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Outcome of stereotactic body radiation for treatment of nasal and nasopharyngeal lymphoma in 32 cats

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Abstract

Background: The safety and efficacy of stereotactic body radiation therapy (SBRT) in the treatment of localized nasal lymphoma in cats has not been described.

Hypothesis: Stereotactic body radiation therapy with or without adjuvant chemotherapy is an effective and well-tolerated treatment for localized nasal lymphoma in cats.

Animals: Thirty-two client owned cats referred to Colorado State University for the treatment of nasal lymphoma.

Methods: Retrospective study of cats treated with SBRT between 2010 and 2020 at Colorado State University. Diagnosis of nasal lymphoma was obtained via cytology or histopathology. Signalment, radiation protocol, concurrent treatments, adverse effects, and survival were recorded.

Results: Progression free survival was 225 days (95% CI 98–514) and median survival time (MST) was 365 days (95% CI 123–531). No significant difference in survival was identified between cats that received 1 versus greater than 1 fraction (MST 427 vs. 123 days, $P = 0.88$). Negative prognostic factors included cribriform lysis (MST 121 vs. 876 days, $P = 0.0009$) and intracalvarial involvement (MST 100 vs. 438 days, $P = 0.0007$). Disease progression was noted in 38% (12/32), locally in 22% (7/32), and systemically in 16% (5/32). No cats developed acute adverse effects. Ten cats developed late adverse effects: keratitis/keratitis sicca ($n = 2$), alopecia ($n = 4$), and leukotrichia ($n = 4$). Twenty-four cats (75%) had signs consistent with chronic rhinitis.

Conclusions: SBRT is effective and well tolerated for treating localized nasal lymphoma in cats. Outcomes for cats with lower stage disease (canine modified Adam's stage 3 and lower) are comparable to historic data of cats treated with fractionated radiation therapy.

KEYWORDS
cat, hypofractionated radiation therapy, lymphosarcoma, SBRT

Abbreviations: CI, conformity index; CSU, Colorado State University; CT, computed tomography; CTV, clinical target volume; GM, gradient measure; GTV, gross tumor volume; HI, heterogeneity index; HR, hazard ratio; MRI, magnetic resonance imaging; OAR, organs at risk; OST, overall survival time; PFS, progression free survival; PTV, planning target volume; SBRT, stereotactic body radiation therapy; VMAT, volumetric arc therapy.

1 | INTRODUCTION

Lymphoma is the most common neoplasm in cats.[1] When evaluating cats with tumors located in the nasal passageways, nasopharynx, and paranasal sinuses, lymphoma accounts for up to 70% of cases.[2-4] Clinical signs associated with nasal disease in cats include nasal discharge, sneezing, stertor, open-mouth breathing, and epistaxis. Historically, both chemotherapy and radiotherapeutic methods have been investigated in the treatment of the disease. Nasal lymphoma is considered a localized disease and can be responsive to either treatment modalities.[5] Median survival times (MST) for treatment with chemotherapy, radiation, or the combination vary widely. In single-modality chemotherapy treatments, MSTs range from 3.3 to 11.9 months.[3,5-7] Survival after treatment including both chemotherapy and radiation ranges from 5.8 to 31.4 months.[5,7,8] Survival times for radiation alone include an overall survival time of 15–30 months. Cats treated with prednisolone alone had an MST of 11–33 days.[3,9]

Lymphoma cells are considered both radiosensitive and radioresponsive, undergoing an apoptotic cell death when treated with radiation.[10,11] Conventional fractionated radiotherapy exploits the differential radiation repair between tumor and normal tissue for a therapeutic advantage. Stereotactic body radiation therapy (SBRT) is a technology that allows for the accurate and precise administration of radiation therapy to a target with a high dose, while sparing normal surrounding tissue.[12] The purpose of this retrospective study was to report response and clinical outcome of 32 cats with nasal lymphoma treated with SBRT at Colorado State University. It was hypothesized that SBRT would provide safe and effective local control of signs associated with nasal lymphoma.

2 | MATERIALS AND METHODS

2.1 | Case selection

Inclusion criteria for the study were cats with histologically or cytologically diagnosed nasal and nasopharyngeal lymphoma treated with SBRT at Colorado State University Veterinary Teaching Hospital between August 2010 and February 2020. Cats required sufficient medical record data to evaluate diagnosis, stage, treatment, and outcome. Exclusion criteria included lymphoma outside of the locoregional lymph nodes. Medical records were reviewed to collect demographics including age, signalment, weight, radiation therapy protocol and dosimetry as well as follow-up data regarding presenting clinical signs, clinical signs after treatment, acute and late normal tissue toxicities, response to therapy, and overall survival time. These data were supplemented with communication from referring veterinarians and clients. Data were collected from staging diagnostic tests which were performed before radiation therapy including complete blood count (CBC), serum biochemical profile, computed tomography (CT) examination, cytological or histopathologic diagnosis, abdominal ultrasound, thoracic imaging, locoregional lymph node aspirates, and magnetic resonance imaging (MRI) when available. Concurrent or previous chemotherapy, antibiotic administration, and glucocorticoid therapy was also recorded.

2.2 | CT examination

CT scans were performed using either a Philips Gemini TF Big Bore 16-slice scanner (Philips Medical Systems, Nederland, B.V.), or Siemens Somaton Force 192-slice scanner (Siemens Medical Solutions, Pennsylvania). All cats were positioned in sternal recumbency, with forelimbs positioned caudally. The head and cervical region were immobilized using a carbon fiber stand, a fixed personalized dental mold, thermoplastic bead facial mask, and Styrofoam cushion.[13]

A non-contrast helical scan was performed of skull through to thoracic inlet, with postcontrast scan performed after intravenous injection of Omnipaque 350 contrast media (GE Healthcare, Princeton, New Jersey; 2.2 ml/kg). Images were reconstructed in 2.0 mm contiguous intervals with 512 matrix and smooth algorithm.

Tumor stage as described by the canine modified Adam's staging system was determined based on retrospective evaluation of CT scans interpreted by American College of Veterinary Radiology certified radiologists.[14] Lymph nodes that were heterogeneously contrast enhancing or enlarged, as interpreted by a radiologist, were recorded.

2.3 | Radiation planning

Both the 2 mm precontrast and postcontrast CT scans were imported and utilized for inverse treatment planning with the Varian Eclipse treatment planning system (Varian Medical Systems, Inc Palo Alto, California). When available, a T1-weighted postcontrast MRI was fused with the CT scan in the treatment planning software to aid with contouring of the tumor volumes. Gross tumor volume (GTV) and organs at risk (OARs) were identified and contoured. In most cases, a 0.5 to 1 cm expansion was created around the GTV for the clinical target volume (CTV) to account for microscopic disease into the ipsilateral and contralateral nasal cavity and sinuses. A planning target volume (PTV) incorporated a 2 mm isotropic expansion from either the GTV or CTV to account for daily set-up error for positioning, as determined by a medical physicist. Contours specifically for lymph nodes were included with previously described asymmetrical expansion for the PTV.[15] The OARs included skin, eyes, lenses, brain, optic chiasm, palatine mucosa, trachea, esophagus, and spinal cord.

Stereotactic body radiation treatment plans were created with coplanar or noncoplanar, isocentrically placed 6 MV radiation beams or coplanar or noncoplanar 6 MV volumetric arc therapy (VMAT). Radiation beams were modulated using sliding-window technique. Radiation plans, at the time of development, were assessed based on the intent to deliver 100% of the radiation prescription to 99% of the GTV and 95% of the PTV. PTV-less structures were created when indicated to remove normal OAR structures from the PTV, and utilized in plan optimization and evaluation. Quality assurance was performed by gamma analysis using Varian portal dosimetry system on individual fields and VMAT arcs. A passing QA score was required before treatment, with minimum of 95% gamma for a 3 mm distance to agreement, and a 3% absolute dose difference.

Radiation plans were later assessed in a retrospective manner with the following data collected: GTV, CTV, PTV with corresponding

less structures when available, volumes and doses to OARs, dose to 99% and 98% of GTV and CTV, dose to 95% of PTV, median, near minimum and near maximum tumor dose, conformity index (CI), heterogeneity index (HI), and gradient measure (GM).[16]

2.4 | Radiation plan parameters

The homogeneity index describes the uniformity of the absorbed dose distribution within the target. HI was defined as $(D_2 - D_{98})/D_p$ where D_2 is the minimum dose to 2% of the target volume, and D_{98} = minimum dose to 98% of target volume. D_p is the prescribed dose. HI values close to 0 reflect a homogeneous dose distribution.[17] The homogeneity indexes were calculated from the PTV of the primary nasal tumor.

Conformity index evaluates the degree of conformity of a high-dose region to the target volume and is described using the equation: $(TV_{PIV})^2/(TV \times PIV)$. TV_{PIV} is the target volume receiving prescription dose, TV is the target volume, and PIV is the volume of body receiving prescription dose. Values of CI range between 0 and 1, with values closer to 1 indicating a more conformal dose coverage of the target volume. Target volumes used in calculation included PTV structures and lymph nodes, when treated.[18]

Gradient measure describe dose fall-off outside of the target. GM was obtained retrospectively from Eclipse planning software and defined as $R_{50} - R_{100}$, where R_{50} = effective radius of the 50% isodose treatment volume, R_{100} = effective radius of the 100% isodose treatment volume. The larger the GM value, the greater the gradient in dose fall off.[19]

2.5 | Radiation treatment

Cats were anesthetized for each radiation treatment. Protocols for anesthesia were variable, and often included an opioid premedication and propofol induction. Cats were maintained on isoflurane gas once intubated. Once anesthetized, cats were positioned in their custom immobilization device created under the initial simulation CT.[13] Position verification was performed daily using an on-board cone beam CT (CBCT) or registration of reconstructed radiograph with setup images obtained using on-board imaging with kilovoltage radiographs. Once positioning was confirmed, treatment was delivered using a Varian Trilogy linear accelerator using coplanar or noncoplanar, isocentrically placed 6 MV radiation beams or coplanar or noncoplanar 6 MV VMAT.

2.6 | Response and follow-up criteria

Response to treatment was evaluated from the first day of SBRT treatment to the last day of follow-up or death via assessment of clinical signs and repeat imaging. Recheck recommendations were physical examination 2 weeks after radiation therapy, with CT scan of the skull 4-6 months after treatment to assess tumor response. Progression free survival (PFS) and overall survival time (OST) were calculated from first day of treatment to the day of disease progression or death, respectively. Disease progression or recurrence was confirmed with cytologic or histopathologic evidence of local and systemic lymphoma or suspected if clinical signs recurred and did not respond with prolonged glucocorticoid or antibiotic therapy. Cats were censored if lost to follow-up or still alive at the date of analysis. Cause of events that lead to death that could not or were not determined were attributed to lymphoma.

Toxicity grading was specified according to the Veterinary Radiation Therapy Oncology Group (VRTOG) morbidity scoring scheme for acute and late radiation effects, with late effects being defined as after 90 days after therapy.[20] Treatment with antibiotic or glucocorticoid therapy after radiation was recorded when available.

2.7 | Statistical analysis

Statistical analysis was performed by a statistically trained author (BL). Deaths of all causes were considered events. Cats still alive at the time of data analysis and those lost to follow-up were censored at the last date known to be alive. A cat that received a second course of stereotactic radiation treatment was censored at the date of second treatment. PFS was calculated from the time of treatment to progression of disease or death.

Kaplan-Meier survival curves were generated for PFS and OST, and median PFS and median OST were compared by log-rank test. Continuous variables included PTV volume, dose to PTV, HI of nasal component and lymph nodes, GTV volume and dose to GTV, CI, and GM. Categorical variables included administering single fraction SBRT versus other SBRT protocols, lymph node treatment, presence of CTV, CTV of 0.5 versus 1 cm, presence of palatal lysis, facial deformity, epistaxis, cribriform lysis, intracalvarial involvement, anemia, glucocorticoid use, and chemotherapy. Univariate Cox proportional hazard model for each continuous predictor was created to calculate hazard ratio (HR) of the PFS and OST. Before performing a 2-sample *t* test, a Shapiro-Wilk test was applied to examine data normality. Continuous variables were evaluated by 2-sample *t* test. Multiple testing was not adjusted. All analyses were performed with commercial software MedCalc v19.6 (MedCalc Software Ltd, Ostend, Belgium). *P* values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Population demographics

Thirty-two cats diagnosed with nasal and nasopharyngeal lymphoma and treated with SBRT were included in the study. No cats met exclusion criteria at the time of first treatment. There were 16 spayed females and 16 castrated males. Median age at time of treatment was 10.7 years (range 4.6–16.6). Breeds included 18 domestic short hair,

3 domestic long hair, 3 Siamese, 2 Maine Coon, and 1 of each of the following: domestic medium hair, Egyptian mix, Cornish Rex, Ragdoll, Persian, and Oriental Shorthair. Median weight was 4.5 kg (range 2.3–9.6 kg)

Cats presented with at least one of the following clinical signs: sneezing, stertor, nasal discharge, epistaxis, ocular discharge, facial swelling and mass effect, hyporexia, blindness, anisocoria, and respiratory difficulty. Diagnosis of lymphoma was cytologic in 4 (13%) cats, and histopathologic in 28 (88%). All cats underwent staging including CBC, chemistry, and CT scan of the skull. MRI images were available for 2 cats. Imaging of the abdomen ($n = 26$, 81%) via ultrasound or CT and thoracic imaging ($n = 30$, 94%) via CT scan or radiographs were performed. Date of thoracic imaging was known in 28 cats, and unknown in 2. Median time between thoracic imaging and treatment was 7 days (1–31 days). Date of abdominal staging was known in 26 cats, with a median of 6 days before treatment (1–30 days). Aspirate of abdominal visceral organs was performed on 3 cats, with no noted metastasis. Aspirates of local lymph nodes were performed if enlarged on exam or abnormal on CT imaging on 14 (44%) cats. One cat had cytologically confirmed evidence of lymphoma in the local lymph node at the time of treatment. Twelve of the 32 cats had facial deformities (38%) noted on physical examination ($n = 11$) and advanced imaging ($n = 1$).

3.2 | Chemotherapy

Eleven of 32 cats (34%) underwent chemotherapy: 1 cat had chemotherapy before radiation treatment, 4 had chemotherapy before and after radiation treatment, and 6 received chemotherapy after treatment. Protocols included a modified CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone), L-asparaginase, cyclophosphamide, cytarabine, chlorambucil, mechlorethamine, and lomustine. Twenty-five (78%) cats were administered corticosteroids before radiation treatment. Median dose of prednisolone before radiation treatment was 1.4 mg/kg/d (range 0.4–4.3 mg/kg/d).

3.3 | Imaging findings

Eleven cats (34%) had either lymphadenopathy or contrast enhancement of the lymph nodes on CT scan. Four (12.5%) had an oral component to their mass. Cats were grouped as stage 1, stage 2 ($n = 1$, 3%), stage 3 ($n = 18$, 56%), stage 4 ($n = 13$, 40.6%) using the canine modified Adam's staging system.[14] Cats in stage 4 were subdivided into stage 4a ($n = 5$), indicating cribriform lysis, and stage 4b ($n = 8$) with intracalvarial involvement.

3.4 | Radiation planning

Seven cats had SBRT protocols that included more than 1 fraction. Protocols included a total of 14 Gy delivered in 2 fractions ($n = 1$), 30 Gy in 3 fractions ($n = 4$), 30 Gy in 5 fractions ($n = 1$), 35 Gy in 5 fractions ($n = 1$), and 20 Gy ($n = 11$) or 18 Gy ($n = 14$) in a single fraction. Fractions were delivered on consecutive business days. Of the cats who had greater than 1 fraction, 2 had alterations during their protocol where treatment re-plans were created due to changes in contours as seen on CBCT. One cat was prescribed 10 Gy for 3 fractions (total 30 Gy), and the second had 5 fractions of 6 Gy (total 30 Gy). A third cat completed their course early due to the changes in the GTV volume and shape. This cat received a dose of 6 Gy followed by a second and final fraction of 8 Gy. A third fraction of 8 Gy was not delivered due to clinical improvement. One cat received a single fraction of 16 Gy as a second course of SBRT 987 days after the first protocol due to recurrence of disease confirmed with cytology. This cat progressed from stage 3 to stage 4b at the time of second treatment. No significance in overall survival was found between cats that received 1 fraction versus greater than 1 fraction of treatment (MST 427 vs. 123 days, $P = 0.88$). Eleven cats had 1 or all locoregional lymph nodes treated concurrently with the nasal tumor. CTV expansions were present in 26 cats. Of these, 17 had a CTV of 1 cm, and 7 had an expansion of 0.5 cm. Two cats had asymmetric CTV expansions ranging from 0.5 to 1 cm which were included in analysis in the presence of CTV, and excluded from comparison of 0.5 and 1 cm. Plan dosimetry is summarized in Table 1.

3.5 | Survival

The median OST for all cats after treatment with SBRT was 365 days (95% CI 123–531 days, Figure 1B). Four cats were censored, 2 due to loss of follow-up, and 2 cats were still alive at the time of data analysis. Seven cats died secondary to local progression consistent with nasopharyngeal signs. Causes of death secondary to systemic spread of disease was noted in 5 cats. Other causes of death were noted in 9 cats including a suspected laryngeal mass, cardiac disease, kidney disease, 2 cats presented laterally recumbent before euthanasia, a hemorrhagic complication from esophageal tube placement the same day after treatment completion of a single fraction of SBRT, 2 cats had declining quality of life, and intranasal squamous cell carcinoma. The remaining causes of death were unknown ($n = 7$). The possibility of lymphoma playing a role as the cause of "unknown" or "other" deaths cannot be excluded.

Median PFS was 225 days (95% CI 98–514 days, Figure 1A). Twelve cats were noted to have progressive disease after SBRT. Five total had spread to multiple distant sites outside of the nasal cavity. Sites included the kidney ($n = 3$), small intestine ($n = 1$), lung ($n = 1$), thoracic lymph nodes ($n = 1$), and peripheral lymph nodes ($n = 1$) diagnosed via histopathology and cytology. Seven cats had progressive local disease.

3.6 | Adverse radiation effects

No acute radiation effects were reported in any cases. Ten cats developed late adverse effects, including: keratitis ($n = 1$), keratitis sicca ($n = 1$), alopecia ($n = 4$), and leukotrichia ($n = 4$). Chronic rhinitis was defined as nasal discharge, sneezing, epistaxis, and stertor that was

TABLE 1 Dosimetry for different SBRT protocols used in cats

	14 Gy	16 Gy	18 Gy	20 Gy	30 Gy	30 Gy	35 Gy
	6 Gy + 8 Gy ($n = 1$)	16 Gy × 1 Fx ($n = 1$)	18 Gy × 1 Fx ($n = 14$)	20 Gy × 1 Fx ($n = 11$)	10 Gy × 3 Fx ($n = 4$)	6 Gy × 5 Fx ($n = 1$)	7 Gy × 5 Fx ($n = 1$)
Volume GTV (cc)	41.1	10.9	12.0 (4.2–66.5)	6.1 (3.9–15.7)	10.1 (6.5–21.2)	19.5	30.4
D_{98} (Gy)	5.5	13.8	16.4 (10.5–19.0)	17.3 (13.7–19.7)	25.8 (25.3–30)	27.1	16.5
Volume GTV lymph nodes (cc)			2.1 (1.3–3.8)	1.7 (1.5–2.2)	1.7 (0.6–2.8)	2.5	
D_{98} (Gy)			16.0 (14.1–17.7)	16.5 (15.0–17.7)	26.7 (22.3–31.0)	23.9	
Volume CTV (cc)		19.1	17.0 (11.9–32.7)	14.2 (9.4–23.7)	10.7 (9.4–12)	22.7	33.2
D_{98} (Gy)		13.2	16.5 (11–17.3)	16.9 (14.0–19.3)	24.6 (23.2–26.0)	33.0	17.6
Volume PTV (cc)	69.7	31.3	25.9 (19.7–51.6)	23.8 (16.1–33.1)	27.0 (19.1–34.9)	34.7	46.3
D_{98} (Gy)	4.8	8.5	12.0 (9.4–15.3)	13.4 (9.7–15.3)	19.2 (18.7–24.5)	17.5	16.1
Volume PTV lymph nodes (cc)			8.9 (4.6–12.3)	8.9 (7.2–9.6)	6.4 (3.0–9.8)	9.8	
D_{98} (Gy)			14.2 (9.0–17.1)	16.0 (11.2–16.9)	22.6 (19.9–25.3)	21.2	
CI	0.1	0.5	0.6 (0.05–0.8)	0.5 (0.3–0.8)	0.6 (0.2–0.8)	0.7	0.3
HI	0.1	0.6	0.4 (0.3–0.7)	0.5 (0.3–0.6)	0.5 (0.3–0.6)	0.6	0.7
GM	2.2	0.8	0.9 (0.7–1.8)	1.1 (0.7–1.6)	1.1 (0.8–1.4)	1.1	1.2

Abbreviations: CI, planning target volume; CTV, clinical target volume; GM, gradient measure; GTV, gross tumor volume; HI, heterogeneity index; PTV, planning target volume.

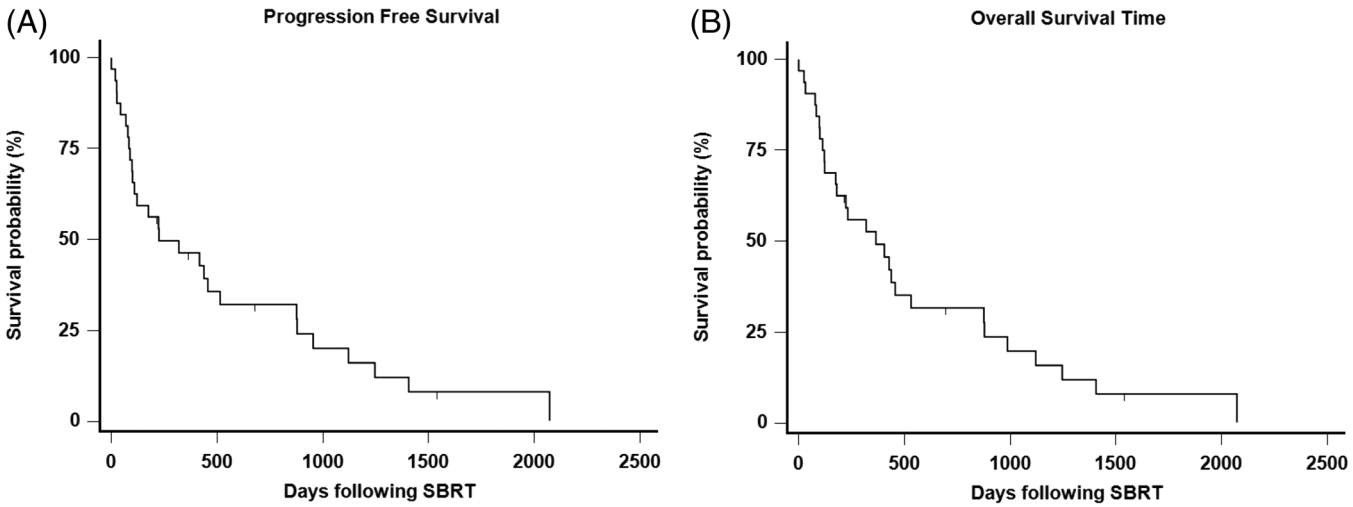

FIGURE 1 Kaplan-Meier curves of progression free survival (PFS) and overall survival time. (A) PFS for all cats was 225 days (95% CI 98–514 days). (B) Median survival time of all cats was 365 days (95% CI 123–531 days)

responsive to antibiotic or anti-inflammatory therapy. Twenty-four cats (75%) were noted to have chronic rhinitis signs that ranged in severity. One cat had a squamous cell carcinoma of the nasal cavity on necropsy 45 months after treatment, which might be evidence of a secondary, radiation-induced tumor type.

3.7 | Follow-up, imaging, and tissue sampling

A clinical response was observed in 21 cats, defined as improved clinicals signs noted after radiation therapy via physical exam findings performed by a veterinarian, or client follow-up. Repeat imaging via CT scan or rhinoscopy was performed for 11 cats. Recheck CT scan was recommended 4–6 months after SBRT, or at the time of clinical sign recurrence. Median time to recheck imaging was 194 days (range 44–1192 days). All 11 cats had improvement of their mass effect on recheck imaging and rhinoscopy. Biopsy or cytology samples were available for 4 cats after radiation therapy to assess for chronic rhinitis versus residual disease. Biopsies revealed chronic moderate lymphoplasmacytic and scattered neutrophilic rhinitis, marked, diffuse, chronic-active mixed rhinitis, marked suppurative inflammation, and subacute to chronic ulcerative necrotizing rhinitis. Cytology of nasal contents on 1 cat revealed marked suppurative inflammation with likely epithelial cell dysplasia.

TABLE 2 Prognostic factors evaluated included epistaxis, facial deformity, palatal lysis, anemia, corticosteroid treatment, and chemotherapy treatment

		Number of cats (total $n = 32$)	Progression free survival (days)	*P* value	Overall survival time (days)	*P* value
Epistaxis	Yes	16	319	0.52	319	0.46
	No	16	121		365	
Facial deformity	Yes	11	109	0.33	180	0.32
	No	21	438		438	
Palate lysis	Yes	13	319	0.68	319	0.65
	No	19	223		405	
Anemia	Yes	6	514	0.44	319	0.46
	No	26	223		531	
Corticosteroid before treatment—single fraction	Yes	19	417	0.30	427	0.30
	No	6	175		405	
Corticosteroid before treatment—all fractions	Yes	24	225	0.68	365	0.69
	No	8	175		319	
Chemotherapy treatment	Yes	11	109	0.11	223	0.23
	No	21	438		438	
CT characteristics						
Cribriform plate lysis	**Yes**	**13**	**98**	**0.0009**	**121**	**0.0009**
	No	**19**	**876**		**876**	
Stage 4A vs. 4B	4A	5	88	0.14	232	0.17
	4B	8	225		100	
Intracalvarial involvement	**Yes**	**8**	**88**	**0.0017**	**100**	**0.0007**
	No	**24**	**438**		**438**	
Radiation therapy						
Fractions	One	25	417	0.92	427	0.88
	>1 Fraction	7	98		123	
Lymph node treated	Yes	11	223	0.43	319	0.50
	No	21	417		427	
Dose per fraction (single)	18 Gy	14	175	0.98	405	0.85
	20 Gy	11	438		438	
Clinical target volume (CTV)	Yes	26	319	0.40	405	0.37
	No	6	98		121	
CTV margin (single fraction)	**0.5 cm**	5	109	0.065	**180**	**0.03**
	1 cm	15	456		**456**	
CTV margin (all treatments)	**0.5 cm**	**7**	**88**	**0.012**	**123**	**0.0047**
	1 cm	**17**	**456**		**456**	
GTV volume (all treatments)	>10.7 cc	16	109	0.95	180	0.95
	<10.7 cc	16	225		365	
GTV volume (one fraction)	>10.7 cc	11	456	0.26	456	0.26
	<10.7 cc	14	223		365	

Note: Other factors evaluated included CT findings such as canine modified Adam's staging including intracalvarial involvement (stage 4B) vs. cribriform lysis alone (stage 4A). Radiation therapy treatment factors evaluated for PFS and MST included number of fractions, lymph node treatment, dose per fraction, presence of clinical target volume (CTV), CTV 0.5 vs. 1 cm, GTV volume for all fractions vs. 1 fraction.

Abbreviations: CT, computed tomography; CTV, clinical target volume; GTV, gross tumor volume.

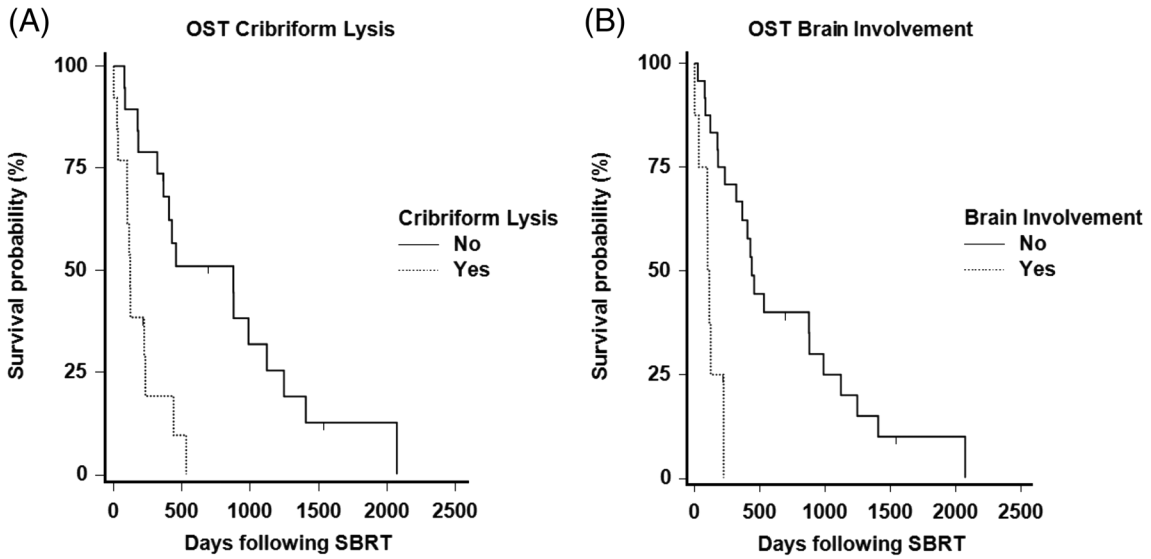

FIGURE 2 Kaplan-Meier curves of overall survival time for cats with and without calvarial extension of disease (A; MST 100 vs. 438 days, $P = 0.0007$) and with and without cribriform lysis (B; MST 121 vs. 876 days, $P = 0.0009$)

3.8 | Necropsy findings

Two cats underwent a necropsy. One cat was euthanized 531 days after SBRT due to difficulty breathing. On thoracic radiographs, a lung mass was present from the diaphragm to the hilus and owners elected euthanasia. Necropsy revealed disseminated B cell lymphoma in lungs and lymph nodes of thorax. A second cat was euthanized 1406 days after treatment, due to recurrence of signs. Necropsy revealed squamous cell carcinoma within mid-rostral region of right nasal and sinus tissues associated with an area of fibrosis and bony lysis. Chronic rhinitis was noted to be diffusely affecting nasal and sinus passages bilaterally. No evidence of recurrent lymphoma was found within the nasal and sinus tissues of this cat.

3.9 | Prognostic factors and HRs

Intracalvarial extension (modified Adam's stage 4b) was statistically significant, as cats with brain involvement ($n = 8$) had an overall MST of 100 days versus those without ($n = 24$) at 438 days ($P = 0.0007$; Table 2). MPFS for cats with intracalvarial extension was also decreased (88 vs. 438 days; $P = 0.002$). Cats with cribriform lysis (modified Adam's stage 4a) had a significantly decreased MPFS (98 vs. 876 days, $P = 0.0009$) and overall MST (121 vs. 876 days, $P = 0.0009$, Figure 2). There was no statistically significant difference between MPFS and overall MST for cribriform lysis as compared with brain involvement (canine modified Adam's stage 4a vs. 4b, $P = 0.14$ and $P = 0.17$ respectively). Anemia, facial deformity, epistaxis, palatal lysis, glucocorticoid use, chemotherapy treatment, and lymph node irradiation did not show statistical significance with PFS or OST (Table 2).

Administered dose to GTV and PTV, GM, HI, and CI were not significant for cats that had either 1 SBRT treatment or greater than 1 fraction for PFS and OST. A statistically significant difference in MST was noted for cats that had a 0.5 cm versus 1 cm expansion in both single fraction protocols (180 vs. 456 days, $P = 0.03$), and all treatment protocols (123 vs. 456 days, $P = 0.005$). CTV size was only significant in PFS when evaluating all treatment protocols (88 vs. 456 days, $P = 0.012$). The presence or absence of a CTV was not statistically significant ($P = 0.40$).

Hazards ratio revealed that an increase in GTV volume was statistically significant for both a shorter PFS (1.0454, $P = 0.01$, 95% CI 1.0105–1.0815) and MST (1.03, $P = 0.03$, 95% CI 1.0042–1.0663). Hazards ratio for PTV volume was significant for shorter PFS (1.0300, $P = 0.04$, 95% CI 1.0014–1.0593). A 2-sample *t*-test did not reveal a significant correlation between the 2 factors GTV volume and CTV of 0.5 versus 1 cm ($P = 0.19$).

4 | DISCUSSION

This study evaluates the treatment of nasal lymphoma with SBRT in felines. The protocol utilized at Colorado State University was adjusted during the study's timeframe from 3 to 5 fractions of radiation to a single treatment. As lymphomatous tumor cells undergo apoptosis, tumor volumes and shape can change rapidly. To appropriately target tissues, information regarding the shape of the tumor, depth of tissues, distance from the radiation source, and electron density of the tissues that the radiation traverses is necessary.[21] This presents challenges with multiple stereotactic fractions, as areas that were previously tumor could result in air, or shift organs at risk in between fractions, leading to altered dosimetry. In the 7 cats that received greater than 1 fraction, 1 cat had their treatment protocol terminated early, and 2 others had plan modifications due to marked changes in tumor volume. The rationale for single fraction SBRT was based on

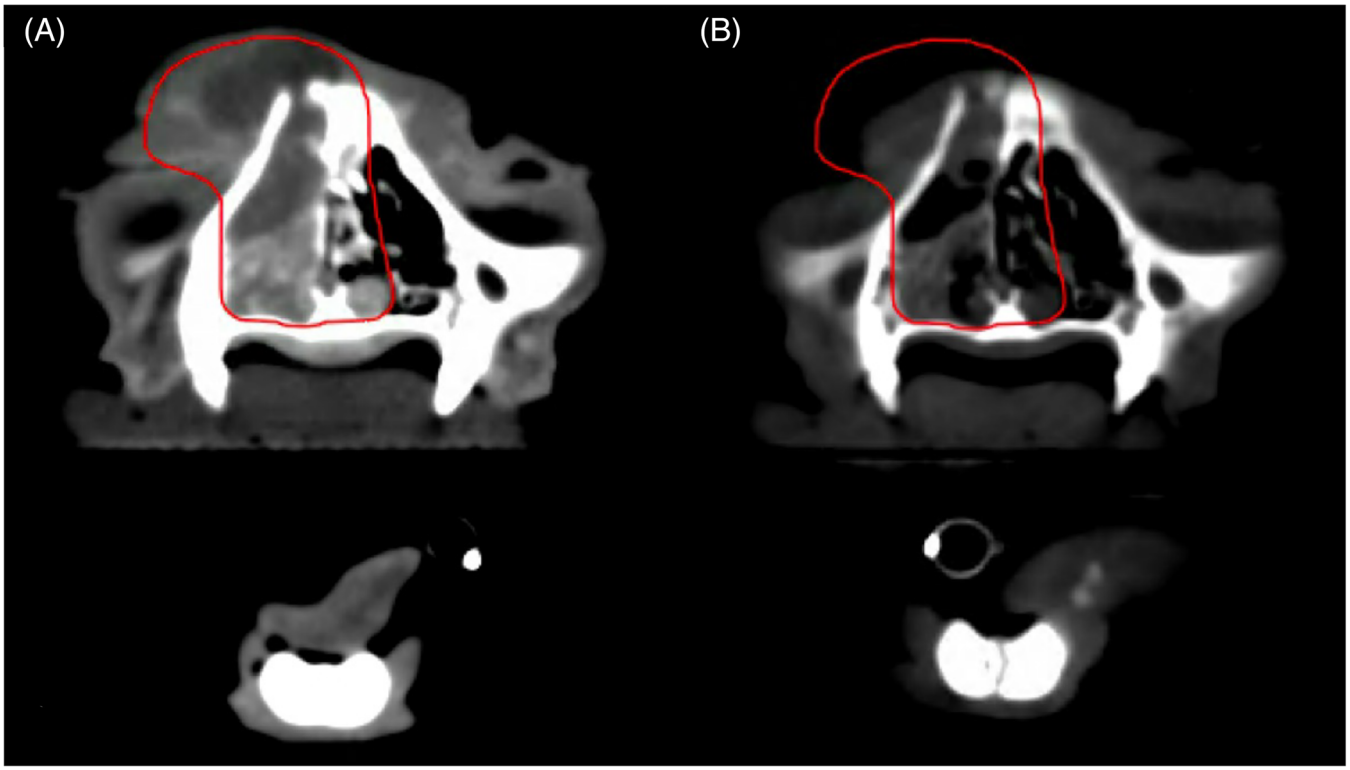

FIGURE 3 Image on left (A) is of a pre-contrast computed tomography (CT) scan of a cat before the first fraction of stereotactic body radiation therapy. The gross tumor volume (GTV) is contoured in red. The image on the right (B) represents the same corresponding location for the cat on fraction 3 of 5, obtained via cone-beam CT (CBCT). GTV contours from original plan are represented on image B

our observation of significant tumor shrinkage as seen on CBCT (Figure 3). It was elected to convert the radiation protocol to decrease inter-treatment variability and potential toxicities or missed tumor tissue. There was no difference in survival between cats that received 1 fraction versus multiple fractions. The basis of treatment planning and delivery relies on accurate target delineation.[21]

A CTV is added to account for potential microscopic disease in the nasal cavity and sinuses ipsilateral and contralateral to the gross tumor volume. On analysis, the presence of a CTV was not statistically significant for PFS and MST. This might be due to the limited number of cats without a CTV expansion. However, there was a statistically significant difference in PFS and MST when evaluating 0.5 versus 1 cm CTV margins. A consideration for this result could be secondary to missed areas of tumor targeting with a smaller CTV volume. The current practice at this institution is to assess the response to SBRT and adverse effects without the use of a CTV in nasal tumors. This study is likely underpowered to detect differences without use of a CTV, which would warrant further investigation into outcome without increasing the amount of potentially normal tissue irradiated.

Previous studies have incorporated a variety of external beam treatment modalities, including orthovoltage x-rays[22] and linear accelerators.[5,7,8] Median doses delivered to nasal tumors ranged from 30 to 49.7 Gy total.[5,7,8,22] The median OST noted in cats that receive treatment for nasal and nasopharyngeal lymphoma is varied from the variety of treatment protocols instituted. In single-modality chemotherapy treatments, MSTs range from 3.3 to 11.9 months.[3,5-7] Multi-modality treatment including both chemotherapy and radiation range from 5.8 to 31.4 months.[5,7,8] Survival times for radiation alone include an OST of 15–30 months, and a disease free survival of approximately 48 months.[5,8] The PFS and MST for cats treated with SBRT in combination with chemotherapy in this study were within the range of those of previous findings. Specifically, cats with modified Adam's stage 3 disease or lower had similar outcomes with those of previous findings.[8]

The prognostic factors cribriform lysis and brain involvement were significant in this study. Cats with modified Adam's stage 4 disease had a significant decrease in overall PFS and MST. These findings are similar to a study where cats with cribriform plate destruction had an MST of 2.5 months versus 42.6 months for those without cribriform involvement.[7] Conversely, non-lymphomatous nasal tumors in dogs treated with SBRT have shown that a canine modified Adam's staging and presence of intracalvarial extension were not predictive for survival.[23] The canine modified Adam's staging system used in this study was developed for the use in dogs, and the imaging parameters were applied for use in cats. Because the brain is inherently sensitive to radiation, a consideration for the decrease in survival time after radiation therapy can be secondary to decrease tumor control at the level of the brain, as normal tissue constraints might limit dose delivered to the level of the cribriform plate. Dose toxicity to the brain was unlikely as in this current study, no cats were noted to have signs

consistent with neurologic dysfunction at the time of treatment, after radiation, or as a cause of death. In stage 4 nasal tumors, a conventionally fractionated protocol would provide larger total dose to this area, with a lower dose per treatment to normal brain.

Treatment with chemotherapy did not significantly improve overall survival time. Systemic progression was noted in approximately 16%, as early as 44 days after SBRT. In a study of 19 cats treated with both radiation therapy and chemotherapy, 17.6% relapsed distantly.[7] Our findings of systemic relapse is similar despite not all cats receiving systemic chemotherapy after treatment. This highlights the importance of full body staging before radiation, and frequent restaging after radiation treatment for potential relapse systemically despite localized disease at time of radiation. Aggressive treatment with adjuvant chemotherapy should be considered if systemic disease is found at restaging. Local progression of disease was noted in as early as 19 days after SBRT. The cat experienced an initial improvement in clinical signs and then progressive facial deformity noted 2 weeks after therapy. A contributing factor to the clinical improvement can include an improvement in the local inflammation surrounding the tumor, as compared to true disease response. This cat was noted to have spread to the retropharyngeal lymph node at time of treatment.

No acute adverse effects were recorded in this cohort of cats. Late adverse effects were minimal in severity, and categorized utilizing the VRTOG morbidity scoring scheme.[20] Rhinitis has not been previously graded in this scoring method. Chronic rhinitis was reported in 75% of cats, with severity of signs ranging from primarily mild intermittent nasal discharge and sneezing to more chronic and increased amounts of nasal discharge and sneezing episodes. Treatment of rhinitis included intermittent to long term glucocorticoid therapy and antibiotic treatment. The protocol proposed by this institution is still being evaluated for efficacy (Table S1[24-27]). Antibiotic doses and treatment follow-up was limited. In human studies evaluating sinusitis and rhinitis secondary to radiation therapy, a blockage at the osteomeatal complex contributes to sinusitis.[28] The mucociliary clearance is altered due to damaged ciliary motility, with delay of exudates.[28] The mucous-secreting cells are also damaged, leading to a decrease in the amount of discharge and a thick mucous.[28] In human patients undergoing intensity modulated radiation therapy (IMRT) for nasopharyngeal carcinoma, chronic rhinosinusitis has been noted in up to 87% of patients.[29] Rhinosinusitis is graded in human medicine using the Lund-Mackay staging system, designating a score for the ostiomeatal complex and each sinus group according to findings on CT scan.[30] At our institution, it is suspected that a combination of tumoral destruction of underlying turbinates combined with altered nasal epithelium contribute to the persistent nasal signs, which can be mistaken for progressive disease in treated cats. Advanced imaging such as CT scan and rhinoscopy with biopsy are recommended to further classify these clinical signs as potential rhinitis versus tumor recurrence or progression.

In this study, 1 cat was noted to have progressive epistaxis and was euthanized 1406 days after treatment. Necropsy revealed squamous cell carcinoma associated with an area of fibrosis and bony lysis, diffuse chronic rhinitis, and no evidence of recurrent lymphoma. Diagnosis of high-grade lymphoma was originally made via histopathology acquired via rhinoscopy. Considerations for the necropsy findings include a neoplastic transformation secondary to radiation therapy as a late-term sequelae from the radiation therapy, versus potential mis-diagnosis at the time of biopsy.

It was noted on referring examinations and Colorado State University documentation that at least half of cats experienced improvement of nasal discharge and sneezing after treatment. However, data regarding complete versus partial resolution of clinical signs was limited, and therefore, assessing clinical response in the form of complete response, partial response, progressive disease, and stable disease was not performed. Repeat imaging via CT scan and rhinoscopy was performed in 11/32 (34%) of cats. Of those with imaging, all 11 had partial to complete resolution of mass effect on recheck imaging and rhinoscopy.

Limitations of this study include its retrospective nature, with lack of complete follow-up physical examination, imaging, and diagnostics performed on cats, and small sample size. Cats received a variety of different treatment protocols, including chemotherapeutic agents, glucocorticoid therapy, and antibiotic treatment. It is possible that due to lack of repeat imaging, that cats with relapse locally were not noted. Cause of events that lead to death that could not or were not determined were attributed to lymphoma.

This study provides encouraging data on the use of single-fraction SBRT treatment of nasal and nasopharyngeal lymphoma, especially in cats who are unable to undergo multiple fractions. Single fraction SBRT allows for broadening of treatment options for cats that could have previously been deemed poor candidates for fully fractionated protocols due to anesthesia or other comorbidities. A previous study evaluating single modality radiation for nasal lymphoma in cats found that canine modified Adam's staging was not predictive of outcome (MST 922 days).[8] Cats with lower stage disease (stage 3 and below) performed comparably to previously reported fractionated protocols with MST of 876 days. For cats with stage 4 disease, a fractionated protocol could be considered due to the decrease in MST, with the goal that the increased overall dose might lead to better control intracranially, lending a longer survival time. Cats tolerated treatment well, and both acute and late adverse effects were minimal in severity. When present, adverse effects were manageable with outpatient care. Due to noted systemic progression of disease in 16% of cats, consistent staging is advised so that a chemotherapeutic or radiation treatment can be recommended pending disease burden. In addition, full body staging would be recommended before treating with a local radiation therapy protocol. A study assessing the use of adjuvant chemotherapy and SBRT can be considered for further evaluation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

The authors declare human ethics approval was not needed for this study.

OFF-LABEL ANTIMICROBIAL DECLARATION

The authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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