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CRITICAL REVIEW

SPINAL CORD TOLERANCE IN THE AGE OF SPINAL RADIOSURGERY: LESSONS FROM PRECLINICAL STUDIES

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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 1970s. 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 preclinical 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. Preclinical 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 are 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. © **2011 Elsevier Inc.**

Spinal cord, Radiation tolerance, Preclinical, Radiosurgery, Animal.

INTRODUCTION

Investigators of single-fraction spinal cord tolerance in the 1970s and 1980s 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-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 before 2003 included approximately 50 patients (2–5), but today one group alone has treated well over 1,000 lesions (6). The recent opening of a prospective Phase II/III study of image-guided radiosurgery/stereotactic body radiation therapy for localized spine metastases by the Radiation Therapy Oncology Group (RTOG 0631) has launched a new era in the investigation of spinal radiosurgery.

Although 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) after 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 more than 1.0 cm^3 of spinal cord to doses

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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. Although 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) follow-up period, c) comorbidity, d) previous therapies, e) neurologic assessment, and 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 four to seven dose groups with four to five subjects per group; thus, conclusions are drawn for a population from the response of 16–30 animals. The reader should consider the margin of error in any study, usually reported as a 95% confidence interval or as standard error. Animal studies frequently include a follow-up 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 follow-up period of 12 months or less, whereas 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, whereas vascular injury can lead to paralysis between 8 and 18 months (13). The authors of a pig study with 70–110 week follow-up reported that the latency for myelopathy was 7.5–16 weeks, but two pigs experienced late myelopathy at 64.5 and 75 weeks after 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 follow-up 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 with 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 dose leading to paralysis in 50% of animals (ED_{50}) 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 preclinical models with an emphasis on practical clinical significance. An understanding of spinal cord tolerance characteristics resulting from uniform irradiation is necessary before 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 $\geq$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} values clustered around 20 Gy. Before 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