Radiotherapy and Oncology 109 (2013) 107–111

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Experimental radiotherapy

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

Paul M. Medin [a,*], Ryan D. Foster [a], Albert J. van der Kogel [b], Jeffrey Meyer [a], James W. Sayre [c,d], Hao Huang [e], Orhan K. Öz [e]

[a] Department of Radiation Oncology, UT Southwestern Medical Center, Dallas, USA; [b] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands; [c] Department of Biostatistics; [d] Department of Radiology, University of California, Los Angeles; and [e] Department of Radiology, UT Southwestern Medical Center, Dallas, TX, USA

ARTICLE INFO

Article history:
Received 15 November 2012
Received in revised form 14 August 2013
Accepted 15 August 2013
Available online 20 September 2013

Keywords:
Spinal nerve tolerance
Radiation neuropathy
Stereotactic ablative radiotherapy
Stereotactic body radiation therapy
Swine

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 ± 0.3 Gy (n = 5), 18.7 ± 0.5 Gy (n = 5), and 24.3 ± 0.8 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 ± 0.2 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 24.9 Gy group.
Results: No pig that received a maximum spinal nerve point dose ⩽19.0 Gy experienced a change in gait while all pigs that received ⩾24.1 Gy experienced paralysis. Extensive degeneration and fibrosis were observed in irradiated spinal nerves of the 24.9 Gy 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.
 Radiotherapy and Oncology 109 (2013) 107–111

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 20 Gy 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 25 Gy 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.

* Corresponding author. Address: Department of Radiation Oncology, UT Southwestern Medical Center, 5801 Forest Park Rd, Dallas, TX 75390-8542, USA.
E-mail address: Paul.medin@utsouthwestern.edu (P.M. Medin).

0167-8140/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2013.08.025

Methods and materials

Seventeen Yucatan minipigs were each irradiated in a single session with a large dose of X-rays 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 35–48 kg when irradiated. Treatment/response parameters for all individual animals are presented in Table 1 Supplement. All animals received a treatment planning CT scan with 0.7–1.5 mm thick slices and a 350–500 cm field of view. Treatment planning calculations were performed using either *Brainscan 5.31* (BrainLAB, AG, Feldkirchen) or *Pinnacle*^{3} *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 Fig. 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" (Fig. 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" (Fig. 1B and C, 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 (Fig. 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 Fig. 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" (Fig. 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,

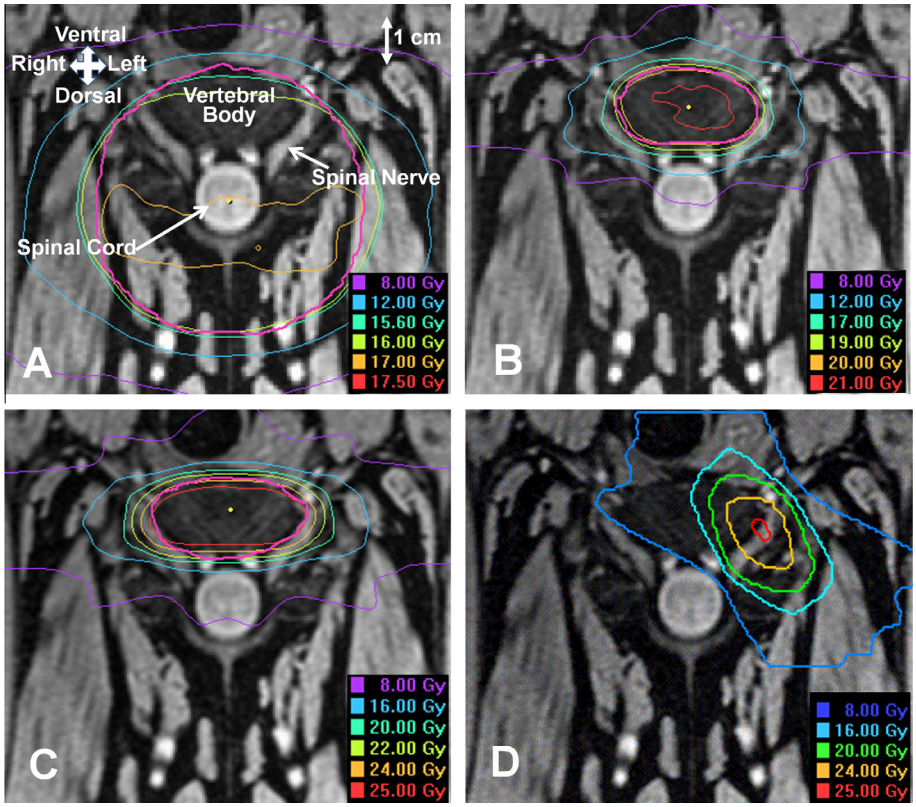

Fig. 1. (A–D) Dose distributions for four dose groups on an axial MR image.