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RADIATION DOSE–VOLUME EFFECTS IN THE SPINAL CORD

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Dose–volume data for myelopathy in humans treated with radiotherapy (RT) to the spine is reviewed, along with pertinent preclinical data. Using conventional fractionation of 1.8–2 Gy/fraction to the full-thickness cord, the estimated risk of myelopathy is <1% and <10% at 54 Gy and 61 Gy, respectively, with a calculated strong dependence on dose/fraction (α/β = 0.87 Gy.) Reirradiation data in animals and humans suggest partial repair of RT-induced subclinical damage becoming evident about 6 months post-RT and increasing over the next 2 years. Reports of myelopathy from stereotactic radiosurgery to spinal lesions appear rare (<1%) when the maximum spinal cord dose is limited to the equivalent of 13 Gy in a single fraction or 20 Gy in three fractions. However, long-term data are insufficient to calculate a dose–volume relationship for myelopathy when the partial cord is treated with a hypofractionated regimen. © 2010 Elsevier Inc.

QUANTEC, Spinal cord, Myelopathy, Radiosurgery.

CLINICAL SIGNIFICANCE

The spinal cord consists of bundles of motor and sensory tracts, surrounded by the thecal sac, which is, in turn, encased by the spinal canal (1). Although the cord proper extends from the base of skull through the top of the lumbar spine, individual nerves continue down the spinal canal to the level of the pelvis. Portions of the spinal cord are often included in radiotherapy (RT) fields for treatment of malignancies involving the neck, thorax, abdomen, and pelvis. In addition, metastatic disease to the bony spine, often requiring RT, is encountered in ~40% of all cancer patients (2). Though rare, RT-induced spinal cord injury (*i.e.*, myelopathy) can be severe, resulting in pain, paresthesias, sensory deficits, paralysis, Brown-Sequard syndrome, and bowel/bladder incontinence (3).

In this analysis, we consider three clinical scenarios for the development of myelopathy following: (1) *de novo* irradiation of the complete spinal cord cross-section via conventionally fractionated external beam RT, (2) reirradiation of the complete spinal cord cross-section after a previous course of conventional external beam RT, and (3) irradiation of a partial cross-section of the cord using high-dose/fraction stereotactic radiosurgery.

ENDPOINTS

Herein, myelopathy is defined as a Grade 2 or higher myelitis, per Common Terminology Criteria for Adverse Events v3.0 (4). Asymptomatic changes in the cord detected radiographically or mild signs/symptoms such as Babinski's sign or L'Hermitte syndrome are not classified as myelopathy for purpose of this analysis. Thus, a diagnosis of myelopathy is based on the appearance of signs/symptoms of sensory or motor deficits, loss of function or pain, now frequently confirmed by magnetic resonance imaging. Radiation myelopathy rarely occurs less than 6 months after completion of radiotherapy and most cases appear within 3 years (5).

In some situations, the question of recurrent tumor can confound the diagnosis of RT-induced myelopathy. Magnetic resonance imaging is useful in this regard with surgical resection/biopsy as indicated for diagnosis and, potentially, therapy.

CHALLENGES DEFINING VOLUMES

In conventional external beam RT, the field generally encompasses the entire circumference of the cord, vertebral body, and spinal nerve roots at the treated levels. Thus, precise organ definition is not critical in conventional RT apart from appropriately identifying the level of the involved cord. Delineation of the cord in body radiosurgery is unsettled (6) with various studies contouring the critical organ in the axial plane as the spinal cord, the spinal cord +2–3 mm, the thecal sac and its contents, or the spinal canal. As the high-dose regions may extend superiorly and inferiorly to

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Table 1. Summary of published reports of cervical spinal cord myelopathy in patients receiving conventional radiotherapy (18)

Institution	Dose (Gy)	Dose/fraction (Gy)	Cases of myelopathy/ total number of patients	Probability of myelopathy*	2-Gy dose equivalent†
Wake Forest (19)	60	2	1/12	0.090	60.0
	65	1.63	0/24	0.000	56.6
Caen (5)	54	3	7/15	0.622	72.8
Brookhaven (20)	19	9.5	4/13	0.437	68.6
Florida (21)	47.5	1.9	0/211	0.000	45.0
	52.5	1.9	0/22	0.000	49.8
	60	2	2/19	0.118	60.0
Yugoslavia (22)	65	1.63	0/19	0.000	56.6

* Calculated using the percentage of patients experiencing myelopathy corrected for overall survival as a function of time by the method in (18).

† Calculated using α/β = 0.87 Gy (18).

the target, several studies extend the critical organ volume above and below the target volume (*e.g.*, 6 mm inferiorly and superiorly in the case of Henry Ford Hospital) (7).

REVIEW OF DOSE–VOLUME DATA

Preclinical studies

A large number of small-animal studies have explored spinal cord tolerance to *de novo* radiation and reirradiation, including time-dependent repair of such damage. Several reports suggest regional differences in radiosensitivity across the spinal cord (8, 9). The clinical endpoint in most studies is paralysis, with the spinal cord showing nonspecific white matter necrosis. The pathogenesis of injury is generally believed to be primarily from vascular/endothelial damage, glial cell injury, or both (3, 9). Using focused protons, Bijl demonstrated large regional differences in rat spinal cord radiosensitivity (10, 11). There was a rightward shift in the dose–response curve from 21 Gy (ED50) with full thickness irradiation vs. 29–33 Gy for lateral cord treatment (wide and narrow geometry, respectively), and 72 Gy when only the central portion of the cord was treated. White matter necrosis was observed in all paralyzed rats, with none seen in animals not exhibiting paralysis. No damage was observed in central grey matter for doses up to 80 Gy. The differences in central vs. peripheral response were attributed to vascular density differences in these regions, with a potential role for differential oligodendrocyte progenitor cell distribution. However, an alternative explanation may be functional differences in the cord white matter regions irradiated, especially given the clinical endpoint of paralysis, which would not be expected if sensory tracts were preferentially irradiated. No similar published reports are available in higher order species, making application of these findings to highly conformal radiotherapy techniques, such as stereotactic body RT (SBRT) or intensity-modulated proton therapy, difficult.

Animal studies support a time-dependent model of repair for radiation damage to the spinal cord (12–17). For example, Ang (13) treated the thoracic and cervical spines of Rhesus monkeys to 44 Gy, and then reirradiated these animals with an additional 57 Gy at 1–2 years, or 66 Gy at 2–3 years, yielding aggregate doses of 101 and 110 Gy, respectively. The study endpoint was lower extremity weakness or balance disturbances at 2.5 years after reirradiation. Of 45 animals evaluated at the end of the observation period, 4 developed endpoint symptoms. A reirradiation tolerance model developed by combining these data with those of a prior study of single-dose tolerance in the same animal model (14) resulted in an estimated recovery of 34 Gy (76%), 38 Gy (85%), and 45 Gy (101%) at 1, 2, and 3 years, respectively. Under conservative assumptions, an estimated overall recovery of 26 Gy (61%) was calculated.

De novo irradiation—conventional radiotherapy in humans

A recent analysis used published reports of radiation myelopathy in 335 and 1,946 patients receiving radiotherapy to their cervical and thoracic spines, respectively (18). Although a few of these patients received relatively high doses/fraction, none were treated using stereotactic techniques to exclude a portion of the circumference of the cord. These data are summarized in Tables 1 and 2. Note that the dose to the cord is the prescribed dose reported in those studies; typically, dosimetric data were not available to calculate the true cord dose. An α/β ratio of 0.87 Gy was estimated from the data and used to calculate the 2-Gy dose per fraction equivalent total dose for each regimen, as described in the following section. Note that this α/β ratio is less than the values of 2–4 Gy frequently encountered in the literature and predicts a more severe effect at larger doses per fraction.

Reirradiation of the spinal cord

In evaluating reirradiation of the spinal cord, one must not only consider the dose regimen for each course and the volume and region (re)irradiated but also the time interval between the courses of RT (35). Table 3 summarizes published reports involving reirradiation of the spinal cord using both conventional, full-circumference external beam RT and SBRT. For purposes of comparing different regimens, an α/β of 3 Gy was used to calculate the biologically equivalent dose in Gy_3 and both α/β values of 1 and 3 Gy were employed to calculate the 2-Gy per fraction equivalent dose. In all of these studies, the median interval between

Table 2. Summary of published reports of thoracic spinal cord myelopathy in patients receiving conventional radiotherapy (18)

Institution	Dose (Gy)	Dose/fraction (Gy)	Cases of myelopathy/total number of patients	Probability of myelopathy*	2-Gy dose equivalent†
MCV (23)	45	3	1/16	0.093	60.7
MGH (24)	45	3	0/75	0.000	60.7
Abramson (25)	40	4	4/271	0.063	67.9
MUSC (26)	40	4	6/45	0.332	67.9
Leicester (27)	40	4	1/43	0.284	67.9
Iowa (28)	40	4	0/42	0.000	67.9
Mt. Vernon (29)	34.4	5.7	13/145	0.278	78.9
Norway (30)	38	3×6 Gy + 5×4 Gy	8/157	0.196	77.0
	38	3×6 Gy + 3×4 Gy + 2×2 Gy	9/230	0.151	67.4
Berlin (31)	66.2	2.45	8/142	0.256	76.5
Virginia (32)	40	5 x 4 Gy + 8 x 2.5 Gy	2/248	0.028	57.4
UK NIRC (33, 34)	18.4	9.2	3/524	0.032	64.5
	39.8	3.06	2/153	0.062	54.5

* Calculated using the percentage of patients experiencing myelopathy corrected for overall survival as a function of time by the method in (18).

† Calculated using $\alpha/\beta = 0.87$ Gy (18).

courses was at least 6 months and only a small number of cases were treated at intervals less than 6 months. Note that few cases of myelopathy are reported despite large cumulative doses, with essentially no cases of myelopathy observed for cumulative doses $\leq$60 Gy in 2-Gy equivalent doses. These data are consistent with the observations of post-RT repair observed in the animal models.

SBRT of the spine in humans

Published reports of radiation myelopathy from SBRT to the spine are summarized in Table 4. These studies include *de novo* RT alone, reirradiation alone, and combination of the two (mixed series.)

FACTORS AFFECTING RISK

Animal studies suggest that the immature spine is slightly more susceptible to radiation-induced complications and the latent period is shorter (13, 57–59). For example, Ruifrok (57) found that the 50% effect dose in 1-week-old rats was 19.5 Gy vs. 21.5 Gy in adult animals ($p < 0.05$). The latency to complications increased from about 2 weeks after irradiation in the 1-week-old rats to 6–8 months in the adults (59). Although the ultimate white matter changes were the same in animals independent of age, vasculopathy increased with increasing age at irradiation (59) Though the literature on radiation-induced myelopathy is sparse, care should be exercised in irradiating the pediatric spine because of the increased sensitivity of the child's developing central nervous system and bone to ionizing radiation (60)

In rats, the use of various chemotherapy agents during radiotherapy has been shown to increase the radiosensitivity of the spinal cord. Administration of intrathecal ara-C (61) or intraperitoneal fludarabine (62) immediately before irradiation of the spinal cord showed an enhanced effect on radiation-induced injury, yielding a dose modifying factor of 1.2–1.3. There are rare reports of radiation myelopathy at relatively low doses in human patients post chemotherapy (63–66). Dosimetry data are limited for this small number of cases and it is difficult to draw any absolute conclusions. Note that many chemotherapeutic agents are neurotoxic in their own right (67) and caution is advised in their concurrent use during irradiation of the central nervous system (68).

MODELS

Conventionally fractionated, full-circumference irradiation

Using the data in Tables 1 and 2, Schultheiss (18, 69) estimated the risk of myelopathy as a function of dose using a probability distribution model. In this model, the probability of myelopathy was derived from the data in Tables 1 and 2 adjusted for estimated overall survival (18). A good fit to the combined cervical and thoracic cord data was not possible and separate analyses were performed. For the cervical cord data, values of $D_{50} = 69.4$ Gy and $\alpha/\beta = 0.87$ Gy were obtained with a Pearson χ^2 statistic of 2.1 for 5 degrees of freedom, providing a reasonable fit of the model as shown in Figure 1. The 95% confidence interval was 66.4 to 72.6 Gy for D_{50} and 0.54 to 1.19 Gy for α/β. At 2- Gy per fraction, the probability of myelopathy is 0.03% at 45 Gy and 0.2% at 50 Gy. However, the further one gets in the tail of the dose–response function, the more dependent the estimates become on the statistical distribution used to model this function.

Because of the dispersion in thoracic data, it is not possible to obtain a good fit to the data. As shown in Figure 2, thoracic cord data points generally lie to the right of the dose–response curve for the cervical cord. This suggests that the thoracic cord is less radiation sensitive than the cervical cord.

Table 3. Summary of published reports involving reirradiation of the spinal cord

Institution	Cases of myelopathy/ total patients	Median F/U (months)	BED, initial course, (Gy_3) Median (Range)	BED, reirradiation (Gy_3) Median (range)	Interval between courses (months) Median (range)	Total BED (Gy_3) Median (range)	2- Gy dose equivalent, α/β = 3 Gy Median (range)	2- Gy dose equivalent, α/β = 1 Gy Median (range)
MSK (36)	0/37	8	60 (10–101)	16 5–50	19 (2–125)	79 (21–117)	47 (13–70)	51 (8–100)
VU (37)	0/34		—	—	—	<100	<60	<60
Munich (38, 39)	0/15	30	70 (34–83)	50 (38–83)	30 (6–96)	115 (91–166)	69 (54–100)	70 (48–107)
Mayo (40)	4/54	4*	60	37	10 (1–51)	97	58	62
Cases with myelopathy	4		All 60	73† (29–115)	9 (5–21)	133 (109–175)	80 (65–105)	83 (69–89)
Henry Ford (41)	0/1	60	75	72	144	147	88	86
UCI (42)	0/1	8	75	42	37	117	70	67
Ontario (43)	0/2	>3–9	(40–56)	(18–35)	(8–20)	(58–91)	(35–57)	(28–51)
VU (44)	0/8		56 (29–78)	42 (36–83)	30 (4–152)	106 (65–159)	64 (39–96)	69 (48–93)
Brescia (45)	0/5	168	47 (32–47)	55 (33–67)	24 (12–36)	94 (80–113)	57 (48–68)	56 (47–67)
Hamburg (46)	0/62	12	29 (29–47)	29 (29–47)	6 (2–40)	69 (59–77)	41 (35–46)	53 (48–57)
Melbourne (47)	0/6	15	All 73	36 (32–39)	15	106 (103–109)	63 (62–65)	66 (64–68)
Princess Margaret (48)	11/–	11	72 (28–96)	42 (14–86)	11 (2–71)	115 (100–138)	69 (60–83)	80 (65–94)
Cases with myelopathy								
Stereotactic body radiotherapy								
Korea (49)	1/3	24	(60–81)	(64–154)	(18–120)	(145–235)	(87–141)	(98–179)
Case with myelopathy	1		81	154	18	235	141	179
No myelopathy	2		60, 81	64, 90	54, 120	145, 150	87, 90	98,114

* Overall survival.

† One patient received two courses of reirradiation, 1 received three courses.

Table 4. Summary of 9 published reports of spinal cord doses and myelopathy in patients receiving stereotactic radiosurgery

Institution (ref.)	Cases of myelopathy/total patients	Total dose (Gy)	Dose/fraction (Gy)	Dose to cord (Gy)	BED to cord (Gy_3)	Proportion of patients previously irradiated to involved segment of spine
Stanford and Pittsburgh (50)	6/1075	12.5–25 ***25*** ***20*** ***21*** ***24*** ***20*** ***20***	5–25 ***12.5*** ***10*** ***10.5*** ***8*** ***2*** ***20***	D_{max}: 3.6–30 ***D_{max}: 26.2*** ***D_{max}: 19.2*** ***D_{max}: 13.9*** ***D_{max}: 29.9*** ***D_{max}: 8.5*** ***D_{max}: 10***	Range: 24–141 Gy_3 ***D_{max}: 141*** ***D_{max}: 81*** ***D_{max}: 46*** ***D_{max}: 129*** ***D_{max}: 33*** ***D_{max}: 43***	>55%
Henry Ford (7)	1/86*	<10–18	<10–18	Mean ± SD D_{max}: 12.2 ± 2.5 D1: 10.7 ± 2.3 D10: 8.6 2.1 Maximum D_{max}: 19.2 D1: 15.8 D10: 13	Mean ± SD D_{max}: 62 ± 4.6 D1: 49 ± 4.1 D10: 33 ± 3.6 Maximum D_{max}: 142 D1: 99 D10: 69	0%
		18†	18	Mean ± SD D_{max}: 13.8 ± 2.2 D1: 12.1 ± 1.9 D10: 9.8 ± 1.5	Mean ± SD D_{max}: 77 ± 3.8 D1: 61 ± 3.1 D10: 42 ± 2.3	
		16	***16***	***Dmax:14.8*** ***D1: 13.0*** ***D10: 9.6***	***Dmax:88*** ***D1:69*** ***D10: 40***	
Korea (49)	2/9	21–44	3–5	Median D_{max}:32.9 D25:11.0 Range Dmax: 11–37 D25: 1.2–24	Median D_{max}:106 D25:21 Range D_{max}: 19–172 D25: 1–88	33%
		30	***10***	***D_{max}: 35.2*** ***D25: 15.5***	***D_{max}:172*** ***D25: 42***	
		33	***11***	***D_{max}: 32.9 D25: 24.0***	***153*** ***88***	
NYMC (51)‡	3/31	Median: 10 ***100*** ***12*** ***20***	Median: 5 ***50*** ***12*** ***5***	Median: 6.0	12	Unknown
UCSF (52)	0/38	24	8	Median $D_{0.1cc}$: 10.5 D_{1cc}: 7.4	Median $D_{0.1cc}$: 23 D_{1cc}: 14	62%
UCSF (53)	0/16	21	7	Median D_{max}: 20.9 $D_{0.1cc}$: 16.6 D_{1cc}: 13.8 Range D_{max}: 4.3–23 $D_{0.1cc}$: 3.4–22 D_{1cc}: 2.8–19	Median $D_{0.1cc}$: 61 D_{1cc}: 22 Range $D_{0.1cc}$: 7–76 D_{1cc}: 6–54	6%
MDACC (54)	0/63	30 patients: 30 33 patients: 27	30 patients: 6 33 patients: 9	30 patients: <10 33 patients:<9	30 patients: <16.7 33 patients: <18	56%
Pittsburgh (55)	0/50	19	19	Mean D_{max}: 10 Range D_{max}: 6.5–13	Mean D_{max}: 21 Range Dmax: 11–32	96%

(*Continued*)

Table 4. Summary of 9 published reports of spinal cord doses and myelopathy in patients receiving stereotactic radiosurgery (*Continued*)

Institution (ref.)	Cases of myelopathy/total patients	Total dose (Gy)	Dose/fraction (Gy)	Dose to cord (Gy)	BED to cord (Gy_3)	Proportion of patients previously irradiated to involved segment of spine
Duke (56)	0/32	Median:18	Median: 7	Mean ± SD D_{max}: 14.4±2.3 D1: 13.1±2.2 D10: 11.5±2.1 Maximum D_{max}: 19.2 D1: 17.4 D10: 15.2	Mean ± SD D_{max}: 46.0±13.2 D1: 39.0±10.8 D10: 31.2±8.1 Maximum D_{max}: 78.3 D1: 59.1 D10: 46.5	58%

All patients within that institutional series are shown in normal font; myelopathy cases shown in ***bold italics.***
* Patients surviving at least 1 year.
† Results for subset of 39 lesions treated at Henry Ford Hospital with a single 18-Gy fraction.
‡ For the NYMC data (51), the cord dose was calculated assuming that the total dose was delivered in two fractions. Although the cord dose for the patients developing myelopathy were not given in the paper, the total BED to the tumor for the 3 patients experiencing myelopathy was 53.3, 60, and ~167 Gy_3 vs. <50 Gy_3 for patients without myelopathy.

The applicability of the linear-quadratic model at high dose per fraction encountered in radiosurgery is controversial and the biologically equivalent doses calculated using $\alpha/\beta = 3$ Gy in Table 4 are intended solely for roughly comparing regimens. In particular, it is not appropriate to extrapolate cord tolerance data obtained at a low dose per fraction to regimens using 10 Gy or more/fraction (70).

SPECIAL SITUATIONS

As discussed in detail previously, hypofractionation via radiosurgery is increasingly employed in the treatment of spinal lesions. Though reports of toxicity are rare, the follow-up time is short and patient numbers small. Caution should be observed in specifying the dose, taking special care to limit the dose to the cord by precise immobilization and image guidance. Predictions based on conventional fractionation should not be applied to such treatments without further careful study. The effect of concurrent chemotherapy is essentially unknown in that situation.

RECOMMENDED DOSE–VOLUME LIMITS

With conventional fractionation of 2 Gy per day including the full cord cross-section, a total dose of 50 Gy, 60 Gy, and ~69 Gy are associated with a 0.2, 6, and 50% rate of myelopathy. For reirradiation of the full cord cross-section at 2 Gy per day after prior conventionally fractionated treatment, cord tolerance appears to increase at least 25% 6 months after the initial course of RT based on animal and human studies. For partial cord irradiation as part of spine radiosurgery, a maximum cord dose of 13 Gy in a single fraction or 20 Gy in three fractions appears associated with a <1% risk of injury.

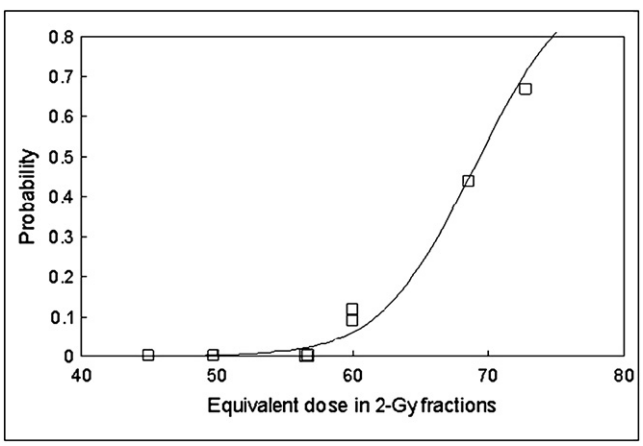

Fig. 1. The dose–response function for the myelopathy of the cervical spinal cord and data points (□) derived from Table 1. The probability of myelopathy was calculated from the data in Table 1, adjusted for estimated overall survival per (18).

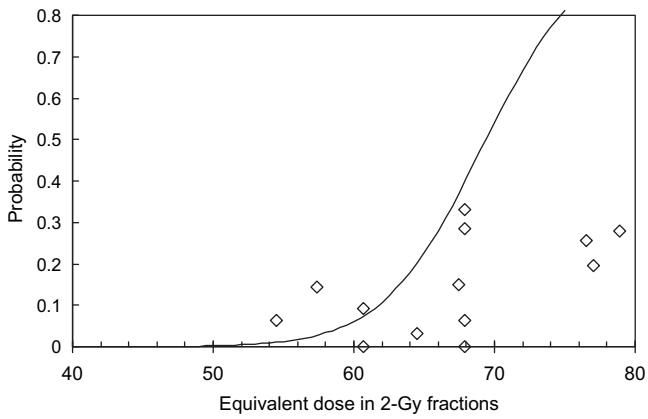

Fig. 2. The dose–response function for myelopathy of the cervical cord (solid line) and data points for the thoracic spinal cord (◇) derived from Table 2. The probability of myelopathy was calculated from the data in Tables 1 and 2, adjusted for estimated overall survival per (18).

FUTURE TOXICITY STUDIES

In cases where it is appropriate to irradiate only a partial circumference of the cord (as in irradiation of vertebral body lesions) or spare the interior of the cord (epidural disease), dose tolerance may be increased. SBRT, particularly using intensity-modulated RT techniques, appears well suited for that purpose, as it can be used to deliver concave-shaped RT dose distributions around organs at risk (56). Studies to better understand the importance of the spatial distribution of dose (and, hence, the utility of partial circumferential sparing) would be useful.

For SBRT of spinal lesions, multi-institutional data need to be carefully collected over several years' time to better estimate the risk of acute and long-term toxicity. At a minimum, participating institutions should report detailed demographics, current treatment factors (anatomic location of the target lesion, cord volume, number of vertebral segments involved, number of fractions, D_{max}, D_1, D_{10}, D_{50}, $D_{0.1cc}$, and $D_{1cc,}$), history of concurrent and prior therapies (including the time interval from, dose and fractionation of previous radiotherapy to the involved levels), and treatment-related toxicity, particularly neurologic deficits.

Given the low frequency of neurologic deficits in patients receiving spinal radiotherapy, further animal studies designed to understand the relationship between dose, fractionation dose distributions, and time between treatment courses would be useful.

TOXICITY SCORING

We recommend that the Common Terminology Criteria for Adverse Events (version 3) be used to score both acute and late spinal cord injury.

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