biol Phys. 2005; 61:543–551. [PubMed: 15667978]
35. Philippens ME, Pop LA, Visser AG, et al. Dose-volume effects in rat thoracolumbar spinal cord: an evaluation of NTCP models. Int J Radiat Oncol Biol Phys. 2004; 60:578–590. [PubMed: 15380595]
36. van Luijk P, Bijl HP, Konings AW, et al. Data on dose-volume effects in the rat spinal cord do not support existing NTCP models. Int J Radiat Oncol Biol Phys. 2005; 61:892–900. [PubMed: 15708272]
37. Philippens ME, Pop LA, Visser AG, et al. Dose-volume effects in rat thoracolumbar spinal cord: the effects of nonuniform dose distribution. Int J Radiat Oncol Biol Phys. 2007; 69:204–213. [PubMed: 17707274]
38. van der Kogel AJ. Radiation tolerance of the rat spinal cord: time-dose relationships. Radiology. 1977; 122:505–509. [PubMed: 834903]
39. Ruifrok AC, Kleiboer BJ, van der Kogel AJ. Reirradiation tolerance of the immature rat spinal cord. Radiother Oncol. 1992; 23:249–256. [PubMed: 1609129]
40. Knowles JF. The radiosensitivity of the guinea-pig spinal cord to X-rays: the effect of retreatment at one year and the effect of age at the time of irradiation. Int J Radiat Biol Relat Stud Phys Chem Med. 1983; 44:433–442. [PubMed: 6605947]
41. Ang KK, Jiang GL, Feng Y, et al. Extent and kinetics of recovery of occult spinal cord injury. International Journal of Radiation Oncology, Biology, Physics. 2001; 50:1013–1020.
42. Ruifrok AC, Stephens LC, van der Kogel AJ. Radiation response of the rat cervical spinal cord after irradiation at different ages: tolerance, latency and pathology. International Journal of Radiation Oncology, Biology, Physics. 1994; 29:73–79.
43. Ryu, S. Phase II/III Study of Image-Guided Radiosurgery/SBRT for Localized Spine Metastasis. Radiation Therapy Oncology Group; 2009. p. 0631
44. Moulding HD, Elder JB, Lis E, et al. Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases. J Neurosurg Spine. 2010; 13:87–93. [PubMed: 20594023]
45. Lovelock DM, Zhang Z, Jackson A, et al. Correlation of local failure with measures of dose insufficiency in the high-dose single-fraction treatment of bony metastases. Int J Radiat Oncol Biol Phys. 2010; 77:1282–1287. [PubMed: 20350795]
46. Chang EL, Shiu AS, Mendel E, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. J Neurosurg Spine. 2007; 7:151–160. [PubMed: 17688054]
47. Lo YC, McBride WH, Withers HR. The effect of single doses of radiation on mouse spinal cord. Int J Radiat Oncol Biol Phys. 1992; 22:57–63. [PubMed: 1727130]
48. Knowles JF. The effects of single dose X-irradiation on the guinea-pig spinal cord. Int J Radiat Biol Relat Stud Phys Chem Med. 1981; 40:265–275. [PubMed: 6974712]
49. van den Aardweg GJ, Hopewell JW, Whitehouse EM. The radiation response of the cervical spinal cord of the pig: effects of changing the irradiated volume. Int J Radiat Oncol Biol Phys. 1995; 31:51–55. [PubMed: 7995768]

Table 1

Dose response for four species (uniform irradiation, length > 16 mm)

Study	Species	Dose Rate (Gy/hr)	Source	ED_{50} (Gy)
Lo, et. al.(47)	mouse	155	250 kV xray	18.9 (17.8–19.9)*
Hopewell, et.al.(31)	rat	Not stated. Similar rad. Technique to Lo	250 kV xray	21.5±0.3SE
Scalliet, et. al.(18)	rat	107.6	^{60}Co	21.3(20.2–22.2)*
Scalliet, et. al.(18)	rat	14.7	^{60}Co	27.2(26.2–28.2)*
Bijl, et. al.(29)	rat	600–900	150–190 MeV proton	20.4 (no error estimate)
Knowles(40,48)	Guinea pig	65.4	250 kV xray	20.5 (no error estimate)
Van den Aardweg, et. al.(49)	pig	12.6–18	^{60}Co	28.3±0.8SE
Medin, et. al.(22)	pig	240–440	6 MV xray	18–20 (preliminary)

* 95% confidence interval

SE = standard error.

Table 2

Longitudinally Homogeneous Dose Response (Length Effect).

Study	Species	Location	Source	Length (mm)	ED50
Bijl, et. al.(29)	rat	cervical	150–190 MeV protons	2	87.8 (80.4–96.4)*
				4	53.7 (49.2–61.9)*
				8	24.9 (21.6–28.6)*
				20	20.4
Hopewell, et.al.(31)	rat	cervical-thoracic	250 kV xray	4	50.98(2.28)SE
				8	30.11(1.45) SE
				16	21.5(0.3) SE
van den Aardweg, et. al.(49)	pig	cervical	^{60}Co	25	28.28(0.78) SE
				50	27.68(0.57) SE
				100	27.02(0.36) SE

* 95% confidence interval

SE = standard error.

Table 3

Split-Dose Spinal Cord Tolerance

Field Arrangement	ED_{50} (Gy)
4 mm + 4 mm with 8 mm separation(27)	45.4 (40–50)*
4 mm + 4 mm with 12 mm separation(27)	41.6 (38–46)*
4 mm single field(29)	53.7 (49–62)*
8 mm single field(28,29)	24.9 (22–29)*

*95% confidence interval

Table 4

"Bath and Shower" Spinal Cord Tolerance.

Field Arrangement	Bath Dose (Gy)	ED_{50} (Gy)
4 mm Symmetric B&S(27)	4	39 (37–40)*
4 mm Symmetric B&S(27)	12	33.4 (32–35)*
4 mm Symmetric B&S(27)	18	31.3 (26–35)*
2 mm Symmetric B&S(28)	4	61.2 (55–68)*
2 mm Symmetric B&S(28)	18	30.9 (NA)
8 mm Symmetric B&S(28)	4	23.1 (22–24)*
4 mm Asymmetric Cranial B&S(27)	18	38.4 (34–43)*
4 mm Asymmetric Caudal B&S(27)	18	37.2 (34–43)*
2 mm Asymmetric Caudal B&S(28)	4	68.6 (64–74)*
2 mm single field(29)	NA	87.8 (80–96)*
4 mm single field(29)	NA	53.7 (49–62)*
8 mm single field(29)	NA	24.9 (22–29)*

* 95% confidence interval

Table 5

"Bath and shower" ED_{50} versus time interval(16).

	Functional ED_{50} (Gy)		Histologic ED_{50} (Gy)	
Time Interval	**Combined Dose B+S**	**Shower Dose**	**Combined Dose B+S**	**Shower Dose**
B+S 8 min	40.8 (38.5–42.8)*	36.8 (34.5–38.8)*	39.9 (37.8–41.7)*	35.9 (33.8–37.7)*
B+S 3 hr	44.4 (43.7–45.0)*	40.4 (39.7–41.0)*	44.2 (43.6–44.9)*	40.2 (39.6–40.9)*
B+S 12 hr	44.8 (42.6–47.1)*	40.8 (38.6–43.1)*	44.5 (42.1–46.8)*	40.5 (38.1–42.8)*
B+S 24 hr	51.9 (50.1–53.7)*	47.9 (46.1–49.7)*	49.3 (47.4–50.7)*	45.3 (43.4–46.7)*
S only	n/a	48.7 (44.7–51.6)*	n/a	46.9 (40.2–50.7)*

* 95% confidence interval

B = bath, S = shower