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Clinical and imaging findings, treatments, and outcomes in 27 dogs with imaging diagnosed trigeminal nerve sheath tumors: A multi-center study

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Abstract

The clinical behavior of canine trigeminal nerve sheath tumors and benefits of previously reported treatments are incompletely defined. Aims of this retrospective, multicenter, observational study were to describe clinical signs, tumor localization characteristics, treatments, and clinical outcomes in a group of dogs with this neoplasm. Databases at four hospitals were reviewed for dogs with a trigeminal nerve sheath tumor diagnosis, magnetic resonance imaging (MRI) studies, and presentation between 2004 and 2014. A single observer recorded medical record findings and two observers recorded MRI characteristics by consensus. A total of 27 dogs met inclusion criteria (15 treated with stereotactic radiation therapy and 12 unirradiated). Two unirradiated dogs were excluded from outcome analyses. The most common presenting signs were masticatory muscle atrophy (26 dogs), neurologic signs referable to intracranial disease (13), and ocular disease (12). Based on MRI findings, all dogs had disease extending centrally at the level of the brainstem. The most commonly affected trigeminal nerve branches were the mandibular (26 dogs), maxillary (22), and ophthalmic (10). Of 15 dogs treated with stereotactic radiation therapy, one had improved muscle atrophy, and six had poor ocular health after treatment. Neurologic signs improved in 4/5 dogs with intracranial signs. Overall median survival time for the 10 unirradiated dogs with available follow-up was 12 days and 441 days for the 15 stereotactic radiation therapy dogs. Mean survival times between these groups were not significantly different (mean 95% CI for unirradiated dogs was 44–424 days and mean 95% CI for stereotactic radiation therapy dogs was 260–518 days).

KEYWORDS

neurooncology, radiation oncology, small animal oncology, stereotactic radiation therapy

1 | INTRODUCTION

In the dog, centrally located nerve sheath tumors can arise from spinal nerves, cranial nerves, or nerve roots. They have been reported to arise from Schwann cells or perineural fibroblasts and commonly occur in the caudal cervical region of the spinal cord.[1,2] The most commonly affected cranial nerve in the dog is the trigeminal nerve.[3] Reported clinical signs in dogs with trigeminal nerve sheath tumors include unilateral masticatory muscle atrophy, reduced facial sensation, diminished palpebral reflex, and reduced corneal sensation.[1,4] Neurologic signs associated with brainstem compression can also occur.[4,5] Differential diagnoses include infectious and inflammatory neuropathies; lymphoma has also been reported to affect the trigeminal nerve.[6] Malignant nerve sheath tumors are classified as soft tissue sarcomas, and in general are thought to have relatively low metastatic potential.[3] To the authors' knowledge, such data have not been reported specifically in canine trigeminal nerve sheath tumors.

Magnetic resonance imaging (MRI) is an established imaging modality upon which a presumptive diagnosis of trigeminal nerve sheath tumor can be made.[3] Previously reported are outcomes of dogs with no treatment, surgical removal, and more recently, stereotactic radiotherapy or radiosurgery.[4,7–9] Untreated dogs with presumptively diagnosed trigeminal nerve sheath tumors have been reported to have a median survival time of 12 months; whereas two dogs treated with surgery survived 4 and 27 months, respectively.[4] The published

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median survival time after stereotactic radiation therapy has been reported to range from 324 to 881 days.[7,8] However, the clinical behavior of trigeminal nerve sheath tumors and comparative benefits provided by these various treatments remain incompletely defined. Aims of the current study were to address these gaps in knowledge by describing clinical signs, tumor localization characteristics, treatments, and clinical outcomes in a comparatively large cohort of dogs treated with or without stereotactic radiation therapy.

2 | MATERIALS AND METHODS

The study was a retrospective, multicenter, observational design. Databases at four referral hospitals were searched for all dogs presenting with a trigeminal nerve sheath tumor. Requirements for study inclusion were a diagnosis of a trigeminal nerve sheath tumor based on neurologic examination and MRI findings, and an admission period between 2004 and 2014. Neurologic examimation findings considered to be suggestive of trigeminal nerve sheath tumor were unilateral temporal and masseter muscle atrophy, enophthalmos, absent or diminished palpebral reflex, absent or diminished corneal reflex, decreased facial sensation, seizures, general proprioceptive ataxia, and/or hemiparesis. Magnetic resonance imaging features considered to be suggestive of a trigeminal nerve sheath tumor were extra-axial mass at the level of the pons, and/or unilaterally enlarged branch or branches of the trigeminal nerve on T2- or T1-weighted images with contrast enhancement of the mass lesion, and enlarged nerve branches on T1-weighted images.[4,10] Neither histologic confirmation of nerve sheath tumor, nor cerebral spinal fluid analysis were required for inclusion. The primary author (K.S.), a board-certified veterinary radiation oncologist (S.L.), a board-certified veterinary radiologist (E.R.), and a board-certified veterinary neurologist (S.M.) made the final decision to include or exclude a patient from the study.

Medical records were reviewed by the primary author and information on patient demographics, history, presenting physical and neurologic examination findings, MRI features, systemic staging, clinical signs after treatment, CT planning images, details of the radiation therapy plans, toxicity, and survival were recorded. Imaging data were retrieved and archived for review via DICOM data transfer.

All MRI studies were retrospectively reviewed together by a board-certified veterinary radiologist (E.R.) and neurologist (S.M.). The reviewers were aware of previous diagnosis and medical record findings at the time of interpretation. A consensus was reached on imaging changes suggestive of diagnosis of trigeminal nerve sheath tumor, branch involvement, and fluid in the tympanic cavity. Findings recorded from imaging studies were laterality of lesion, presence or absence of an intracranial component, the branch or branches of the trigeminal nerve affected, and changes suggestive of fluid in the tympanic cavity. A branch was considered affected if it was contrast enhancing on post-contrast T1-weighted sequences, or enlarged and contrast enhancing relative to the contralateral nerve within or distal to its exiting foramen or canal.

For dogs having undergone stereotactic radiation therapy, radiation toxicity was retrospectively graded according to the criteria of the Veterinary Radiation Therapy Oncology Group.[11] The primary author (K.S.) graded the radiation toxicity and was aware of medical record data. Acute radiation effects were considered possible in dogs that had a transient decline in neurologic status during the course of, or up to 3 weeks after stereotactic radiation therapy, or in dogs that had imaging after stereotactic radiation therapy in that timeframe that showed increased peritumoral edema. Early delayed radiation side effects were considered possible if transient neurologic decline occurred 3 weeks to 6 months after treatment or if there was increased peritumoral edema with stable to decreased tumor size in MRI after treatment. Late effects were considered possible if there were nontransient, progressive neurologic signs greater than 6 months following radiation treatment without imaging evidence of tumor progression.[12–14]

In all dogs, brain and tumor volumes were contoured by either the primary author (unirradiated dogs) or by a radiation oncology resident (irradiated dogs) using radiation planning software. The volume measurements for the brain and tumor volumes were extracted from the radiation planning software by the primary author. For dogs receiving stereotactic radiation therapy, a combination of CT and MRI was used to contour the brain. In unirradiated dogs, only the MRI was used to contour the brain. In all subjects, the MRI was used to contour tumor volumes. Brain-to-tumor volume ratio was determined in all dogs, and was calculated by dividing the total brain volume in milliliters (mL) by the total intracalvarial tumor volume in milliliter.

2.1 | Statistics

Analyses were performed using commercially available software (SigmaPlot Version 12, Systat Software, Inc., San Jose, CA; or SAS Version 9.4, SAS Institute Inc., Cary, NC). Data for statistical analysis were selected by the primary author (K.S.) and analyses were performed by the primary author and a biostatistician (S.R.). The Kaplan-Meier product limit method was used to calculate disease-specific survival times, from the time of imaging diagnosis by MRI to death of tumor-related cause. Dogs that died of a nontumor related cause, or that were alive or lost to follow up at the time of analysis were censored at the time of last contact. Similarly, overall survival time was calculated from the time of imaging diagnosis by MRI to time of death of any cause. Log-rank tests were used to assess differences in survival times, absolute intracalvarial tumor volumes, and brain-to-tumor volume ratios between dogs treated with stereotactic radiation therapy and unirradiated dogs. In an attempt to eliminate potential outcome bias associated with severity of clinical signs, and allow for a more conservative outcome comparison between dogs treated with stereotactic radiation therapy and unirradiated dogs, overall and disease-specific survivals not including dogs euthanized at diagnosis were additionally evaluated. In all dogs, logistic regression analysis was used to determine association between dogs displaying ataxia or vestibular signs at presentation with imaging changes suggestive of fluid in the middle ear. Logistic regression analysis was used in all dogs to determine association of ophthalmic branch involvement apparent on imaging and those dogs with history of ocular disease. In dogs treated with stereotactic radiation therapy, various plan parameters, including the dose that was delivered to 99% of intracalvarial gross tumor volume, 95% dose to the intracalvarial

planning target volume, volume of the intracalvarial tumor, volume of normal brain (calculated as the intracalvarial volume, excluding grossly identifiable tumor) at 24 Gy, and the ratios of brain-to-tumor volumes, were evaluated using nonparametric Spearman's rho to find correlation between these parameters and radiation-associated side effects. Linear regression was used to determine the association of the continuous data of ratio of brain/tumor volume with overall survival time. Statistical significance was defined as a *P* value less than 0.05.

3 | RESULTS

3.1 | Clinical findings

Twenty-seven dogs met the inclusion criteria. Clinical outcome data were missing for two dogs following imaging diagnosis. These two dogs were excluded from outcome and survival analyses. There were 14 spayed females, 12 castrated males, and 1 intact male. Age ranged from 5 to 13.5 years with a mean of 9 years. Weight ranged from 4.4 to 55.5 kg with a mean of 21.7 kg. Breeds were variable and included mixed breed (8), Labrador retriever (4), Pug (2), Jack Russell Terrier (2), and one each of the following: Staffordshire Terrier, Cocker Spaniel, Miniature Pinscher, Shih Tzu, Coonhound, Border Collie, Pomeranian, Newfoundland, French Bulldog, American Pitbull Terrier, and Gordon Setter.

The most common presenting clinical signs at the time of diagnostic MRI were as follows: unilateral muscle atrophy (26), absent palpebral reflex (7), decreased menace (7), enophthalmos (10), facial paresis (4), intracranial signs (13), and ocular disease (12). Ocular disease in the population herein was considered neurogenic and tumor associated if it was ipsilateral and included corneal ulceration and/or keratoconjunctivitis sicca.[15] The occurrence of ocular disease in this study population included ipsilateral corneal ulceration (6/12), ipsilateral keratoconjunctivitis sicca (3/12), and previous ocular surgery for one of those two causes (3/12). No dog had a history of ocular disease contralateral to the tumor. Of the 13 dogs presenting with signs supportive of intracranial disease, five dogs presented with recent seizure activity, four with general proprioceptive ataxia, four with postural reaction deficits, and six with abnormal mentation/behavior (circling, pacing, head pressing or vocalization). As recorded on physical and neurological examination, 11 dogs presented with right-sided masticatory muscle atrophy and 14 dogs presented with left-sided masticatory muscle atrophy. One dog had no reported muscle atrophy and one dog had generalized muscle atrophy. The dog with no reported muscle atrophy presented with seizures that prompted workup. The dog with generalized muscle atrophy was counted as having masticatory muscle atrophy.

3.2 | Magnetic resonance imaging techniques and findings

Technical acquisition parameters are summarized in Table 1. Magnetic resonance imaging studies were acquired using 1.0–1.5 Tesla magnets (GE, General Electric Company, Boston MA; or Siemens; Siemens Medical Solutions, Inc. Malvern, PA) and either a human extremity or head coil. Contrast medium (Magnevist, gadopentetate dimeglumine; 0.5 mmol/mL; Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ; or Dotarem, gadoterate meglumine; 0.5 mmol/mL, Guerbet LLC. Bloomington, IN) was administered by manual boluses at a dose of 0.22 mL/kg and time delays between contrast injection and acquisition of postcontrast sequences ranged from immediately following injection to 4 minutes. All studies were acquired in 2D and included at least T1-weighted pre- and postcontrast, and T2-weighted sequences in the transverse plane. Most studies also included dorsal and sagittal plane images, in varying sequences.

Imaging findings for the 27 included dogs were as follows: left-sided lesion (14), right-sided lesion (13), mandibular branch involvement (26), maxillary branch involvement (22), ophthalmic branch involvement (10), intracalvarial extension (27), tympanic cavity effusion (8). The number of dogs with one, two, or three branches involved was 5, 13, and 9, respectively. Eight dogs had ipsilateral imaging changes suggestive of fluid in the tympanic cavity. One of the eight dogs had bilateral changes in the middle ear, with the ipsilateral ear more profoundly affected. Clinical otitis was reported historically in only one dog. In that dog, the otitis was treated successfully with anti-inflammatories about 2 years prior to presentation and had no clinical recurrence. Two dogs had a myringotomy performed at the time of imaging. Only cytology results of one of the dogs was available which showed proteinaceous fluid with few neutrophils. Appendix 1 details each of the subjects' MRI findings. Total tumor volumes in all dogs ranged from 0.4 to 18.73 mL with a mean and median of 2.9 and 2.2 mL, respectively. Tumor volumes are further detailed in Table 2 and Appendices 2 and 3.

3.3 | Stereotactic radiation therapy techniques

3.3.1 | Stereotactic radiation therapy planning

Radiotherapy simulation is CT image acquisition performed prior to radiation treatment with a patient specifically positioned and immobilized in treatment position. The imaging is used for tumor localization, radiotherapy contouring, dose calculation, and treatment positioning. In all stereotactic radiation therapy dogs, simulation imaging was performed under general anesthesia using a variety of anesthetic protocols based on patient needs. At both institutions, dogs were positioned for CT and treatment in sternal recumbency and in a bite block apparatus, as previously described.[16] For imaging at Colorado State University (CSU), a Philips Gemini TF Big Bore 16-slice scanner (Philips Medical Systems, Andover, MA) was used to obtain 2 mm nonoverlapping slices in a 512 × 512 matrix. At North Carolina State University (NCSU), a Siemens Somatom Sensation 64 (Siemens Medical Solutions, Inc. Malvern, PA) was used for CT imaging with similar slices and matrix.

For all 15 stereotactic radiation therapy cases, CT images were manually coregistered with an MRI (T1 postcontrast and/or T2-weighted) and used to contour structures for treatment planning. Primary planning CT images were either precontrast (6) or postcontrast (9). The GTV was based on the contrast-enhancing lesion as seen on the T1-weighted images, while CT images delineated exiting

TABLE 1 Technical parameters used for magnetic resonance imaging studies in all dogs in the current study population

Sequence		Repetition Time	Echo Time	Inversion Time	Flip Angle	Number of Acquisitions (NEX)	Slice Thickness	Gap	Field of View	Matrix
T1W										
	Transverse	200–1150	4.5–18	100–200	68–180	1–6	2–5	2–5.5	111–220 × 130–220	224–512 × 224–512
	Sagittal	200–516	5–11	120–260	70–90	1–4	2–3	2–3.3	120–260 × 120–260	256–512 × 256–512
	Dorsal	800	11.5	200	90	1.5	3	3.3	200 × 200	512 × 512
T1W + C										
	Transverse	350–800	8–18	130–200	90–180		1–4	1.5–5.5	111–250 × 140–250	224–512 × 224–512
	Sagittal	350–900	8–24	150–270	90	1–4	2–4	2–4.5	111–270 × 150–270	256–512 × 256–512
	Dorsal	350–800	9.5–24	140–240	90	1–4	2.5–4	3–4.5	111–240 × 140–240	240–512 × 240–512
T1WFS + C										
	Transverse	400–756	11–14	150–190	90–180	1–2	2–4	2–4	111–190 × 150–190	256–512 × 256–512
	Sagittal	450–800	11–12.5	160–260	90	1–2	2–3	2–3	160–260 × 160–260	256–512 × 256–512
	Dorsal	450	11	160	90	4	3	3.3	160 × 160	512 × 512
T2W										
	Transverse	3072–6416	26–130	150–250	20–180	1–4	2–4.5	2.5–5.5	111–270 × 140–270	256–512 × 256–512
	Sagittal	2442–5490	11–131	140–260	90–180	1–4	2–4	2.5–4.5	111–260 × 140–260	256–512 × 256–512
	Dorsal	3500–4716	100–115	150–220	90	1–4	2.5–3	2.5–4	170–220 × 170–220	256–512 × 256–512
FLAIR										
	Transverse	6000–9000	78–142	129–190	90–180	0.5–2	2–5	2.5–5.5	111–250 × 150–250	256–512 × 256–512
T2*W GRE										
	Transverse	350–1105	15–28	140–190	20–40	1–3	3–5	3–5.5	140–220 × 140–220	256–512 × 256–512

Notes. Repetition, inversion, and echo times reported in milliseconds. Slice thickness, gap, and field of view reported in millimeters. T1W, T1-weighted; T1W + C, T1-weighted postcontrast; T1WFS + C, T1-weighted postcontrast with fat saturation; T2W, T2 weighted; FLAIR, Fluid-attenuated inversion recovery; T2*WGRE, T2*weighted gradient echo.

TABLE 2 Intracalvarial and total tumor volumes in all dogs

	Unirradiated Dogs ($n = 10$)		SRT Dogs ($n = 15$)	
	IC Tumor Volume	Total Tumor Volume	IC Tumor Volume	Total Tumor Volume
Minimum	0.20	0.40	0.40	1.28
Maximum	2.47	3.98	4.57	18.73
Mean	1.36	1.77	1.50	3.95
Median	0.9	1.3	0.93	2.57
SD	1.14	1.36	1.37	4.40

Notes. Volumes listed in units of milliliters. IC, intracalvarial; SD, standard deviation; SRT, stereotactic radiation therapy.

foramina of the trigeminal branches. The GTV was broken into two portions: the intracalvarial GTV and extracalvarial GTV, with the intracalvarial GTV including only the tumor portion sitting inside the skull. Once within an exiting foramen, the tumor was considered extracalvarial GTV. There was no additional clinical target volume expansion to account for microscopic disease. The intracalvarial planning target volume expansion was either 1 or 2 mm and the extracalvarial planning target volume ranged from 1 to 3 mm. During positioning for daily stereotactic radiation therapy delivery, the cone beam match was preferentially based on alignment of the intracalvarial disease, so a larger planning target volume was applied to the extracalvarial component to ensure the entire length of the tumor was dosed as intended. Contoured organs at risk were contoured based on CT/MRI registration and included external body contour, bones, ear canal, cochlea, optic chiasm (defined by the optic canal), eyes, lenses, brain, skin, palate mucosa, pharynx, and spinal cord. Skin was contoured by extracting a 2 mm margin inward from the external body contour. Normal brain was contoured as the intracalvarial volume, excluding grossly visible tumor. Eyes were contoured to include the whole globe as seen on CT, and the lenses were contoured on CT to include the well marginated area of increased opacity within the globe.

Treatment plans were generated with 7–11 6 and/or 10 MV photon beams in a coplanar arrangement, and with inverse treatment planning, using Varian Eclipse computer software versions 8.6, 10.0 or 11.0 (Varian Eclipse, Varian Medical Systems, Inc., Palo Alto, CA). Heterogeneity correction and AAA photon dose calculation algorithm were employed. Patient-specific plan quality assurance was performed for each field comprising the treatment plan by gamma analysis comparing treatment plan data to that measured with the MapCHECK2^{R} system (Sun Nuclear Corporation, Melbourne, FL) (NCSU) or Portal Dosimetry system (Varian Medical Systems, Inc.,) (CSU). 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.

3.3.2 | Stereotactic radiation therapy delivery

All dogs were treated in three fractions of 8–10 Gy and total treatment time ranged from 3 to 6 days with weekends or holidays creating variation in total treatment time. In all but one dog, on-board cone beam CT imaging was used to verify patient positioning prior to each daily treatment. In one dog, orthogonal planar kilovoltage radiographs were used for position verification. All pretreatment positioning image matches were performed manually and position corrections were applied prior to each treatment. At CSU, a Varian Trilogy linear accelerator delivered megavoltage radiation to 13 patients, and a Varian Novalis TX delivered megavoltage radiation to two patients treated at NCSU. All plans had beams coinciding at a defined isocenter. In six cases, 30 Gy was prescribed to the entire planning target volume; in nine cases, 30 Gy was prescribed to the extracalvarial planning target volume, whereas 24 Gy was prescribed to the intracalvarial planning target volume. Using previously reported normal brain dose constrains as a guideline, (briefly, <1 cubic centimeter of brain > 24 Gy, and falloff to 21.6 Gy within 2 mm of the planning target volume),[17] in all cases, dose to the margin of the intracalvarial planning target volume was lower than that delivered to the extracalvarial planning target volume .

3.4 | Outcome findings

Follow-up information had been gathered from referring veterinarian records and communication records from the radiation treatment institutions. All stereotactic radiation therapy dogs were evaluated after radiation. However, follow-up schedule was widely variable throughout the population and reasons for reevaluations were inconsistent. Reasons for reevaluation varied from presumed clinical problems associated with the tumor, to routine health rechecks. Range of reevaluation was 2 days to the latest censor time of 682 days. Two dogs did not have follow-up information after imaging diagnosis and were excluded from outcome analyses. Of dogs with available follow-up information, 10 were conservatively managed (no treatment, prednisone, antiepileptics, or a combination of prednisone and antiepileptics), and 15 were treated with definitive-intent stereotactic radiation therapy. Thirteen were treated with stereotactic radiation therapy at CSU, and two at NCSU. Of the dogs not receiving stereotactic radiation therapy, one was seen at CSU, two at NCSU, six at Bush Veterinary Neurology Service, and one at Purdue University.

3.4.1 | Unirradiated dogs

Ten dogs did not receive stereotactic radiation therapy. Pretreatment staging information recorded or available for review was as follows: Nine thoracic radiographs, none with evidence of metastatic disease, 10 biochemistry profiles and complete blood counts, and two urinalyses, none of which showed more than mild deviation from normal. Analysis of CSF in four dogs showed albuminocytological dissociation (2), minimal mononuclear pleocytosis (1), or normal fluid (1). Seven dogs presented with signs supportive of intracranial disease, three of which were having seizures. Only 1/7 dogs with intracranial signs lived longer than 2 weeks. During the follow-up period, all dogs presenting with unilateral masticatory muscle atrophy had progressive or stable atrophy. Six dogs presented with ipsilateral ocular disease and that disease remained in 2/6 dogs living longer than 2 weeks. Four dogs were euthanized within 3 days of diagnosis because of owner preference. Of the remaining six dogs, two were euthanized within 2 weeks of diagnosis because of progressive neurologic signs. Four dogs were censored at the last communication date. One was lost to follow up, and three were alive at the time of writing. Median follow-up time for censored subjects was 250 days (range: 104–577 days). Of these four dogs surviving longer than 2 weeks, two dogs were prescribed ocular medications, one dog was prescribed antiseizure medications, and three were prescribed prednisone. In the three dogs prescribed prednisone, clinical signs remained stable (stable muscle atrophy). One of those three dogs had reduced seizure activity (this dog was prescribed antiseizure medications in addition to prednisone). Oral prednisone doses were recorded for two patients and were 0.5 and 0.6 mg/kg delivered daily.

Overall and disease-specific survival times in unirradiated dogs ranged from 1 to 577 days. The disease-specific and overall median survival time was 12 days. The median disease-specific and overall survival times had a 95% confidence interval of 0–25 days. Forty percent were alive at 1 year. Overall and disease-specific survivals not including unirradiated dogs euthanized at diagnosis were evaluated. In these dogs ($n = 6$), overall and disease-specific survival ranged from 11 to 577 days. Only two of these six dogs had a defined date of death after initial diagnosis, so median survival times could not be defined for those unirradiated subjects. Individual case characteristics for unirradiated dogs are summarized in Appendix 2.

3.4.2 | Stereotactic radiation therapy treated dogs

Pretreatment staging information available for the 15 dogs treated with stereotactic radiation therapy was as follows: thoracic radiographs (14), complete blood count and biochemistry profile (14), urinalysis (4), and abdominal ultrasound (3). None of the dogs with thoracic or abdominal imaging were found to have evidence of metastasis. Blood work and urinalysis results showed no to mild deviations from normal, none of which categorized patients as inappropriate anesthetic or treatment candidates. Two dogs had CSF collected; the fluid was considered normal in both. Five dogs presented with signs supportive of intracranial disease, two of which were having seizures. Six dogs presented with ipsilateral ocular disease. One dog had stereotactic radiation therapy for a pituitary tumor 3 years prior to diagnosis of the trigeminal nerve sheath tumor. Seizures caused by the pituitary

tumor resolved after treatment, and the trigeminal nerve sheath tumor was diagnosed upon presentation for unilateral masticatory muscle atrophy and enophthalmos. Time from initial diagnosis by MRI and the first fraction of stereotactic radiation therapy ranged from 1 and 59 days (median 22 days).

Two dogs were reported to have improvement in unilateral muscle atrophy (1) or facial paresis (1) after stereotactic radiation therapy. One dog presented with facial rubbing with no improvement after stereotactic radiation therapy and two dogs developed facial rubbing. Three dogs had resolution of ipsilateral corneal ulceration, and three dogs developed ipsilateral corneal ulceration, or KCS. Of the three dogs in which ocular disease developed, one had no tear production evident on the last day of treatment and had an enucleation performed immediately following the final fraction. Another had a deep corneal ulcer diagnosed 3 days following treatment, at which time an enucleation was performed. The third dog had KCS diagnosed approximately 3 months following radiation therapy that eventually led to an enucleation approximately 15 months following treatment. Three of the six dogs initially presenting with ocular disease had no improvement of ocular health. In total, four dogs eventually required ocular surgery (tarsorrhaphy or enucleation). No dog had development of contralateral ocular disease. In the timeframe of presentation through follow up, 10 dogs were prescribed ocular medications and two dogs were prescribed antiseizure medications. One dog was prescribed levetiracetam after having two generalized seizures approximately five and a half months after radiation therapy, and the second dog was prescribed levetiracetam prophylactically after intermittent stumbling episodes, approximately 10 months following radiation therapy. Fifteen dogs treated with stereotactic radiation therapy were discharged with oral prednisone with doses ranging from 0.26 to 1.2 mg/kg daily. Six of these dogs had prednisone initiated at the time of the imaging diagnosis, and in all six dogs the same dose was continued at discharge following stereotactic radiation therapy. The duration of, and dose of prednisone following radiation varied considerably among patients, and was impacted by clinician preference, and clinical status of the patient.

Magnetic resonance imaging studies after treatment were performed within 10 months of stereotactic radiation therapy in five dogs for either routine recheck, or in response to development of altered neurologic status. Recheck images were not consistently available for review, and recheck imaging information was obtained from the written record and/or radiology report. Because of this, exact tumor volumes could not be directly compared to pretreatment volumes and responses were considered subjective depending on the interpreting radiologist or neurologist, and not in accordance with standardized RECIST criteria. One dog had imaging changes suggestive of early delayed effects (two and a half months following stereotactic radiation therapy) and one dog had progression of the tumor at the level of the brainstem (6 months following stereotactic radiation therapy).[14,18] In the remaining three dogs (four MRIs), the tumor was considered stable to subjectively decreased in size. Only one postmortem examination was completed. In the dog with evidence of tumor progression, postmortem evaluation of tissues showed a grade 3 soft tissue sarcoma at the left trigeminal ganglion with multifocal areas of necrosis and fibrinosuppurative inflammation. The brainstem white matter adjacent to the tumor was effaced by the mass, and the adjacent normal tissue displayed no histologic changes suggestive of radiation injury.[12,14]

Either acute or early delayed radiation-induced brain injury was presumed to have occurred in five dogs. One dog showed transient grade I CNS toxicity 2 days following radiation therapy.[11] That same dog developed grade III CNS toxicity (seizures) approximately two and a half months following treatment. The MRI report noted a subjectively decreased tumor size (both intracalvarial and extracalvarial), with increased edema throughout the brainstem. The dog's clinical signs failed to improve with increased prednisone and it was euthanized about 1 month following imaging. The intracalvarial 99% GTV and 95% planning target volume doses in this dog were 26.3 and 24.4 Gy, respectively. The doses were comparable to the average doses for both GTV and planning target volume within this stereotactic radiation therapy study population (Table 3). The other four dogs developed transient grade I CNS toxicity between 5 weeks and 4 months following radiation therapy. One dog was categorized as having a possible late radiation injury. That dog displayed grade I CNS toxicity 10 months after treatment with stable tumor size on follow up imaging. Lack of follow-up imaging or necropsy in patients experiencing neurologic decline in the period consistent with development of late effects prevented further assessment of late radiation effects in this population.

Neurologic signs referable to intracranial disease improved in 4/5 dogs, within 2 months of stereotactic radiation therapy. Two dogs presenting with seizures had no further reports of seizures following therapy and in those dogs seizure activity was considered improved.

One dog was euthanized 71 days after stereotactic radiation therapy following a diagnosis of multicentric T-cell lymphoma and one dog was euthanized 583 days after stereotactic radiation therapy because of a progressive mass at the level of the intermandibular area. The mass was neither aspirated nor biopsied prior to euthanasia. Seven dogs died of progressive neurologic signs. Six dogs were censored from the survival analysis because they were lost to follow up (4) or alive at the time of manuscript preparation (2); median follow-up time for the censored subjects was 329 days (range 45–682 days). Overall and disease-specific survival times in the stereotactic radiation therapy treated dogs ranged from 45 to 682 days. Overall median survival time for stereotactic radiation therapy dogs was 441 days and 95% confidence intervals of mean and median survival times were and 260–518 days and 160–721 days, respectively, with 55% alive at 1 year. The disease-specific median survival time was 441 days, with a 95% confidence interval of 159–723 days. Sixty percent were alive at 1 year. Tables 3 and 4 display doses delivered to tumor volumes and organs at risk, respectively. Individual case characteristics for dogs treated with stereotactic radiation therapy are summarized in Appendix 3. In the 10 unirradiated dogs with available follow-up, overall median survival time was 12 days and 95% confidence intervals of mean and median survival times were 44–424 and 0–25 days, respectively.

3.5 | Statistical comparisons

No significant correlation existed between aural effusion ($n = 8$) and ataxia or vestibular signs ($n = 7$). There was no association between ophthalmic branch involvement ($n = 10$) as seen on MRI and dogs

TABLE 3 Average dose delivered to treatment volumes and conformity indices

	GTV Intracalvarial D_{99}	GTV Extracalvarial D_{99}	PTV Intracalvarial D_{95}	PTV Extracalvarial D_{95}	PTV Intracalvarial CI	PTV Extracalvarial CI
Minimum	23.21	27.42	22.69	27.06	0.41	0.63
Maximum	32.01	31.49	28.83	30.17	1.00	0.97
Mean	26.54	29.26	25.34	28.63	0.84	0.84
Median	26.24	29.60	24.55	28.63	0.88	0.85
SD	2.69	1.27	2.09	0.95	0.17	0.10

Notes. Average dose delivered to treatment volumes. D_x refers to the radiation dose (in gray) delivered to *X*% of the respective treatment volume. Conformity index = (prescription isodose volume)2/ (total PTV volume) × (prescription isodose volume)[26]. CI, conformity index; GTV, gross tumor volume; PTV, planning target volume; SD, Standard deviation.

TABLE 4 Average dose delivered to organs at risk in all SRT treated dogs in the current population

	Normal Brain Volume at 24 Gy	OC* Max Point Dose	Lens Max Point Dose	Eye (Globe) Max Point Dose	Eye (Globe) (Ipsilateral) Mean Dose
Minimum	0.05	8.37	0.18	0.40	0.20
Maximum	2.77	31.50	7.56	25.9	5.45
Mean	1.00	18.90	3.03	8.79	1.46
Median	0.71	17.00	1.90	9.80	0.50
SD	0.77	5.99	2.84	7.53	1.73

Notes. Average dose (in gray) delivered to normal brain, *optic chiasm, lens, or eye. Volumes listed in units of mL. Brain volume at 24 Gy is reported here to maintain consistency with previously reported guidelines for normal brain.[17] Max point doses are inclusive of both eyes. OC, optic chiasm; SD, standard deviation; SRT, stereotactic radiation therapy.

presenting with a history of ocular disease (n = 12). There were no statistically significant differences in brain to tumor volumes or absolute intracalvarial tumor volumes when dogs in the stereotactic radiation therapy group (n = 15) were compared to dogs in the unirradiated group (n = 10). For the dogs treated with stereotactic radiation therapy and with available outcome data (n = 15), none of the potential predictive factors of radiation associated effects outlined in the methods section were found to be significant. Survival times for dogs treated with stereotactic radiation therapy (n = 15) versus unirradiated dogs (n = 10) were not statistically different. In the unirradiated cohort, overall and disease-specific survivals not including dogs euthanized at diagnosis were further evaluated to compare to the stereotactic radiation therapy cohort. Owing to the high censor rate of the longer survivors, median survival time in that population could not be determined and complete survival comparison could not be achieved. In dogs treated with stereotactic radiation therapy, a statistically detectable difference in survival could not be detected when outcomes were compared for dogs presenting with (n = 5) and without intracranial signs (n = 10) (441 days and 583 days, respectively). There was not a statistically significant association between the brain/tumor volume and survival time.

4 | DISCUSSION

This study aimed to describe clinical and imaging characteristics, and outcomes of dogs with trigeminal nerve sheath tumors. To our knowledge, this is the first published report to describe lesion localization characteristics in a multicenter sample of dogs with trigeminal nerve sheath tumors. In this study, all dogs with trigeminal nerve sheath tumors had intracranial extension of bulky tumor at the level of the trigeminal ganglion and the most commonly affected portion of the fifth cranial nerve was the mandibular branch, with up to 81% of dogs having more than one branch affected. Clinical signs in this population were similar to a previous report[4] and survival times were within the range of previous reports (324–881 days).[7,8] In this study, stereotactic radiation therapy appeared to have benefitted most of the dogs presenting with intracranial signs referable to trigeminal nerve sheath tumor, but did not yield improved ocular health or contribute to resolution of masticatory muscle atrophy in the majority of affected dogs. Since all dogs treated with stereotactic radiation therapy were prescribed at least prednisone, and some were prescribed antiepileptics, potential improvement associated with medical treatment should not be overlooked. In this study, it is impossible to discern if the improvements in dogs with intracranial signs were solely attributable to stereotactic radiation therapy.

The current study did not identify a significant difference in survival times for stereotactic radiation therapy dogs versus unirradiated dogs. This was primarily due to an overlap in the mean 95% CI's for the two groups. Also, in stereotactic radiation therapy dogs, the median time from diagnosis to initiation of stereotactic radiation therapy was 22 days; longer than the median survival time 12 days in the unirradiated group. This difference is evidence of a selection bias. Some dogs in the unirradiated group were more clinically compromised than dogs in the stereotactic radiation therapy group, and owners elected euthanasia instead of stereotactic radiation therapy. Potential biases are obvious limitations of this study. To address the problem of selection bias for the unirradiated group, we attempted to find the survival of dogs in the unirradiated group, not including dogs euthanized at diagnosis. Unfortunately, median survival time in the population could

not be determined, and a complete survival comparison could not be achieved.

Late radiation brain side effects associated with radiotherapy can occur 6 months or more following radiation therapy.[12–14] The effects are often localized to the area of the tumor and clinical signs associated with a late radiation effect can be indistinguishable from those associated with tumor progression. Further complicating the ability to differentiate between the two diagnoses, is the fact that both late radiation effects and tumor progression may occur at similar times following radiation. The lack of consistent follow-up imaging or postmortem examinations in this study made assessment of late radiation side effects impossible.

The functional and gross anatomy of the trigeminal nerve can explain the clinical findings within our study population, including: facial nerve dysfunction (facial paresis and decreased menace), muscle atrophy, ocular disease, and tympanic cavity effusion. Ocular disease in dogs with trigeminal nerve dysfunction is caused by decreased corneal innervation and decreased innervation of the parasympathetic fibers of lacrimation (also innervated by the facial nerve).[15] The facial nerve is in close proximity to the trigeminal nerve, at the level of the brainstem,[19] and inflammation or compression caused by the trigeminal nerve sheath tumor may compromise function of the adjacent facial nerve. The mandibular branch of the trigeminal nerve supplies motor innervation to muscles of mastication, and innervates the tensor veli palatini muscle.[20] Lack of innervation to the masticatory muscles can lead to denervation atrophy,[1] and disrupted innervation to the tensor veli palatine muscle may lead to tympanic cavity effusion.[21] In humans, denervation of the tensor veli palatini muscle can affect normal auditory tube function.[22,23] When a nonfunctioning auditory tube fails to allow equalization between atmospheric pressure and middle ear, extracellular fluids can be drawn into the middle ear. The clinical significance of fluid in the middle ear of these dogs is unknown; there was no correlation between tympanic cavity effusion and vestibular signs. Interestingly, only one dog in our population lacked mandibular branch involvement, and was the only dog without masticatory muscle atrophy (initial diagnostic workup was prompted by signs suggestive of intracranial disease). If the motor root of the mandibular branch is not disrupted by a tumor, masticatory muscle atrophy may not occur and neurologic workup may be delayed.

It would be difficult based on imaging, to identify which dogs will develop ocular disease. The ophthalmic branch is the smallest of the branches, and microscopic or minor changes in the nerve may be missed on imaging. Moreover, innervation could be disrupted at the level of the trigeminal ganglion or sensory nuclei, prior to the branching of the nerve into the discretely identifiable ophthalmic branch.

In dogs, the cause for facial rubbing may be associated with altered sensation or discomfort. In this study population, one dog presented with facial rubbing and two developed facial rubbing after stereotactic radiation therapy. In humans with trigeminal nerve tumors, altered facial sensation or pain are the most common reported symptoms and pain following irradiation of the trigeminal nerve has been reported.[24] It is possible that dogs experience similar pain sensations, and appropriate pain management should be considered in dogs displaying clinical signs of discomfort. The cause for sensation changes may be related to the tumor, stereotactic radiation therapy, or both.

At the authors' institutions, stereotactic radiation therapy is intended to stabilize trigeminal nerve sheath tumor size, slow progression of disease, and improve quality of life in dogs experiencing intracranial signs caused by the tumor. However, conventionally fractionated, full-course radiation may provide benefit over stereotactic radiation therapy in some dogs with trigeminal nerve sheath tumors. A fractionated protocol would better spare late responding nervous tissue,[25] and may allow eventual return of nerve function and improved clinical outcome (improved atrophy and ocular health) in some patients. Further, trigeminal nerve branches follow a tortuous path, making contouring for stereotactic radiation therapy difficult, potentially leading to geographic miss. Use of conventional fractionation in these treatments would allow a generous clinical target volume expansion, thus helping ameliorate concerns for geographic miss, and potentially resulting in improved local tumor control, as compared to stereotactic radiation therapy.

It was interesting that 4/5 dogs presenting with intracranial signs experienced clinical improvement after stereotactic radiation therapy. While the clinical improvement may also be associated with the addition of prednisone or antiepileptic drugs, the role of stereotactic radiation therapy in this scenario is unclear, and larger studies would be needed to define the role of stereotactic radiation therapy in this subpopulation of dogs with trigeminal nerve sheath tumors.

In conclusion, all dogs with a trigeminal nerve sheath tumor sampled in the current study had a portion of disease extending centrally, and central disease progression was the apparent cause of death in almost all dogs with tumor-related deaths. Muscle atrophy and ocular health did not improve in dogs medically managed or treated with stereotactic radiation therapy. Findings indicated that stereotactic radiation therapy may be a beneficial treatment option in dogs with neurologic signs referable to intracranial disease associated with trigeminal nerve sheath tumor but further studies are needed to validate its role in this setting. Further studies are also needed to determine optimal fractionation and treatment schedules.

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(c) Analysis and Interpretation of Data: Swift KE, Nolan MW, LaRue S, McGrath S, Randall E, Rao S, Leary D

Category 2

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Category 3

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REFERENCES

1. Lorenz MD, Kornegay JN, Oliver JE. *Handbook of Veterinary Neurology*. 4th ed. Philadelphia, PA: Saunders; 2004.
2. Chijiwa K, Uchida K, Tateyama S. Immunohistochemical evaluation of canine peripheral nerve sheath tumors and other soft tissue sarcomas. *Vet Pathol*. 2004;41(4):307–318. https://doi.org/10.1354/vp.41-4-307.
3. Withrow SJ, Vail DM, Page RL. *Small Animal Clinical Oncology*. St Louis, MO: Elsevier; 2013.
4. Bagley RS, Wheeler SJ, Klopp L, et al. Clinical features of trigeminal nerve-sheath tumor in 10 dogs. *J Am Anim Hosp Assoc*. 1998;34(1):19–25.
5. Dewey CW. *A Practical Guide to Canine and Feline Neurology*. 2nd ed. Ames, IA: Wiley-Blackwell; 2008.
6. Mayhew PD, Bush WW, Glass EN. Trigeminal neuropathy in dogs: a retrospective study of 29 cases (1991–2000). *J Am Anim Hosp Assoc*. 2002;38(3):262–270.
7. Mariani CL, Schubert TA, House RA, et al. Frameless stereotactic radiosurgery for the treament of primary intracranial tumours in dogs. *Vet Comp Oncol*. 2015;13(4):409–423.
8. Hansen KS, Zwingenberger AL, Theon AP, Pfeiffer I, Kent MS. Treatment of MRI-diagnosed trigeminal peripheral nerve sheath tumors by stereotactic radiotherapy in dogs. *J Vet Intern Med*. 2016;30(4):1112–1120.
9. Zwingenberger AL, Pollard RE, Taylor SL, Chen RX, Nunley J, Kent MS. Perfusion and volume response of canine brain tumors to stereotactic radiosurgery and radiotherapy. *J Vet Intern Med*. 2016;30(3):827–835.
10. Schultz RM, Tucker RL, Gavin PR, Bagley R, Saveraid TC, Berry CR. Magnetic resonance imaging of acquired trigeminal nerve disorders in six dogs. *Vet Radiol Ultrasound*. 2007;48(2):101–104.
11. LaDue TK. Toxicity criteria of the veterinary radiation therapy oncology group. *Vet Radiol Ultrasound*. 2001;42(5):475–476.
12. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: a review. *Front Oncol*. 2012;2:1–18.
13. Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. *Int J Radiat Oncol Phys*. 1980;6(9):1215–1228.
14. Valk PE, Dillon WP. Radiation injury of the brain. *AJNR Am J Neuroradiol*. 1991;12(1):45–62.
15. Maggs DJ, Miller PE, Ofri R, Slatter DH. *Slatter's Fundamentals of Veterinary Ophthalmology*. 5th ed. St. Louis, MO: Elsevier; 2013.
16. Harmon J, Van Ufflen D, Larue S. Assessment of a radiotherapy patient cranial immobilization device using daily on-board kilovoltage imaging. *Vet Radiol Ultrasound*. 2009;50(2):230–234. Epub 2009/04/30.
17. Griffin LR, Nolan MW, Selmic LE, Randall E, Custis J, LaRue S. Stereotactic radiation therapy for treatment of canine intracranial meningiomas. *Vet Comp Oncol*. 2016;14(4):158–170.
18. Walker AJ, Ruzevick J, Malayeri AA, et al. Postradiation imaging changes in the CNS: how can we differentiate between treatment effect and disease progression? *Future Oncol*. 2014;10(7):1277–1297.
19. DeLahunta A, Glass E, Kent M. *Veterinary Neuroanatomy and Clinical Neurology*. 4th ed. St. Louis, MO: Elsevier; 2015.
20. Evans HE, Miller ME. *Miller's Anatomy of the Dog*. 3rd ed. Philadelphia, PA: W.B. Saunders; 1993.
21. Kent M, Glass EN, de Lahunta A, Platt SR, Haley A. Prevalence of effusion in the tympanic cavity in dogs with dysfunction of the trigeminal nerve: 18 cases (2004-2013). *J Vet Intern Med*. 2013;27(5):1153–1158. Epub 2013/07/24.
22. Monsell EM, Harley RE. Eustachian tube dysfunction. *Otolaryngol Clin North Am*. 1996;29(3):437–444.
23. Dyer RK, McElveen JT. The patulous eustachian tube: management options. *JAMA Otolaryngol Head Neck Surg*. 1991;105(6):832–835.
24. Schmidt RF, Yick F, Boghani Z, Eloy JA, Liu JK. Malignant peripheral nerve sheath tumors of the trigeminal nerve: a systematic review of 36 cases. *Neurosurg Focus*. 2013;34(3):1–10.
25. Hall EJ, Giaccia AJ. *Radiobiology for the Radiologist*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.
26. Paddick I. A simple scoring ratio to index the conformity of radiosurgical treatment plans. Technical note. *J Neurosurg*. 2000;93 (Suppl 3):219–222.

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APPENDIX 1: SUMMARY OF MAGNETIC RESONANCE IMAGING CHARACTERISTICS FOR INDIVIDUAL DOGS

Subject	Mandibular	Maxillary	Ophthalmic	Tympanic Effusion
1	Yes	Yes	No	Yes
2	Yes	Yes	No	Yes
3	Yes	No	No	No
4	Yes	Yes	Yes	No
5	Yes	Yes	Yes	No
6	Yes	Yes	No	No
7	No	Yes	Yes	No
8	Yes	No	No	No
9	Yes	Yes	No	No
10	Yes	Yes	No	No
11	Yes	Yes	No	Yes
12	Yes	Yes	No	No
13	Yes	Yes	Yes	No
14	Yes	No	No	No
15	Yes	No	No	Yes
16	Yes	No	No	Yes
17	Yes	Yes	Yes	No
18	Yes	Yes	No	No
19	Yes	Yes	Yes	Yes
20	Yes	Yes	Yes	Yes
21	Yes	Yes	Yes	Yes
22	Yes	Yes	No	No
23	Yes	Yes	Yes	No
24	Yes	Yes	Yes	No
25	Yes	Yes	No	No
26	Yes	Yes	No	No
27	Yes	Yes	No	No

APPENDIX 2: SUMMARY OF INDIVIDUAL CASE CHARACTERISTICS: UNIRRADIATED DOGS

Subject	Breed	Presenting Clinical Signs/CC	TTV	ICV	BTV	Follow up MRI	Survival/Time to Censor (days)
1†	Miniature Pinscher	Muscle atrophy, disorientation, circling	2.61	2.47	22	None	3
2†	Shih Tzu	Seizures, ataxia, muscle atrophy, disorientation	2.6	1.9	29	None	1
3*	Labrador	Muscle atrophy	0.4	0.2	402	None	250
4	Coonhound	Seizures, ataxia, muscle atrophy	3.9	3.2	34	None	11
5	Border Collie	Muscle atrophy, disorientation, torticollis	3.7	2.8	28	None	12
6*	Labrador	Muscle atrophy	0.7	0.6	156	None	321
7*,†,‡	Pomeranian	Seizures	0.7	0.5	132	None	104
8	Mixed breed	Muscle atrophy, positional nystagmus	1.2	0.5	157	None	No follow up
9	Mixed breed	Muscle atrophy, disorientation, torticollis, positional nystagmus	0.7	0.4	185	None	1
10*	Labrador	Muscle atrophy, nonambulatory vestibular	1.9	1.2	75	None	3
11	Jack Russel	Muscle atrophy	0.5	0.3	206	None	577
12	Boxer Mix	Muscle atrophy	0.7	0.4	233	None	No follow up

*Patient prescribed prednisone.
†Patient prescribed antiepileptic medications.
‡Patient's presenting clinical signs improved with treatment.
CC, Chief complaint; TTV, Total Tumor Volume (mL); ICV, Intracalvarial Tumor Volume (mL); BTV, Brain-to-tumor volume.

APPENDIX 3: SUMMARY OF INDIVIDUAL CASE CHARACTERISTICS: STEREOTACTIC RADIATION THERAPY DOGS

Subject	Breed	Presenting Clinical Signs/CC	TTV	ICV	BTV	RT Rx	Follow up MRI	CI (Intracal-varial)	Toxicity	Survival/Time to Censor (days)
13*	Mixed breed	Muscle atrophy	6.92	4.57	17	8–24/10–30	None	0.98	Early Delayed	364
14*	Mixed breed	Muscle atrophy	3.08	1.30	51	10–30/10–30	None	0.81	Early Delayed	682
15*	Labrador	Muscle atrophy	2.57	0.57	154	8–24/10–30	None	0.64		48
16*,†	Staffordshire Terrier	Muscle atrophy	1.95	0.45	192	8–24/10–30	Stable disease at 6 months and 10 months post-SRT.	0.65	Possible late effect	583
17*	Mixed breed	Muscle atrophy	4.22	1.72	50	10–30/10–30	None	0.81		315
18*	Pug	Muscle atrophy	0.56	0.40	150	8–24/10–30	None	0.88		45
19*,‡	Cocker Spaniel	Muscle atrophy lethargy, mild disorientation	2.22	1.82	43	8–24/10–30	None	0.92	Early Delayed	180
20*	French Bulldog	Muscle atrophy lethargy, mild disorientation	2.40	0.43	194	8–24/10–30	None	0.98		71
21*,‡	Pug	Muscle atrophy seizures, KCS	2.64	1.21	56	10–30/10–30	Stable disease at 2.5 months post-SRT.	0.41		441
22*,†	Mixed breed	Muscle atrophy	1.87	0.63	129	10–30/10–30	Increased tumor size at ventral aspect of cranial vault 6 months post-SRT. (Post mortem evaluation supported tumor progression).	0.95		218
23*	Mixed breed	Muscle atrophy	1.93	0.67	115	8–24/10–30	Stable disease 4 months post-SRT.	0.68		344
24*,‡	Newfoundland	Muscle atrophy, confusion, mental dullness	18.73	2.63	39	10–30/10–30	None	0.98		574
24*,‡	Bichon	Muscle atrophy, head tilt, seizures, circling.	5.47	4.43	15	10–30/10–30	None	0.76	Early Delayed	191
26*	Jack Russel	Muscle atrophy	1.28	0.71	82	8–24/10–30	Decreased tumor size with increased edema throughout the brainstem 2.5 months post-SRT.	1.0	Acute and early delayed	125
27*	Gordon Setter	Muscle atrophy	3.43	0.93	109	8–24/10–30	None	0.89		329

*Patient prescribed prednisone.

†Patient prescribed antiepileptic medications.

‡Patient's presenting clinical signs improved with treatment.

CC, Chief complaint; TTV, Total tumor volume (mL); ICV, Intracalvarial tumor volume (mL); BTV, Brain to tumor volume; RT Rx, Radiation therapy prescription: fraction size (in Gy) – total dose (in Gy) intracalvarial/fraction size (in Gy) – total dose (in Gy) extracalvarial; CI, Conformity index; SRT, stereotactic radiation therapy.