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Journal

Veterinary and Comparative Oncology, 21(3)

ISSN

1476-5810

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Publication Date

2023-09-01

DOI

10.1111/vco.12900

Title:

Conventional Fractionated Radiotherapy Outcomes for Young Dogs with Nephroblastoma of the Spinal Cord: 5 Cases

Running head:

Radiotherapy for Nephroblastoma

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Disclaimers: No disclaimers are declared by any authors.

Sources of Support: None

Word Count: 3885

Number of Figures: 2, Number of Tables: 3

Conflict of interest disclosure: The authors declare no conflict of interest.

Abstract:

Published radiotherapy results for spinal nephroblastomas in dogs are limited. In this retrospective longitudinal study (1/2007-1/2022), five dogs with a median age of 2.8 years received post-operative 3-D conformal, conventional fractionated radiotherapy (CFRT) for an incompletely resected nephroblastoma. Clinical findings prior to surgery included one or more of the following: pelvic limb paresis (5), faecal incontinence (2), flaccid tail (1), non-ambulatory (2), and deep pain loss (1). All masses were located between T11-L3 and surgically removed via hemilaminectomy. Dogs received 45-50 Gray (Gy) in 18-20 fractions, and no dogs received chemotherapy post-radiation. At analysis, all dogs were deceased, with none lost to follow-up. The median overall survival (OS) from first treatment to death of any cause was 3.4 years (1,234 days; 95% CI 68 days-upper limit not reached; range: 68-3607 days). The median planning target volume was 51.3 cc, with a median PTV dose of 51.4 Gy and median D98 = 48.3 Gy. Late complications or recurrence were difficult to fully determine in this small dataset; however, some degree of ataxia persisted throughout life in all dogs. This study provides preliminary evidence that post-operative radiotherapy may result in prolonged survival times dogs with spinal nephroblastomas.

Key Words:

Wilms tumour, spinal tumour of young dogs, radiation

Introduction:

Nephroblastoma of the spinal cord is a rare neoplasm, typically affecting young, large-breed dogs, and arises from the embryonic remnants of the immature kidney.[1] It is most often intradural/extramedullary and located in the caudal thoracolumbar region.[2] In humans, nephroblastoma is the most common primary renal tumour of childhood (i.e., Wilms tumour) but intraspinal lesions are not reported except in cases of metastatic spinal invasion.[3,4] Spinal cord nephroblastoma in dogs is generally considered to be locally aggressive, although metastasis has been reported.[5] Clinical signs routinely observed in dogs with spinal nephroblastoma include progressive paraparesis, paraplegia, or ataxia secondary to spinal cord compression.[6,7] In most cases, a preliminary diagnosis of a spinal cord tumour is obtained through imaging, historically with myelography, but more commonly now with MRI. Imaging frequently reveals an intradural/ extramedullary space-occupying mass, but there are occasional reports of intramedullary/extradural, as well as multifocal presentations.[5,8]

On histopathology, nephroblastomas are composed of epithelial, blastemal and stromal cells. The location of the tumour (T10-L3), compatible clinical signs, and histologic characteristics are sufficient for establishing a diagnosis in dogs. The WT-1 gene is expressed within glomerular podocyte nuclei, stem cells, and mesothelial cells and is overexpressed in Wilms tumours, and immunohistochemical analysis with a WT-1 antibody is routinely used to confirm renal origin of

Wilms tumours in children.[9,10] In a retrospective study, positive WT-1 staining was detected in 9/11 dog nephroblastoma samples.[7]

In humans, treatment consists of a combination of surgical excision, chemotherapy, and radiotherapy.[3,11,12] There is little information regarding treatment outcomes in dogs with spinal nephroblastoma, and reports are mostly limited to single cases.[1,6,13] In dogs, palliative treatment with pain medications and prednisone is reported with a 55-day median overall survival (OS).[14] Surgical resection alone is reported in dogs, and can result in substantial clinical improvement by resolving the mass effect immediately; however, OS with surgery alone was 70.5 days in the largest published cohort[7], and another case report described local recurrence one year post-surgery.[13] Complete excision is difficult because wide surgical margins are not possible to preserve neurological function, and residual tumour tissue carries risk for rapid recurrence.[13]

Radiotherapy is frequently used as an adjuvant therapy for other canine cancers, and may play a role in preserving neurologic function while preventing recurrence for spinal nephroblastomas.[7] Adjuvant radiotherapy represents an attractive option for spinal nephroblastomas, as surgery will allow for decompression and alleviation of clinical signs, but, on its own, is not likely curative. Of particular interest is conventional fractionated radiotherapy (CFRT), which involves multiple daily treatments over several weeks, using relatively lower dose-per-fraction. Fractionation of the radiation dose allows normal tissues to recover while achieving high target dose. Following resection, CFRT may limit adjacent spinal cord damage due to the lower dose-per-fraction used with CFRT compared to hypofractionated protocols.[15] A further advantage of conventional fractionation may be decreased risk of radiation-induced cancer in a population of young

animals, as this complication has been reported with higher dose-per-fraction treatments and these dogs may have prolonged survivals.[16,17]

Combined surgical resection and radiotherapy of spinal cord nephroblastoma in dogs has been described, albeit with limited radiotherapy planning data reported.[1,6,7,13] Specifically, adjuvant radiotherapy with conventional fractionation is published in three case reports, with outcomes ranging from 8.8 months to 5.5 years.[7,14,16] A palliative radiation report also described improved limb function and survival of the patient for at least 16 months.[1] However, radiotherapy details are limited, and the protocols used were variable in these published cases. This study assesses survival outcome in dogs receiving post-operative CFRT of histologically-confirmed nephroblastomas, with more consistent fractionation between dogs, and contemporary dosimetry reporting.

Methods:

This retrospective study was performed at the University of California, Davis Veterinary Medical Teaching Hospital from 1/2007-1/2022. Animals were cared for in accordance with hospital policies. Due to the retrospective nature of this study, informed consent was not obtained. Electronic medical records were searched for dogs having received a single, post-operative CFRT course following resection of a histopathologically confirmed spinal nephroblastoma. Other therapies such as antibiotics, corticosteroids, and non-steroidal anti-inflammatories were allowed. Included dogs were retrospectively identified by a radiation oncologist.

Patient demographics, including age, weight, sex, and breed were recorded. Diagnostic results (bloodwork, thoracic radiographs, abdominal ultrasound, MRI and CT imaging), clinical signs at diagnosis, radiotherapy parameters, follow-up visit information, and survival times were recorded. Where outcome data was not available in the record, local veterinarians and owners were contacted for records and date of death. Follow-up imaging was not an inclusion criterion.

Prior to their radiation treatment, all cases had a simulation CT scan with a helical scanner (Hispeed or Lightspeed 16 General Electric Co., Milwaukee, WI). Patients were positioned in a vacuum-lock bag (SecureVac, Bionix Development Corporation, Toledo, OH). Those in sternal recumbency were also placed on an indexed board and secured with a thermoplastic body mask (Q-fix systems, Avondale, PA) as previously described.[18] Non-contrast and contrast-enhanced images with 1.3-2.5 mm slices were acquired.

All CT images were imported into the treatment planning system (Eclipse v. 8 or 11, Varian Corporation, Palo Alto, CA).[19,20] Relevant target volumes were contoured, including the post-operative clinical target volume (CTV) and planning target volume (PTV) based on attending clinician recommendations. The relevant organs at risk (OARs) were contoured, commonly including the spinal cord, lung, or kidneys, based on attending clinician recommendation.

3D-conformal calculations were performed with the Pencil Beam Convolution (PBC 7518 or 8118) or AAA_11031. Tissue heterogeneity correction, to account for dose variation in tissues, was used except for PBC 7518 calculations. Treatment plans were evaluated based on PTV dose-volume histogram (DVH) coverage and dose to the OARs per clinician. When possible, 90-95%

of the PTV was covered by the prescription dose, and standardized OAR constraints were not in place.

All treatments were delivered with 6 or 10 MV photons using a linear accelerator (Clinac 2100, or TrueBeam, Varian Medical Systems, Palo Alto, CA) with an 80-leaf or high-definition multi-leaf collimator (MLC). For Clinac-delivered plans, daily orthogonal MV-setup images (Clinac 2100) or CBCT (Truebeam) were acquired, prior to each treatment and matched to digitally reconstructed reference images. For Clinac administered plans, couch adjustments were measured on the DRR, adjustments were manually introduced on the couch and verified by re-imaging, and dose was then delivered. For TrueBeam administered plans, couch adjustments were determined from the CBCT overlayed onto the diagnostic imaging CT and shifts determined and made after imaging approval by the clinician. Dose was then delivered according to the treatment plan.

Recheck visits were recommended 2-3 weeks post-radiation therapy, 8-12 weeks post-radiation therapy to assess for pneumonitis as appropriate, and every 3-6 months thereafter. Data from all rechecks were collected, including acute side effects (defined as within 3 months post-radiation), late side effects, long-term clinical signs, and survival.

For statistical analysis, all graphs and statistical analyses were made using commercially available software (STATA 14.2, Stata Corporation, College Station, TX; Microsoft Excel 2008 for Mac, Version 12.1, Microsoft Corporation, Redmond, WA). Due to the small sample size, non-parametric tests were used for continuous variables, and descriptive statistics are reported as

medians and ranges. The Kaplan-Meier method was used to calculate median overall survival times (OS). Survival time was defined as the time between the first radiotherapy treatment and death. For censoring, all deaths were considered events. A p value < 0.05 was considered statistically significant.

Results:

Five dogs met the inclusion criteria. Notable patient and treatment details are summarized in Table 1. The breeds represented were as follows: Labrador retriever (2), American bulldog, Great Dane, and mixed breed. Four dogs were male castrated and one was an intact female. The median age at treatment was 2.8 years (range: 1.8-6.2 years). The median weight at treatment was 38.7 kg (range: 27.2-53.7 kg).

Clinical findings at diagnosis included one or more of the following: pelvic limb paresis (5), faecal incontinence (2), flaccid tail (1), non-ambulatory (2), and deep pain loss (1). Diagnosis was based histopathology by a board certified pathologist. All dogs had an MRI revealing a contrast-enhancing mass in the spinal canal between T11 and L3, but the MRI report did not describe the intra/extra-dural or medullary location for two dogs. All masses were surgically removed by board-certified neurologists via hemilaminectomy, with approach reported from the left (2), right (2), and one case approached from opposite sides for consecutive vertebral spaces. Post-surgical MRI was not performed in any patient. Histopathology confirmed the diagnosis of nephroblastoma in all five dogs. Immunohistochemistry was used in three cases. One sample was pan-cytokeratin positive, vimentin negative, and GFAP negative, and the monoclonal Wilms

tumour antibody was applied but was not readable. One case was cytokeratin positive, and one exhibited strong nuclear WT-1 immunoreactivity.

Prior to irradiation, bloodwork was unremarkable for three dogs, a mild hypercalcemia (11.5 mg/dL, range 9.6-11.2) was noted in one dog, and a mild increase in ALT (86 IU/L, range 21-72), and GGT (7 IU/L, range 0-5) was noted in one dog. Thoracic radiographs were available from diagnosis in 2/5 dogs and were unremarkable except for a mild narrowing of the T12-T13 intervertebral disc space in one dog. Abdominal ultrasound was performed in 3/5 dogs at diagnosis, revealing an unremarkable abdomen in one dog, a distended urinary bladder with mild right adrenal enlargement in the second dog, and a thickened bladder wall consistent with cystitis and a urinary tract infection which was subsequently confirmed by urinalysis and culture in the last dog. No dogs were reported to have co-morbidities, consistent with their relatively young age.

All dogs had improved mobility after surgery and could walk independently or with a sling for assistance. However, serial and complete neurological examination records were not available to provide a better timeline of neurological improvement after surgery and radiation. All dogs had a post-operative CT scan for radiotherapy planning and commenced radiation within 30 days after surgery. Patients were positioned either in right decubitus (2) or sternal (3), and 4/5 were pelvic limb-first while one was head-first towards the CT gantry. The CT characteristics were as follows: No obvious mass remained post-operatively on the radiation planning CT (5/5), contrast enhancing material adjacent to the hemilaminectomy site suspected to be post-operative changes (3/5), and spinal cord with slightly irregular shape and attenuation at the surgery site (1/5).

Because no gross mass remained, GTV (gross tumour volume) was not contoured. CTV contouring was variable between clinicians: all CTV contours included the cord that was touching or involved in the mass on the pre-surgical MRI, and the bony defect post-surgery. Based on the diagnostic CT and surgeon recommendations, the CTV variably included 3-10 mm of cord cranial and caudal to the laminectomy site, 2-10 mm of bone and soft tissue around the bony defect, and variable portions of the surgical tract in the epaxial muscle and incised skin. PTV was a 3-5 mm isometric expansion around the CTV (Figure 1A).[19,21,22] OARs, and specifically the normal spinal cord, were not cropped from the PTV. A summary of CTV and PTV volumes are shown in Table 2: the median CTV was 28.3 cc, (range 5-644 cc) and the median PTV was 51.3 cc (range 18.5-805 cc).

Prescriptions ranged from 18-20 fractions of 2.4-2.5 Gy/fx for a total dose of 45-50 Gy. The dose was normalized to cover 93-95% of the PTV. A calculation grid size of 2.5 mm was used for 4/5 plans and not available for one dog. All cases used a single isocenter with wedged, conformal fields (Figure 1 B). Wedge angles ranged from 15-45 degrees and were applied to each field. 4/5 cases were treated with 2 equally-weighted, parallel-opposed fields. In one case, a parallel-opposed field set and a second set of angled fields were used, for a total of 4 fields with different weights. A 1.5 cm bolus was used in one dog to increase subcutaneous dose in the PTV. Beam energies were either 6 MV (2) or 10 MV (3) to optimize dose distribution. Field lengths ranged from 4.4-22 cm. The recommended radiation reporting data for the PTV and spinal cord are described in Table 3.[23] The median dose to all PTVs was 51.4 Gy (range: 48.6-54.9 Gy), and an example isodose colorwash and DVH are shown in Figure 1B-C. D2 and D98 are values that

may better represent dose heterogeneity to the PTV, with D2 representing the hottest 2% of the target and D98 representing the coldest 2%. The median PTV D2= 52.4 Gy (range: 50.5-53.6 Gy), median D98= 48.3 Gy (range: 35.65-49.45). Conformity Index (CI), heterogeneity index (HI), and Gradient Index (GI) were not calculated for these forward-planned cases.

The median total dose to the spinal cord was 2.9 Gy. The maximum point dose to the spinal cord in any case was 54.6 Gy, which equated to a maximum cord point dose of 2.7 Gy/fraction in this dog (Table 3). The length of the cord included in the PTV, and thus receiving the prescription dose, ranged from 2.9-11.7 cm, and the median hotspot in the cord was 52.4 Gy (total dose range: 50.0-54.6 Gy). Kidney values were available for two cases with dose near the kidneys, with a median left kidney dose of 0.3 Gy (total dose range: 0.1-3.5 Gy), and median right kidney dose of 2.2 Gy (total dose range: 0.2-38.4 Gy). Lung values were available for two cases, with a median lung dose of 0.6 Gy (total dose range: 0-50.5 Gy).

There was one fraction delay for a patient, in which a partial treatment was delivered due to machine failure mid-treatment, and the remaining dose was distributed over the next three treatments by giving 2.92 Gy/fx for the subsequent three fractions (original dose per fraction: 2.5 Gy). Early adverse effects were limited to mild alopecia (n= 2) and pyoderma (n= 1) in the radiation field. Three dogs commenced 0.4-0.5 mg/kg PO daily prednisone halfway through treatment or continued prednisone started at diagnosis and were tapered off the drug starting 2-5 weeks post-radiation therapy. Two dogs did not receive steroids during radiation therapy. One dog received 14.7 mg/kg PO q 12 hour amoxicillin trihydrate/clavulanate potassium (Zoetis, Parsippany-Troy Hills, NJ) for a urinary tract infection, and one dog received cefpodoxime

proxetil (Zoetis, Parsippany-Troy Hills, NJ) during radiotherapy due to the reported pyoderma. Due to limited records on neurologic evaluations, and the expected protracted improvement after spinal surgery, improved ambulation specifically due to radiotherapy could not be assessed.

All five dogs were deceased at analysis, with no dogs lost to follow-up. The OS from first treatment to death by any cause was 3.4 years (1,234 days; 95% CI 68 days-upper limit not reached; range: 68-3607 days, Figure 2). One dog had CT-diagnosed recurrence with recrudescence of clinical signs 400 days after treatment and was ultimately euthanized at 425 days. One dog had progressive disease (both intra/extra-dural) 68 days after treatment both within and out of the radiation field. Necropsy revealed pathologically distinct, WT-1 negative nodules that were not consistent with a diagnosis of nephroblastoma, despite the original, surgically-removed mass being WT-1 positive and pathologically consistent with a nephroblastoma. This dog had multiple intra and extra-dural nodules of polygonal, blastemal-like cells in the lumbar canal on necropsy. The sample was reviewed by several pathologists after necropsy. Because there were only five cases, only one necropsy (on the shortest-surviving case), no consistent recheck or re-staging ultimately performed, and no way to confirm the presence of any residual disease in the three longest-surviving cases, cause-specific survival was not assessed, and prognostic factors were not assessed statistically.

Discussion:

This study provides preliminary evidence that adjuvant 3D-conformal CFRT may be an effective treatment for post-operative nephroblastomas of the spinal cord, with an OS of 3.4 years (1,234 days). As noted in previous reports, the dogs in this study were young in age and generally larger

breeds.[24] The limited number of cases in this study precluded statistical analysis for prognostics factors. Currently there are no data on long-term benefits of surgery as the sole treatment, and most surgery-only cases in the literature suggest limited survival.[7] As suggested in the referenced study,[7] and through the data presented here, radiation may prolong outcomes markedly compared to surgery-alone.

All dogs had improved clinical signs after surgery and were able to ambulate alone or with assistance of a sling. However, serial and complete neurological examination records were not available, so the exact timeline of improvements in ataxia, knuckling, and faecal incontinence are not well-described in this cohort. Although dogs continued to have neurologic improvement reported during or after radiotherapy, it is difficult to attribute improved mobility specifically to the radiation treatment as this may have been because of the protracted improvements that can be seen after spinal surgery. Two patients were also reported to engage in canine rehabilitation exercises with an integrative medicine and rehabilition centre to improve mobility; however, the small numbers and limited records prevent conclusions on the benefit of rehabilitation in the current study. Previous literature shows that postoperative rehabilitation after spinal cord injury might contribute to clinical improvement, with one study showing return to more full neurologic function than the control group after hemilaminectomy[25] while another study used several rehabilitation techniques to improve neurologic function.[26] However, a randomized, blinded, prospective clinical trial assessed the benefit of early post-operative rehabilitation in dogs after thoracolumbar intervertebral disk herniation, and reported early rehabilitation post-surgery was safe but did not improve the rate or level of recovery.[27]

291 Distant metastasis was not reported in any case. However, the shortest-surviving dog appeared to
292 have co-development of a second, more aggressive tumour alongside the pathologically-
293 confirmed nephroblastoma, with these new nodules invading the spinal canal and resulting in
294 euthanasia within weeks of finishing radiation therapy. It is unclear if this tumour was already
295 present at the time of radiotherapy and was not identified in the original surgical histopathology.
296 It may also be that the originally resected mass was not a nephroblastoma, but pathology review
297 did not conclude as such. Post-treatment changes in architecture at radiation sites have been
298 previously reported, including increased fibrinous and necrotic regions, vessel wall thickening,
299 and glandular atrophy, along with nuclear and cytoplasmic enlargement and degenerative
300 changes. In tumour cells, nuclear polymorphism, degeneration, pyknotic cells, and tumour cells
301 detaching from one another is also reported.[28,29] The results of the dog's post-mortem pathology,
302 with sheets of cells and lack of features consistent with radiation-induced cell damage, does not
303 directly support a radiation-induced change in nephroblastoma cells as the cause of the differing
304 histopathology.
305
306 The small data set limits our conclusions regarding best fractionation. The Biological Equivalent
307 Dose (BED) for the protocols used: 50 Gy in 20 fractions (BED_{10} 62.5, BED_3 91.67), 48 Gy in 20
308 fractions (BED_{10} 59.52, BED_3 86.4), and 45 Gy in 18 fractions (BED_{10} 56.25, BED_3 82.5) are
309 somewhat similar. The patient receiving the lowest BED_{10} received a total dose of 45 Gy, likely
310 due to the large target site and necessarily wide region of cord being irradiated, but also had one
311 of the shorter survivals (425 days) and likely recurrence on CT scan imaging. However, more
312 cases would be needed to recommend a specific radiotherapy protocol. Although the PTV
313 volume in the three longest surviving dogs was mid-range (18.5-58.2 cc), because they were

treated with parallel-opposed fields or with 4 fields, the volumes of near-prescription dose were quite large as depicted in Figure 1. Therefore, the approach in this study does not directly inform outcomes with more advanced conformal techniques such intensity-modulated or volumetric-arc radiotherapy (IMRT/VMAT).

Additionally, radiation-induced cancer is a rare but well-recognized phenomenon in humans. Radiation-induced osteosarcoma was also reported in 3.4% of dogs treated with external beam radiotherapy between 1.7-5 years after irradiation. In this report, a large dose per fraction (> 3.5 Gy) may have increased the incidence of radiation-induced osteosarcoma. This type of complication may inform risks of hypofractionated or stereotactic protocols in young dogs for nephroblastomas.[30]

Targets around the spinal cord are frequently limited to avoid unnecessary dose and risk of spinal cord damage. Finer fractionation, as was performed in these dogs, can also help to mitigate late effects on the spinal cord. The reported risk of myelopathy from conventional fractionation to the full-thickness cord appears rare in humans, with less than 1% and 10% risk at a total of 54 Gy and 61 Gy, respectively.[31] In one study the histopathologic response of the spinal cord to fractionated doses of radiation (4 Gy fractions, total dose 44-68 Gy), as investigated in laboratory beagles and severe late radiation effects such as white matter necrosis, haemorrhage, and parenchymal atrophy were seen mostly 1-2 years after irradiation.[31-33] Overall, the planned cord doses in this study did not exceed 2.7 Gy/fraction, and by using parallel-opposed planning the global hotspots were located in the epaxial muscles and away from the cord. The dog requiring extra dose for 3 fractions after machine failure did not exceed 3 Gy/fraction for those doses.

These doses would be considered acceptable for the spinal cord based on the literature available.[31] The plans in this study did not exceed dose constraints for lung and kidney with conventional fractionation.[34-36] Overall, the doses delivered to normal tissues were acceptable, albeit with limited follow-up.

It is difficult to elucidate late-radiation vs. tumour-related effects, especially without follow-up imaging and/or necropsy examination. Therefore, patients with worsening ataxia could have spinal signs referable to other spinal disease, tumour progression or late radiation effects. As such, we cannot make conclusions about the rate of late effects on this series. There are other limitations to this study as well. The numbers are small, and there was no control group to indicate the disease course in untreated dogs with similar clinical signs. Additionally, lack of progression was based on clinical signs rather than serial 3D-imaging. A larger cohort would better represent the late effects to the cord or secondary tumours that could arise in a long-lived population of nephroblastoma dogs. Further, necropsy examinations would better elucidate any pathologic late effects. Importantly, different contouring and treatment protocols limit this study's conclusions.

Overall, 3D-conformal planning appears to be an effective treatment option for post-operative nephroblastomas and may provide clinical improvement and prolonged survival. Further assessment of radiotherapy techniques, time-dose-fractionation, and follow-up with 3D-imaging would be helpful to determine the best treatment strategy for these patients.

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Table 1: Clinicopathological, Treatment Data, and Outcome for Dogs with Spinal Nephroblastoma

Dog	Imaging modality: Tumour location	Clinical signs at diagnosis	Surgical procedure	Radiation Therapy Planning			
				Total Dose	Dose per fraction	Technique	Survival (Days)
1	MRI: T13-L1 intradural extramedullary	2 weeks progressive paraparesis, worse on left, faecal incontinence	Hemilaminectomy (left)	50 Gy	2.5 Gy	Parallel opposed	3607
2	MRI: L2-L3 ‡	3 weeks progressive left pelvic limb weakness with absent CP†, reduced CP on right pelvic limb, faecal incontinence	Hemilaminectomy (left)	50 Gy	2.5 Gy	Parallel opposed	1234
3	MRI: L1-L2 intradural extramedullary	Non-ambulatory, deep pain loss	Hemilaminectomy (right)	50 Gy	2.5 Gy	Parallel opposed	68
4	MRI: T13 ‡	6 months duration progressive paraparesis and tail pain, worse on right. Non-ambulatory paraparesis for 2 days	Hemilaminectomy (right)	48 Gy	2.4 Gy	4 fields: 2 parallel-opposed (90° & 270°), and 2 angled fields (30° & 330°)	2505
5	MRI: T11-T12 intradural extramedullary & intramedullary component	6 weeks duration progressive paraparesis and pain	Hemilaminectomy (bilateral) 4 medium screws with cement at vertebral bodies of T12-T13	45 Gy	2.5 Gy	Parallel opposed	425

† Conscious proprioception (CP)

460 ‡ Incomplete imaging location reported

Table 2: Mean, Median, and Range for Clinical and Planning Target Volumes in Centimetres Cubed (cc)

	CTV[†] (cc) n= 5	**PTV[‡] (cc) n= 5**
Mean	145.9	196.4
Median	28.3	51.3
Range	5.0-644	18.5-805

[†] Clinical Target Volume (CTV)
[‡] Planning Target Volume (PTV)

Table 3: Dose Characteristics for Planning Target Volume and Spinal Cord in Gray (Gy)

	PTV (n= 5)			Spinal Cord (n= 5)		
	Overall Mean (Gy)	**Overall Median (Gy)**	**Overall Range (Gy)**	**Overall Mean (Gy)**	**Overall Median (Gy)**	**Overall Range (Gy)**
Min[†]	38.9	41.3	19.1-47.6	0.34	0	0-1
Max[‡]	54.3	52.55	51.3-61.9	52.4	52.4	50-54.6
Mean[§]	51.1	51.1	47.4-54.9	17.0	20.3	5.8-24.5
Median[¶]	51.4	51.4	48.6-54.9	4.4	2.9	0.1-11.2
D2[††]	52.1	52.4	50.5-53.6			
D98[‡‡]	45.9	48.3	35.7-49.5			

[†] Minimum dose to the planning target volume (PTV) or spinal cord
[‡] Maximum dose to PTV or spinal cord
[§] Mean dose to PTV or spinal cord
[¶] Median dose to PTV or spinal cord
[††] D2= dose to 2% of PTV (i.e., highest dose to PTV)
[‡‡] D98= dose to 98% of PTV (i.e., lowest dose to PTV)

Figures Legends:

Figure 1: Representative planning for a nephroblastoma radiation case. A, Contouring for the Clinical Target Volume (CTV- dark blue), planning target volume (PTV- red) and spinal cord (light blue). B, Field distribution for a wedged, 2-field conformal plan. The dose colorwash gradient ranges from 10% (blue) to 100%+ (red). C, Dose-Volume Histogram demonstrating the dose to targets and organs at risk, with CTV (dark blue), PTV (red), and spinal cord (light blue).

Figure 2: Kaplan Meier survival curve. Median overall survival (OS) for 5 dogs receiving radiation therapy for post-operative nephroblastomas from first radiation fraction to death by any cause was 3.4 years (1,234 days; 95% CI 68 days-upper limit not reached; range: 68-3607 days).