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Spinal cord tolerance

Spinal cord tolerance to single-session uniform irradiation in pigs: Implications for a dose-volume effect

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ABSTRACT

Background and purpose: This study was performed to test the hypothesis that spinal cord radiosensitivity is significantly modified by uniform versus laterally non-uniform dose distributions.

Materials and methods: A uniform dose distribution was delivered to a 4.5–7.0 cm length of cervical spinal cord in 22 mature Yucatan minipigs for comparison with a companion study in which a laterally non-uniform dose was given [1]. Pigs were allocated into four dose groups with mean maximum spinal cord doses of 17.5 ± 0.1 Gy ($n = 7$), 19.5 ± 0.2 Gy ($n = 6$), 22.0 ± 0.1 Gy ($n = 5$), and 24.1 ± 0.2 Gy ($n = 4$). The study endpoint was motor neurologic deficit determined by a change in gait within one year. Spinal cord sections were stained with a Luxol fast blue/periodic acid Schiff combination.

Results: Dose–response curves for uniform versus non-uniform spinal cord irradiation were nearly identical with ED_{50}'s (95% confidence interval) of 20.2 Gy (19.1–25.8) and 20.0 Gy (18.3–21.7), respectively. No neurologic change was observed for either dose distribution when the maximum spinal cord dose was $\leqslant$17.8 Gy while all animals experienced deficits at doses $\geqslant$21.8 Gy.

Conclusion: No dose-volume effect was observed in pigs for the dose distributions studied and the endpoint of motor neurologic deficit; however, partial spinal cord irradiation resulted in less debilitating neurologic morbidity and histopathology.

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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 [2]. Early efforts to investigate dose-volume effects in the spinal cord were limited to characterizing the influence of irradiated length on response [3–5]. Pioneering work in frame-based spinal radiosurgery at the University of Arizona [6], followed by the development of image-guidance and dose-shaping technologies, provided tools to localize and irradiate lesions of the spine while minimizing dose to the spinal cord but the effect of the resulting complex dose distributions on spinal cord tolerance was unknown. Since 2001, many studies performed in rats have demonstrated that spinal cord tolerance is modified by non-uniform dose distributions [7] including steep lateral dose gradients [8–10], longitudinal dose inhomogeneity [3,11], and selective regional irradiation [9]. These studies were never repeated in a large animal. A general perception that dose-volume effects play a role in human spinal cord tolerance permeates the radiosurgery literature [12–15].

In this study, pigs received de novo single-session irradiation using a uniform dose distribution for comparison to a previous study in which the same cervical spinal cord segments received a steep lateral dose gradient [1]. Spinal cord tolerance to uniform irradiation has not previously been studied in a large animal under conditions relevant to clinical stereotactic body radiotherapy and the lateral dose-volume effect has not previously been studied in a model with spinal cord dimensions equivalent to humans. The inclusion of human clinical treatment parameters in this study may be responsible for the difference between these results and those of previous studies and may serve to refine models of normal tissue complication probability [16].

Methods and materials

This study conformed to all national and local regulations regarding the use of animals for research and was approved by the Institutional Animal Care and Use Committee. A total of 50 female Yucatan minipigs were enrolled to study dose-volume effects in the cervical spinal cord. Pigs were randomly assigned to receive either uniform or partial-volume single-session irradiation to the same spinal cord segments. Twenty-two pigs received uniform

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Table 1
Dose and time parameters for individual irradiated animals.

ID#	Rx dose (Gy)	Irradiated spinal cord length (cm)	Irradiated spinal cord level	Image-guidance/ irradiation platform	Maximum spinal cord dose (Gy)	Age at SRS (weeks)	Follow-up period (weeks)	Latency (weeks)	Overall Tx time (min)
1	16	4.5	MidC4–midC7	X/N	17.6	45	56	NA*	14
2	16	5.1	MidC4–midC7	X/N	17.6	43	55	NA*	10
3	16	6.8	C5–C7	X/N	17.4	45	52	NA*	11
4	16	7.0	C5–C7	X/N	17.4	45	53	NA*	14
5	16	7.0	C5–C7	X/N	17.4	45	53	NA*	8
6	16	7.0	C5–C7	X/N	17.6	45	53	NA*	10
7	16	7.0	C5–C7	X/N	17.8	46	53	NA*	10
8	18	5.1	C5–midC7	X/N	19.2	102	25	8	12
9	18	5.1	C5–midC7	X/N	19.4	99	54	NA*	12
10	18	5.1	C5–midC7	X/N	19.2	99	54	NA*	10
11	18	5.1	MidC4–midC7	V/S	19.7	46	54	NA*	22
12	18	5.1	MidC4–midC7	V/S	19.7	46	51	NA*	25
13	18	5.1	MidC4–midC7	V/S	19.7	47	52	NA*	25
14	20	5.1	MidC4–midC7	X/N	21.8	43	55	10	12
15	20	5.1	MidC4–midC7	X/N	22.0	42	14	9	10
16	20	5.1	MidC4–midC7	V/S	22.1	45	11	10	19
17	20	5.1	MidC4–midC7	V/S	21.9	47	14	13	17
18	20	5.1	MidC4–midC7	V/S	21.9	45	11	10	20
19	22	5.1	MidC4–midC7	V/S	24.0	46	9	9	26
20	22	5.1	MidC4–midC7	V/S	24.1	46	12	12	24
21	22	5.1	MidC4–midC7	V/S	24.1	45	11	11	23
22	22	5.1	MidC4–midC7	V/S	24.4	47	10	10	20

C = cervical.
X = Stereoscopic X-ray.
N = Novalis.
V = Volumetric cone beam computed tomography.
S = Synergy S.
* No motor neurologic deficits were observed in stated follow-up period.

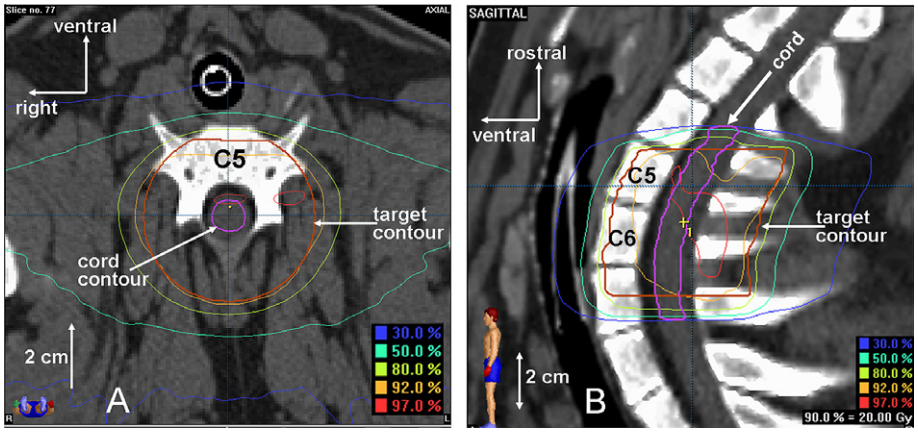

Fig. 1. Dose distributions in the axial (A) and sagittal (B) planes.

irradiation and are described here. Twenty-six pigs were assigned to receive partial-volume irradiation and have been reported previously [1]. Two pigs served as unirradiated controls.

Animals that received uniform spinal cord irradiation were 42–102 weeks old and weighed approximately 35–60 kg when irradiated. Treatment parameters for all individual animals are presented in Table 1 including: (a) prescription dose group, (b) irradiated spinal cord length, (c) irradiated spinal cord level, (d) image-guidance/irradiation platform, (e) maximum spinal cord dose, (f) age, (g) follow-up period, (h) latency to response, and (i) overall treatment time. All animals received a treatment planning CT scan with 0.75–1.5 mm thick slices and a 300-500 cm field of view. Treatment planning calculations were performed using either *Brainscan 5.31* software (BrainLAB, AG, Feldkirchen) or *Pinnacle*^{3} *8.0m* (Philips Electronics N.V., Eindhoven). Radiation was delivered in a single session to a cylindrical target volume 4.5–7.0 cm in length and 5 cm in diameter that was centered on the spinal cord. In the rostral/caudal direction, the target volume was centered at the level of the sixth cervical vertebral body. Dose distributions in the axial and sagittal planes are shown in Fig. 1. Treatment plans consisted of a series of 4–6 dynamically-shaped arcs or 12 conformal fields arranged with the goal of creating a uniform dose distribution through the spinal cord. The spinal cord volume was defined on CT images by contracting the thecal sac contour by 1.5 mm in the axial plane. This method was based on CT/MRI fusion of two animals and is consistent with the method used in a companion study [1]. The spinal cord was contoured 5.5–6.5 mm beyond the irradiated volume in the rostral and caudal directions and the dose calculation grid resolution through the spinal cord ranged from 1.5 to 1.8 mm. Dose distributions were normalized