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Paralysis following stereotactic spinal irradiation in pigs suggests a tolerance constraint for single-session irradiation of the spinal nerve

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Abstract

Background and Purpose—Paralysis observed during a study of vertebral bone tolerance to single-session irradiation led to further study of the dose-related incidence of motor peripheral neuropathy.

Materials and Methods—During a bone tolerance study, cervical spinal nerves of 15 minipigs received bilateral irradiation to levels C5–C8 distributed into three dose groups with mean maximum spinal nerve doses of $16.9 \pm 0.3 \text{ Gy}$ ($n=5$), $18.7 \pm 0.5 \text{ Gy}$ ($n=5$), and $24.3 \pm 0.8 \text{ Gy}$ ($n=5$). Changes developing in the gait of the group of pigs receiving a mean maximum dose of 24.3 Gy after 10 – 15 weeks led to the irradiation of two additional animals. They received mean maximum dose of $24.9 \pm 0.2 \text{ Gy}$ ($n=2$), targeted to the left spinal nerves of C5 – C8. The followup period was one year. Histologic sections from spinal cords and available spinal nerves were evaluated. MR imaging was performed on pigs in the 24.9Gy group.

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Conflicts of Interest Notification

Paul Medin teaches in radiosurgery courses sponsored by BrainLAB AG. Ryan Foster has received research funding from Elekta, Ltd. Remaining authors declare no conflicts of interest.

Results—No pig that received a maximum spinal nerve point dose 19.0Gy experienced a change in gait while all pigs that received 24.1Gy experienced paralysis. Extensive degeneration and fibrosis were observed in irradiated spinal nerves from the 24.9Gy animals. All spinal cord sections were normal. Irradiated spinal nerve regions showed increased thickness and hypointensity on MR imaging.

Conclusion—The single-session tolerance dose of the cervical spinal nerves lies between 19.0 and 24.1 Gy for this model.

Keywords

spinal nerve; radiation neuropathy; stereotactic ablative radiotherapy; stereotactic body radiation therapy; swine

Introduction

Animal studies of spinal cord tolerance to single-session irradiation have been ongoing since the 1970's (1) but the effort toward characterizing the radiation response of the peripheral nervous system has been comparatively minimal. There is no consensus regarding the radiation tolerance of the peripheral nervous system. Much of the information regarding tolerance of peripheral neural tissue to high-dose radiation arises from studies in dogs in which the sciatic nerve and/or lumbosacral nerve plexus was exposed to a radiation source in a way that mimicked the scenario of intra-operative radiation therapy (IORT) (2–4). The outcomes of these IORT studies were variable which is in contrast to studies of spinal cord tolerance in animals that report very homogeneous results (ED_{50} 's close to 20Gy for rats (5–7), guinea pigs(8), mice(9) and pigs(10)).

Relevance of data from IORT studies to stereotactic ablative radiotherapy (SAbR) can be questioned since surgical skeletonization of nerves may not reflect tolerance in the setting of non-invasive external beam irradiation. Vujaskovic et al. (2) noted that surgical exposure of a nerve may lead to a degree of devascularization sufficient to induce hypoxia resulting in radioprotection; alternatively, repair of the nerve may be hindered in the setting of devascularization. Lin et al. (11) reported an animal (rabbit) model of SAbR, in which high-dose radiation was delivered to the rabbit sciatic nerve. A 7.7 mm diameter collimator was used to deliver a 25Gy radiation dose. At seven months post-treatment, none of the 12 rabbits treated displayed functional consequences, although subsequent histologic analysis revealed areas of axonal degeneration and necrosis.

In a recent study of vertebral body bone tolerance in pigs, we observed paralysis in all five animals that received maximum point doses of 24.3 ± 0.8 Gy to cervical spinal nerves adjacent to the targeted vertebral bodies. This observation led to an analysis of the dose received by the involved spinal nerves and spinal cord of all fifteen animals in the bone study. Subsequently, two additional animals received targeted spinal nerve irradiation to evaluate the cause of paralysis, to provide magnetic resonance (MR) imaging data and to provide nerve tissue for histologic analysis.

Methods and Materials

Seventeen Yucatan minipigs were each irradiated in a single session with a large dose of xrays in compliance with protocols approved by the Institutional Animal Care and Use Committee. Fifteen of the seventeen pigs were included in a study of cervical vertebral body bone tolerance and received partial irradiation of bilateral spinal nerve levels C5–C8 as an unavoidable consequence of vertebral body irradiation. The final two pigs received targeted

unilateral irradiation to left-side nerve levels C5–C8 only. One additional animal functioned as an unirradiated control.

Animals were 45–54 weeks old and weighed approximately 35–48kg when irradiated. Treatment/response parameters for all individual animals are presented in Table 1 supplement. All animals received a treatment planning CT scan with 0.7–1.5mm thick slices and a 350–500cm field of view. Treatment planning calculations were performed using either *Brainscan 5.31* (BrainLAB, AG, Feldkirchen) or *Pinnacle³ 9.0* software (Philips Electronics N.V., Eindhoven). Each animal was irradiated according to one of four dose distributions. Axial planes of the four dose distributions used are presented in Figure 1A–D. The axial planes are representative of the dose distributions throughout the irradiated volume because treatment plans were generated with the goal of creating a uniform distribution in the right/left and rostral/caudal directions. Treatment plan “A” (Figure 1A) consisted of a series of 6 dynamically-shaped arcs arranged with the goals of uniformly irradiating the C5–C7 vertebral bodies and spinal cord while minimizing the dose to the esophagus. The spinal cord was intentionally irradiated in group “A” because these animals were also enrolled in a companion study investigating spinal cord tolerance (10). Treatment plans “B” and “C” (Figures 1B and 1C, respectively) consisted of a series of 10 conformal fields arranged with the goals of uniformly irradiating the C5–C7 vertebral bodies while minimizing the dose to the spinal cord and esophagus. Treatment plan D (Figure 1D) consisted of a series of 15 conformal fields arranged with the goals of uniformly irradiating the C5–C8 left proximal spinal nerves while minimizing the dose to the spinal cord. All dose distributions in Figure 1 are shown on the same axial MR image (multi-echo fast field echo) from an age-matched pig that was fused to the original CT-based treatment plans because MR imaging was not performed prior to irradiation. The quality of image fusion was considered to be very good based on visual comparison of the spinal anatomy.

Treatment planning dose-length or dose-volume statistics for the spinal nerves and spinal cord are summarized in Table 2 supplement including separate entries for ‘left’ and ‘right’ nerves for animals in group “D.” Dose statistics reported for the spinal nerves were determined by observing the dose distributions displayed on axial CT images with the aid of an axial MR imaging series from an age-matched pig that was fused to the original CT-based treatment plans after irradiation. The methods used for contouring the spinal cord, image guidance, immobilization, anesthetization and irradiation have been described previously (10).

After radiosurgery, animals were followed for 52–55 weeks or until paralysis was observed. The general health of animals was observed daily with attention toward unusual restlessness, vocalizing, loss of mobility, licking, biting, or guarding of a painful area, failure to groom, unkempt appearance, open sores, skin lesions, loss of appetite, and weight loss. Gait was observed approximately weekly with the animal walking freely in a large space. Response was defined as any study-related paralysis. A veterinarian evaluated all responders for symptoms indicative of pain. Magnetic resonance (MR) imaging at 3-Tesla (Achieva, Philips Medical Systems, Best, The Netherlands) was performed on both pigs in the dose group “D” (Figure 1D) within three days of presentation with motor neurologic deficits. Fast field echo (FFE), T2-weighted fluid attenuation inversion recovery (FLAIR) and T1-weighted turbo spin echo (TSE) sequences were acquired before contrast, and T1-weighted TSE images were acquired after contrast (gadopentetate dimeglumine, 0.2 mmol/kg, Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ). Images were reformatted into sagittal or axial planes and interpreted by a radiologist.

Bilateral spinal nerves were harvested from all animals, except those in group “C” (Figure 1C). Individual spinal nerves were skeletonized to a length of approximately 1.5–2.0 cm and

removed from levels C5, C6, C7, C8, and T1. Nerves were fixed in formalin before being sectioned and processed for embedding in paraffin. Longitudinal and axial sections were cut from the left-sided spinal nerves at each level as illustrated in Figure 2. The inset in Figure 2 shows the regions of nerve cut for longitudinal “A,” and axial “B” sections. All sections were stained with a Luxol fast blue/periodic acid Schiff combination and were examined for histology. Bilateral spinal nerves were stained for the two animals in group “D” (Figure 1D). The cervical spinal cords of all animals were removed and fixed in formalin before being sectioned and processed for embedding in paraffin. Five uniformly distributed axial sections through the irradiated volume of each animal were cut and stained with a Luxol fast blue/periodic acid Schiff combination and were examined for histology.

The dose-related incidence of paralysis was used as an endpoint to obtain quantal data that was then analyzed by probit analysis (12).

Results

The observation of paralysis during a study of bone tolerance led to further investigation of spinal nerve toxicity in pigs. Pigs in dose groups “A,” “B,” and “C,” (Tables 1 and 2) were enrolled in the original bone study while pigs in group “D” were subsequently added to evaluate the cause of paralysis, to provide MR imaging data and to provide nerve tissue for histologic analysis. Duration of follow-up, latency until response and dosimetric parameters for all dose groups are presented in Tables 1 and 2. A clear dose-response relationship was observed as all pigs that received maximum spinal nerve doses 24.1Gy developed front limb paralysis on the irradiated side(s) while all pigs that received 19.0Gy maintained their normal gait. A probit analysis was performed but with the minimal dose range and small numbers, an adequate fit was not possible. A probit model incorporating non-parametric density estimation was also performed with convergence failure. Though a complete probit model could not be performed, a point estimate of 22.1Gy for ED₅₀ was obtained. Paralysis presented initially as a mild limp and progressed to limb weakness and/or immobility within 1–3 weeks. The latent period for the first observed indication of paralysis ranged from 10–15 weeks. A non-steroidal anti-inflammatory drug (Carprofen, *Pfizer Inc., New York*, 200mg per day, 3–10 days) was given to 4 pigs in group “C” (Figure 1C) after their initial response but no consistent response was observed. No changes were observed on the unirradiated side of the two unilateral-irradiated pigs (#16 and #17 in Table 1). Two animals in group “C” experienced loss of appetite which may be indicative of pain.

T1-weighted signal hyperintensity was observed in vertebral bodies C5–7 (Figure 3A). The spinal nerves on the irradiated side were thickened and generally showed decreased signal intensity on all signal sequences (Figure 3B–D). Irregular contrast enhancement was seen as a minor feature involving few spinal nerves (data not shown).

No spinal nerve degeneration was observed in any of the animals in groups “A” or “B” (pigs #1 through #10 in Table 1). Spinal nerves were not harvested from animals in group “C” (pigs #11 through #15 in Table 1). Histology of spinal nerves from an animal in group “D” is presented in Figure 4 supplement. Longitudinal and axial sections from the unirradiated side are shown on the left (Figures 4A, 4C) while sections from the irradiated side are shown on the right (Figures 4B, 4D). All sections are from nerve segments that received 24–25 Gy and were stained with Luxol Fast Blue and periodic acid Schiff. Observed changes consist mostly of extensive fibrosis, while individual nerve fibers show swollen axons and disrupted myelin sheaths (Figures 4B, 4D). The replacement of myelinated fibers by fibrotic tissue is clearly seen in the irradiated nerves while the unirradiated side is normal. No histologic damage was observed in the white or gray matter from the spinal cord tissue of any animal in this study.

Discussion

Previous animal studies sought to characterize the tolerance of peripheral nerves (2–4) in the setting of IORT but the relevance of data from these studies to SAbR can be questioned due to the significant differences between these procedures. For example, IORT studies included surgical intervention and irradiation of large volumes which may both alter radiation response. Lin et al. (11) investigated the tolerance of the rabbit sciatic nerve to a single 25Gy dose of external beam irradiation and observed no functional consequences up to 7 months after irradiation. The comparatively large nerve tolerance reported for the rabbit model appears to contradict our finding in the pig but significant differences in study designs may account for contradictory outcomes. In the rabbit study, a single nerve was irradiated with a 0.77 cm diameter field while four consecutive spinal nerves were irradiated to approximately 1.6cm lengths in the pigs presented here. Irradiated length has been observed to influence spinal cord tolerance profoundly within this length range. For the spinal cord, a treatment field length of 0.8 cm results in ED₅₀'s for paralysis ranging from 24.9Gy(5) to 30.1Gy(6) as compared to 20.4–21.5Gy for lengths of 1.6–2.0 cm. Alternatively, results from the rabbit and pig studies may disagree due to differences in the radiation response of the rabbit versus the pig or differences in the radiation biology of the spinal nerve versus the sciatic nerve.

Peripheral neuropathy has been reported by at least three investigators following irradiation of lung tumors with SAbR. Forquer et al. (13) reported that 7 of 37 patients treated with apical lung tumors developed brachial plexopathy. Maximum dose of >26Gy (in four fractions) was associated with a 46% risk of developing plexopathy by two years. Chang et al. (14) reported one case of partial arm paralysis after 20% of the brachial plexus received 40Gy in four fractions and Kawase et al. (15) observed thumb numbness in a patient that received an estimated mean dose of 47Gy in five fractions to the brachial plexus. In a review of 104 spinal metastasis treated with single-fraction SAbR, Yamada et al. (16) observed no case of radiculopathy even though the spinal nerve roots often received the prescription dose of 18–24Gy. The absence of radiculopathy in patients that received 24Gy appears to contradict the present results in pigs but this contradiction may be explained by differing lengths of nerve treated in humans versus pigs or by the fact that pigs in our study were irradiated to 4 consecutive spinal nerve levels while the human group was most often treated to a single level. A detailed analysis of spinal nerve lengths irradiated was not presented by Yamada et al. (16)

Ideally, all pigs in this report would have received identical dose distributions but multiple dose distributions were delivered consistent with the design and evolution of the bone study from which the majority of this neurologic data originated. The bone study aimed to compare multiple measures of bone health following SAbR to 16Gy (group A) or 24Gy (group C). The group “A” dose distribution (Fig. 1A) was chosen to accommodate a companion study, (10) thereby minimizing the use of animals. The group “C” dose distribution (Fig. 1C) was designed to spare the spinal cord and esophagus primarily. The spinal nerves were not considered to be at risk for functional deficits given the clinical experience (16) and rabbit study (11) described above. Paralysis observed in all five animals in group “C” required that they be humanely killed and led to the addition of the replacement group “B” to receive a reduced dose (20Gy, Fig. 1B). The relative dose distribution for group “B” (Fig. 1B) was modified slightly from the group “C” (Fig. 1C) relative dose distribution to reduce the dose to the spinal nerves. Dose distribution “D” (Fig. 1D) was created as a study with neurologic endpoints to evaluate the cause of paralysis at a dose level similar to group “C”, to provide magnetic resonance (MR) imaging data and to provide spinal nerve tissue for histologic analysis.

The accuracy of dose-length and dose-volume data reported in this study is limited by CT-based contouring. MR imaging of individual animals prior to irradiation would have been preferable but would likely not have a large impact on the dose statistics reported because the dose distributions used were very uniform in the right/left and rostral/caudal directions and the spines of age-matched pigs are very similar anatomically. The shapes of the dose distributions used (Figure 1) make the dose-length data for the spinal nerves relatively insensitive to shifts in the ventral/dorsal and rostral/caudal directions while a 2mm shift in the right/left direction could change the maximum spinal nerve dose ± 5 –10% (Figures 1B and C). The spinal cord dose-volume histogram is relatively insensitive to shifts in the right/left and rostral/caudal directions while a 2mm shift in the ventral/dorsal direction could change the maximum spinal cord dose ± 15 –20% (Figure 1B and C).

The expected latent period for the onset of motor deficits following SAbR of the spinal nerves is not well-established. Latencies reported from IORT studies in dogs (3, 4) vary widely with the majority being from 1–18 months with an outlier as late as 52 months (3). Potentially more cases of radiation myelopathy would have been observed in a longer follow-up period. The follow-up period of the current study (52–55 weeks) is considered long enough to observe the initial phase of spinal cord radiation myelopathy as commonly reported for guinea pigs(8), rats(5, 6), mice(9) and pigs(10) (2–6 months). The latency (2.5–3.5 months) to response observed in the present study is in close agreement with the latency observed for pigs that received a maximum spinal cord dose similar to the spinal nerve dose reported here (10, 17, 18). Species-specific variations in the expression of radiation toxicity to the spinal nerves in the context of SAbR is unknown but the response of rats(5–7), guinea pigs(8), mice(9) and pigs(10) to single-session uniform spinal cord irradiation is relatively homogeneous with ED₅₀'s very close to 20Gy. The biologic mechanism(s) that resulted in paralysis in this study are not clear. Paralysis may have been the result of demyelination due to loss of Schwann cells, or indirectly by vascular injury, in either case followed by progressive fibrosis.

Magnetic resonance imaging, with its high soft tissue contrast, is the method of choice for evaluating the nervous system and changes in the marrow space. Irradiated vertebral bodies undergo a fatty marrow transition that is easily shown on MRI. T1W images display fat as bright (Figure 3A). Soft-tissue like nerves, following irradiation, will first undergo an inflammatory process that is expected to be bright on T2W or FLAIR images followed by scarring which will be hypointense relative to normal tissue. Since at the time of imaging, hypointensity of the irradiated spinal nerves was mainly observed on both T1W and T2W FLAIR images (Figure 3B–C) we predicted scarring would be observed on pathological examination. Thickening of the affected spinal nerves was clearly observed on the small field of view fast field echo image (Figure 3D). Scattered areas of irregular contrast enhancement were observed on some spinal nerves consistent with remaining active inflammation/demyelination. Histopathologic observations were consistent with imaging changes in that fibrosis and demyelination were both present. Signs of inflammation, such as infiltrating lymphocytes or macrophages, were not observed in the histology.

Conclusion

The neurologic and histologic tolerance dose of the cervical spinal nerves to single-session irradiation lies between 19.0 and 24.1Gy for the pig model. Both the tolerance dose and latency to motor neurologic deficit for the spinal nerves are consistent with the spinal cord as determined in companion studies (10, 17, 18).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
A–D. Dose distributions for four dose groups on an axial MR image.

Figure 2. Illustration of spinal nerve with superimposed dose distribution. Insets “A” and “B” show nerve segments cut for longitudinal and axial histopathologic sections, respectively.

Figure 3.

A–D MR images of the cervical spine of a pig that developed peripheral neuropathy. A) turbo spin echo T1-weighted sagittal image showing hyperintensity in marrow space of C5–7, B) turbo spin echo T1-weighted axial image showing thickened hypointense C6 nerve root, C) fast field echo axial image showing thickening to good advantage and mild hypointensity, D) fluid attenuation inversion recovery axial image showing hypointensity to better advantage.