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Stereotactic radiation therapy for treatment of canine intracranial meningiomas

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Abstract

The objective of this study is to determine the rate of toxicity, median survival time (MST) and prognostic factors in dogs with presumed intracranial meningiomas that were treated with stereotactic radiation therapy (SRT). Patient demographics, neurological history, details of SRT plans and response to treatment (including toxicity and survival times) were examined for potential prognostic factors. Overall MST (MST) due to death for any cause was 561 days. There was a mild to moderate exacerbation of neurological symptoms 3-16 weeks following SRT treatments in 11/30 (36.7%) of dogs. This presumed adverse event was treated with corticosteroids, and improvement was seen in most of these dogs. Death within 6 months of treatment as a result of worsening neurologic signs was seen in 4/30 (13.3%) of dogs. Volume of normal brain that received full dose at a prescription of 8Gy × 3 fractions was predictive of death due to neurological problems within this 6-month period.

Keywords
Comparative Oncology, Oncology, Pathology, Radiation Oncology, Small Animal

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Introduction

Meningiomas are extra-axial tumors that arise from the meningothelial cells of the arachnoid cap and pia mater overlaying the brain, optic nerve and spinal cord. Meningiomas are the most common primary intracalvarial tumors found in dogs, representing 35–45% of masses diagnosed.[1] Meningiomas rarely metastasize, but can cause clinical symptoms resulting from compression, invasion and inflammation of the surrounding central nervous system tissue. Meningiomas tend to be solitary, broad based, strongly homogenously to heterogeneously contrast enhancing lesions with a dural tail sign. These features facilitate image based diagnosis.[2,3] Meningiomas are the most common primary intracalvarial tumors found in dogs, representing 35–45% of masses diagnosed.[1]

Primary treatment for intracranial meningiomas in dogs is often surgery; however, complete excision is difficult due to the friable and infiltrative nature of these tumors. Surgery is often not feasible because of location and size of the tumor. Forebrain and caudodorsal cerebellum or medulla masses can be accessible, unlike masses found in the brainstem or hypothalamic region.[4] Morbidity associated with brain surgery, particularly in the caudal fossa and brainstem, can be quite high; reported complications include hemorrhage, pneumocephalus, increased intracranial pressure, seizures, brain herniation, infections and aspiration pneumonia. [5,6] Median survival times (MSTs) following surgical excision of meningiomas ranges from 120 to 210 days.[7–9] When surgery is combined with radiation for the treatment of meningiomas the MST

is increased to 540–900 days.[7,10,11] In cases where radiation is used as a primary treatment for all types of intracranial tumors a MST of 250–699 days has been reported.[12–14] In these cases radiation prescriptions varied from coarse fractionation to curative intent, finely fractionated protocols. By comparison, canine meningiomas treated with conservative medical management (i.e. corticosteroids, anticonvulsants, etc.) have a reported MST of 70 days.[15]

Conventional fractionation protocols (12-20 fractions of 2.5–4 Gy) have historically been used for curative-intent external beam irradiation of brain tumors. [12,14,16] Daily doses are dictated by the surrounding normal brain tissue and their tolerance for radiation. In veterinary medicine acute toxicities following brain irradiation may include otitis, pharyngeal mucositis, conjunctivitis, keratoconjunctivitis and corneal ulceration.[6,11] Brain edema and worsening of neurologic signs is a reported but unusual consequence of brain irradiation in the peritreatment period.[17,18]

In human medicine other adverse radiation effects (ARE) reported include early delayed encephalopathies, which can occur within weeks to months following completion of radiation. This ARE is related to transient, diffuse demyelination and perilesional reaction and can be seen in 15–40% of brain irradiation cases depending on location and/or fractionation protocol.[8,17,19] Signs are typically transient and responsive to steroid administration.[17,19]

Late effects can be seen anywhere from 6 months to several years following brain irradiation.[19]

Late toxicosis reported in association with brain irradiation of veterinary patients includes cataract formation, leukotrichia, alopecia, keratitis and deafness.[11] More seriously there can be radionecrosis (in human studies reported in approximately 5–20% of cases at 5 years[17,20]) or secondary tumor induction (seen in 1.4–3.7% of children treated with high-dose brain irradiation[17,21]).

Recent technological advances have made it possible to deliver radiation therapy in an increasingly precise and conformal manner. Use of steep dose gradients and patient positioning verification prior to (and often during) therapy aids in limiting the dose deposition in normal tissues. This has allowed for the dose per fraction of radiation to be escalated, which in the extreme form involves a hypofractionated form of therapy called stereotactic radiation therapy (SRT). SRT is commonly used for treatment of metastatic brain lesions and small- to medium-sized intracalvarial tumors in physician-based medicine, particularly recurrent lesions or ones in locations not surgically accessible.[22] More recently SRT has become available for treatment of intracalvarial tumors in veterinary patients.[23]

The purpose of this study was to determine the safety and response to curative-intent SRT, as prescribed herein, when used for the treatment of presumed canine intracranial meningioma. Dose–response relationships for toxicity and overall survival time were described, and potential prognostic factors were evaluated.

Materials and Methods

Dogs with an image-based diagnosis of presumed meningiomas that were treated with curative-intent SRT at the Colorado State University Veterinary Teaching Hospital (CSU-VTH) between July 2008 and November 2012 were included in this study. Medical records were reviewed to determine the nature and severity of presenting clinical signs, anatomic location of tumor, medications administered, adverse events, response to therapy and survival time. Severity of presenting clinical signs was based upon previously established guidelines where grade 1 was seizures only or mild neurological signs identified on neurological examination, grade 2 was moderate to marked neurological signs in an ambulatory dog and grade 3 was stuporous or non-ambulatory.[24] When evaluating plans the endpoints used were as follows: Gross tumor volume (GTV), GTV to intracalvarial volume ratio (GTV/ICV), dose to 95% of the planned target volume (PTV), the maximum dose, minimum dose and mean doses to the PTV. Volume of normal brain 2-mm outside of the PTV that was receiving >90% of the prescribed dose and volume of normal brain at 100% prescription was determined. Dose to normal brain was calculated as the contoured brain (i.e. ICV) minus the GTV. Biological

Table 1. Percentage of meningiomas in this case series with imaging characteristics typical of this tumor type

Imaging characteristic (previously reported incidence)	% Seen in this case series
Dural Tail (60%[45], 80%[46])	100% (30/30)
Broad Based (100%[47])	100% (30/30)
Well Defined Margins (86%)[48]	90% (27/30)
Strongly Contrast Enhancing (100%)[46]	100% (30/30)
Homogenously Contrast Enhancing (60-70%[2])	90% (27/30)
Peritumoral Edema (40% [2], 82%)[46]	66.7% (20/30)
Calcification	6.7% (2/30)
Hyperostosis (23%)[49]	13.3% (4/30)
Cystic (12.5–31.2%)[47,48]	50% (15/30)

All advanced imaging was retrospectively reviewed by one-boarded radiologist (ER).

equivalent doses (BED) were calculated for comparison of plans based on the following formula:

$BED = nd\ [1 + (d/(\alpha/\beta)]$ where n is the number of fractions, d is the dose per fraction and the α/β was assumed to be 10 for a tumor

All dogs were presented for evaluation of neurological signs. An MRI had been performed in 29/30 of these dogs prior to presentation leading to an image-based diagnosis of a meningioma. Patients had systemic staging prior to radiation therapy that included complete blood cell count, biochemical profile, +/− urinalysis, +/− thoracic radiographs, +/− abdominal ultrasound.

Diagnosis of tumor type was based on imaging characteristics. In dogs where masses were considered accessible, a diagnostic biopsy and/or surgical excision was offered to owners. In all instances this option was declined. MRIs and CTs were initially evaluated for margins of the mass, contrast enhancement, presence of thickened meninges (i.e. dural tails), location, and presence of edema to support a diagnosis of meningioma.[2] All CTs and MRIs were later evaluated retrospectively and scored by one American College of Veterinary Radiology (ACVR) board-certified veterinary radiologist (ER) to support the diagnosis of meningioma (see Table 1).

All patients were placed in a foam trough in sternal recumbency with their forelimbs pulled caudally for radiation planning CT scans. Patients were further immobilized using a previously described system consisting of a carbon fiber plate, bite block stand, a thermoplastic bite block (Bite block beads, Patterson Medical, Cedarburg, WI) and mask system (Thermoplastic face mask, Civco model MT-APU, Civco Systems, Orange City, IA, USA). [25] A Styrofoam bead style cushion (Vaculok pillow, Civco model MT-VL-37, Civco Systems, Orange City, IA, USA) was used to provide ventral support to the cervical region.

The CT examination was performed using either a Picker PQ2000 CT single slice helical scanner (prior to November 2009), Picker PQ2000 (Picker Medical Systems, Cleveland, OH, USA) CT helical scanner, or a Philips Gemini TF Big Bore 16-slice scanner (Philips Gemini TF Big Bore 16-slice scanner Philips Medical Systems, Nederland, B.V.).

A non-contrast volumetric (helical) dataset was obtained through the skull. 2.2 ml per kilogram Omnipaque™ 350, Omnipaque™ 350 (GE Healthcare, Princeton, NJ, USA), contrast media was then injected intravenously prior to the post-contrast series. Images were reconstructed at 2.0 mm contiguous intervals with a 512 matrix, using the smooth algorithm.

The 2-mm post-contrast CT scans were utilized for inverse treatment planning performed using a Varian Eclipse™ treatment planning system (Varian Eclipse™, Varian Medical Systems, Inc. Palo Alto, CA). CTs were manually co-registered with available MRI sequences. Normal structures and organs at risk (OAR's) were contoured using the CT scan; OAR's included brain, skin, palatine mucosa, ocular lenses, optic chiasm, pharynx, bone and esophagus. A GTV was contoured based off of the CT, using the fused MRI sequences when possible to assist with differentiation between tumor and normal brain, bone and edema. The first 4 dogs treated at our institution with SRT for intracranial meningioma had a 2-mm clinical target volume (CTV) expansion to account for potential microscopic extension of disease; the field was expanded an additional 2 mm to account for inter- and intra-fraction motion and setup inaccuracies (PTV). A CTV expansion was not applied to later cases, and a 1–2 mm isotropic PTV expansion encompassed the GTV.

Inverse-planning was employed; all plans were designed such that coplanar, isocentrically placed 6 MV radiation beams were centered around a single isocenter. Radiation beams were modulated using

sliding-window technique. Dosing goal was 100% of the radiation prescription to 95% of the PTV. Normal tissue constraint for brain at this institution dictated that the 90% isodose line be 2 mm outside of the PTV, attempting to keep the volume of normal brain at this level to less than 0.1 cc. All radiation plans were reviewed and approved by an ACVR board-certified veterinary radiation oncologist.

An American Board of Radiology certified therapeutic medical physicist reviewed and performed quality assurance on all radiation plans. Quality assurance (QA) was done with gamma analysis utilizing the Varian portal dosimetry system on individual fields. A minimum of 95% gamma for a 3 mm distance to agreement and a 3% absolute dose difference was defined as a passing QA score.

Dogs were anesthetized for the delivery of radiation. Anesthetic protocols varied but in most cases consisted of an opioid premedication followed by a propofol (Dipravan, AstraZeneca, London, UK) induction and maintenance with isoflurane(Aerrane, Baxter, Haryana, India) gas. Four dogs required mannitol (Mannitol, B. Braun Medical Inc., Bethlehem, PA) (dose 0.5–1g/kg intravenously) during initial imaging when there was evidence of a possible increase in intracranial pressure.

Once anesthetized, dogs were repositioned in the immobilization devices utilized during their initial imaging. Daily patient position verification was performed by online registration of the simulation CT with images of the daily setup obtained via an on-board cone beam CT (CBCT), or registration of a digitally reconstructed radiograph with setup images obtained via on-board imaging (OBI) with kilovoltage radiographs. Allowable setup inaccuracies corresponded to the planned PTV margin. When large table shifts or repositioning was required to allow for accurate alignment repeat imaging and registration was performed. Therapy was delivered using a Varian Trilogy™ linear accelerator (Varian Trilogy™ linear accelerator, Varian Medical Systems, Inc. Palo Alto, CA).

Following radiation all dogs were monitored to evaluate for potential adverse effects and overall survival time. Recommended recheck scheduling was for a physical examination and full neurological evaluation to be performed at 2 weeks, 4 weeks, then every month following radiation therapy until the patient was 6 months post treatment. Any change in behavior or mentation would warrant an immediate appointment with the referring veterinarian or specialist.

Survival time was calculated as the time between the first day of treatment and death. Survival analysis was performed on an intent-to-treat basis; events included death from any cause. Kaplan–Meier survival curves were created using a commercial statistical program, SigmaPlot® Version 12.0 (SigmaPlot® Version12 Systat Software, Inc. San Jose, CA). Dogs were censored at the time of analysis if they were still alive or lost to follow up. One dog was counted as an event at time of retreatment. Log rank tests were used to assess categorical variables including age, sex, weight, presenting clinical signs, severity of presenting clinical signs, location, GTV volume, GTV/ICV, dose to 95% of the PTV, volume of brain at 90% isodose line, volume of normal brain receiving the prescription dose and BED.

Additionally a subset analysis was performed to look for prognostic factors. Patients were separated into two groups to evaluate dogs that had neurological difficulties (including seizures, ongoing or recurrent lethargy, worsening neurological status and/or death) in the initial 6 months (i.e. Probable acute effects or subacute demyelination) versus dogs that did not. Following tests for normality utilizing a Shapiro–Wilk test, Mann–Whitney rank sum tests or t-tests were used to compare survival to GTV volume, GTV/ICV, dose to 95% of the PTV, volume of brain at 90% isodose line, volume of normal brain receiving the prescription dose, and BED between groups based upon death as a binary variable. These same tests were then repeated to compare dogs that had died due to worsening neurological problem within 6 months of treatment [Veterinary Radiation Therapy Oncology Group (VRTOG) score ≥ 3)[26] to those that survived more than 6 months. A P value of less than 0.05 was considered significant.

Results

Signalment

Thirty dogs met criteria in the study, including 18 spayed females (60%), 10 castrated males (32.3%)

Table 2. Chemotherapy administered

Dog	Reason for Treatment	Chemotherapy	Dose	Weight
3	Hemangiosarcoma	CCNU	40 mg q3weeks PO	22 kg
12	Small Cell Lymphoma	Chlorambucil	2 mg q3days PO	22 kg
14	Presumed pulmonary metastasis	Cyclophosphamide	25 mg q7days PO	7 kg
18	Meningioma	Hydroxyurea	1500 mg q3days PO	43 kg
23	Plasma Cell Tumor	Melphalan	Cycle of 2 mg q24 hours PO × 5 days then off 14 days, repeat	5 kg
26	Meningioma	Hydroxyurea	300 mg q3days PO	6 kg

and 1 intact male (3.2%) and 1 intact female (3.2%). Breeds included mixed breed ($n = 7$, 23.3%), Golden Retrievers ($n = 5$, 16.7%), Shetland Sheepdogs ($n = 3$, 10%), Boxer ($n = 3$, 10%), and 1 (3.3%) each of the following breeds: Labrador Retriever, Poodle, Boston Terrier, Shar Pei, West Highland Terrier, Water Spaniel, Rottweiler, Rhodesian Ridgeback, Irish Wolfhound, Pomeranian, Beagle and Great Dane. Ages ranged from 3 years to 15 years old with a median of 10 years. Weights ranged from 4.2 to 60.4 kg with a median of 25.0kg.

Presenting signs and imaging

Out of 30 dogs, 15 dogs(50%) presented primarily for seizures, 14/30 dogs (46.7%) primarily had difficulties with ambulation due to head tilts, ataxia and/or stumbling and 1/30 dogs (3.3%) presented for acute onset lethargy. Secondary complaints related to neurological disease varied, and included nystagmus (4/30, 13.3%), facial paralysis (4/30, 13.3%), weakness (4/30, 13.3%), and visual deficits (3/30, 10%). Severity of presenting signs had 20/30 dogs (66.7%) with grade I, 9/30 dogs (30%) with grade II and 1/30 (3.3%) with grade III.

The majority of lesions identified on advanced imaging were located within the cerebrum (17/30, 56.7%) with 6/30 (20%) in the cerebellum and 7/30 (23.3%) in the brainstem.

Image review supported the original diagnosis in all cases. Imaging characteristics are presented in Table 1.

Medications and other treatments

All dogs were taking corticosteroids at the initiation of radiation treatment. Dosages ranged from a prednisone equivalent (assuming that 1 mg of prednisone is the equivalent of 0.15 mg of dexamethasone) of 0.80 – 1.64 mg/kg/day (mean 1.05 mg/kg/day) given daily or split into a twice daily dosing. Dosing regimes and duration of medicating with steroids varied widely between cases. Eleven of the 30 dogs (36.7%) were on phenobarbital prior to and following SRT. Other anti-seizure medications included levetiracetam (4/30, 13.3%), and potassium bromide (3/30, 10%). Post-irradiation chemotherapy was administered in 6/30 (20%) of the dogs. Chemotherapeutic agents used included CCNU, cyclophosphamide metronomics, chlorambucil, melphalan and hydroxyurea (see Table 2).

As per owners' decision, no dogs had surgical biopsy or excision prior to radiation. No dogs had prior radiation therapy before the initiation of SRT. Dog 8 had a second course of SRT performed 534 days after the initiation of its first course when it developed progressive disease identified on imaging. This dog was counted as an event at 534 days.

One dog was lost to follow up and censored at day 497. At that time the dog was doing well clinically.

Radiation planning and treatment

All dogs were treated on consecutive treatment days (Monday through Friday). Total treatment time varied from 2 to 10 days. Radiations prescriptions varied, but the dose per fraction was generally escalated as we became more experienced with normal tissue tolerance. The initial radiation prescription of 6Gy × 5 fractions was based upon human phase II trials for use of hypofractionated SRT for treatment of brain metastasis.[27] Three dogs were treated with a total of 30 Gy delivered in 5 daily fraction of 6 Gy; 3 dogs were treated with a total of 28 Gy delivered in 4 daily fractions of 7 Gy, and 23 dogs were treated

with a total of 24 Gy in 3 daily fractions of 8 Gy. One dog was treated with only 2 fractions of 8 Gy with the intent to treat to a total of 24 Gy; SRT was discontinued at the owners request after their dog was diagnosed with a splenic hemangiosarcoma.

Size of the diagnosed meningioma was compared by total volume and also a ratio of GTV to ICV to help standardize for brain size variation.[28] As of yet there is no established cut-off volume for canine meningiomas that would preclude them from treatment. Dose parameters delivered to PTV were analyzed. Dose constraints to OAR (i.e. the normal brain) were evaluated and summarized.

There was no statistically significant effect of any of these parameters on overall survival.

These results are summarized in Table 3.

Survival and adverse effects

MST due to death from any cause was 561 days (95% CI: 423–875 days). At the time of analysis 18/30 (60%) of the dogs had been euthanized (see Table 3). The 1- and 2-year survival rates were 60.8 and 33.2%, respectively. Follow up time for censored cases ($n = 12$) was at least 6 months with a median of 386 days (range: 198–794 days). Four dogs were euthanized for reasons unrelated to their neurological status. Dog 18 died after one treatment of radiation (day 1) due to a gastric perforation; dog 25 died on day 94 due to newly diagnosed carcinomatosis; dog 4 died on day 105 from chronic kidney failure that had been diagnosed prior to the onset of neurological signs; dog 9, who was diagnosed with pulmonary metastatic disease at the time of treatment, died of respiratory failure on day 581. Excluding these four dogs, MST for death due to progressive neurological dysfunction was still 561 days.

There was no statistical difference in overall MST based on sex ($P = 0.208$), age ($P = 0.950$) and weight ($P = 0.336$). Survival versus GTV ($P = 0.340$), GTV/ICV ($P = 0.322$), volume of normal tissue included at the 90% isodose line ($P = 0.547$), and dose to 95% of the PTV ($P = 0.886$) were also not significant. Initial clinical signs ($P = 0.602$), location of mass ($P = 0.538$) and severity of neurological disease ($P = 0.532$) did not significantly impact survival. Biological effective dose (BED) to compare different radiation prescriptions was calculated and reviewed and found to not have a significant impact on survival ($P = 0.879$).

Based upon recheck examinations in the month following SRT there was no evidence of acute radiation effects to the periocular tissues, eyes or ears as described by the VRTOG morbidity scoring.[26] There was no clinical evidence of peritreatment (in this case during radiation or within the first 2 weeks following radiation) brain edema (i.e. worsening of neurological status).

Dogs that had a worsening of their neurologic status in the first 6 months ($n = 14$, of which 4/14 died due to the severity of the problem) versus those that did not have a worsening of neurological status ($n = 14$) were evaluated. There were 10/14 (71.4%) of dogs with mild to moderate problems (lethargy, problems walking, etc.) who consequently had a subjective clinical improvement, usually in conjunction with an increase in steroid doses (VRTOG morbidity score of Grade 1).[26] Because of the transient nature and timing of these episodes (3–16 weeks post irradiation) it is assumed these patients developed subacute demyelination. There is no scoring system available for subacute radiation effects. There were no prognostic factors identified that put animals at risk for this. Prednisone dosages varied so widely between patients at the time of onset of these signs and during resolution of them that no conclusions regarding medication administration could be made. There was no significant difference in survival between the 10 dogs with subacute demyelination that recovered and the 14 dogs that did not develop these effects. Two dogs were excluded from this analysis as they were euthanized for non-neurological problems prior to the 6-month time point and did not suffer from any noted effects in this time period.

Dogs that suffered a fatal worsening of neurological status (VRTOG morbidity score of late effects ≥ 3)[26] in the first 6 months ($n = 4$, 13.3%) versus dogs that survived for greater than 6 months ($n = 22$) were compared. Four dogs, 2 of which had possible subacute demyelination but then exhibited clinical improvement, were not included in this analysis as they were euthanized for non-neurological reasons within 6 months of treatment. In 3/4 of dogs with fatal worsening there was a sudden, severe increase in seizure activity

Table 3. Summary of Radiation Planning parameters, survival and doses to normal brain tissue

Dog	Survival (days)	GTV vol (cc)	(Dose/fx) × (Fractions)	GTV/Br	PTV dose cGy	PTVmin cGy	PTVmax cGy	Brain-PTV + 2mm at 90% Isodose (cc)	Brain Volume at Full Prescription (cc)
1	[a]1434	2.2	6 × 5	13.636364	3043.1	2873	3252	0.04	2.64
2	[a]861	3.5	7 × 4	8	2653.6	2399	3273.3	0.339	1.8
3	[a]225	1.3	7 × 4	21.538462	2639.9	1877.6	2941.5	0.008	1.52
4	[a, b]105	2.4	6 × 5	12.5	2719.5	2482.7	2985.8	0	0
5	[a]561	2.4	6 × 5	12.5	2528.8	1978.8	3155.5	0.065	0.03
6	[a]594	2	8 × 3	12	2126.3	1919.8	2479.1	0	0.01
7	[a]367	5.5	7 × 4	5.0909091	2545.2	1192.5	3020.1	0	0.22
8	[a]532	4.2	8 × 3	5.7142857	2400.4	1813.3	3055.2	0.001	1.04
9	[a, b]581	4.7	8 × 3	5.106383	2409.2	2168.2	2752.9	0.002	1.2
10	[a]497	4.7	8 × 3	3.4042553	1590.84	1397.6	1891.1	0.016	1.26
11	[a]104	1.3	8 × 3	18.461538	2366.5	2239.5	2673.9	0.039	0.65
12	798	7.5	8 × 3	3.2	2295.7	2035.5	2776.7	0	0.53
13	777	2.3	8 × 3	10.434783	2399.4	2210.1	2945.5	0.038	0.65
14	[a]357	3.7	8 × 3	6.4864865	2401	2255	2831.4	0.087	1.44
15	615	5	8 × 3	4.8	2420.6	2297.9	2964.3	0.121	1.25
16	546	4.3	8 × 3	5.5813953	2381.9	2200.9	2823.6	0.03	1.24
17	[a]93	7.1	8 × 3	3.3802817	2394.4	2127.1	2891.2	0.001	1.83
18	[a, b]1	6.5	8 × 3	3.6923077	2394.9	2206.4	2963.2	0	1.38
19	420	3.9	8 × 3	6.1538462	2329.4	2027.2	3025.1	0.001	0.71
20	391	2.3	8 × 3	10.434783	2399	2129.1	2853	0.003	1.06
21	390	0.4	8 × 3	60	2403.1	2012.5	2922.3	0.005	0.47
22	377	2.7	8 × 3	8.8888889	2394.2	2270.4	2845.9	0.042	0.91
23	370	7.2	8 × 3	3.3333333	2422.3	2249.6	2687.6	0.011	2.61
24	[a]94	3.9	8 × 3	6.1538462	2409.3	2231.1	2688.3	0.018	1.46
25	[a, b]274	5.2	8 × 3	4.6153846	2397.1	2040.7	3203.6	0	1.09
26	288	0.2	8 × 3	120	2391.4	2078.4	2766.2	0.038	0.31
27	[a]24	3.4	8 × 3	7.0588235	2237.5	1682.4	2766.9	0.024	1.62
28	202	5.7	8 × 3	4.2105263	2434	2048.4	2816.4	0.012	2.06
29	[a]99	2.4	8 × 3	10	2391.2	2157.8	2677.1	0.003	1.41
30	[a]123	12.7	8 × 3	1.8897638	2356.8	1663.6	2767.2	0.23	3
Median	373.5	3.8		6.3201663	2399.2	2128.1	2849.45	0.0115	1.22
Mean (±CI)		4.02 (±0.95)		13.28 (±8.5)	2409.2 (±83.5)	2075.5 (±117.96)	2856.5 (±96.5)	0.039 (±0.0276)	1.18 (±0.29)
Minimum	1	0.2		1.8897638	1590.84	1192.5	1891.1	0	0
Maximum	1434	12.7		120	3043.1	2873	3273.3	0.339	3

[a]Survival times of dogs that were euthanized or counted as an event at time of analysis.
[b]Cause of death reasons other than neurological.

that could not be controlled with medications. Recurrence of seizures was seen in all three of these dogs at time points varying from 4 to 16 weeks post irradiation. One dog became progressively more lethargic following radiation, was not responsive to medications and the owner elected euthanasia due to a decline in quality of life. Analysis of this small subset of patients showed that the volume of normal brain receiving the prescription dose was significantly associated with fatality (mean 1.97 cc in dogs with survival <6 months vs. 1.09 cc in dogs with survival >6 months, $P = 0.019$) (see Table 4).

Necropsy examination was performed on Dog 29 (in the 8 Gy × 3 fractions = 24 Gy group) that died on Day 99 following >24 hours of seizure activity and evidence of non-cardiogenic pulmonary edema. Histopathology of the brain showed degeneration and necrosis within the meningioma and locally extensive reactive glial scarring and vacuolization in the surrounding neuropil. There was an extensive focus of encephalomalacia and spongy change within the cerebrum. These findings are compatible with radiation effects. Retrospective analysis of the radiation plan showed that there was

Table 4. Comparison of survival times and normal brain volumes in dogs that died <6 months following radiation due to increased severity of neurological issues to dogs that survived >6 months

Dogs with Survival <6 months		
Dog	**Survival (days)**	**Brain volume at full prescription (cc)**
17	93	1.83
28	24	1.62
30	99	1.41
31	123	3
Mean	**84.75**	**1.97**
Dogs with Survival >6 months		
Dog	**Survival (days)**	**Brain volume at full prescription (cc)**
1	1434	2.64
2	861	1.8
3	225	1.52
5	561	0.03
6	594	0.01
7	367	0.22
8	532	1.04
9	581	1.2
10	497	1.26
12	798	0.53
13	777	0.65
14	357	1.44
15	615	1.25
16	546	1.24
19	420	0.71
20	391	1.06
21	390	0.47
22	377	0.91
23	370	2.61
25	274	1.09
27	288	0.31
29	202	2.06
Mean	**520.77**	**1.09**

Statistically different volume of brain at full prescription ($P = 0.019$).

1.41 cc of normal brain irradiated at full radiation dose (24 Gy in 3 fractions of 8 Gy per fraction).

In comparison, Dog 1 was euthanized 1434 days post-SRT (6 Gy × 5 fractions = 28Gy) for recurrent neurological signs. Necropsy was performed; histopathology showed necrosis and hemorrhage within the center of a progressive meningioma. There was hypergliosis and occasional gitter cells in the adjacent neuropil. There was no histological evidence of telangiectasia, demyelination or malacia within the surrounding brain tissue, indicating no radionecrosis. Retrospective analysis of the radiation plan showed that there was 2.67 cc of normal brain irradiated at full radiation dose (28 Gy in 4 fractions of 7 Gy per fraction).

Discussion

When evaluating volume of normal brain receiving full prescription dose there was a significant association with serious neurologic deterioration leading to death with in the first 6 months ($n = 4$ dogs in this group). A further evaluation of other types of brain tumors treated in dogs with SRT is warranted to confirm these results. The results of this study suggest that volume of normal brain at prescription dose should be kept below 1.1 cc. However, the small number of dogs in this group makes drawing definitive conclusions difficult. Establishing normal constraints for veterinary patients is an important part of practicing veterinary radiation oncology. Inherent species differences are expected so complete reliance on the more established human data is not possible. The 2010 American Association of Physicists in Medicine (AAPM) guidelines on normal tissue constraints suggests that the brainstem should receive no more than 18 Gy of radiation in 3 fractions (6Gy/fraction) with a maximum allowed dose of 23.1 Gy[29]. There are no recommended constraints for the remainder of the brain.

When examining Table 4 there are 10/22 (45.5%) of dogs with survival that was more than 6 months who had a volume of normal brain included at full radiation dose greater than the suggested constraint of 1.1 cc's. However, all the dogs who died of neurological issues in less than 6 months (4/4, 100%) had more than 1.1 cc's of normal brain included at full radiation dose, with the minimum volume in this group actually being 1.4 cc's. Given the variability in individual radiation response, it is impossible to reliably predict for all cases what volume of normal brain is safe to irradiate. The normal tissue constraint of 1.1 cc's is likely conservative. Depending upon future response to therapy this constraint may require adjustments to allow for higher volumes of normal brain to be included.

The overall MST of 561 days following our SRT protocol appears comparable to previously

reported outcomes following surgery and/or radiation therapy.[6,12,14,16] The treatment time required for delivery of SRT (3–5 fractions) means a significant reduction in the number of anesthetic events when compared to conventional fractionated radiation. The small number of cases in this series made it hard to discern any possible prognostic factors associated with overall survival following this SRT protocol.

The ability to achieve conformal dosing means that some of the previously reported acute effects of brain irradiation (dermatitis, keratoconjunctivitis sicca and otitis) are avoidable, keeping the patient more comfortable during the peritreatment period.[30,31]

There were no dogs that had evidence of radiation-related neurological effects during the treatment period. Studies in human medicine have shown that acute effects are generally experienced within a week or two of radiation therapy.[17] These are rare in conventionally fractionated radiation protocols, but large dose per treatment protocols can lead to an acute exacerbation of neurological signs.[19] Many of these problems are associated with spike in intracranial pressure due to edema.[19] Acute edema related to radiation would be considered a treatment-related toxicity and could potentially be prevented by appropriate anti-inflammatory doses of steroids throughout a defined risk period. As a result of the referral nature of this institution follow-up care was not under the direct control of the radiation oncologist, leading to wide variations in dosing regimes and duration of prednisone administration. The retrospective nature of the study meant that medical records from different hospitals had to be reviewed to determine time of onset of clinical signs, severity of clinical signs and dosages of medication. Given this variability it was not possible determine an optimum dosing regime.

A concerning aspect of escalating dose per fraction during brain irradiation is the potential for worsening of delayed and late effects in CNS tissue. There is a continuum of brain inflammation following irradiation that makes it difficult to separate early edema from subacute demyelination and late radionecrosis. This inflammation is mediated by cascading release of cytokines. There is an excessive generation of reactive oxygen species (ROS) following brain irradiation that quickly overwhelms the anti-oxidant protective systems, leading to oxidative stress. The glial cells and neurons of the central nervous system appear to have a comparatively low antioxidant enzyme reserve.[32] As well, the high levels of peroxidizable fatty acids in myelin membranes make the brain particularly sensitive to ROS' and cytokine inflammatory processes. This can eventually progress to injury in the white matter following endothelial change and fibrosis of cerebral blood vessels.[18,33,34]

The mild to moderate worsening neurological problems up to 24 weeks after SRT is possibly due to subacute demyelination (also referred to as an early delayed effect). Subacute demyelination is a problem recognized in people undergoing radiation therapy for brain tumors.[19] It occurs 1–6 months following completion of radiation therapy and is thought to be related to the death and subsequent release of cytokines from tumor cells leading to transitory axonal demyelination of oligodendrocytes and/or disruption of the integrity of the blood brain barrier.[19] The problem is often transient and responsive to increased steroid doses.

The continuous nature of radiation effects makes it hard to exactly define the cause of these problems without histopathology. Reports would claim that radionecrosis would be more likely to be seen beyond the 6-month time point, but it is hard to distinguish this from tumor recurrence. [19] Effects seen prior to 6 months are more likely to be acute or subacute treatment-related effects. The subset analysis using 6 months as a time point cut off was chosen in an attempt to determine the causative factors of a true radiation effect while decreasing the risk of tumor progression as a confounding factor.

In the case of Dogs 29 and 1 where histological evaluation of irradiated CNS tissue was available there was >1.1 cc's of normal brain included in both radiation plans. In Dog 29 (1.41 cc's of normal brain included in the 100% isodose line in an 8Gy × 3 fraction plan) this resulted in ARE including encephalomalacia and vacuolization of the neuropil. In Dog 1 (2.67 cc's of normal brain included in the 100% isodose line in a 6 Gy × 5 fraction plan) there was minimal ARE noted in the neuropil adjacent to the tumor and it is presumed that progressive disease was responsible for the recurrence

of neurological signs. All dogs that died as a result of worsening neurological signs within 6 months of treatment were in the 8 Gy × 3 fraction group. There were not enough dogs in the 7 Gy × 4 fraction and 6 Gy × 5 fraction groups to find a statistical significance between survival in groups, or to determine if volume of normal brain included in the 100% isodose line was more detrimental with larger dose per fraction. Adverse events have been shown to vary based upon dose per fraction[35] and are likely playing a role in this study. Future studies or collaborative research to compare different fractionation protocols may help to better define tolerance of normal brain tissues in our veterinary patients.

Due to the lack of histological confirmation of radionecrosis in most patients in this case series, it was not possible to determine whether there were parameters contributing to late effects. When clinical signs recur months to years following irradiation it is hard to clinically distinguish tumor progession from radiation necrosis; it is important to distinguish between the two processes, as they are managed very differently and may influence an SRT protocol. For example, if tumor progression is more common than late encephalopathies, radiation dose escalation would be indicated; conversely, if toxicity is more common than recurrence, the protocol exceeds normal tissue tolerance and more restrictive constraints should be placed on the OAR.

At this time more evidence obtained through advanced imaging modalities, such as spectroscopy and diffusion weighted imaging, and histopathology of irradiated brain tissue following SRT (either at time of post mortem or via stereotactic guided sampling)[36] is required to standardize tolerance doses and radiation prescriptions in canine patients.

The OAR dose constraint of having the 90% isodose line fall within 2 mm of the PTV expansion is based up on a physics requirement for steep dose drop off at the CSU-VTH. Future dose constraints will also include evaluating the volume of normal brain at prescription dose. Larger masses, or masses with long dural tails, particularly along the falx, can easily meet the criteria of fall off of dose within 2 mm, but may have an increased volume of normal brain at prescription as a result of their location. A combination of the two evaluation methods should help to limit effects.

There are multiple papers[2,3,37] that define imaging characteristics associated with various brain tumors found in dogs. In this case series there was one ACVR board-certified radiologist that retrospectively reviewed all pre-treatment imaging to support the initial diagnosis. In all cases the imaging had multiple properties that would be seen with a meningioma. While this does not provide definitive diagnosis, we feel that we have taken a consistent and repeatable approach that can be used in future studies. Ideally a biopsy would be obtained prior to treatment, however morbidity associated with brain biopsies ranges from 12 to 26% of cases[38–40].

Manual co-registration of MRIs and planning CTs is performed at this facility. Rigid co-registration of imaging modalities is commonly practiced in human medicine, but it has been our experience that the variation between size and conformation of the patients seen in veterinary medicine makes these programs of limited use. In addition the immobilization devices required for obtaining planning CTs are not MRI compatible, making most of the soft tissues difficult to align. Planning CTs are created using a 2-mm slice thickness, meaning that if the MRI slice thickness is greater than this the computer algorithm must employ interpolation methods to make up the difference. Given the sub-millimeter accuracy that is our goal in these cases this is considered inadequate for precise planning. The majority of these patients have an MRI that was utilized for diagnostic purposes. In between this initial imaging and the imaging for a planning CT, many patients have been placed on anti-inflammatory doses of steroids, which may also affect the GTV margins. As a result a second planning MRI with limited sequences (axial T1, axial T1 post contrast and axial T2 images) with 2-mm slice thickness is often obtained on the same day as a planning CT to allow for precise registration. Ideally, in masses with minimal peritumoral edema, the initial diagnostic MRIs would be done in 2-mm slices so that interpolation during planning would not be necessary, which would negate the need for additional, expensive imaging

The advantage of chemotherapy in the treatment of meningiomas in veterinary medicine has not been clearly defined. *In vitro* studies have shown

that hydroxyurea inhibits the growth of meningioma cells and has been shown in human studies to occasionally have a dramatic effect for the treatment of recurrent meningiomas.[41] Other human studies have questioned the effectiveness of any type of cytotoxic chemotherapy in treatment of meningiomas.[42] There are only a few case reports of the use of chemotherapy for the treatment of meningiomas in veterinary medicine.[43–45] In this retrospective study we have six dogs that were on some form of anti-neoplastic medication after SRT. There was no evidence that chemotherapy significantly impacted survival.

Limitations of this study included the retrospective nature, the limited case number, lack of consistent follow up, variation in protocols, variations in medications, lack of histological diagnosis and limited necropsy examinations.

Conclusion

In conclusion it is felt that SRT for the treatment of canine meningiomas, as prescribed and delivered in this case series, is associated with an acceptable toxicity profile and provides a survival times comparable to other treatment modalities. In addition it is associated with fewer anesthetic episodes and a shorter total treatment time than conventionally fractionated protocols. As a result of this retrospective analysis we have defined a normal tissue tolerance for our institution in patients being treated with 3 fractions of SRT. It states that the volume of normal brain receiving greater than or equal to 24 Gy in 3 fractions should be kept below 1.1 cc's. As the establishment of these constraints there have been only a few mild episodes of subacute demyelination and no treatment-related deaths [$n = 48$ dogs treated with SRT for intracalvarial tumors with 17/48 (35.4%) of these being meningiomas]. Dogs are either on no steroids or low doses of steroids that are weaned off within 1–2 months with no episodes of recurrent neurological issues (personal communication, Dr. Susan LaRue). Continued follow up on these cases is required to attempt to evaluate dogs for late effects and impact on overall survival. Ultimately the goal would be to decide if dose escalation (in the case of tumor recurrence) versus dose de-escalation at the periphery of the radiotherapy field (in the case of radionecrosis) is required.

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