





STANDARD ARTICLE

Retrospective evaluation of intranasal carcinomas in cats treated with external-beam radiotherapy: 42 cases

Hiroto Yoshikawa^{1,2}  | Tracy L. Gieger^{1,2}  | Corey F. Saba³  |
 Kirsha Fredrickson³ | Lyndsay Kubicek⁴ | Siobhan Haney⁵ | David Ruslander⁶ |
 Krista L. Kelsey⁷ | Margaret C. McEntee⁸ | Michael W. Nolan^{1,2} 

¹College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina

²Comparative Medicine Institute, North Carolina State University, Raleigh, North Carolina

³College of Veterinary Medicine, University of Georgia, Athens, Georgia

⁴Angell Animal Medical Center, Boston, Massachusetts

⁵Hope Veterinary Specialists, Malvern, Pennsylvania

⁶Veterinary Specialty Hospital of the Carolinas, Cary, North Carolina

⁷Carolina Veterinary Specialists, Matthews, North Carolina

⁸Cornell University Hospital for Animals, Ithaca, New York

Correspondence

Tracy L. Gieger, 1052 William Moore Drive, Raleigh, NC 27607.
 Email: tlgieger@ncsu.edu

Abstract

Background: Little is known regarding the comparative efficacy of various irradiation strategies used to treat intranasal carcinomas (INC) in cats.

Objectives: Investigate outcomes and prognostic factors associated with survival for cats with INC.

Animals: Forty-two cats with INC that underwent radiotherapy (RT).

Methods: Single-arm retrospective study. Medical record review for cats with INC that underwent RT at 1 of 7 veterinary RT facilities. Irradiation protocols categorized as: definitive-intent fractionated RT (FRT), definitive-intent stereotactic RT (SRT), and palliative-intent RT (PRT). Median overall survival time (OST) and disease progression-free survival (PFS; documented by advanced transverse imaging, or recurrence of symptoms) were calculated. Associations between tumor stage, RT protocol/intent, and adjunctive treatment usage and outcome were calculated.

Results: Cats underwent SRT (N = 18), FRT (N = 8), and PRT (N = 16). In multivariate modeling, cats received definitive-intent treatment (DRT; FRT/SRT) had significantly longer median PFS (504 days, [95% confidence interval (CI): 428–580 days] vs PRT 198 days [95% CI: 62–334 days]; $p = 0.006$) and median OST [721 days (95% CI: 527–915 days) vs 284 days (95% CI: 0–570 days); $p = 0.001$]. Cats that underwent second DRT course at time of recurrence lived significantly longer than cats that received 1 RT course (either DRT or PRT [median OST 824 days (95% CI: 237–1410 days) vs 434 days (95% CI: 277–591 days); $p = .028$]).

Conclusion: In cats with INC, DRT is associated with prolonged OST and PFS as compared to PRT. If tumor progression occurs, a second course of DRT should be considered.

KEYWORDS

head and neck cancer, nasal cancer, nasal tumor, radiation therapy

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; CI, confidence interval; DRT, definitive-intent radiation therapy; FRT, fractionated radiation therapy; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiation therapy; INC, intranasal carcinomas; OST, overall survival time; PFS, progression-free survival time; PRT, palliative-intent radiation therapy; SRT, stereotactic radiation therapy.

Tracy L. Gieger and Michael W. Nolan contributed equally.

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1 | INTRODUCTION

Nonlymphomatous intranasal tumors are typically seen in older, FIV/FelV-negative cats.^{1,2} Carcinomas are more common than sarcomas.¹⁻³ Intranasal carcinomas (INC) in cats are typically locally invasive and slow to metastasize to locoregional lymph nodes, other organs (ie, lungs), or both.^{4,5} Since complete excision cannot be achieved with surgery, and chemotherapy alone has minimal efficacy for the treatment of gross disease,^{6,7} external beam radiotherapy (RT) is generally regarded as the treatment of choice for INC in cats; however, there is a paucity of published data describing clinical outcomes after treatment with modern irradiation protocols.^{4,8}

A 1989 publication describing use of orthovoltage RT for intranasal tumors in cats demonstrated that RT can provide long-term tumor control.⁹ All cats with INC in that study (N = 3) received a total of 45 Gy in 10 fractions and lived more than 20 months (although 2 of them also underwent rhinotomy). More recently, megavoltage RT was used for a total of 24 cats with various nonlymphomatous intranasal tumors.^{1,2} The RT protocols varied and included 12 fractions of 4.0 Gy (administered on Monday, Wednesday, and Friday), 6 weekly fractions of 6 Gy, and 4 weekly fractions of 8 Gy. Reported 1-year survival rates are 44% and 63% and the median overall survival times (OSTs) are 11.5 months and 12.6 months, respectively.^{1,2} Due to the lack of a specific staging scheme for nasal tumors in cats, a staging scheme for nasal tumors in dogs is applied to cats with intranasal cancer in the previous study, though it is not a statistically significant predictive factor.^{2,10}

In the past few decades, sophisticated irradiation techniques have been adopted in veterinary oncology, including image-guided RT (IGRT) utilizing cone-beam CT scan, intensity modulated RT (IMRT), and stereotactic RT and radiosurgery (SRT/SRS).¹¹ The primary goal of utilizing these technologies is to minimize dose to normal tissues while precisely delivering RT to target (ie, tumor) tissues. Cats with INC treated with 10 daily (Monday-Friday) fractions of 4.2 Gy, and 89% of cats were treated with IMRT-based treatment plans had median OST of 269 days while 11% treated with more traditional 3D conformal radiation therapy (3D-CRT) methods had median OST of 452 days.⁸ To date, there are no published data available which describe clinical outcomes of SRT for INC in cats. The goal of this multi-institutional retrospective study was to evaluate clinical outcomes in cats with INC that were treated with various palliative- and definitive-intent irradiation protocols, and to identify factors which might aid in predicting treatment outcomes.

2 | MATERIALS AND METHODS

A medical records review was performed to search for eligible cases at 7 sites: North Carolina State University Veterinary Hospital, University of Georgia, Cornell University Hospital for Animals, Hope Veterinary Specialists, Angell Animal Medical Center, Veterinary Specialty Hospital of the Carolinas, and Carolina Veterinary Specialists. Eligibility requirements included cats with a cytological or histological

diagnosis of INC that was treated with external beam megavoltage RT. Cross-sectional imaging to determine tumor stage before treatment was not required for inclusion into the study. Cases were excluded if they received surgical debulking before RT, if no follow-up information was available, or if details of the RT protocol were not available. A standardized abstracting form was distributed to each site. The RT and medical records were searched for details including treatment intent, treatment schedule and dates, dose/fraction, total dose, and treatment outcome for all cases. Data collected are described in detail in the Supporting Information.

2.1 | Data interpretation

Definitive-intent full course RT (FRT) was defined as a total radiation dose of at least 40 Gy given in ≥ 10 fractions. Definitive-intent SRT was defined as a minimum fractional dose of 8 Gy and interfraction interval of no greater than 2 business days. The RT protocol was considered as SRT only if it was planned and delivered with stereotactic technique as previously reported (ie, stereotactic administration).¹¹ Palliative-intent RT (PRT) was defined as a non-SRT and non-FRT protocol, with the primary goal of improving a cat's quality of life. For statistical purposes, definitive-intent treatment (DRT) includes cats that received either FRT or SRT as their first-line treatment.

Primarily retrospectively by medical record review, adverse events were graded according to the Veterinary Radiation Therapy Oncology Group (VROG) criteria.¹²

2.2 | Statistical analyses

Kaplan-Meier analysis was used. The OST was defined as the number of days from the initiation of RT until death due to any cause; cases were censored if alive at the time of analysis, or if lost to follow-up. Disease progression-free survival (PFS) was defined as the number of days from initiation of RT until local or systemic disease progression; findings considered an event were; local tumor progression evident on follow-up CT or MRI or suspected based on follow-up physical examination, and death potentially associated with the INC or RT (including anesthesia-associated complications). Because of the retrospective nature of the current study, timing of follow-up physical and imaging examinations was not standardized. Cases were censored if they died of causes that were presumed not to be related to the nasal tumor (no clinical or radiological evidence of local tumor progression at the time of death) or if they were alive without clinical or radiological evidence of tumor progression. If the cause of death was unknown, the case was not censored, and was instead considered an event. Postmortem examination was not required for inclusion into the study.

To assess the value of various clinical and radiological variables with regard to their ability to predict clinical outcome, a Cox univariate analysis was performed; and variables with $P < .1$ were included for Cox multivariate analysis. Variables analyzed are listed in Tables 1 and 2 and the Supporting Information.

TABLE 1 Summary of signalment, clinical signs, clinical/physical examination and staging findings, and adjunctive treatments in cats of intranasal carcinoma treated with radiation therapy grouped by treatment intent (definitive- vs palliative-intent)

		Definitive-intent treatment (SRT + FRT) (N = 26)	Palliative-intent treatment (N = 16)	
Signalment	Mean age (y)	12.1	15.4	
	Mean body weight (kg)	5.3	4.2	
	Sex	CM	13	11
		SF	13	5
	Histological/cytological diagnosis	Adenocarcinoma	18	10
		Carcinoma	7	6
Transitional nasal carcinoma		1	0	
Clinical signs and physical/ clinical examination findings	Signs of neurological dysfunction ^a	Yes	2	1
		No	24	15
	Sneezing	Yes	16	14
		No	10	2
	Epistaxis	Yes	9	7
		No	17	9
	Facial deformity	Yes	5	11
		No	21	5
	Dyspnea	Yes	15	4
		No	11	12
	Nasal discharge	Yes	16	10
		No	10	6
	Reduced ocular retropulsion	Yes	4	2
		No	22	14
	Duration of clinical signs before diagnosis of intranasal carcinoma	<1 mo.	2	1
		1-6 mo.	12	9
6-12 mo.		10	3	
>12 mo.		2	3	
Cytological evaluation of regional lymph nodes ^b	Nonmetastatic	13	4	
	Metastatic	1	4	
Pre-RT treatment	Corticosteroids	Yes	16	4
		No	10	12
	NSAIDs ^b	Yes	2	2
		No	21	14
CT findings	Disease laterality ^b	Bilateral	13	10
		Unilateral	13	5
	Nasopharynx involvement ^b	Yes	20	6
		No	6	9
	Subcutaneous/submucosal involvement	Yes	4	13
		No	22	3
	Cribriform plate lysis ^b	Yes	7	8
		No	19	7
	Modified Adams stage ^b	I	2	0
		II	0	0
III		17	7	
IV		7	8	

TABLE 1 (Continued)

			Definitive-intent treatment (SRT + FRT) (N = 26)	Palliative-intent treatment (N = 16)
Post-RT treatment	Corticosteroids	Yes	11	6
		No	15	10
	NSAIDs	Yes	2	0
		No	24	16
	Chemotherapy	Yes	3	4
		No	23	12

Abbreviations: CM, castrated male; CT, computed tomography; FRT, fractionated radiotherapy; NSAIDs, nonsteroidal anti-inflammatory drugs; SF, spayed female; SRT, stereotactic radiotherapy.

^aHead tilt (N = 1), seizures (N = 2).

^bInformation was not available in all cats.

Commercial software was used for all statistical analyses (SigmaPlot, ver. 14, Systat Software, Inc, San Jose, California; Graphpad Prism, ver. 8.4, GraphPad Software, San Diego, California). Statistical significance was defined by $P < .05$.

3 | RESULTS

3.1 | Case population

A total of 42 cats (24 neutered male and 18 neutered female) met inclusion criteria. Treatment centers included 13 cases from Hope Veterinary Specialists (treated with CyberKnife; Accuray, Inc, Sunnyvale, California), 9 from North Carolina State University (treated with Varian Novalis TX; Varian Medical Systems, Inc, Palo Alto, California), 8 from Cornell University (treated with Siemens Primus; Siemens Medical Systems, Concord, California), 5 from University of Georgia (treated with Trilogy; Varian Medical Systems, Inc), 5 from Angell Animal Medical Center (treated with TrueBeam; Varian Medical Systems, Inc), and 1 each from Carolina Veterinary Specialists (treated with 2100C; Varian Medical Systems, Inc) and Veterinary Specialty Hospital of the Carolinas (treated with Varian 2100C/D; Varian Medical Systems, Inc). The cohort included 36 domestic short-haired cats, 2 domestic long-haired cats, and 1 each of domestic medium hair, Maine Coon, Scottish Fold, and Siamese. The mean age and body weight at the time of diagnosis were 13.3 years old (range, 5.0-21.0 years old) and 4.9 kg (range, 2.5-8.5 kg), respectively.

Clinical signs that prompted a nasal workup, initial physical exam findings, and adjunctive treatments are summarized in Table 1. All but 1 cat underwent a CT scan for RT planning as part of the initial workup. This cat was diagnosed as INC based on facial deformity, nasal discharge and epistaxis, lack of airflow from nares, and cytology of a tissue sample obtained by nasal flush. Diagnosis of intranasal carcinoma was based on histology in 33 cats and cytology in 9 cats. Cytologic evaluation of regional lymph nodes for metastasis was performed in 22 cats, and confirmed metastasis in 5 (4 cats in the mandibular and 1 in the retropharyngeal lymph nodes). The reason that prompted lymph node

evaluation for each case varied or was unknown because of the retrospective nature of this study (ie, routinely evaluated by the clinician vs based on physical examination or tomographic appearance). Thoracic imaging was performed in 39 cats (radiographs in 25 cats, CT scan in 10 cats, and both in 4 cats); in 3 cats (based on CT scan in 2 cats and radiographs in 1 cat), 1 or more pulmonary nodules were found. Fine needle aspirate and cytology of the lung nodule was performed in 1 cat, and revealed a benign cyst (this cat died of aspiration pneumonia 14 days after initiation of a PRT course). In the other 2 cats, cytological/histological evaluation of the lung nodules was not performed. One of these cats died of congestive heart failure 342 days after initiation of a PRT course (censored from PFS analysis) and the other cat died of an unknown reason at home 98 days after initiation of a PRT course. It was reported that signs of nasal tumors in this cat were stable but the cat was showing progressive neuropathy in the hind limbs (considered as an event for PFS analysis). Abdominal imaging was performed in 13 cats (ultrasound in 11 cats, CT scan and radiographs in 1 cat each); results were normal in 6 cats and abnormal in 7 (liver nodule and/or hyperplasia in 4 cats, bilateral nephropathy in 2 cats, and gastric wall masses in 1 cat [aspirated with inconclusive cytology]).

3.2 | Radiotherapy details

All RT plans used 6 megavoltage photon beams, with either coplanar or noncoplanar beam arrangements. Eighteen cats received SRT (10 Gy \times 3 daily, N = 15; and N = 1 for each of: 17 Gy \times 1, 10 Gy \times 2 daily, and 9 Gy \times 3 daily), 8 cats received FRT (3 Gy \times 16 daily, N = 4; 3 Gy \times 18 daily, N = 2; and N = 1 for both 4.2 Gy \times 10 daily and 2.7 Gy \times 20 daily), and 16 cats received PRT (8 Gy \times 4 weekly, N = 5; 4 Gy \times 5 daily, N = 5; 4 Gy \times 4 twice daily, N = 3; and N = 1 for each of: 10 Gy \times 2 [5 days apart], 5 Gy \times 4 daily, and 6 Gy \times 6 weekly). Generally, daily fractionation refers to once-daily treatments given on a Monday through Friday basis.

For the 26 cats that underwent DRT, computer-based inverse treatment planning (IMRT) was used in 20 (linear-accelerator-based

TABLE 2 Summary of Cox univariate analyses in 42 cats with intranasal carcinoma that underwent 1 or 2 course(s) of radiation therapy and in 35 cats that underwent only 1 course of radiation therapy

		All cats (N = 42)			Cats that underwent only 1 course RT (N = 35)		
		P value			P value		
		N	OST	PFS	N	OST	PFS
Signalment, history, clinical signs, staging							
Age		42	.31	.52	35	.47	.7
Body weight		42	.28	.25	35	.14	.53
Sex	CM	24	.32	.68	22	.56	.42
	SF	18			13		
Tumor histology	Adenocarcinoma	28	.44	.14	24	.61	.18
	Carcinoma	13			10		
	Transitional nasal carcinoma	1			1		
Treatment intent	Definitive	26	<.001	.006	21	.02	.01
	Palliative	16			14		
Signs of neurological dysfunction	No	39	.64	.03	32	.52	.04
	Yes	3			3		
Sneezing	No	12	.98	.56	12	.48	.36
	Yes	30			23		
Epistaxis	No	26	.13	.75	21	.31	.64
	Yes	16			14		
Facial deformity	No	26	.12	.3	20	.49	.23
	Yes	16			15		
Dyspnea	No	23	.3	.6	16	.45	.44
	Yes	19			19		
Nasal discharge	No	16	.14	.5	13	.93	.66
	Yes	26			22		
Ocular retropulsion	Normal	36	.61	.9	30	.9	.87
	Reduced	6			5		
Duration of clinical signs	<1 mo.	3	.92	.12	3	.85	.22
	1-6 mo.	21			15		
	6-12 mo.	13			12		
	>12 mo.	5			5		
Cytological evidence of lymph node metastasis ^a	No	17	.022	.022	16	.03	.03
	Yes	5			4		
Pre-RT treatment							
Corticosteroids	No	22	.21	.94	17	.72	.89
	Yes	20			18		
NSAIDs ^a	No	35	.33	.11	28	.28	.17
	Yes	4			4		
		All cats (N = 42)			Cats that underwent only 1 course RT (N = 35)		
		P value			P value		
		N	OST	PFS	N	OST	PFS
CT findings							
Disease laterality ^a	Unilateral	18	.12	.03	13	.19	.007
	Bilateral	23			21		

TABLE 2 (Continued)

		All cats (N = 42)			Cats that underwent only 1 course RT (N = 35)		
		N	P value		N	P value	
			OST	PFS		OST	PFS
Nasopharynx involvement ^a	No	15	.88	.28	11	.17	.23
	Yes	26			23		
Subcutaneous/submucosal involvement	No	25	.05	.15	20	.24	.09
	Yes	17			15		
Cribriform plate lysis ^a	No	26	.38	.14	21	.39	.25
	Yes	15			13		
Modified Adams stage ^a	I	2	.02	.48	0	.4	.22
	II	0			0		
	III	24			21		
	IV	15			13		
Post-RT treatment							
Corticosteroids	No	25	.55	.19	22	.05	.25
	Yes	17			13		
Chemotherapy	No	35	.21	.74	28	.44	.7
	Yes	7			7		
NSAIDs	No	40	.11	.03	33	.07	.05
	Yes	2			2		

Abbreviations: CM, castrated male; CT, computed tomography; NSAIDs: nonsteroidal anti-inflammatory drugs; OST, overall survival time; PFS, progression-free survival; RT, radiotherapy; SF, spayed female.

^aInformation was not available in all cats.

p-values <0.05 are shown in bold.

IMRT in 11 cats and CyberKnife treatment in 9 cats) and computer-based forward treatment planning (3D-CRT) was used in 6. In the 16 cats that underwent PRT, IMRT was used in 7 cats, 3D-CRT in 8 cats, and nongraphic planning (ie, manual setup) was used in 1 aforementioned cat that did not undergo CT scan of the head. Modified Adams stage of this cat was determined to be at least stage III due to the presence of subcutaneous lesion (excluded from the prognostic value evaluation). Details about radiotherapy planning and treatment administration are described in the Supporting Information. Regional lymph nodes were simultaneously irradiated in 8 cases—5 cats with known lymph node metastases and 3 cats prophylactically.

3.3 | Oncologic outcomes

Five cats did not complete the first course of RT due to: unexpected death in the hospital of unknown cause (N = 1, ST = 2 days), development of life-threatening comorbidities including anemia, acute dyspnea, and aspiration pneumonia (N = 1 each, ST = 1 day, 4 days, and 14 days, respectively), or euthanasia due to worsening of anorexia and weight loss (N = 1, ST = 43 days, received only 2/4 planned fractions). Two of these 5 cats underwent postmortem examination, and tumor progression was not suspected to be the cause of acute decline. Those 5 cats were included in the OST and PFS analysis and

all were considered as an event. A total of 35 cats underwent only 1 course of RT with intent to treat. Seven cats received a second course of RT after local tumor progression was confirmed by cross-sectional imaging; 3 cats received 2 courses of SRT (N = 2 : 2 courses of 10 Gy × 3 daily, N = 1 : 9 Gy × 3 daily then 10 Gy × 3 daily), 2 cats received 2 courses of PRT (N = 1 each: 2 courses of 4 Gy × 5 daily, 8 Gy × 4 weekly then 5 Gy × 5 daily), and 2 cats received SRT as reirradiation after initial FRT (N = 2 : 3 Gy × 18 daily then 10 Gy × 3 daily). Among the 2 cats that received 2 courses of PRT, 1 had evidence of regional lymph node metastasis at the time of the first course of PRT.

The median OST for all 42 cats was 591 days (95% confidence interval [CI] = 315-867 days). One- and 2-year survival rates were 60.1% and 29.0%, respectively. Nineteen cats were censored from the survival analysis; 10 were lost to follow-up and 9 were alive at the time of data analysis. The median follow-up time for the 19 censored cases was 342 days (range, 38-925 days). Of the 23 cats that died and were considered as an event, 12 cats died or were euthanized because of documented local progressive disease (including 5 treated with SRT, 4 treated with FRT, and 3 treated with PRT), 3 cats died because of probable anesthesia-related acute decompensation (all cats received postmortem examination and gross sinonasal tumor was present but exact cause of death was unclear), and the cause of death was unknown in 8 cats.

TABLE 3 (Continued)

All cases (N = 42)		PFS	
OST		Median	95% CI
	P value		
Cases that underwent only 1 course of RT (N = 35)			
OST		PFS	
	P value	Median	95% CI
Treatment intent	.02	Definitive (N = 21) Palliative (N = 14) Hazard ratio (definitive) 95% CI of hazard ratio	224-958 days 0-977 days 0.3 0.11-0.84
		Treatment intent	Definitive (N = 21) Palliative (N = 14) Hazard ratio (definitive) 95% CI of hazard ratio
Post-RT corticosteroids use	.06	Disease laterality	.06
Post-RT NSAID use	1	Signs of neurological dysfunction	1
When lymph node status (data available in 20 cats) is included in the analysis		Post-RT NSAID use	1
Cytological evidence of lymph node metastasis	.2	When lymph node status (data available in 20 cats) is included in the analysis	
Treatment intent	.26	Cytological evidence of lymph node metastasis	.32
Post-RT corticosteroids use	.51	Treatment intent	.33
Post-RT NSAID use	1	Disease laterality	.16
		Signs of neurological dysfunction	1
		Post-RT NSAID use	1

Note: Variables that showed P value <.1 in the univariate analysis were included in the multivariate analysis. Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OST, overall survival time; PFS, progression-free survival; RT, radiotherapy.

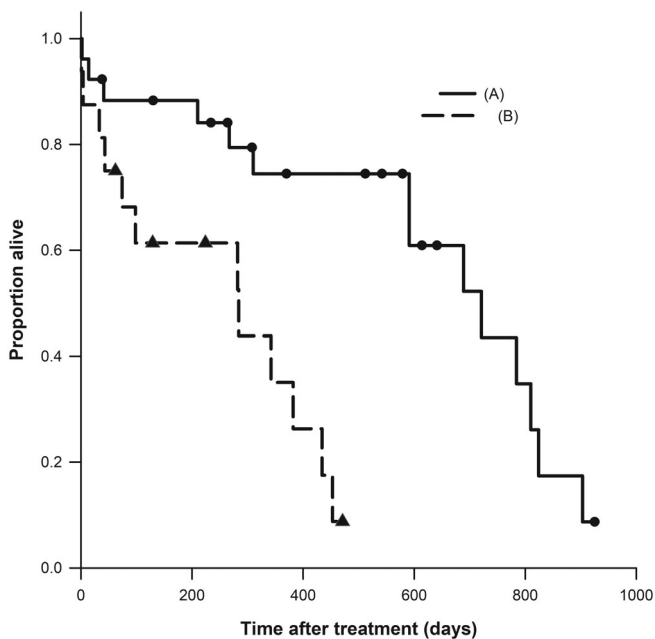


FIGURE 1 Kaplan-Meier survival curves showing overall survival times (OST) in all cats (N = 42) with intranasal carcinoma treated with radiation therapy, grouped by treatment intent. A, Definitive; solid line, N = 26, median OST: 721 days, 95% confidence interval (CI): 527 to 915 days; B, Palliative; dashed line, N = 16, median OST: 284 days, 95% CI: 0 to 570 days. *P* value (<.05) of Cox univariate proportional hazard model comparing OST between treatment intent groups; (A) vs (B): <.001. Black symbols indicate censored cases

The median PFS for all 42 cats was 459 days (95% CI = 292-626 days). One- and 2-year PFS rates were 52% and 0%, respectively. Sixteen cats were censored from PFS analysis (6 were alive without evidence of tumor progression, 8 were lost to follow-up but had no evidence of disease progression at the last follow-up, and 2 died of unrelated reason; 1 each of hypertrophic cardiomyopathy and a mass on a limb). The median follow-up time for the censored cases was 309 days (range, 38-614 days). Twenty-six cats were considered as an event for PFS assessment (including 11 treated with SRT, 5 treated with FRT, and 10 treated with PRT). Of the 26 cats, progressive disease was determined based on follow-up CT/MRI examination in 11 cats, based on physical examination findings in 8 cats (development of facial deformity = 3, recurrent clinical signs = 5), and based on clinical signs that are potentially related to the INC or RT in 2 cats (development of signs of neurological dysfunction). Of the remaining 5 cats, 3 cats died acutely or were euthanized during or immediately after RT and 2 cats died of an unknown reason. Fourteen cats had follow-up CT or MRI scan(s) and details can be found in the Supporting Information. In summary, 7/18 cats that underwent SRT, 3/8 cats that underwent FRT, and 4/16 cats that underwent PRT had follow-up CT or MRI scan(s). All 7 cats that underwent a second RT course had an evidence of local tumor progression on the follow-up CT or MRI scan.

When assessing survival statistics in the 35 cats that underwent only 1 course of RT, the median OST was 591 days (95% CI = 384-798 days) and the median PFS was 504 days (95% CI = 287-721 days).

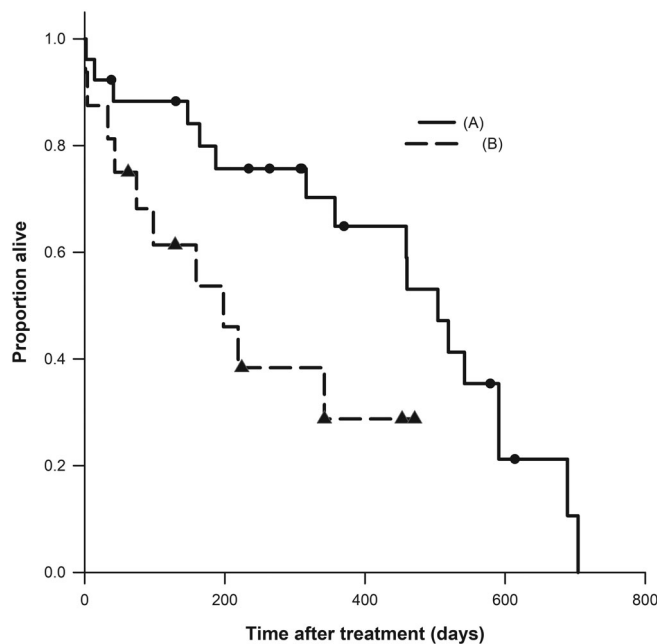


FIGURE 2 Kaplan-Meier survival curves showing progression-free survival (PFS) in all cats (N = 42) with intranasal carcinoma treated with radiation therapy, grouped by treatment intent. A, Definitive; solid line, N = 26, median PFS: 504 days, 95% confidence interval (CI): 428 to 580 days; B, Palliative; dashed line, N = 16, median PFS: 198 days, 95% CI: 62 to 334 days. *P* value (<.05) of Cox univariate proportional hazard model comparing PFS between treatment intent groups; (A) vs (B): .006. Black symbols indicate censored cases

The median interval between the first and second courses of RT was 316 days: for the 5 cats that underwent 2 courses of DRT, it was 357 days (range, 187-519 days) whereas for the 2 cats that underwent 2 courses of PRT, the intervals were 159 and 198 days. The median time between the second course of RT and death (all 7 cats treated with second courses of RT were deceased at the end of the study) was 364 days (range, 84-637 days) for all 7 cats: for the 5 cats that underwent 2 courses of DRT, it was 465 days (range, 122-637 days) whereas for the 2 cats that underwent 2 courses of PRT, the intervals were 84 and 125 days. When comparing OST in cats that underwent only 1 course of RT (including the 5 cats that did not complete it) (N = 35, 434 days) vs those that underwent reirradiation (N = 7, 824 days), the difference was statistically significant (*P* = .03). Further analysis revealed that cats that underwent 2 courses of DRT had significantly longer OST (N = 5, 824 days) than those that underwent 1 course of DRT (N = 21, 591 days) (*P* = .05) and 1 course of PRT (N = 14, 342 days) (*P* = .02). The OST in the 2 cats that underwent 2 courses of PRT was 282 and 284 days.

There was no statistically significant difference in OST or PFS between cats that received SRT (N = 18) vs FRT (N = 8) as a first RT course (median OST: 721 days vs 591 days, *P* = .67; median PFS: 460 days vs 519 days, *P* = .66, respectively).

Treatment intent, subcutaneous/submucosal disease invasion, regional lymph node metastasis, and modified Adams' stage were significantly predictive of OST in the univariate analysis (Table 2). For PFS,

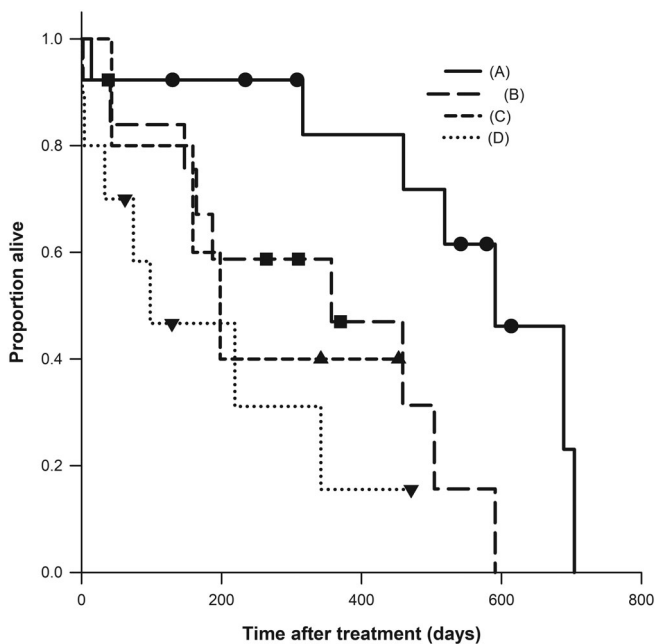


FIGURE 3 Kaplan-Meier survival curves showing progression-free survival (PFS) in all cats (N = 41; information about disease laterality was not available in 1 cat) with intranasal carcinoma treated with radiation therapy, grouped by treatment intent (definitive vs palliative) and disease laterality (unilateral vs bilateral). A, Definitive, unilateral; solid line, N = 13, median PFS: 591 days, 95% confidence interval (CI): 439 to 743 days; B, Definitive, bilateral; long dashed line, N = 13, median PFS: 357 days, 95% CI: 56 to 658 days; C, Palliative, unilateral; short dashed line, N = 5, median PFS: 198 days, 95% CI: 114 to 282 days; D, Palliative, bilateral; dotted line, N = 10, median PFS: 98 days, 95% CI: 0 to 271 days. *P* value (<.05) of Cox univariate proportional hazard model comparing PFS between treatment intent groups: (A) vs (D) = .02. Black symbols indicate censored cases

treatment intent, disease laterality, regional lymph node metastasis, signs of neurological dysfunction, and post-RT use of nonsteroidal anti-inflammatory drugs (NSAIDs) showed statistical significance in the univariate analysis ($P < .05$) (Table 2). Upon multivariate analysis, treatment intent (SRT/FRT vs PRT) was the only statistically significant variable ($P = .05$) with regard to predicting OST (Table 3, Figure 1) when the presence of regional lymph node metastasis (yes/no) was excluded from this analysis because data for that variable were only available in 22 cats. When the regional lymph node metastasis data were included, it was the only significant variable for predicting OST; for PFS, treatment intent and disease laterality both showed statistical significance (Figure 2) when the regional lymph node metastasis data were excluded. When it was included, none of the variables were significant (Table 3). Further assessment of the impact of treatment intent and disease laterality on the PFS was performed (Figures 3 and 4). Statistical difference was found between cats with unilateral disease that were treated with DRT (591 days, 95% CI = 439-743 days) and those with bilateral disease that were treated with PRT (98 days, 0-271 days) ($P = .02$) (Figure 3).

In the Cox multivariate analysis, when only cats that underwent 1 course of RT were analyzed (N = 35), treatment intent was the only

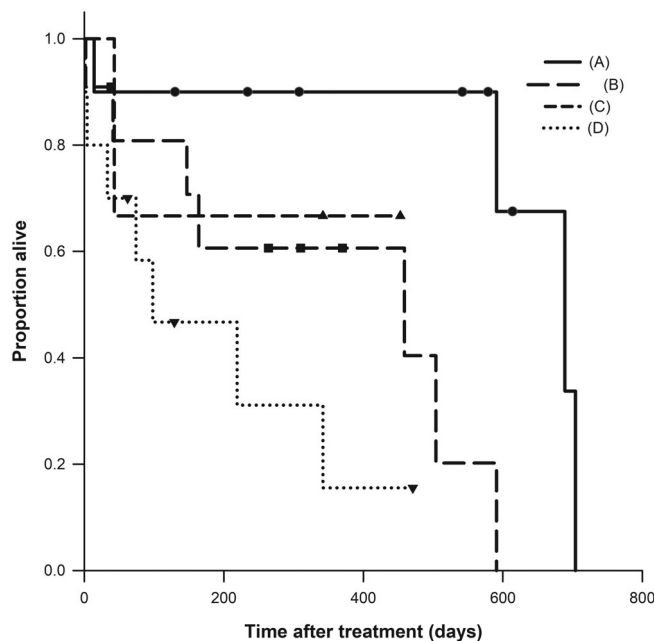


FIGURE 4 Kaplan-Meier survival curves showing progression-free survival (PFS) in cats with intranasal carcinoma that underwent only 1 course of radiation therapy (N = 34), grouped by treatment intent (definitive vs palliative) and disease laterality (unilateral vs bilateral). A, Definitive, unilateral; solid line, N = 10, median PFS: 689 days, 95% confidence interval (CI): 541 to 837 days; B, Definitive, bilateral; long dashed line, N = 11, median PFS: 459 days, 95% CI: 0 to 1015 days; C, Palliative, unilateral; short dashed line, N = 3, median PFS: not reached, mean PFS: 316 days; D, Palliative, bilateral; dotted line, N = 10, median PFS: 98 days, 95% CI: 0 to 271 days. *P* value (<.05) of Cox univariate proportional hazard model comparing PFS between treatment intent groups: (A) vs (D) = .03. Black symbols indicate censored cases

significant variable when the regional lymph node metastasis data were excluded: both OST and PFS were significantly longer with DFT in the Cox multivariate analysis (Table 3). When the regional lymph node metastasis data were included, none of the variables showed significance in either OST or PFS analysis (Table 3). Because the disease laterality showed near-significant *P* value for PFS analysis when the regional lymph node metastasis data were excluded, further assessment of the impact of treatment intent and disease laterality on the PFS was also performed in these 35 cats. Cats with unilateral disease that were treated with DRT (N = 10, 689 days, 95% CI = 541-837 days) had significantly longer PFS than cats with bilateral disease that were treated with PRT (N = 10, 98 days, 0-271 days) ($P = .03$) (Figure 4).

3.4 | Adverse events and improvement in clinical signs

All cats were assessed for any RT-associated toxicoses after RT by a veterinarian at 1 of the authors' institutions or a referring veterinarian. However, because of the retrospective nature of the study, the timing and frequency of the follow-up examination varied. Among the 37 cats

that completed at least 1 RT course, 9 cats were reported to have developed acute radiation toxicoses; 3 cats developed grade 1 alopecia (1 each received SRT, FRT, or PRT), 1 cat that received FRT developed transient coughing, 5 cats developed oral mucositis (2 with VRTOG grade 1 mucositis [both FRT], 1 grade 2 (FRT), 2 unknown grade [1 each in PRT or SRT]). Among these 9 cats, there were 2 cats that also developed grade 1 acute ocular toxicoses; both were treated with 3D-CRT treatment plans (1 FRT and 1 PRT).

One cat that received PRT (8 Gy × 4 weekly fractions) developed possible early delayed neuropathy (characterized by mental confusion and seizure activity) and was euthanized 33 days after initiation of the PRT course. This cat had sneezing and nasal discharge as the original clinical signs (no signs of neurological dysfunction) and was diagnosed with modified Adams stage IV INC. An IMRT plan was used to spare surrounding normal tissues. Since neither follow-up images nor post-mortem examination was performed, the cause of the neuropathy (early delayed neuropathy vs local disease progression) could not be determined. For PFS analysis, this cat's death was considered as an event.

Information about late toxicoses (those occurring >3 months after RT) was available in 31 cats. The 5 cats that did not complete an RT course were excluded from this analysis. Observed late toxicoses were clinically mild in all cases and described in detail in the Supporting Information.

Among the 37 cats that completed the first RT course for whom information about post-RT clinical signs was available, improvement of clinical signs was appreciated in 34 cats (91.8%); 15/16 in SRT-, 5/6 in FRT-, and 14/15 in PRT-treated animals. Information about timing of improvement after RT and duration of the improved clinical signs was not consistently available.

3.5 | Neoadjuvant and adjuvant treatment

Four cats were treated with an NSAID (meloxicam) before RT, with variable duration. Twenty cats were treated with corticosteroids before RT, with variable duration, dose, and route of administration.

Seven cats received chemotherapy after RT including carboplatin in 3 cats, toceranib in 1 cat, vinorelbine in 1 cat (with regional lymph node metastasis), chlorambucil in 1 cat (with regional lymph node metastasis), and chlorambucil followed by toceranib in 1 cat (to treat gastrointestinal lymphoma). Two cats received NSAIDs for variable duration after an RT course; that included meloxicam and robenacoxib. There were 17 cats that received prednisolone for variable duration after RT.

4 | DISCUSSION

The median OST and PFS of 42 cats with INC treated with variable protocols of external beam RT in the current study are comparable to those of studies published between 2014 and 2020. In a study of 65 cats with nasal tumors (various histotypes including lymphoma)

treated with hypofractionated (weekly) megavoltage (4 MV) irradiation, the median OST in 36 cats with nonlymphomatous nasal tumors (including carcinomas, sarcomas, and other histotypes) was 450 days, and 5/36 received multiple courses of RT.¹³ A median OST of 342 days in for 28 cats with nasal tumors that underwent coarse-fractionated, PRT was also reported in another study.¹⁴ Also, a study of 27 cats of INC treated with 10 daily (M-F) fractions of 4.2 Gy reported median OST and PFS of 452 days and 269 days, respectively.⁸ Although direct comparison between studies is challenging due to differences in protocols and cat populations, the present study further emphasizes that RT of any type could improve clinical signs and quality of life; we found that irrespective of treatment intent, most (>90%) irradiated cats had improvement in clinical signs. All RT protocols were well tolerated; the incidence of mild to moderate (VRTOG grade I-II) acute toxicosis was low, and no cats were reported to have developed moderate or severe (grade III or higher) adverse events. Clinically meaningful late toxicoses were also reportedly rare.

Our results suggest that definitive-intent treatment with either FRT (total dose >40 Gy given in 10 or more fractions) or SRT provides significantly better outcome (median OST = 721 days) as compared to PRT (median OST = 284 days). Furthermore, the current study revealed that a second course of DRT (in our study, all SRT) after local tumor progression after the first course of DRT (either FRT or SRT) can prolong survival time significantly. Although this finding needs to be verified in a future study with a larger pool of cats with INC, this might indicate that definitive-intent reirradiation after local failure after a DRT course is a valid treatment option, assuming good integrity of the surrounding normal tissues. The ideal RT protocol (ie, the best outcome with the least toxicosis) has yet to be determined. In addition to concluding that treatment intent is predictive for outcome, our data also allow certain conclusions to be made with regard to factors which are potentially prognostic for outcome in cats with INC.

The finding of cytological evidence of metastasis in 5/22 cats whose lymph nodes were sampled emphasizes the importance of fine needle aspiration and cytology of the regional lymph nodes in cats with INC. Because of the retrospective nature of this study, it was difficult to discern from the medical records whether the lymph nodes were aspirated due to palpable enlargement or tomographic evidence of abnormalities that could suggest metastasis (like heterogenous contrast enhancement). Although the numbers of cats with lymph node metastasis in our study were small, this finding was a negative prognostic factor for both OST and PFS in the Cox univariate analysis (Table 2). This statistical significance was not retained after adjusting for confounding factors using a multivariate analysis (Table 3). In fact, 4/5 cats with a metastatic regional lymph node underwent 1 (N = 3) or 2 (N = 1) course(s) of PRT. This treatment selection, potentially made based on the advanced disease status, might have biased them for a poorer treatment outcome and falsely made the lymph node status possess prognostic value. Moreover, the lymph node cytology was performed only in 22/42 cats and 5/22 were positive for metastasis, drawing a conclusion of its prognostic value challenging with lower statistical power. Future investigation warrants uniform regional

lymph node assessment in all cats with INC before RT to determine the significance of this finding.

In the cats of our study, those with more advanced local disease (bilateral nasal cavity involvement) had shorter duration of local tumor control. One plausible explanation for this finding is that while it is possible that these findings reflect a truly more aggressive disease phenotype, it is also possible that these cats were simply undertreated (half of the cats with bilateral disease received PRT), possibly as a result of clinician bias toward recommending PRT due to their perception that cats with more locally advanced cancers have a worse prognosis. One aspect of radiation treatment planning that could have impacted outcome in our study is that for the 8 cats treated with SRT, intentional skin-sparing in hopes of avoiding late radiation toxicoses (ie, fistulas), might have also lead to inadvertent underdosing of parts of the tumor near the skin. In dogs, the modified Adams' tumor stage is prognostic for outcome in some, but not all studies describing nasal tumor irradiation in dogs.^{10,15,16} We demonstrated here that cats might not easily fit into the defined modified Adams' stages, since 15/17 cats with unilateral disease were classified to be in Adams stage III or IV due to extra-sinonasal cavity involvement. This might indicate that for cats with INC, use of modified Adams' stage might not be appropriate to evaluate as a prognostic factor for outcome. The fact that cats with unilateral tumors treated with DRT had the longest PFS might emphasize the importance of diagnosing INC at an early stage, followed by an aggressive treatment with DRT. Even at the time of local tumor recurrence, another course of DRT might be worthwhile to consider to improve survival time and cat's quality of life.

The authors acknowledge some limitations in the current study, mostly related to the retrospective nature of it. First, many cats did not undergo postmortem examination, potentially biasing the cause of death. Second, even though the total number of cats was large compared to previous reports, the number of cats in most subcategories was low, making determinations of the usefulness in specific treatment protocols or adjunct treatments difficult. The small population of cats might also have made eliminating a bias caused by treatment selection (ie, PRT was recommended for cases with more advanced stage) challenging. Also, due to the possible inaccuracy of linear-quadratic model in cats receiving high doses per fraction (ie, >8 Gy/fraction) and different calculation algorithms that were used between institutions, comparison of calculated doses to the target structures and surrounding normal tissues between different RT protocols could not be performed.^{17,18} Because of the retrospective nature of the study, lack of standardized follow-up after RT (physical examination and cross-sectional imaging) might have caused an inaccuracy in treatment outcome and RT-related toxicosis evaluation. For example, this might have resulted in an overestimation of PFS because follow-up imaging was not routinely performed and some of the cats that died without obvious worsening of clinical signs might have already had local tumor recurrence that was not appreciated. Also, RT-related toxicosis might have been underestimated because no standardized follow-up schedule and grading scheme were employed at the time of follow-up examination. Assessment of the

impact of the adjunctive treatments was also challenging in the current study because of a wide variation of the drug type, dosing frequency/duration, and lack of systematic method for their efficacy assessment. Details of RT and adjunctive treatments were not consistently available from all cases, and thus recommended publication recommendations regarding radiation reporting could not be fully adhered to.^{19,20} A randomized, controlled prospective study is advised to ensure adequate radiation reporting, toxicosis documentation, and response assessment. Additionally, in 9 cats, diagnosis of INC was solely based on cytology and histological examination of the nasal tumor was not performed. This inconsistency could carry a risk of misdiagnosis.²¹

In conclusion, the RT protocols reported herein were safe and reliably associated with improved clinical status. Definitive-intent treatment is associated with prolonged tumor control and survival. Cats with advanced stage disease had inferior treatment outcome, though improved outcomes could be achievable with routine recommendation for definitive-intent therapy, dose escalation to target volumes, or both. A second course of definitive-intent therapy should be considered as it might extend the duration of local tumor control.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Hiroto Yoshikawa  <https://orcid.org/0000-0001-8249-1525>

Tracy L. Gieger  <https://orcid.org/0000-0003-4889-4560>

Corey F. Saba  <https://orcid.org/0000-0003-0590-0801>

Michael W. Nolan  <https://orcid.org/0000-0002-4432-9700>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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