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Research Article

Outcomes of a Stereotactic Protocol for Canine Nasal Tumors with a Combined Dose to Head and Neck Lymph Nodes: 10 Cases (2016 - 2020)

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Abstract

Objectives: To present results from stereotactic radiation on a linear accelerator for nasal cavity tumors in canine patients. In addition results from mandibular and retropharyngeal lymph nodes receiving a prophylactic dose of radiation are included.

Methods: Medical records were analyzed for dogs treated with stereotactic radiation treatment for nasal tumors. Standardized treatment was a total of 24Gy delivered in three treatments (8Gy) every other day. In addition head and neck lymph nodes received 5Gy at the same time. The planning target volume margins were less than or equal to 3mm. Dose optimization was accomplished by following the inverse planning method.

Results: Ten dogs met the inclusion criteria. Eight of the dogs had stage 3 cancer and two of the dogs had stage 1 (Adams modified). The median overall survival for the series was 432 days. Minimal acute and late effects were observed. These were defined as no higher than grade 1 toxicity using the Veterinary Radiation Treatment Oncology Group classification system.

Clinical Significance: Hypofractionated intensity-modulated radiotherapy with a dose of 8Gy every other day might be a reasonable treatment option for dogs with nasal cavity stage 1 - 3 cancer. Patient's stage selection is essential before enrolling them with hypofractionated treatment for nasal tumors when treated with linear accelerators not specifically designed for those techniques. Physics criteria selection, such as a sharp gradient index and a conformity index close to one, improves the treatment dosimetry quality. Further study is needed on the lymph nodes treatment relevance and the enrollment of a larger group to confirm the findings of this study.

Keywords: *Stereotactic Radiation; Nasal Cavity Tumor*

Introduction

Hypofractionated stereotactic treatments have become very popular for canine nasal tumors. Dogs enrolled with those treatment types [1-5] have similar survival expectancy as compared to conventional fractionated protocols [6,7]. The advantage for the patient

and its owner is the short duration of the course, less than a week, and less hospitalization, and anesthesia. Radiation oncologists have reduced the number of required treatment fractions from 16 - 20 to one to three. Three fractions are currently the most popular choice. Improvement in linear accelerators (LINAC) technology through the development of fine or ultrafine multileaf collimators (MLCs) and/or the adaptations of stereotactic cones with the association of complex software treatment plans (Intensity-modulated radiation therapy (IMRT), arc therapy allows the radiation oncologist to bring more dose within the tumor with fewer treatments while sparing the critical structures (eyes and lens, brain, spine cord). Some machines are dedicated to this practice: Cyberknife, Gamma knife. Upgraded linear accelerators can deliver 1000 - 2000 monitor units (Mu) per minute, with less required time for dose delivery after removing the flattening filters. These dedicated radiosurgery machines have a more precise isocenter (< 1 mm), an associated robotic couch for positioning in 6 directions, on-board-image cone-beam, Kilovolt (kV) panels, and tracking options to assist with an ultraprecise patient set-up.

Our institution is equipped with a second LINAC generation upgraded with IMRT capacity.

The Machine was not specifically designed for radiosurgery treatment. Patients with nasal cavity tumors are treated with hypofractionated treatments of 8 Gray (Gy) every other day (EOD). A strict patient set-up utilizing a bite block and immobilization of the head with a moldable cushion and a thermoplastic mask is used. The head base is set, and the patients body is in a vacuum bag. Indentation bars secure the head frame and the body bag to the treatment table. Historically at our institution stereotactic radiation (SRT) was used as a salvage procedure for recurrent tumors. Today this protocol is a potential primary treatment option as the service gained confidence in the technique. 8Gy is delivered every other day to the tumor itself and 5Gy to the patients mandibular and retropharyngeal lymph nodes. The patient position is verified with port films before each set. Based on our experience, we consider that this method is safe, and we think that our results are comparable with previously published work for selected patients with the added benefit of minimal side effects.

Materials and Methods

Our Radiation Service conducted a retrospective study for canine patients with nasal tumors from 2016 to 2020 who were treated with SRT as a single modality.

Patient selection

Patient medical records from 2016 to 2020 were retrieved. Patients were selected if they had been treated for a nasal tumor with SRT which utilized three fractions of 8Gy EOD for a total dose of 24Gy. Characteristics such as sex, age at presentation, breed, date of death, and cause of death were reported. Tumor histopathology results were retrieved. Patients who presented for a second treatment were excluded. All patients had a complete examination prior to treatment which included CBC, serum biochemical analysis, computed tomography (CT) of the thorax and abdomen, or the combination of thoracic radiographs and abdominal ultrasound. Each patient stage was classified according to the Adams modified classification shown in table 1. In addition, cytologic examinations of enlarged regional lymph nodes were performed during the clinical exam or through the imaging process. Each patient was also treated with a total dose of 15 Gy which was split into three fractions delivered EOD for both retropharyngeal and mandibular lymph nodes.

Stage	Description
1	One nasal passage, paranasal sinus or frontal sinus, no bone involvement beyond turbinates.
2	Bone involvement beyond turbinates without orbit, subcutaneous or submucosal mass.
3	Involvement of the orbit, nasopharynx or subcutaneous or submucosal mass.
4	Lysis of the cribriform plate caused by the tumor.
4a	Brain invasion of the tumor.

Table 1: *Adams modified classification for Staging Canine Nasal Neoplasia.*

Note. Extracted and modify from "Withrow et al., 2013" by Adams et al., 2009.

All the patients had an updated follow-up either through medical rechecks at our institution or at the primary veterinarian's office. However, without any precise update in the medical record, the radiation team reached the primary veterinarian or the owners. Based on the absence of strict periodic follow-up with CT imaging this retrospective study could not provide a disease-free interval evaluation. Instead, the retrospective study targeted overall survival, quality of life, and side effects. The patients' clinical assessments are reported. The Veterinary Radiation Therapy Oncology Group (VRTOG) scoring scheme is used to describe the acute and late effects of radiation therapy [8].

Radiotherapy plans and treatments

The radiology department acquired contrast and non-contrast CT (GE lightspeed VCT, 64 slice CT scan, Milwaukee, WI) images from the patient with 0.625 mm slice thickness. The patients head was placed in a thermoplastic mask (CIVCO™ Orange City, IA) with the maxillary bone fixed by a bite block laying on a cushion and a head-frame base. Each anesthetized dog was placed in a vacuum bag (CIVCO™ Vac-Lok™ Cushions Urethane, Orange City, IA) in sternal recumbency "The position was secured to the table with two indexing bars (head and body bag). When brain involvement was suspected (neurologic signs), a magnetic resonance imaging (MRI) exam was included (GE 1.5T 8 channel-23x, Milwaukee, WI). We realized a MRI-CT fusion tumor volume appreciation. Treatments were administered via a 2100EX Varian Clinac (©Varian Medical Systems, Inc**.** Palo Alto, CA, USA) with 120 MLC and IMRT capacity.

IMRT generates multiple radiation beams with different directions angles and variation of dose intensity within the path converge to the tumor center while sparing normal structures. The radiation oncologist or the dosimetrist used inverse method planning and set up the dose objectives to the tumor and the critical structures. The computer generated the dose for each beam, optimized the angle for the beam, and processed the variation of dose within each beam, known as fluency. MLC leaves were individually motorized and moved at different speeds during the treatment in order to reproduce the dose variation. The goal was "to paint the treatment dose at the tumor level" while limiting the dose delivery to normal structures [9].

The radiation oncologist was responsible for designing the treatment plan assisted with Varian Eclipse® software v11.0 (©Varian Medical Systems, Inc. Palo Alto, CA, USA**),** AAA_11031 anisotropic analytical algorithm version 11.0.31 dose calculation for photons, a grid size of 0.25, field normalization to 100% to isocenter, and heterogeneity correction. A quality analysis check before treatment delivery was completed using a Mapcheck2© (©Sun Nuclear Corporation, USA) device. A physicist approved the final plan. Patient positioning was verified before each radiation fraction using port films and their digitalization after acquisition (©Kodak ACR-2000i, Single-cassette system).

For contouring methodology, the gross tumor volume (GTV) was contoured on CT contrast slices or after MRI-CT Fusion, contrast enhancing regions were determined as the GTV based on the radiation oncologist experience. For the study reported herein the authors excluded patients with brain involvement. The clinical tumor volume (CTV) was set as equal to the the planned tumor volume (PTV) in cm^3. The PTV was determined as GTV plus 1 - 3 mm, except near the eyes, or brain to avoid structural damage. The normal tissue structures at risk were the brain, left and right eye, skin, left and right lacrymal gland, and palate.

The biological dose (BED) associated with the selected treatment and the dose equivalent at 2 Gy (EQ2) were evaluated. Those parameters were retrieved from the radiobiology linear-quadratic survival curves [10]. Conformity index (CI), homogeneity index (HI), and gradient index (GI) was calculated for each patient following the guidelines in Radiation Therapy Group (RTOG) report 63 (Reft., *et al* 2003). The conformity index was the ratio of the reference isodose volume (VRI) to the target volume (TV). The conventional homogeneity index was the ratio of the maximum dose (Dmax) to the minimum dose (Dmin) [11,12]. The gradient index, which specifies the rapid decline of the dose outside the target volume was determined by calculating the ratio of volume dose isocenter v50% by v100% at isocenter% [13]. Analysis for correlation between conformity index, homogeneity index, gradient index, size of the tumor, and survival of patients [10,14].

Statistical analysis

Descriptive statistics on patient sex, age, weight, pathology diagnosis, clinical stage, and treatment plan were utilized. Quality metrics were independent variables placed in Excel® software to obtain median, mean, standard deviation, and minimum and maximum values. The Kaplan-Meier method for the survival curve design and the report of the overall median was used. The overall median survival time represents the time elapsed from the beginning of treatment to the patients date of death. Patients alive at the end of the study were censored. The statistical software R, version R 4.11 with functions (Surfvit, Hmisc, Rcoorr) [15-17] was used for correlation analysis and generated a Spearman correlation matrix with rho values and P-values. P values below < 0.05 were considered significant.

Results

Population

Ten patients meet our inclusion criteria to be included for further analysis, their characteristics are shown in table 2. All patients completed the SRT course without delay or treatment modification. The SRT plan corresponded to three fractions of 8Gy EOD for a total dose of 24Gy.

Variable	Result
Weight, Median (Mean - standard deviation; min-max)	11Kg† (18 – 15; 6.9-15.3)
Age, Median (Mean - standard deviation; min- max)	12y‡ (11 - 3)
Sex:	
Percentage of Neuter male	60%
Percentage of Spayed Female	30%
Percentage Intact male	10%
Histopathology:	
Carcinoma	30%
Adenocarcinoma	20%
Osteosarcoma	20%
Non-diagnostic simple	30%
Stage:	
I	20%
III	80%

Table 2: *Patients Characteristics: Clinical characteristics of dogs that fulfill our selection criteria to be included in the research. The variables presented are weight, age at presentation, sex, histopathology diagnosis, and stage classification. The stage classification is based on the Adams modified classification system for nasal neoplasia presented in table 1. (Percentages are base in the total of the sample, n=10).*

Table 2: *Patients Characteristics.*

(n = 10), † Kilogram, ‡ Year.

Patient characteristics

The median age of the ten dogs was 12 years, with a minimum range of 6.9 years, and a maximum range of 15.3 years. The median weight of all patients was 11 kg, with a minimum weight range of 5.4kg, and a maximum range of 52 kg. Breeds represented were Minia-

ture Schnauzers (2), mixed breed (2), and 1 each of Cairn Terrier, Labrador Retriever, Newfoundland, Poodle, Scottish Terrier, and Silky Terrier. Seven dogs were male and six were neutered and one was intact. Three dogs were spayed females.

Pathology reports showed 3 non-specified types of carcinomas, 2 adenocarcinomas, 2 osteosarcomas, and 3 patients having no specific diagnosis due to poor sample quality. Eight of the patients (n = 8) had stage III tumors and two had stage I. This was determined using the Adams modified classification (Table 1) [18] None of the patients had signs of metastasis at the time of treatment. Therefore, no additional chemotherapy, surgery, or immunotherapy treatments were combined with the radiation treatments.

Dosimetry metrics

All patients received three fractions of 8Gy EOD for a total dose of 24Gy with no interruptions or modifications during treatment. The BED_3 was 88Gy with an EQD_2 of 52.80Gy. The BED_{10} was 43.20Gy with an EQD_2 of 36Gy. The gross tumor volume (GTV) median was 19cm^3 (mean, 25; min-max 1.90-82.40), the median PTV was 30cm^3 (mean, 34; min-max 3.70-82.40). The PTV max dose median was 114% corresponding to 27.38Gy (mean, 115-2766; min-max; 110.10%-26.42Gy, 125.70%-30.16Gy**).** The conformity index median was 0.76 (mean, 0.71**;** min-max, 0.4623-0.87). The homogeneity index median was 1.35 (mean, 1.14; min-max, 1.1-1.25), the gradient index median was 1.55 (mean, 0.67; min-max, 1.14-2.56) (Table 3).

Variable	Median	Mean	Minimum	Maximum
GTV† (cm3)	19.80	25.39	1.90	82.40
PTV‡ (cm3)	30.10	34.87	3.70	82.40
PTV Max Dose in percentage	114.05	115.25	110.10	125.70
PTV§ Max Dose (Gy§)	27.38	27.66	26.42	30.16
Conformity index	0.77	0.72	0.46	0.87
Homogeneity index	1.14	1.15	1.10	1.25
Gradient index	1.55	1.67	1.14	2.56

Table 3: *Dosimetry quality metrics of the treatment plans: Dosimetry quality metrics retrieved from the treatment plans of the dogs that fulfill our selection criteria were retrieved. The evaluated variables are gross tumor volume (in cm3), planning target volume (in cm3), The maximum dose received by the planning target volume (in percentage and gray), conformity, homogeneity, and gradient indexes (absolute numbers).*

(n=10, Confidence interval 95%.) † Gross tumour volume ‡Planning target volume §Gray.

For the organs at risk, the brain's median maximum dose was 22Gy (mean, 19). The skin median maximum dose was 16Gy (mean, 15). The skin was defined as a contouring line 2 mm inside the body. The median maximum dose for the right eye was 11Gy, and the left eye was 10Gy (mean, 11 - 11). The right lacrimal gland median maximum dose consisted of 8Gy, and 6Gy for the left one (mean, 8 - 7). The maximum dose to the palate was of 19Gy (mean, 18) (Table 4).

Variable	Median	Mean	Minimum	Maximum
V15 Gy† Brain (%)	0.67	0.92	0.00	2.50
V25 Gy Brain (%)	0.00	0.00	0.00	0.01
V15 Brain (cm^3)	0.44	0.72	0.00	2.26
V25 Brain (cm^3)	0.00	0.03	0.00	0.34
Mean V50 Dose Gy Brain (%)	2.77	3.17	1.75	4.79

Max Dose Brain (Gy)	22.60	19.13	6.88	27.10
Dose Max Skin (Gy)	16.64	15.29	6.00	21.12
V12 Gy right eye (%)	0.00	0.95	0.00	7.00
V12 right eye (cm^3)	0.00	0.04	0.00	0.33
Mean Dose V50 right eye (Gy)	4.56	4.35	1.49	7.24
Max Dose right eye (Gy)	11.17	11.30	3.84	20.09
V12 left eye Gy (%)	0.00	2.08	0.00	12.30
V12 left eye (cm^3)	0.00	0.08	0.00	0.39
Mean Dose V50 left eye (Gy)	4.14	4.39	2.12	7.46
Max Dose left eye (Gy)	10.30	11.87	5.52	20.40
Mean Dose V50 right lens (Gy)	3.71	3.49	1.36	4.78
Mean Dose V50 left lens (Gy)	3.53	3.45	2.10	4.98
Max Dose Right Lacrimal Gland (Gy)	8.60	8.06	3.40	12.24
Max Dose Left Lacrimal Gland (Gy)	6.60	7.32	3.40	12.24
Palate Max Dose (Gy)	19.68	18.59	9.33	23.50
(n=10) † Gray				

Table 4: *Organs at risk maximum dose in Gy. The maximum dose received by the structures determined as the organs at risk during the treatment plan were retrieved. The organs at risk are brain, skin, eye, lens, lacrimal gland, and palate. Additional values (V15, V25, V12, V50) of the structures are presented.*

(n=10) † Gray.

Eight out of the ten patients developed acute effects according to the VRTOG acute morbidity scoring scheme (Table 5). Side effects include transient decreased tear production (n = 3), and dry desquamation in the skin (n = 6). Additionally, four owners reported a transient nasal discharge increase at different moments during treatment. Four out of the 10 patients developed mild late effects according to the VRTOG (grade1) late radiation morbidity scoring scheme (Table 5). Late effects consisted of alopecia (n = 2), and mild keratoconjunctivitis Sicca (n = 2). Additionally, Three of the owners reported mild periodic nasal discharges, however, less than compared before treatment.

Percentage of patients affected by acute and late effects grade I VRTOG morbidity scheme			
% Acute effects Grade I:			80%
	% Decrease Tear Production	30%	
	% Nasal Discharge	40%	
	% Dry Desquamation	60%	
% Late effects Grade I:			40%
	% Nasal Discharge	30%	
	% Alopecia	20%	
	% Keratoconjunctivitis Sicca	20%	

Table 5: *Acute effects Vs. Late effect. Acute and late effects after receiving three fractions of eight gray every other day were evaluated in all the patients after treatment. The effects are presented as the actual manifestation sign and quantified in percentage. The signs were classified according to the Veterinary Radiation Therapy Oncology Group (VRTOG), according to this classification the patients only developed grade 1 acute and late effects (n=10).*

SRT median survival time

Survival analysis through the Kaplan-Meier method resulted in an overall median survival time (MST) of 432 days (Figure 1). Nine out of the ten patients were dead at the writing of this study. One patient was still alive. Therefore, it was censored and not included in the MST analysis. The minimum survival time (ST) range was 216 days, and the maximum ST range was above 1,500 days. Conversations were held with the patient primary veterinarian if the last follow-up was not done at our institution to identify the date and possible cause of death. This information helped to assess the decision of censoring a patient or not. Due to the nature of the type of follow-up of patients, an inference was possible of cancer involvement at the time of death. Those deaths events were not censored.

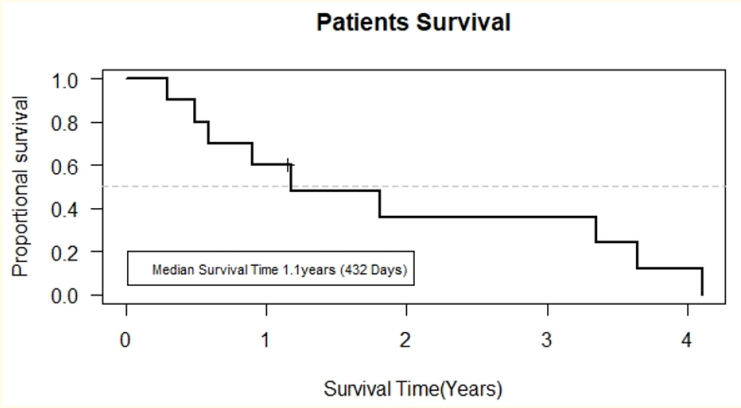

Figure 1: *Overall median survival time of canine nasal tumor patients treated with SRT to tumor and to head and neck lymph nodes. Kaplan Meier curve, the overall median survival time of the patients. The X-axis displays the survival time in years, and the Y-axis shows the proportional survival of patients. The lowest range corresponds to approximately one-half year, and the highest corresponds to approximately four years. The overall median survival time was estimated at 1.2 years, as marked by the dotted transverse line in the curve. The vertical line-forming cross corresponds to the only censored patient.*

Conformity index and survival

The association analysis (Figure 2) between conformity index and survival showed a moderate negative association with a rho value of -0.68. A negative association indicates that it is likely that if one of the values decreases, the other one will also decrease. This association was statistically significant with a p-value of 0.04. The homogeneity index and the size of the tumor (GTV) showed rho values considered a low negative association with survival. The association was not statistically significant. The gradient index did not show a relevant rho or p-value that was considered significant (Table 6).

Spearman correlation test					
	Survival	**Conformity Index**	**Homogeneity index**	**Gradient Index**	**GTV†**
Survival	1	-0.68	-0.46	0.25	-0.49
Conformity Index	-0.68	1.00	0.10	-0.04	0.36
Homogeneity index	-0.46	0.10	1.00	-0.40	0.46
Gradient Index	0.25	-0.04	-0.40	1.00	-0.45
GTV	-0.49	0.36	0.46	-0.45	1.00

P-values*					
	Survival	Conformity Index	Homogeneity index	Gradient Index	GTV
Survival		0.03	0.18	0.49	0.15
Conformity Index	0.03		0.79	0.91	0.31
Homogeneity index	0.18	0.79		0.25	0.18
Gradient Index	0.49	0.91	0.25		0.19
GTV	0.15	0.31	0.18	0.19	

Table 6: *Risk Factors in treatment planning. The conformity index, homogeneity index, gradient index, and the size of the tumor (represented by the gross tumor volume "GTV") were evaluated in relation to the survival of the patients through a spearman's correlation test. A matrix composed of the Rho values from the spearman test with their correspondent P-value was constructed. The conformity index and survival show a negative association with statistical significance (P-value < 0.03).*

(n=10) † Gross tumor volume.

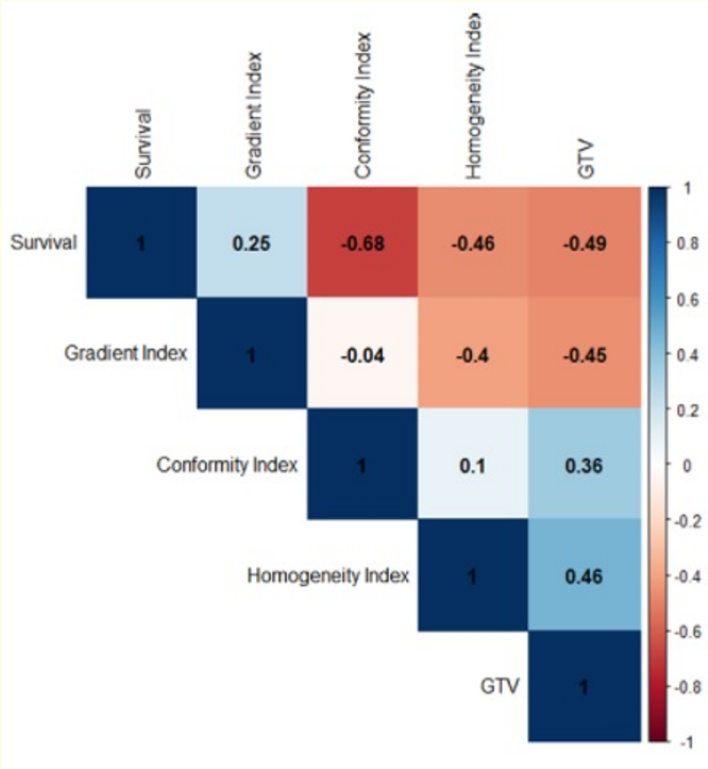

Figure 2: *Heat map showing the association analysis between four parameters (gradient index, conformity index, homogeneity index, gross tumor volume, and survival). The numbers inside the boxes correspond to the Spearman rho value. Blue corresponds to a positive correlation, while red corresponds to a negative correlation. Conformity index and survival display a moderate negative correlation with a rho value of -0.68. All other variables show rho values that can be described as non-relevant.*

Discussion

A disease-free interval for the patients was not provided because the follow-up methods were not standardized. There was an absence of consistent rechecks, which would have included a physical exam at our institution, and Imaging with CT. This made it difficult to detect early recurrence and differentiate side effects associated with radiation therapy versus tumor progression. The median survival for these ten patients treated EOD 8Gy for three fractions was 432 days. Compared to other publications [1-5]. There was an extra day off during fractionation, It has been shown that fractionation in SRT can result in reduce toxicities, and an extra day could support a better repair process of normal tissues compared to consecutive protocols while maintaining the same local controls [19]. The treatment dose was equal or less than other institutions (Table 7) [1-5]. The tumor volume was not boosted [2,3]. The margins were minimal compared to previous publications: an average of 1 - 3 mm versus 6 - 10 mm [2,3], and 5 - 6 mm contralateral cavity. Based on these minimum margins, these patients may have been more prone to local recurrence. However, the survival analysis data were very similar. Today modern linear accelerators are provided with tight machine isocenter, CT and KV onboard imaging, Plus sub-millimetric patient positioning is possible with the addition of a robotic couch. all those improvements have made radiosurgery techniques safer for the patients with the avoidance of severe late effects [8,20]. Late effects such as oro-nasal fistula, bone necrosis, blindness, or suspicion of brain necrosis (Table 1) were not seen. Possibly because the total dose was conservative, and minimal margins were selected helping to avoid serious side effects based on the limits of the equipment like no on-board imaging (OBI), high definition MLC collimator, and fine isocenter. There is no consensus on the necessary margins around the GTV essential to apply for PTV contouring for the treatment of nasal tumors with stereotactic radiation therapy [21]. Stereotactic radiation therapy treatments present radiobiological advantages compared to fractionated treatments: improvement of tumor cell killing, dose, dose rate [22], the potential destruction of tumor vasculature [23]. Besides the mitotic death of the cancer cells, other biological effects can be possible with higher doses per fraction, such as vascular endothelial apoptosis and immunologic effect. In cancer in humans, doses from 8 - 14 Gray per fraction may be of interest to immunologists as there is a stimulation of the native immune response, which could be seen in massive liberation of tumor antigens, release of stress signal proteins such as calreticulin and HGBM1, or activation of lymphocytes T (sting pathway and the production of interferon 1) [24]. Could those added effects change the paradigm of treating all of the tumor volumes? This has been of recent interest in the world of human oncology [25].

Parameter	Glasser., *et al.* 2014	Kubicek., *et al.* 2016	Gieger., *et al.* 2017	Mayer., *et al.* 2019	Fox-Alvarez., *et al.* 2020	Study reported herein
Total Dose	24-36Gy†	18.75Gy–56Gy	30Gy	27-30Gy or 20Gy	24-30Gy	24Gy
Fraction size	8–12Gy	18.75Gy–56Gy	10Gy	9-10Gy or 20Gy	8-10Gy	8Gy
Protocol	Consecutive	Single dose	3-5 days	Consecutive or single dose	3-7 days	Every other day
Boost	No	No	yes	No	yes	No
Lymph node Treatment	No	No	1 patient, metastasis	1 patient, prophylactically	No	all patients
Dosimetry Quality Metrics (Median)	CI‡: No Data HI§: 1.27 GI¶: No Data	CI: No Data HI: No Data GI: No Data	CI: 0.82 HI: No Data GI: 2.7	CI: 0.5 HI: 1.4 GI: 3.9	CI: 0.99 HI: 1.1 GI: 3.34	CI: 0.77 HI: 1.14 GI: 2.56
Median Survival Time	399 days	255 days	586 days	388 days	563 days	432 days

Table 7: *Comparative analysis between previous publications. The data from the most recent publications in the field addressing stereotactic radiotherapy for the treatment of nasal tumors in dogs was extracted to construct a table with their most relevant parameters for comparison with the data reported herein. The variables extracted were the total dose, fraction size, the protocol to deliver the fractions (how many days or rest days between fractions), boost (yes/no), the treatment of lymph nodes (yes/no), dosimetry quality metrics (conformity, homogeneity, and gradient indexes), and the median survival time.*

Note. †Gray ‡Conformity index., §Homogeneity index, ¶Gradient index.

This study included mainly stage 3 tumors. There were no patients with stage 4, so it cannot be said with certainty if the absence of severe late side effects in the brain or optical chiasma was related to the lack of stage 4 (and more particularly stage 4a). No skin necrosis or palate fistula was observed. The AAPM recommendations [26] for dosimetry objectives were followed. No patients were treated with an added Radiation dose boost. The maximum dose in the PTV is less than that delivered in most studies [1-5]. Also, an additional day between treatments might benefit the normal structures by allowing time for repair. All head and neck lymph nodes (both mandibular and retropharyngeal) received three fractions of 5Gy during the course of treatment. The rationale for this protocol for the lymph nodes was an empirical clinical decision made by the senior radiation oncologist. Previous experience in treating primary nasal carcinoma where relapse had occurred in the lymph nodes led to a conservative approach and supported the clinical decision.

The statistical analysis revealed a potential correlation between the conformity index and the survival with a p-value < 0.05. An ideal conformity index is 1. The conformity index is related to the prescription of dose for precise coverage target volume. The gradient index specifies the rapid decline of the dose outside the target volume. The gradient index was low (1.55), this was the result of a selection of a sharp dose fall-off outside the target for the IMRT optimization process by our physicist. The conformity index was similar to other studies [1-5] However, the calculation model was the RTOG method. Variability to calculate the CI exists through different methods like the Paddick calculation method [27]. The homogeneity index was similar to previous references. A homogeneous dose within the PTV is of prime importance for fractionated treatment. The radiosurgery world has more tolerance to inhomogeneities within the PTV; variations are common, and some hot spots could be desirable for suspected resistant areas [28].

Limitations

The overall survival was 432 days, which is comparable to other reports. However, the sample size was small, and it is not known if there was a bias due to the small sample size. This study did not include any patients with advanced-stage 4 disease. There may have been some preference to limit the patient enrollment to less advanced stages of disease given the equipment at this institution and also for prognosis purposes. Patients with advanced cases at our institution might have a fractionated IMRT course or a palliative 5x4Gy depending on the prognosis and the owner's choice. This selection bias might artificially lead to less severe late side effects in comparison to other studies.

It is not known how much the tumor volume impacts the biological response for this type of treatment, so the comparable survival results in other studies might be a confounding factor to a lower stage per series. Furthermore, this study does not differ in treatment results, but the number of patients enrolled was small. In addition to small numbers of cases tumor histology for all 10 cases was not available. Finally, the pertinence of treating the lymph nodes with stereotactic protocols is not known. Some radiation oncologists might argue that the risk of metastasis is limited (10 - 20%). However, they are none randomized powerfully studies for verification. Analyzing recent data on immunotherapy abscopal response to radiation therapy in human patients [25], might lead to restricting the treatment of lymph nodes in future studies without pathology confirming metastatic invasion.

Conflict of Interest

No conflicts of interest have been declared.

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Volume 7 Issue 7 July 2022