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Dynamic contrast-enhanced computed tomography in dogs with nasal tumors

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Abstract

Background: Treatment of nasal tumors in dogs is associated with high morbidity and reliable prognostic factors are lacking. Dynamic contrast-enhanced computed tomography (DCECT) can be used to assess tumor perfusion.

Objectives: To assess perfusion parameters of nasal tumors (correlating with tumor type) before and during radiotherapy (RT) and find potential correlation with survival.

Animals: Twenty-four client-owned dogs with nasal tumors, including 16 epithelial tumors and 8 sarcomas.

Methods: Prospective cross-sectional study. All dogs had baseline DCECT to assess fractional vascular volume (BV), blood flow (BF), and transit time (TT). Thirteen dogs had repeat DCECT after 12 Gy of megavoltage RT. Survival times were calculated.

Results: Median BV was 17.83 mL/100 g (range, 3.63-66.02), median BF was 122.63 mL/100 g/minute (range, 23.65-279.99), and median TT was 8.91 seconds (range, 4.57-14.23). Sarcomas had a significantly lower BF than adenocarcinomas ($P = .002$), carcinomas ($P = .01$), and other carcinomas ($P = .001$), and significantly lower BV than adenocarcinomas ($P = .03$) and other carcinomas ($P = .004$). Significant associations were found between epithelial tumors and sarcoma for change in tumor volume ($P = .01$), width ($P = .004$), and length ($P = .02$) in that epithelial tumors decreased in volume whereas sarcomas increased in volume. Perfusion parameters were not correlated with survival.

Conclusions and Clinical Importance: Nasal sarcomas have lower BV and BF than nasal carcinomas, and sarcomas have a lower size reduction than carcinomas early on during RT. Baseline results and changes in perfusion parameters may not be correlated with survival.

Abbreviations: BF, blood flow; BV, blood volume; CT, computed tomography; DCECT, dynamic contrast-enhanced computed tomography; NSAID, non-steroidal anti-inflammatory drugs; RT, radiotherapy; TT, transit time.

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KEYWORDS
DCECT, dogs, nasal tumor, perfusion CT, radiotherapy

1 | INTRODUCTION

Tumors of the nasal cavity and paranasal sinuses are relatively common neoplasms in dogs, representing approximately 1% to 2% of all cancers.[1] Approximately two-thirds of nasal tumors are carcinomas and one-third are sarcomas, most commonly chondrosarcomas.[2-5] Dogs with nasal tumors can be treated using surgery, chemotherapy, radiotherapy (RT), or some combination of these. Megavoltage RT often is used in these patients, with median survival times ranging from 350 to 650 days.[3,4,6-13] The relationship between tumor type and prognosis is unclear, but carcinomas tend to respond better than sarcomas to RT in terms of size reduction, but without a significant difference in survival time between the 2 groups.[14] Radiotherapy can be associated with morbidity caused by radiation toxicity, requires owner commitment, and entails considerable financial expense.[15] Current assessment of response to treatment in solid tumors often relies on changes in clinical signs and tumor size on CT using Response Evaluation Criteria in Solid Tumors (RECIST).[16] These variables do not seem to be accurate predictors of progression-free interval,[17] and there is a need to develop pre-treatment prognostic indicators that might help tailoring treatment on an individual basis.

Dynamic contrast-enhanced computed tomography (DCECT) is a functional imaging technique that allows assessment of blood flow in the capillary network by continuous or intermittent scanning of a volume of tissue during IV administration of contrast medium.[18-20] Correlations exist between DCECT-derived perfusion parameters of solid tumors with hypoxia, and among tumor hypoxia, malignant progression, and treatment failure.[21] In human beings with head and neck cancer, DCECT (also referred to as perfusion CT), has shown promise as a prognostic indicator, and is used to assess response to treatment and to detect local recurrence.[22-25]

Dynamic contrast-enhanced computed tomography has been used in dogs, and several proof-of-principle studies have assessed normal tissues and tumors, and compared DCECT to 18F-fluorodeoxyglucose positron emission tomography-computed tomography.[26-42] Two studies specifically reported DCECT in nasal tumors but did not find correlation with histogenesis or survival.[33,39] Our objectives were (a) to assess baseline perfusion parameters in dogs with nasal tumors based on histopathological type, (b) to characterize changes in perfusion parameters with changes in tumor volume after the start of RT, and (c) to evaluate if a correlation existed of either objective 1 or objective 2 with survival. Our hypothesis was that carcinomas and sarcomas would have different perfusion parameters and that alterations in these parameters during RT would be correlated with survival.

2 | MATERIALS AND METHODS

2.1 | Experimental design

2.1.1 | Case selection

Prospective cross-sectional study. Client-owned dogs presented to the Small Animal Teaching Hospital of the University of Liverpool for suspicion of nasal tumors were prospectively enrolled from January 2017 to January 2020. Owner consent for diagnostic tests including DCECT was obtained before inclusion in the study. To meet the inclusion criteria, a histological diagnosis of nasal tumor was required, and dogs must have undergone at least baseline DCECT. Dogs that had already received RT, tyrosine kinase inhibitors or chemotherapy were excluded. Dogs receiving other non-chemotherapeutic medical treatments for nasal tumor (eg, anti-inflammatory or antimicrobial medications) were not excluded.

2.2 | Clinical data

Duration and type of clinical signs, treatment received at the time of DCECT, heart rate and systolic blood pressure during DCECT, side and histological type of the nasal tumor, treatment administered for the nasal tumor and survival time from referral consultation were recorded. Treatment administered before the consultation was categorized as corticosteroids, non-steroidal anti-inflammatory drugs (NSAID), none or other (eg, vitamin K, antimicrobials). Histological type was classified as adenocarcinoma, carcinoma, other carcinoma (comprising transitional carcinoma, undifferentiated carcinoma and papillary carcinoma) and sarcoma for baseline DCECT. Too few dogs were present in each group for repeat DCECT, therefore adenocarcinomas, carcinomas and other carcinomas were grouped together and designated epithelial tumors. Treatments received for the nasal tumor were categorized as RT, chemotherapy (1 dog), none or palliative (eg, NSAID, paracetamol). Finally, any clinically relevant comorbidity was recorded.

2.3 | Dynamic contrast-enhanced computed tomography

All dogs but 1 were anesthetized, with a single dog receiving sedation (medetomidine, 0.005 mg/kg and butorphanol 0.3 mg/kg). Premedication varied depending on the attending anesthetist, but most dogs received medetomidine (0.003 to 0.01 mg/kg) in association with butorphanol, buprenorphine or methadone, with 1 dog receiving acepromazine (0.02 mg/kg) instead of medetomidine. Dogs were induced

using propofol or alfaxolone (to effect) and anesthesia was maintained using sevoflurane. The DCECT was performed using an 80-slice CT scanner (Aquilion Prime 80, Canon Medical System) with dogs in sternal recumbency. Dogs for which owners elected RT were immobilized using a thermoplastic mask and customized head support, secured to a plastic head frame with 4 points of fixation, as part as the standard RT planning.

Pre-contrast scan of the head, thorax and abdomen was performed. Scanning parameters were 120 kV, variable mAs using automatic exposure control, pitch factor 0.625, and images were reconstructed at 1 mm slice thickness using bone and soft tissue (head), lung and soft tissue (thorax) and only soft tissue (abdomen) reconstruction algorithms. The DCECT planning was performed using the pre-contrast soft tissue reconstruction in a soft tissue window (window width, 200 Hounsfield unit [HU]; window level, 40 HU).

A 4-cm length field of view was chosen to include the entirety of the tumor or the tumor center if the total mass was longer than 4 cm.

A 60-second continuous scan starting with IV injection of 2 mL/kg body weight of iodinated contrast medium (Ioversol 300 mg/mL iodine) using a power injector set at 3 mL/second injection rate (maximal allowable injection pressure set at 150 psi) and followed by a bolus of saline (1 mL/kg) at the same injection rate. Scanning parameters were 80 kV, 200 mA, 0.75 second rotation time, 0.5 mm scan slice thickness, 1 second time interval, and 2 mm reconstruction slice thickness. Images were reconstructed using a soft tissue reconstruction algorithm.

A post-contrast scan of the head, thorax, and abdomen was performed immediately after the perfusion CT (90 seconds after IV injection of iodinated contrast medium), using the same scanning parameters as for the pre-contrast scan.

Fourteen dogs had a second DCECT using the same anesthetic protocol (all under general anesthesia) and the same scanning technique as described above, after receiving 12 Gy in 3 fractions. Median time between the first and second DCECT was 15 days (range, 10-23).

2.4 | Radiation therapy

Dogs received RT using a linear accelerator (Clinac 2100 or VitalBeam, Varian Medical Systems, Palo Alto, California). Definitive RT was administered with 12 fractions of 4 Gy on a Monday, Wednesday, Friday basis. All treatments were carried out at 6 MV and were 3-dimensionally (3D)-planned from CT images using Pinnacle version 8/9 (Pinnacle, Phillips Radiation Oncology Systems, Phillips Healthcare, Andover, Massachusetts) or Eclipse 15.1 (Varian Medical Systems, Palo Alto, California) with intention to include ≥95% of the planning treatment volume (clinical target plus 0.5 cm) in the 95% to 105% isodose. Organs at risk were segmented. Plans utilized 3 or 4 coplanar beams, with beam collimation using multileaf collimator beam modification and dynamic wedges where appropriate. Dogs were immobilized as described for the CT scans. Portal imaging was carried out at least twice during the treatment protocol to verify position.

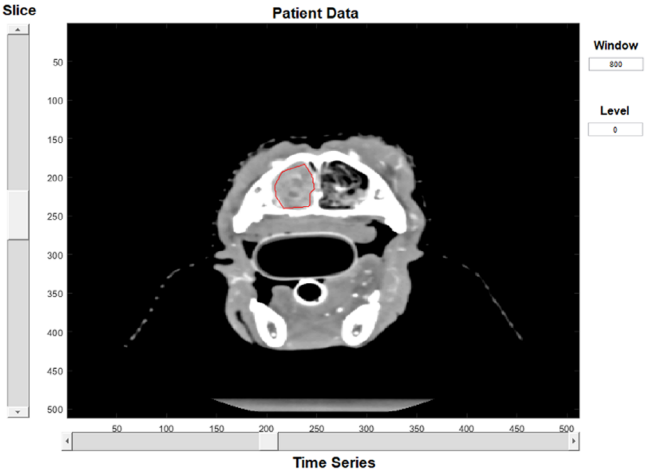

FIGURE 1 Computed tomographic image of a nasal tumor in transverse plane and soft tissue window using the perfusion analysis software and showing the contouring of the mass (red line) for subsequent perfusion analysis. *x*-axis and *y*-axis are the time series and CT slices, respectively.

2.5 | Images and perfusion analysis

Conventional CT images of the head were reviewed by a European College of Veterinary Diagnostic Imaging board-certified radiologist (JM) blinded to the clinical data of the dogs, using a Macintosh workstation and an image viewer (OsirixMD, Pixmeo). Images were viewed using both a soft tissue window (window width, 200 HU; window level, 40 HU) and a bone window (window width, 4500 HU; window level, 450 HU). Multiplanar reconstruction was performed for each dog. Length, width, and height of the mass with planes parallel and orthogonal to those of the head were measured and the volume of the tumor (using the ellipsoid formula, $V = 4/3 \times \pi \times L \times W \times H$) was calculated. Heterogeneity of the masses pre- and post-contrast were subjectively graded from 0 (homogeneous) to 3 (markedly heterogeneous). The degree of contrast enhancement of the masses was subjectively assessed and graded on a 0 (none to poor) to 3 (marked) scale. Margination of the masses also was subjectively graded from 0 (poorly marginated) to 3 (well marginated). Stage of the tumor according to the modified Adam's staging system was determined.[43] Presence of lymphadenomegaly also was noted when the height of the mandibular or width of the medial retropharyngeal lymph nodes was >1 cm or when a size difference was noted between the left and right lymph nodes.[44,45] The CT images of the thorax and abdomen were reviewed, and any abnormality noted was recorded.

Dynamic contrast-enhanced computed tomographic images were analyzed using an adiabatic approximation to the tissue homogeneity (ATH) model implemented with MATLAB (MathWorks, Massachusetts), designed as part of a previous study.[39] An arterial input function was first contoured, and a time-attenuation curve displayed to verify it had a shape consistent with arterial blood flow. The artery selected for the

arterial input function was the deep lingual artery because it was consistently the largest artery included in the field of view not surrounded with bone. To appropriately contour the artery without selecting peripheral lingual tissue the image was zoomed in and contoured on the arterial phase (veins not contrast-enhanced). Only the center of the artery was included when possible. The nasal mass then was contoured manually slice by slice on every slice containing suspected tumoral tissue (Figure 1). Care was taken not to include bone within the contouring. Therefore, the most peripheral sliver of tumor tissue was not included in the contouring when the tumor was contacting the bones of the nasal passage. Similarly, when present, parts of the tumor that were extending outside the nasal cavities were not included if they were too small or contained bone. Perfusion parameters obtained from the analysis were blood flow (BF) and transit time (TT). Vascular fraction (blood volume [BV]) then could be calculated using the formula: $BV = TT \times BF$. Perfusion analysis was performed by a trained operator (JM).

2.6 | Statistical analysis

All statistical analyses were performed using the software packages SPSS 24.0 (SPSS Inc, Chicago, Illinois, USA) and R (R version 3.2.0, The R Foundation for Statistical Computing). All dependent and independent variables were derived from the signalment data, clinical data, CT examinations and histopathological examinations. Descriptive statistics were calculated for data where appropriate. Categorical variables were summarized as frequencies with 95% confidence intervals (CI) and continuous variables as medians with interquartile ranges (IQR). Categorical variables with multiple categories, categories containing small numbers or both were reviewed and collapsed if required. The distribution of any continuous variable was assessed for deviation from normal both graphically and using the Kolmogorov-Smirnov test.

Three primary individual outcomes were considered: BF, TT, BV, and associations between these continuous variables and the collected independent variables were estimated using linear regression. All independent variables showing potential association with an outcome on univariable analysis (P value <.25) were considered for inclusion in the final multivariable model for that outcome. Variables showing evidence of correlation (correlation coefficient >0.7), were examined and only the variable with the smallest P value was selected for entry in the multivariable models developed. Final models were developed using a manual backwards stepwise methodology with retention of variables with P values <.05. Additionally, for the 14 dogs that were re-scanned, linear regression was used to compare the change in tumor variables (length, width, height, volume, BF, BV, TT) between epithelial tumors and sarcomas and to evaluate associations between tumor volume and perfusion parameters (BF, BV, TT).

Survival times were calculated from time of first visit until death. Dogs alive at the time of data collection were considered censored, as were dogs lost to follow-up (censored at date of last known contact). Median survival times were calculated using Kaplan-Meier product limit (survival) analysis. Univariable comparison of survival times and associations between survival and independent variables were examined using the log rank test for categorical variables and Cox proportional hazard regression analysis for continuous variables. Multivariable regression models were constructed using a similar approach, including all variables with univariable P value <.25 and a backwards stepwise approach with retention of P values <.05.

3 | RESULTS

3.1 | Patient demographics and clinical data

Twenty-four dogs met the inclusion criteria. All dogs had baseline DCECT and 13 dogs had repeat DCECT. There were 13 spayed females, 2 intact males, and 9 neutered males. Breeds varied and included 6 cross breeds, 3 West Highland white terriers, 2 border collies, 2 English springer spaniels, 1 cocker spaniel, 1 boxer, 1 rottweiler, 1 Labrador retriever, 1 Staffordshire bull terrier, 1 Yorkshire terrier, 1 lurcher, 1 Rhodesian ridgeback, 1 Airedale terrier, 1 Irish setter, and 1 Cavalier King Charles spaniel. Median age of the dogs was 9.9 years; median weight was 19.1 kg.

Fourteen nasal masses were left-sided and 10 were right-sided. There were 5 adenocarcinomas, 6 carcinomas, 5 other carcinomas (3 transitional carcinomas, 1 papillary carcinoma, and 1 unclassified carcinoma), and 8 sarcomas (4 chondrosarcomas, 1 hemangiosarcoma, and 3 sarcomas of undetermined cell lineage).

At presentation, 5 dogs were receiving a NSAID, 3 dogs were receiving corticosteroids, 4 dogs were receiving a treatment classified as other (gabapentin and loratadine in 1 dog, trimethoprim-sulfamethoxazole in 1 dog, amoxicillin-clavulanate in 1 dog, and vitamin K1 in 1 dog) and 12 dogs were receiving no treatment at the time of presentation.

At repeat DCECT, 12/13 dogs were receiving corticosteroids and 1 dog was receiving a NSAID. In addition, 9 dogs were receiving acetaminophen and 7 dogs were receiving antibiotics for minor infections. One dog was receiving amlodipine.

Fourteen dogs had RT, 1 dog had chemotherapy without RT (carboplatin 10 mg/kg once a week for 3 weeks), 6 dogs had palliative treatment only, and 3 dogs had no treatment.

In total, 21/24 dogs had a record of their heart rate during the baseline DCECT, at the time of injection of contrast medium. All were considered appropriate by the attending anesthetist and ranged from 40 to 110 beats per minute (bpm; median, 85 bpm). Similarly, systolic blood pressure was obtained for 14 dogs and ranged from 80 to 140 mmHg (median, 100 mmHg).

Of the 19/24 dogs that had cytological analysis of the mandibular lymph nodes, only 1 had metastasis detected. This dog did not have lymphadenomegaly on CT.

Two patients had clinically relevant comorbidity; 1 had metastatic adenocarcinoma of the anal gland and another had systemic hypertension (the dog treated with amlodipine).

TABLE 1 Median baseline perfusion parameters in different histological types of nasal tumors in dogs.

	Median blood volume (min-max) (mL/100 g)	Median blood flow (min-max) (mL/100 g/min)	Median transit time (min-max) (s)
Adenocarcinomas (n = 5)	30 (54.4-163.4)	257.3 (89.1-280)	9.1 (7.1-12.2)
Carcinomas (n = 6)	15.3 (7.8-37.1)	125.9 (73.1-280)	8.2 (4.6-10.7)
Other carcinomas (n = 5)	29.7 (8.5-66)	255.4 (107-274.2)	10.6 (5.1-14.2)
Sarcomas (n = 8)	8.2 (3.6-18.3)	61.2 (23.7-121.5)	9.4 (5.6-12.3)

3.2 | Imaging findings

3.2.1 | Baseline DCECT

Imaging and perfusion analysis results are detailed in File S1.

Median mass length, width, height, and volume were 4.9 cm (range, 1.9-7.2), 2.1 cm (range, 1-4), 1.2 cm (range, 1.4-4.4), and 127 cm^3 (range, 14.5-408.8), respectively. Median volume for the different tumor types was 61.6 cm^3 for adenocarcinomas, 160.2 cm^3 for carcinomas, 50.2 cm^3 for other carcinomas, and 140.5 cm^3 for sarcomas. Median grade for tumor margination, heterogeneity, intensity of contrast enhancement, and heterogeneity of contrast enhancement were 2, 1.5, 2, and 2, respectively. For dogs that had repeat DCECT, median tumor volumes pre-treatment were 49.6 cm^3 (mean, 82.5) for epithelial tumors and 150.8 cm^3 (mean, 141.9) for sarcomas.

Six dogs were stage 1, 3 dogs were stage 2, 10 dogs were stage 3, and 5 dogs were stage 4. Five dogs had mandibular lymphadenomegaly, all of which were not metastatic on cytological analysis, and 3 dogs had pulmonary nodules.

Median BV was 17.83 mL/100 g (range, 3.63-66.02), median BF was 122.63 mL/100 g/minute (range, 23.65-279.99), and median TT was 8.91 seconds (range, 4.57-14.23). Results for the different groups of tumors are shown in Table 1. Sarcomas had a significantly lower BF than adenocarcinomas ($P = .002$), carcinomas ($P = .01$), and other carcinomas ($P = .001$), and significantly lower BV than adenocarcinomas ($P = .03$) and other carcinomas ($P = .004$). The weight of the dog was negatively associated with both BF ($P = .002$) and BV ($P = .04$). No significant association was found between tumor stage, imaging characteristics and perfusion parameters.

3.2.2 | Repeat DCECT

Imaging and perfusion analysis results are detailed in File S1.

Significant associations were found between epithelial tumors and sarcomas for change in tumor volume ($P = .01$), width ($P = .004$), and length ($P = .02$) between the first and second DCECT. Median decrease in tumor volume was 11 cm^3, with a median decrease in volume of 18.6 cm^3 in the epithelial tumors group and a median increase in volume of 28 cm^3 in the sarcoma group. Only 1/5 dog in the sarcoma group experienced tumor volume reduction and only 1/8 dog in the epithelial tumor group showed an increase in tumor volume based on repeat DCECT.

Median and mean changes in perfusion parameters for epithelial tumors and sarcomas are presented in Table 2. Changes in perfusion parameters between the first and second DCECT were not significantly different between epithelial tumors and sarcomas.

3.3 | Survival analysis

At the end of the study 17 dogs were dead, 16 because of progression of their nasal tumor and 1 because of metastatic anal sac adenocarcinoma, and 7 were either still alive or lost to follow-up.

Median survival time was 321 days (95% CI, 252-390) for all dogs, 374 days for dogs that received RT, 333 days for dogs that received palliative treatment and 116 days for dogs that had no treatment. The only dog that received chemotherapy had a survival time of 88 days.

Raw data from the study are shown in Table S1.

On multivariate analysis, only the type of treatment received for the nasal tumor was associated with survival ($P = .01$). More specifically, dogs receiving no treatment had the shortest survival time. Perfusion parameters were not significantly associated with survival in the final statistical model.

4 | DISCUSSION

We assessed CT-based morphological characteristics and DCECT perfusion parameters of different histological types of nasal tumors at baseline and during RT in dogs. Sarcomas had lower baseline BV and BF than epithelial tumors, and sarcomas experienced a smaller reduction in size than epithelial tumors during the early course of RT. Neither CT-based morphological characteristics nor DCECT perfusion parameters were significantly associated with survival.

A previous study of 31 dogs with spontaneous tumors (15 carcinomas and 16 sarcomas of various origins and localizations) in which semi-quantitative perfusion analysis was performed showed that soft tissue sarcomas had significantly lower BF than carcinomas and bone sarcomas.[30] These results are in agreement with our results and could be explained by the presence of a dense stroma and extracellular matrix in most nasal chondrosarcomas and osteosarcomas.[46] Stroma can represent zones of hypoxia in tumors and BF and BV are negatively correlated with the degree of tumor hypoxia.[47,48] However, tumor microenvironment and its relationship with hypoxia and

TABLE 2 Median change in perfusion parameters between baseline and repeat dynamic contrast-enhanced computed tomography in dogs with nasal tumors.

	Median Δ blood volume (min-max) (mL/100 g)	Median Δ blood flow (min-max) (mL/100 g/min)	Median Δ transit time (min-max) (s)
Epithelial tumors (n = 8)	5.3 (−22.8 to 27.7)	6.9 (−30 to 92.4)	1.4 (−4.8 to 5.9)
Sarcomas (n = 5)	−3.4 (−8.5 to 3.9)	11.7 (−27.3 to 75.3)	−4.9 (−8.4 to 1.4)

vascularization in human and veterinary medicine are complex, and findings in the literature are inconsistent, and therefore assumptions should be avoided.

The clinical relevance of volume changes during RT is poorly understood. In extremity soft tissue sarcomas in humans, volume increase (requiring plan adaptation) is reported during pre-operative RT, but increased volume is not definitively associated with worse surgical outcomes.[49,50] Apparent tumor volume may increase because of edema, necrosis, and inflammation rather than progressive disease, a phenomenon called pseudoprogression. We found no significant correlation between perfusion parameters and tumor size reduction during treatment, or between perfusion parameters and survival.

Consistent with the results presented here, a recent study reported higher volume reduction of nasal carcinomas compared to nasal sarcomas within 3 months of completing a full course of definitive megavoltage RT.[14] This finding could be explained by the lower perfusion of sarcomas compared to carcinomas, because the effectiveness of RT is positively associated with tumor perfusion in tumors of humans.[23,51] Correlations among tumor types, response to RT and survival seldom have been explored in the veterinary literature, with variable results,[4,5,14,52] and an early study suggested that volume reduction during RT could be associated with more aggressive tumors and inversely correlated with progression-free interval.[17] Sarcomas in our study generally were larger than epithelial tumors (approximately twice the size), which could have had an impact on the initial response to RT measured after administration of 12 Gy. Indeed, large tumors tend to develop hypoxic or necrotic areas, inducing resistance to RT.[53] Finally, the smaller volume reduction of sarcomas also could be explained by lower cell loss factor.[54]

Previous studies reported perfusion parameters of nasal tumors in dogs.[33,39] A study of 9 dogs with nasal tumors reported BF ranging from 145 to 249 mL/minute/100 g with mean and median values of 118 and 102 mL/minute/100 g, respectively.[33] These results are comparable to ours despite differences between DCECT acquisition protocols and data analysis. In our study, the whole tumor was contoured apart from the rostral and caudal extremities for masses longer than 4 cm. On the other hand, the previous study selected 2 small square-shaped regions of interest on a single 5-mm thickness slice to perform their perfusion analysis.[33] The type of computational method used in their perfusion model also was different from ours. They used a single-compartment model, which can cause an underestimation of BF, whereas we used a dual-compartment model.[20] Eight of their dogs had epithelial tumors and 1 dog had a sarcoma, but the perfusion parameters for each dog were not detailed.

The parameters obtained in our study differed slightly from a previous study of 11 dogs with nasal tumors (7 carcinomas and 4 sarcomas).[39] The authors found means for BF of 72, 69, and 51 mL/minute/100 g using 3 different perfusion software packages (including that used in our study), which were lower in comparison to BF obtained in our study (mean, 122.63 mL/minute/100 g). Similarly, means for BV using the 3 perfusion software packages were lower in comparison to that of our study (means for BV, 6.6, 6.2, and 7.7 mL/100 g[39]; mean BV in our study, 17.83 mL/100 g). Transit time on the other hand was similar to that found in our study (means of TT, 5.7, 6.4, and 10.2 seconds[39]; mean TT in our study, 8.91 seconds). Although the method of data analysis was similar, these differences could be explained by variations in tumor and arterial contouring between operators, differences in DCECT acquisition protocols or both.

Correlations between tumor perfusion parameters on DCECT and response to treatment and survival in oncology in human medicine have been inconsistent. However, most studies found that head and neck tumors with high pre-treatment BV and BF had better prognoses, both in terms of response to treatment and survival time.[51,55-59] A large reduction of BF and BV during chemoradiation also generally is associated with good local control.[23,59,60]

In humans, DCECT also has been used to predict tumor grade,[61-65] define tumor margins and detect local tumor recurrence,[25,66] differentiate benign from malignant lesions,[67,68] and detect lymph node metastases.[69]

In veterinary medicine, DCECT mostly has been used for fundamental research and proof of concept.[36,38,39,41] The largest clinical study described 34 dogs with brain tumors treated using stereotactic RT and showed that BV and BF decreased significantly between baseline and 3-month follow-up DCECT.[40] No association however was identified between perfusion parameters and survival. For nasal tumors, 2 studies reported non-specific changes in perfusion during RT in 12 dogs.[33,41] However, neither study compared perfusion parameters to tumor type, response to treatment or survival.

One unexpected and interesting finding of our study is the negative association between the weight of the dog and both BF and BV. This observation could be explained by the fact that smaller dogs tend to have smaller nasal cavities and possibly smaller tumors. Large tumors can overgrow their neovascularization capabilities and develop hypoperfused and necrotic areas, decreasing the overall perfusion parameters of the tumor. Alternately, this association could also be a consequence of technical differences in the perfusion analysis between small and large dogs, particularly in terms of vessel

segmentation for the arterial input function. Partial volume effect might have been higher in small dogs, artifactually decreasing BF and BV in this population.

Our study had some limitations. The overall number of dogs recruited was small, especially when divided into the different histological categories. In addition, obtaining an accurate histological diagnosis can be challenging with small tissue samples from nasal biopsies and some of the cases could have been misclassified. The number of dogs receiving RT was even smaller, and although all RT plannings were similar and performed by the same radiation oncologist, the variety of treatments used in our population highly biased our survival analysis. Additional studies with higher numbers of dogs and standardized treatments would be interesting to further assess the potential value of perfusion parameters in dogs with nasal tumors.

Some dogs received anti-inflammatory drugs before the first and repeat DCECT, or before both; others did not. The effects of anti-inflammatory drugs on DCECT perfusion parameters have not been studied, but their anti-cyclooxygenase activity has an anti-angiogenic action that could be responsible for changes in perfusion parameters.[70]

The DCECT protocol used in our study meets the recommendations for use in humans except for injection rates of contrast medium and saline irrigation. Indeed, because of catheter size limitations leading to excessive pressure during injection, we could not meet the recommended 4 to 8 mL/second injection rate and instead used 3 mL/second. However, the smaller size of dogs compared to human beings likely balances out this limitation.

Intra- and inter-observer variability were not calculated in our study but would have been interesting, especially because it represents the highest contributor to overall variability in DCE-CT.[71] A previous study found a coefficient of variation within patients ranging from 22% to 30% because of variability of arterial input function area under the curve and variability in tumor area under the curve.[39] On the other hand, patient blood pressure was not found to have a significant impact on the perfusion analysis. Finally, a peripheral sliver of neoplastic tissue was omitted from the contouring so as not to include peri-tumoral bone tissue in the perfusion analysis. Although this was unavoidable, it could have changed the overall perfusion analysis of the mass, especially in small dogs.

In conclusion, we showed that nasal sarcomas have lower BV and BF than nasal carcinomas and that epithelial tumors experience a decrease in volume early in the course of RT whereas sarcomas tend to grow. This information could facilitate further understanding of tumor vascularization and its implications for response to treatment, and provide more accurate prognostic information that potentially could improve treatment of nasal tumors.

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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

Approved by the Committee on Research Ethics at the Institute of Veterinary Science of the University of Liverpool (VREC560a).

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

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

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