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# Dynamic contrast-enhanced computed tomography in 11 dogs with orofacial tumors

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**OBJECTIVE**
Treatment of orofacial 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. The objectives of this study were to describe the perfusion parameters of different types of orofacial tumors and to describe the changes in perfusion parameters during radiotherapy (RT) in a subset of them.

**ANIMALS**
11 dogs with orofacial tumors prospectively recruited.

**CLINICAL PRESENTATION AND PROCEDURES**
All dogs had baseline DCECT to assess blood volume (BV), blood flow (BF), and transit time (TT). Five dogs had repeat DCECT during megavoltage RT.

**RESULTS**
5 squamous cell carcinomas, 3 sarcomas, 1 melanoma, 1 histiocytic sarcoma, and 1 acanthomatous ameloblastoma were included. Blood volume and BF were higher in squamous cell carcinomas than in sarcomas, although no statistical analysis was performed. At repeat DCECT, 4 dogs showed a reduction in the size of their tumor during RT. Among these dogs, 3 showed an increase in BV and BF and 1 a decrease in these parameters between the baseline and the follow-up DCECT. The only dog whose tumor increased in size between the first and the second DCECT showed a decrease in BV and BF.

**CLINICAL RELEVANCE**
Perfusion parameters derived from DCECT were described in a series of dogs with various types of orofacial tumors. The results suggest that epithelial tumors could have higher BV and BF than mesenchymal tumors, although larger sample sizes are needed to support these preliminary findings.

Orofacial tumors are frequent in dogs. The most common malignant types are malignant melanoma, squamous cell carcinoma, and sarcoma (fibrosarcoma, less frequently osteosarcoma), whereas the most common benign oral tumors are odontogenic tumors, especially acanthomatous ameloblastoma.[1–3] The treatment of choice for maxillary and mandibular tumors is excisional surgery, alone or with adjuvant radiotherapy (RT) and chemotherapy or other medical therapy depending on the type of tumor.[4–11] However, facial surgery is associated with significant morbidity and esthetic consequences that might discourage owners,[2] and RT alone (or in association with chemotherapy) is sometimes preferred. Apart from the treatment type, several other prognostic factors for oral tumors have been described in the veterinary literature, including the type, size, stage, and location of the tumor, histological grade, margins after surgical resection, proliferation, and other prognostic markers.[7,8,12,13] Surgery is the mainstay of treatment in most studies.

Dynamic contrast-enhanced computed tomography (DCECT) is a functional imaging technique that allows the assessment of blood flow (BF) in the capillary network by continuous or intermittent scanning of a volume of tissue during intravenous (IV) administration of contrast medium.[14–16] In humans, correlations exist between DCECT-derived perfusion parameters

of solid tumors and hypoxia, and similarly between tumor hypoxia, malignant progression and treatment failure.[17] In humans with head and neck cancer, perfusion parameters derived from DCECT, particularly blood volume (BV) and BF, have shown promises as prognostic indicators, to assess response to treatment and to detect local recurrence.[18–21] Dynamic contrast-enhanced computed tomography has been previously described in dogs with cancer, but its potential value as a clinical tool remains unknown.[22–29]

The aims of this study were (1) to describe the perfusion parameters of various types of orofacial tumors in a small population of dogs and (2) to describe the changes in perfusion parameters during RT in a subset of them.

## Materials and Methods

### Experimental design

This is a prospective cross-sectional and longitudinal case series.

### Case selection

Client-own dogs presented at the Small Animal Teaching Hospital (SATH) of the University of Liverpool with a diagnosis of orofacial tumor were prospectively enrolled from January 2017 to January 2020. Ethical approval was granted by the Committee on Research Ethics at the Institute of Veterinary Science of the University of Liverpool (VREC560a) and owner consent allowing for diagnostic tests including DCECT was obtained before inclusion into the study. To meet the inclusion criteria, a final diagnosis of the orofacial tumor had to be made by cytology and/or histology and dogs must have undergone at least a baseline DCECT. Dogs who had already received RT or chemotherapy were excluded. Dogs receiving other medical treatments for their tumor (anti-inflammatory and antimicrobial medication) were not excluded.

### Clinical data

Treatment received at the time of DCECT, heart rate and systolic blood pressure during DCECT, localization and histological type of the tumor, and treatment administered to treat the tumor were recorded. Histological types were subclassified as squamous cell carcinoma, sarcoma (unclassified sarcoma, fibrosarcoma), and other (1 melanoma, 1 acanthomatous ameloblastoma, and 1 histiocytic sarcoma) for baseline DCECT. Palliative medical treatment received for the tumor was NSAID, acetaminophen, and/or metronomic chemotherapy.

### Dynamic contrast-enhanced CT

All dogs were anesthetized. Premedication slightly varied depending on the attending anesthetist but most dogs received a combination of medetomidine (0.003 to 0.01 mg/Kg IV) and butorphanol (0.05 to 0.2 mg/Kg IV) or methadone (0.2 mg/Kg IV). One dog did not have an anesthetic record. Dogs were then induced using IV propofol or alfaxolone (to effect), intubated, and anesthesia was maintained using sevoflurane. Dynamic contrast-enhanced computed tomography was performed using an 80-slice CT scan (Aquilion Prime 80; Canon Medical System) with dogs in sternal recumbency. Dogs for which owners elected for RT were immobilized using a thermoplastic mask and customized head support, secured to a plastic head frame with 4 points of fixation, as part of the standard RT planning.

Pre-contrast scan of the head 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 reconstruction algorithms. Dynamic contrast-enhanced computed tomography planning was done using the pre-contrast soft tissue reconstruction in a soft tissue window (window width: 200 HU, window level 40 HU). A 4-cm length field of view was chosen to include the entirety of the tumor or its center if the mass was longer than 4 cm in length.

A 60-second continuous scan starting with intravenous injection of 2 mL/Kg body weight of iodinated contrast medium (Ioversol 300 mg/mL iodine) using a power injector set at 3 mL/s injection rate (maximal allowable injection pressure set at 150 psi) and followed by a bolus flush 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 was performed immediately after the perfusion CT (90 seconds after initiation of the intravenous injection of iodinated contrast medium), using the same scanning parameters as for the pre-contrast scan. Five 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 of radiation in dogs with definitive RT and 8 Gy in the dog with palliative RT.

### Radiation therapy

The 5 dogs who had repeat DCECT received RT using a linear accelerator (Clinac 2100 or VitalBeam; Varian Medical Systems). Definitive RT (4 dogs) was administered with 12 fractions of 4 Gy on a Monday, Wednesday, and Friday; palliative RT (1 dog) was administered as 4 fractions of 8 Gy on a once weekly basis. All treatments were carried out at 6 MV and were 3D planned from CT images using Pinnacle version 8/9 (Pinnacle, Phillips Radiation Oncology Systems, Phillips Healthcare) or Eclipse 15.1 (Varian Medical Systems), with intention to include at least 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 multi-leaf collimator (MLC) beam modification and dynamic wedges where appropriate. Dogs were immobilized as described for the CT scans. Point-by-point calibration using portal imaging was carried out at least twice during the treatment protocol to verify position.

## Images and perfusion analysis

Conventional CT images of the head were reviewed by an ECVDI board-certified veterinary radiologist (J.M.) blinded to the clinical data of the dogs, using a Mac 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 and window level: 450 HU). Multiplanar reconstruction was performed for each dog. Length, width, and height with planes parallel and orthogonal to those of the head were measured and the volume of the mass (using the ellipsoid formula V = 4/3.π.L.W.H) was calculated. Masses were first classified as mandibular, maxillary, palatal, frontal, or incisive depending on the bone from where it originated.

DCECT images were analyzed using an adiabatic approximation to the tissue homogeneity (ATH) model implemented with MATLAB, designed as part of a previous study.[28] An arterial input function was first contoured, and a time-attenuation curve was displayed to verify it had a shape consistent with arterial BF. The artery selected for the arterial input function was the lingual artery as it is the largest artery that was consistently included in the field of view and not surrounded by bone. To appropriately contour the artery without selecting peripheral lingual tissue the image was zoomed in and contoured on the arterial phase (with veins not contrast-enhanced). Only the center of the artery was included when possible. The tumor was then contoured manually slice-by-slice on every slice containing suspected tumoral tissue **(Figure 1)**. Care was taken not to include bone or large vessels within the contouring. Therefore, when present, the small part of the mass in contact with these structures was excluded from contouring. Perfusion parameters obtained from the analysis were BF, vascular fraction, and transit time (TT). BV could then be calculated using the following formula: BV = TT X BF. Perfusion analysis was performed by one trained operator (J.M.).

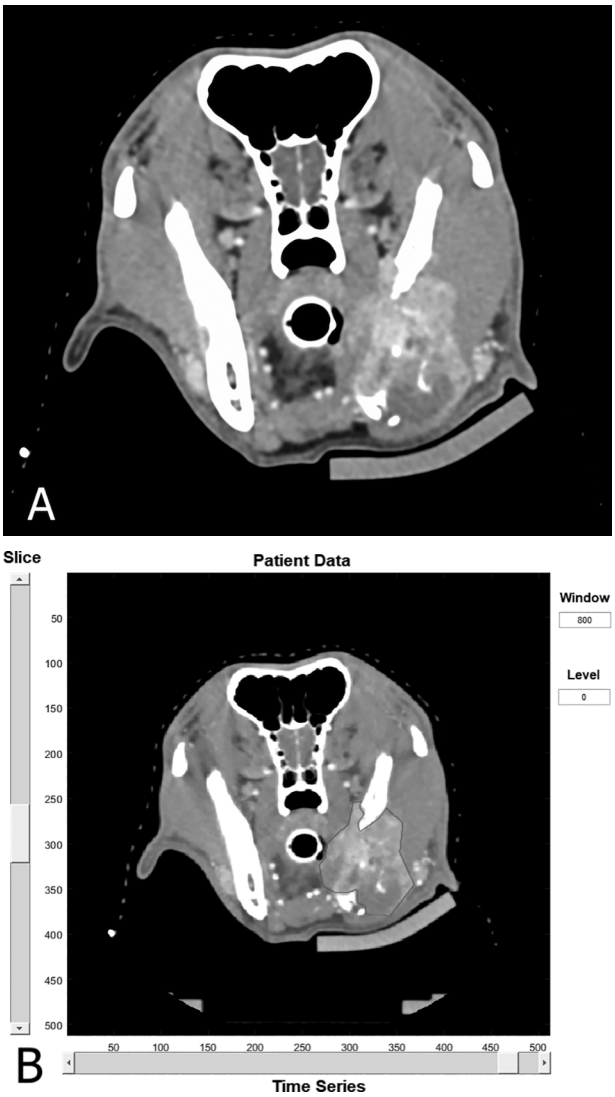


**Figure 1**—A computed tomographic image of the head of a dog with squamous cell carcinoma centered on the left mandible, in the transverse plane and soft tissue algorithm (A). The same image is displayed by the perfusion software, showing tumor contouring (B).

# Results

Eleven dogs met the inclusion criteria. All dogs had a baseline DCECT. Five dogs had a repeat DCECT 11 to 33 days (median 17 days) after the first DCECT. There were 2 intact females, 2 spayed females, 2 intact males, and 5 neutered males. Breeds were varied and included 2 Labrador retrievers, a cross breed, and 1 dog of several breeds (including Cocker Spaniel, Bernese Mountain dog, Cairn Terrier, Border Terrier, Jack Russel terrier, Pug, Bearded Collie, and Beagle). Median age of the dogs was 8.9 years old and median weight was 14.2 Kg.

There were 5 squamous cell carcinomas, 3 sarcomas (1 fibrosarcoma and 2 undifferentiated sarcomas), 1 melanoma, 1 acanthomatous ameloblastoma, and 1 histiocytic sarcoma.

In terms of location, there were 4 maxillary masses (1 histiocytic sarcoma, 1 melanoma, 1 squamous cell carcinoma, and 1 fibrosarcoma), 3 palatal masses (2 undifferentiated sarcomas and 1 squamous cell carcinoma), 2 mandibular masses (both squamous cell carcinoma), 1 frontal mass (squamous cell carcinoma), and 1 incisive mass (acanthomatous ameloblastoma).

Five dogs were receiving meloxicam (0.1 to 0.2 mg/Kg PO q 24 hour) including 2 dogs with squamous cell carcinoma, the dog with histiocytic sarcoma, the dog with acanthomatous ameloblastoma, and the dog with melanoma. Six dogs had not received any treatment at the time of presentation.

Seven dogs had a record of their heart rate during the baseline DCECT at the time of injection of contrast medium. All heart rates were considered appropriate by the attending anesthetist and ranged from 60 to 130 bpm (median 70 bpm). Similarly, systolic blood pressure was obtained for 4 dogs and ranged from 100 to 130 mmHg (median 115 mmHg).

In the 5 dogs who had repeat DCECT, tumor types were: 2 squamous cell carcinomas, 1 melanoma, 1 sarcoma, and 1 acanthomatous ameloblastoma. At repeat DCECT the 1 dog with squamous cell carcinoma was receiving prednisolone (0.4 mg/Kg PO q 24 hour), 1 dog with melanoma was on robenacoxib (1 mg/Kg PO q 24 h) and 2 dog (1 with a squamous cell carcinoma, 1 with a sarcoma) were not receiving any medical treatment.

## Imaging Findings

### Baseline DCECT

Imaging and perfusion analysis results are detailed elsewhere **(Supplementary Appendix)**. Median mass length, width, height, and volume were 3.2 cm (1–5.6), 2.3 cm (1.3–6.1), 2.5 cm (0.8–5.3), and 83.8 $cm^3$ (6.8–472.2), respectively. Median tumor volume was 12.9 $cm^3$ (12.7, 12.9, 320.8) in the sarcoma group and 31.8 $cm^3$ (6.8, 21.8, 31.8, 92.7, 426.3) in squamous cell carcinomas. Mass volume for the other tumor types were 472.2 $cm^3$ for the histiocytic sarcoma, 111 $cm^3$ for the melanoma, and 83.8 $cm^3$ for the acanthomatous ameloblastoma.

Median BV was 4.79 mL/100 g (2.5–18.1), median BF was 52.6 mL/100 g/min (22.4–261.7), and median TT was 5.1 seconds (3.8–6.93). Results for the different types of tumors are shown **(Table 1)**.

### Repeat DCECT

Perfusion parameters before and during RT and the percent change in tumor volume are presented **(Table 2)**. Four dogs showed a reduction in the size of their tumor during RT, with a mean decrease in size of 28.3 $cm^3$ (48%, 10–72%). Amongst these dogs, 3 showed an increase in BV and BF between the baseline and follow-up DCECT, and 1 a decrease in both (the dog who received palliative RT). The only dog whose tumor increased in size between the first and the second DCECT (45%) showed a decrease in BV and BF.

## Discussion

This study described the perfusion parameters of various types of orofacial tumors in dogs and although no inferential statistical analysis was performed due to the small sample size, these results suggest that epithelial tumors could have higher BV and BF than mesenchymal tumors. A previous study on 31 dogs with spontaneous canine tumors (15 carcinomas and 16 sarcomas of various origins and localizations) where the authors performed a semi-quantitative perfusion analysis showed that soft tissue sarcomas had significantly lower BF than carcinomas and bone sarcomas.[25] These results are also in keeping with studies in humans, where soft tissue sarcomas tend to have lower BV and BF than carcinomas.[30,31] Most epithelial tumors were squamous cell carcinomas in the current study, and this tumor type tends to have strong tumor-associated inflammation, which could partly explain their higher vascularization compared with sarcoma.[32]

With too few dogs undergoing repeat examination, it was not the aim of this study to correlate the baseline perfusion parameters and the changes in tumor size during RT, but it is noteworthy that the only tumor that showed an increase in size during RT also had the second highest BV and BF. Results of similar studies in human patients with head and neck cancer are inconsistent, yet most studies have found that high pre-treatment BF and BV were associated with a better response to treatment, locoregional control, or survival.[20,33–38] This could be explained by the fact that well vascularized and well oxygenated tumors are generally better responders to RT.[39]

In the current study, 3 out of 4 dogs who showed a reduction in size of the tumor during RT also showed an increased in BF and BV at 12 Gy. Functional imaging, including DCECT, has previously been done in 2 dogs with orofacial tumors at baseline and at 5 of the treatment sessions during intensity-modulated RT.[23,26] One dog showed an increase

**Table 1**—Baseline perfusion parameters and volume of orofacial tumors in 11 dogs.

| Tumor types | Median (mean) blood volume (mL/100 g) | Median (mean) blood flow (mL/100 g/min) | Median (mean) transit time (s) | Median (mean) volume ($cm^3$) |
|---|---|---|---|---|
| Squamous cell carcinomas (n = 5) | 10 (7.7) | 107.6 (93.4) | 4.8 (5.2) | 31.8 (45.1) |
| Sarcomas (n = 3) | 2.8 (3.8) | 32.3 (20.7) | 5.9 (11.4) | 12.9 (37.4) |
| Melanoma (n = 1) | 4.2 | 49.8 | 5.1 | 111 |
| Histiocytic sarcoma (n = 1) | 2.8 | 42.2 | 5.1 | 472.2 |
| Acanthomatous ameloblastoma (n = 1) | 11.1 | 161.2 | 4.3 | 83.8 |

**Table 2**—Perfusion parameters before radiotherapy and after 12 Gy, and associated change in tumor volume in 5 dogs with orofacial tumors.

| | Before radiotherapy | | | After 12 Gy | | | |
|---|---|---|---|---|---|---|---|
| Tumor types | Blood volume (mL/100 g) | Blood flow (mL/100 g/min) | Transit time (s) | Blood volume | Blood flow | Transit time | Volume change (%) |
| Squamous cell carcinoma | 18.1 | 261.7 | 4.2 | 23.6 | 267.3 | 5.2 | −72 |
| Squamous cell carcinoma | 4.8 | 52.6 | 5.8 | 5 | 54.4 | 5.5 | −54 |
| Sarcoma | 7.7 | 104.1 | 4.5 | 8.7 | 211.8 | 2.5 | −10 |
| Melanoma | 4.2 | 49.8 | 5.1 | 3.9 | 43.7 | 6 | −56 |
| Acanthomatous ameloblastoma | 11.1 | 161.2 | 4.3 | 8.8 | 84.6 | 6.3 | 45 |

in contrast enhancement during RT, whereas the other one showed a decrease in contrast enhancement. Although these results are similar to those of the current study, their DCECT technique was based on semi-quantitative evaluation of tumor contrast enhancement, and changes in perfusion parameters and tumor volume did not seem well correlated. Studies in humans with head and neck tumors treated with RT showed that an initial increase in BV or BF during treatment followed by a decrease in these perfusion parameters was associated with better locoregional control.[37,40,41] One hypothesis to explain these results is an initial increase in tumor microvessels and vascular permeability, allowing a good response to RT, followed by occlusion or destruction of tumoral vessels in good responders.[41] Persistently low BF and BV after RT, also associated with good locoregional control, could demonstrate a lack of tumor repopulation. On the other hand, an early decrease in perfusion parameters during RT could illustrate the development of hypoxic areas that would decrease the sensitivity of the tumor to further RT sessions. However, current knowledge on tumor environment, its modification during treatment and the relationship with response to therapy is still scarce.

This study has important limitations. The main one is the small number of dogs, preventing inferential statistical analysis. However, the objective of this study was only descriptive.

The tumors included in this study were of various sizes, histological types, and locations, further adding important bias to the statistical analysis. As regards tumor size, large tumors can develop areas of hypoperfusion, necrosis, or cavitation that could have decreased their overall perfusion. However, correlation between tumor size and perfusion parameters has been inconsistent in human literature, as numerous interconnected environmental factors play a role in tumor perfusion, such as interstitial fluid pressure, growth rate, neoangiogenesis, and microvascular density, amongst others.[42–44]

Some dogs received inflammatory drugs before the first or the repeat DCECT, other did not. The effects of anti-inflammatory drugs on DCECT perfusion parameters have not been studied, yet their anti-COX-2 activity have an anti-angiogenic action and could be responsible for changes in the perfusion parameters.[45] Finally, the slight variation in anesthetic protocols and the difference in blood pressure and heart rate among dogs might also have had an impact on the perfusion parameters.

The DCECT protocol used in this study meets that recommendation for use in people but for the injection rates of contrast medium and saline flush. Indeed, due to catheter size limitations leading to overpressure during injection, a 5 mL/s injection rate was not feasible. However, the smaller size of dogs compared with human beings likely balances out this limitation. Finally, intra- and inter-observer variability have not been calculated in this study, but would have been interesting; especially because it likely represents the highest contributor to overall variability in DCECT.[46] La Fontaine (2017) found a coefficient of variation within patients ranging from 22% to 30% due to variability of the arterial input function area under the curve and variability in the tumor area under the curve in dogs with nasal tumors, using the same perfusion analysis software as the one used in this study.[28]

In conclusion, the perfusion parameters derived from DCECT might be different in epithelial and mesenchymatous tumors of the head, with epithelial tumors having higher BV and BF than sarcomas in this small population. Three out of 4 dogs who showed a reduction in the volume of the tumor during RT also showed an increase in BV and BF at repeat DCECT, suggesting that there could be a relationship between changes in volume and in perfusion parameters in dogs with orofacial tumors, as it is the case in humans.

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## Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org.