Case Series

jfms OPEN REPORTS

Journal of Feline Medicine and Surgery Open Reports
1–6
© The Author(s) 2024
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/20551169231213499
journals.sagepub.com/home/jfmsopenreports

This paper was handled and processed by the European Editorial Office (ISFM) for publication in *JFMS Open Reports*

Sage

Electrochemotherapy for the treatment of basal cell tumours of the nasal planum in three cats

Alvaro Salmoral, Chiara Penzo and Stephen Baines

Abstract

Case series summary Malignant basal cell tumours may be seen on or near the nasal planum in cats, and include basal cell carcinomas, which are common, and basosquamous carcinomas, which are rare. Reported treatments for these tumours include surgical excision, radiotherapy, photodynamic therapy and cryosurgery. This report describes the successful management of basal cell tumours with electrochemotherapy (ECT), including calcium electroporation, in three cats.

Relevance and novel information All patients had a complete response lasting at least 9 months to 1 year. The adverse effects of this treatment were minimal and were limited to nasal discharge, sneezing and scabs at the treatment site. ECT and calcium electroporation are a safe, minimally invasive and effective option for the treatment of feline basal cell carcinoma and basosquamous carcinomas.

Keywords: Neoplasia; basosquamous carcinomas; basal cell carcinoma; electrochemotherapy

Accepted: 23 October 2023

Introduction

Basal cell carcinoma (BCC) is a subtype of basal cell tumour. In dogs, cats and humans, it is considered a low-grade tumour of unknown origin,[1] arising from the basal cells of the inter-follicular epidermis.[2] In humans, BCC is the most common neoplasm in Caucasian individuals[3] and is associated with ultraviolet radiation exposure.[4,5] Surgery is the treatment of choice in humans and animals, and the probability of local tumour recurrence depends on the aggressiveness of this procedure.[4,6] Radiotherapy, systemic chemotherapy and electrochemotherapy (ECT) may be considered when surgery cannot be performed.

Basosquamous carcinomas (BSCs) are included within the basal cell tumour group. This entity is rare in cats[7] and is a rare skin cancer in humans. BSC is a variant of basal cell carcinoma;[8] it is transitional between BCC and squamous cell carcinoma (SCC), which occupies opposite poles of a spectrum of differentiation.[7] This tumour is often pigmented, has increased nuclear and cellular pleomorphism and has a greater metastatic rate compared with BCC.[8]

ECT is a therapy that uses systemic or local administration of anticancer agents followed by the application of permeabilising electrical pulses with specific amplitude (<1000 V/cm), duration (50–100 µs) and waveforms (unipolar/monophasic at 1 Hz pulse delivery rate).[9] This temporary increase in cellular permeability to lipophilic drugs (reversible electroporation) improves drug efficacy and reduces patient morbidity.[10] In veterinary medicine, the most common agents are bleomycin, administered intravenously or intralesionally, and cisplatin, administered intralesionally. Intralesional calcium can be used in reversible electroporation as it can increase absorption, which leads to severe ATP and water depletion associated with cancer cell death. Calcium electroporation has been shown

Willows Referral Service, Solihull, West Midlands, UK

Corresponding author:
Chiara Penzo, DVM, PhD, DipECVIM-CA (Oncology), MRCVS, Willows Referral Service, Highlands Road, Shirley, Solihull, West Midlands B90 4NH, UK
Email: Chiara.Penzo@veterinarycentre.co.uk

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

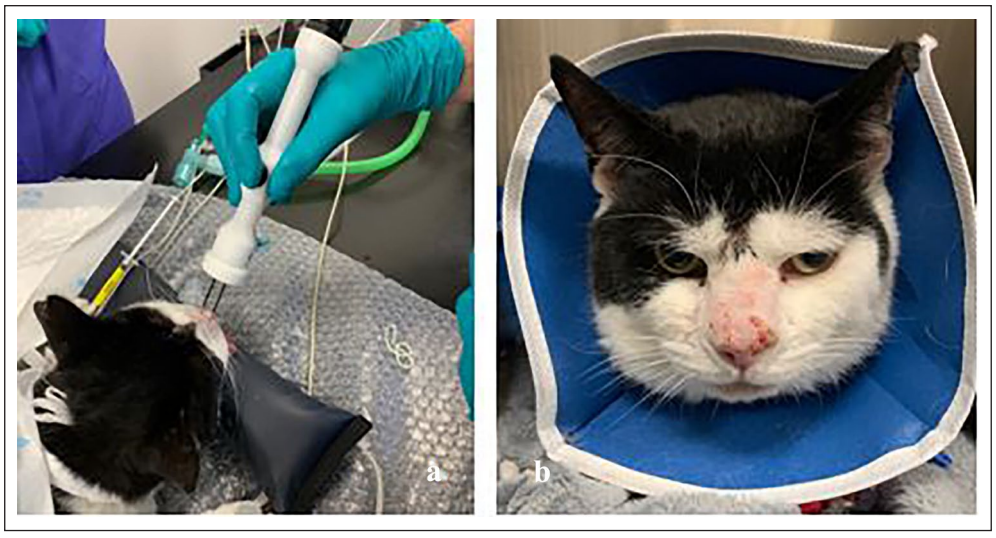

Figure 1 A 10-year-old neutered male domestic shorthair cat (case 1) with basosquamous cell carcinoma treated with electroporation techniques. (a) Application of permeabilising biphasic electric pulses and (b) the same patient 24 h after one of the treatments of electrochemotherapy with expected grade 1 toxicity (nasal planum swelling and mild erythema)

to be a safe and efficient anti-cancer treatment in human clinical studies with cutaneous metastases and recurrent head and neck cancer. Interestingly, both clinical data and preclinical studies have indicated a systemic immune response induced by calcium electroporation.[11] Irreversible electroporation consists in the use of repeated high-voltage electrical pulses (>1000 V/cm, similar duration and waveform as in reversible electroporation) that generate irreversible nano-sized structural defects and pores leading to cell death.[12] ECT equipment modified for veterinary use is available today.[9,13] In cats, ECT is used successfully for treating SCC of the nasal planum, with an overall 100% response rate and a 77% complete response;[14] however, to our knowledge, no report is available for the treatment of feline BCC.

Human ECT can achieve a local cure in 85–92% of patients with BCC, improving to 100% after re-treatment, with a low risk of local recurrence.[15] Local administration of calcium chloride and irreversible electroporation help improve the outcome in more complex tumours.[3,6,13] Only one clinical study is available describing the use of calcium electroporation in horses but there are none in cats.[16] While several preclinical studies are available on the use of irreversible electroporation in veterinary medicine, only one describes its clinical use in dogs.[5]

The aim of the present study was to describe the use of ECT, calcium electroporation and irreversible ECT in cats with BCC or BSC. To the authors' knowledge, these treatments have not been previously described for this tumour type in veterinary medicine.

Case series description

Materials and methods

Privately owned cats with histologically confirmed BCC or BSC of the nasal planum and surrounding skin were included. A complete history, physical examination, haematology, serum biochemistry and thoracic imaging (radiographs or CT) were performed in each patient. Urinalysis and cytology of the regional palpable lymph nodes were inconsistently performed.

Patients were pre-medicated with 0.01 mg/kg medetomidine IV and 0.2 mg/kg methadone IV. General anaesthesia was induced with alfaxalone or propofol to effect and maintained with Isoflurane. Two ECT treatments were performed 2–6 weeks apart, depending on response.

The patients were prepared by clipping and aseptically preparing the areas. Maropitant (Cerenia; Vetimed) 1 mg/kg IV was administered as an antiemetic. All patients were given a slow IV bolus of bleomycin (Bleomicina Solfato; Aventis Pharma) at 15 or 20 mg/m^2 followed by an intralesional injection of a volume of calcium (calcium chloride; Martindale Pharma) (14.7% diluted with NaCl 0.9% to a concentration of 10 mg/ml) that would cause mild skin blanching up to a maximum of 1 mg/kg/cat. Cisplatin (Cisplatin; Accord-Healthcare) (1 mg/ml solution, diluted 1:1 with saline to a concentration of 0.5 mg/ml) was also injected intralesionally in case 1 at a volume of 0.15 ml (0.075 mg) that would not cause blanching (Figure 1).[17] After a standard 5 mins interval from the bleomycin injection, sequences of permeabilising pulses were applied to the lesions and an area of normal tissue around the lesion to allow a treatment margin of at least 1 cm. Trains of eight biphasic electric pulses lasting 50 + 50 µs each with interpulse intervals of 1 ms were delivered with a veterinary electroporator (Onkodisruptor EXP-Vet; Biopulse). The electrodes were a double-plate stainless-steel electrode for surface treatments (60 mm in length) and two double-needle stainless-steel electrodes (45 mm in length) shielded and treated with a special insulating resin, suitable for subcutaneous use.[9]

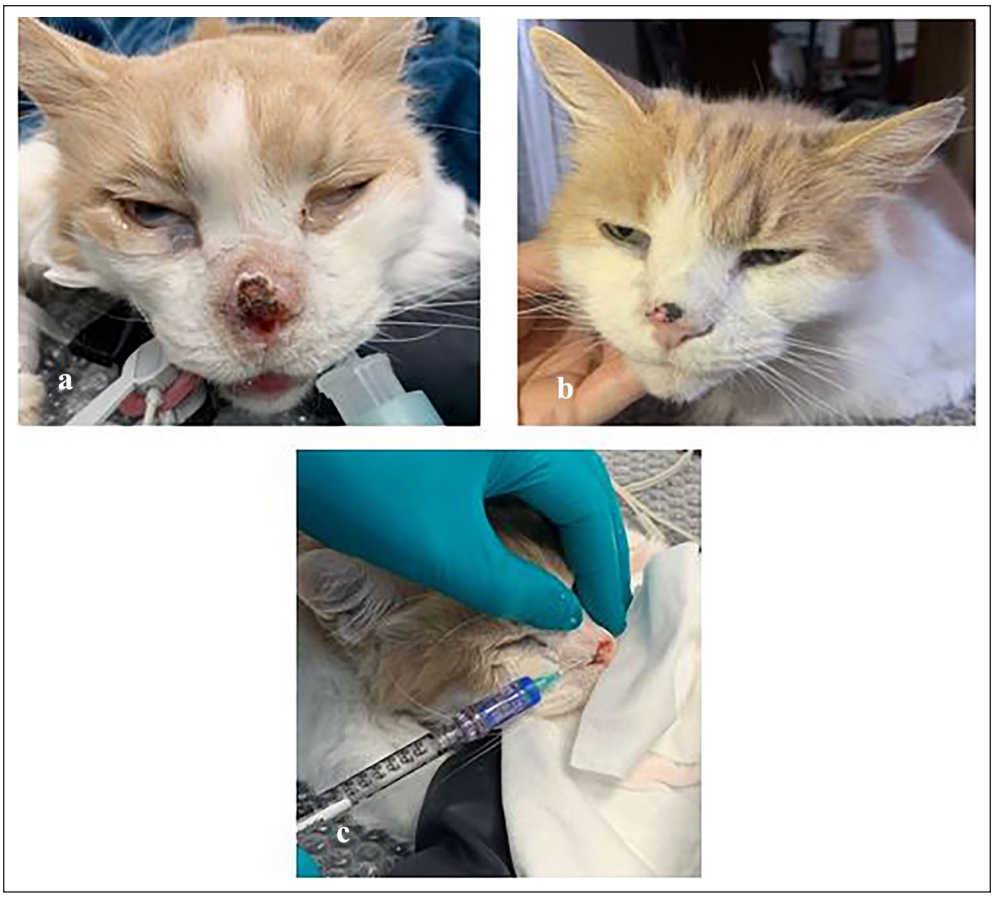

Figure 2 A 13-year-old neutered male domestic longhair cat (case 2) with basal cell carcinoma treated with electroporation techniques. (a) Patient at presentation; note the extensive crusty erosion; (b) local injection of a 0.5% solution of cisplatin within the tumour bed; and (c) the same cat at the point of the completion of its treatment

Reversible electroporation was performed by applying one train of pulses per site at 1300–800 V/cm with a double-plate electrode on a stick probe. In cases 1 and 2, irreversible electroporation was also performed with the application of five trains of pulses per site at 1000 V/cm with double needles on a stick probe (Figure 2).

Electroconductive gel with aloe vera (aloe vera gel; Aloe Pura Laboratories) was used to optimise contact between the patient and probes and avoid burns. Two of the patients were discharged on the same day for both treatments and one required one night of hospitalisation for practical reasons. Postoperative analgesia was given on the day of treatment with meloxicam (Metacam; Boehringer) 0.1 mg/kg SC and buprenorphine (Vetergesic; Ceva Animal Health) 0.02 mg/kg IV. All cats were discharged with maropitant (Cerenia; Vetimed) 2 mg/kg q24h, to be used as needed, and meloxicam (Metacam; Boehringer) 0.05 mg/kg q24h for 7 days.

After each ECT treatment, response and local toxicity were assessed weekly by email and photographic correspondence with the owner to determine the most appropriate inter-treatment interval based on visual response. After treatment, haematology, serum biochemistry and urinalysis would only be repeated if there was any concern on pre-treatment assessment or the patient became unwell. After treatment completion, physical examinations or phone call follow-ups were available. Given the mechanism of action of ECT and expected apoptotic and necrotic changes to the treated area and the small size of the treated tumours, local complications were considered to be present when ulceration and necrosis of the treated area (grade 3) had not healed within 4 weeks or progressed beyond this time. Given the lack of veterinary-specific guidelines to interpret local reactions after application of electroporation techniques, toxicity grading according to the VCOG-CTCAE after infusion site extravasation/reaction was used as a reference.

Case presentation

Patient signalment, tumour characteristics and results of investigations are summarised in Table 1. The results of general health assessment and clinical staging were unremarkable except for mild hypercalcemia in case 3.

Table 1 Clinical and treatment information

ID	Case 1	Case 2	Case 3
Breed	DSH	DLH	Norwegian Forest
Age (years)	10	13	12
Location	Nose	Nose	Nose and right pinna
Tumour size (mm)	12 × 8	7–8	Nose: 5 × 8 Ear: 3 × 2
Electroporation	Onkodisruptor	Onkodisruptor	Onkodisruptor
Pulse protocol	Reversible: one train of pulses at 1300 V/cm Irreversible: five trains of pulses at 1000 V/cm	Reversible: one train of pulses 800 V/cm Irreversible: five trains of pulses at 1000 V/cm	Reversible: One train of pulses at 900 V/cm
Drug in the treatment	IV: Bleomycin Intralesional: Cisplatin + $CaCl_2$	IV: Bleomycin Intralesional: $CaCl_2$	IV: Bleomycin Intralesional: $CaCl_2$
Response after first treatment	CR	PR	PR
Response after second treatment	x	CR	CR
Weight (kg)	4.27	4.76	5.37
Histological diagnosis	BSC	BCC	BSC
General health assessment	Haematology and serum biochemistry: NAD	Haematology and serum biochemistry: NAD	Haematology and serum biochemistry: mild hypercalcaemia
Clinical staging	Radiographs of the chest (3 views) and FNA of the mandibular lymph nodes: no evidence of metastasis	Radiographs of the chest (3 views) and FNA of the mandibular lymph nodes: no evidence of metastasis	Contrast CT scan of the head, neck and thorax: no evidence of metastasis
Treatment interval (weeks)	0	6	6
Local disease-free interval (months)	12	12	9

In-house clinical electroporation was performed with certificated electroporator (Onkodisruptor EXP-Vet; Biopulse)
BCC = basal cell carcinoma; BSC = basosquamous cell carcinoma; CR = complete remission; DLH = domestic longhair; DSH = domestic shorthair; NAD = nothing abnormal discovered; PR = partial remission; VCOG–CTCAE = Veterinary Cooperative Oncology Group – Common Terminology Criteria for Adverse Events

The mandibular lymph nodes were palpably unremarkable in size in all patients, but lymph node cytology was not available for case 3. The results of incisional biopsies yielded a diagnosis of BSC in cases 1 and 3 and BCC in case 2. One week after treatment, case 1 presented mild erythema with scabbing and nasal discharge, which caused sneezing and inappetence (grade 2 toxicity); the cat appeared in complete remission after 12 weeks and at the 1-year telephone follow-up. A small scab also formed on the rostral dorsal aspect of the rhinarium after the first ECT treatment in case 2 but this caused no concern. However, 5 days later, the patient became inappetent with bilateral nostril occlusion by a scab (grade 2 toxicity). Sedation was required to remove the scab and the patency of the nostrils was established by removing a large mucus plug from each nasal passage; inappetence resolved. At the 7-month recheck, after the second ECT treatment, the wound was completely healed with no further lesions. The same was reported at a follow-up telephone appointment 1 year after the last treatment. In case 3, 6 weeks after the first treatment, all lesions had decreased in size except for the left pinna lesion, which was covered by a large crust that was asymptomatic (grade 3). An excisional biopsy performed to monitor the progress and rule out other causes showed no evidence of residual disease of the BSC previously diagnosed. This lesion was excised under the same general anaesthetic for the second treatment of the other lesions. Nine months after the second treatment, during a telephone follow-up, the owner reported that the wounds had completely healed with no further lesions noted.

Discussion

What is documented in the scientific literature reflects how these patients have been presented clinically. Feline BCC usually presents as discrete, encapsulated, plaque-like nodules that may be pigmented and have an ulcerated surface.[8] Lesions typically range from 2 mm to ⩾12 mm in diameter.[12] The average age at presentation is 8–12 years. The most affected sites are the head (primarily nose and ear) and neck (31.5%), trunk and dorsum (35.5%), limbs (21.8%) and other sites (11.3%).[8]

The present study shows that ECT can be effective for the palliative treatment of basal cell tumours of the nasal planum in cats when surgery is not feasible. Two treatments for two patients and one treatment for another patient at intervals of 3–6 weeks after intravenous bleomycin were used, as the general approach is used for feline SCC. All patients also underwent calcium electroporation and one patient underwent irreversible electroporation. Adverse effects were grade 2 in two cases and grade 3 in one case according to the Veterinary Cooperative Oncology Group – Common Terminology Criteria for Adverse Events (VCOG-CTCAE) grades, with no differences between the cases treated with both irreversible and reversible electroporation or just reversible electroporation.[18] A common adverse effect was the formation of a scab at the treatment site with no surgical debridement required. After complete remission, a follow-up of 3–6 months should be performed to monitor any toxicity after administration of these drugs.

ECT has the advantage of preserving healthy tissue, fewer adverse reactions, less invasiveness, fewer drug doses and better tolerability compared with other treatment options. In addition, all patients in this case report had a complete response lasting at least 9–12 months.

Our cases showed that calcium electroporation and irreversible electroporation are safe for the treatment of feline BCCs. However, their additive or synergistic role with reversible electroporation after intravenous administration of bleomycin only and/or intralesional cisplatin is to be clarified.

ECT with biphasic electric pulses and the intravenous administration of bleomycin is a safe and effective option for the treatment of BCCs in cats.[17] Further studies are needed to investigate the effect of the possible therapeutic enhancement of intralesional calcium or cisplatin administration, and/or irreversible electroporation in addition or instead of ECT with intravenous bleomycin only in the treatment of nasal planum carcinomas in cats. In addition, a recent study indicated that a lower dose of bleomycin (10 mg/m^2) may achieve the same response rate and should be considered in future treatments.[4]

Conclusions

The present study shows that ECT can be effective for the palliative treatment of malignant basal cell tumours of the nasal planum in cats.

Conflict of interest The authors disclosed the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Linnaeus Veterinary Limited supported the costs of the Open Access Publication Charges.

Funding Linnaeus Veterinary Limited supported the costs of the open access publication charges. The Linnaeus Associate affiliation stipulated in the paper is Willows Referral Service, part of Linnaeus Veterinary Limited.

Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals and procedures that differed from established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient. The study therefore had prior ethical approval from an established (or ad hoc) committee as stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

ORCID iD Alvaro Salmoral https://orcid.org/0000-0001-5688-5117

References

1 Scott DW, Miller WH and Griffin CE. **Basal cell tumors**. In: Scott DW, Miller WH and Griffin CE (eds). Muller Kirk's small animal dermatology 6th ed. Philadelphia, PA: WB Saunders, 2001, pp 1259–1263.
2. Carucci JA and Leffell DJ. **Basal cell carcinoma**. In: Wolff K, Goldsmith L, Katz S, et al. (eds). Fitzpatrick's dermatology in general medicine. 7th ed. New York: McGraw Hill, 2008, pp 1036–1042.
3 de Bree R and Wessel I. **Electrochemotheraphy in the head and neck area: an addition to the treatment armamentarium.** *Curr Opin Otolaryngol Head Neck Surg* 2020; 28: 112–117.
4 Dos Anjos DS, Sierra OR, Spugnini EP, et al. **Comparison of two different doses of bleomycin in electrochemotherapy protocols for feline cutaneous squamous cell carcinoma nonsegregated from ultraviolet light exposure.** *Sci Rep* 2020; 10: 18362. DOI: 10.1038/s41598-020-75472-0.
5 Butty EM, Forsyth B and Labato MA. **Irreversible electroporation balloon therapy for palliative treatment of obstructive urethral transitional cell carcinoma in dogs.** *J Am Anim Hosp Assoc* 2022; 58: 231–239.
6 Bellahammou K, Lakhdissi A and Akkar O. **Metastatic giant basal cell carcinoma: a case report.** *Pan Afr Med J* 2016; 24. DOI: 10.11604/pamj.2016.24.157.9233.
7 Cotchin E. **Further examples of spontaneous neoplasms in the domestic cat.** *Br Vet J* 1956; 112: 263–272.
8 Goldschmidt MH. **Basal and squamous-cell neoplasms of dogs and cats.** *Am J Dermatopathol* 1984; 6: 199–206.
9 Spugnini EP, Citro G and Porrello A. **Rational design of new electrodes for electrochemotherapy**. *J Exp Clin Cancer Res* 2005; 24: 245–254.
10 Spugnini EP, Renaud SM and Buglioni S. **Electrochemotherapy with cisplatin enhances local control after surgical ablation of fibrosarcoma in cats: an approach to improve the therapeutic index of Highly toxic chemotherapy drugs.** *J Transl Med* 2011; 9. DOI: 10.1186/1479-5876-9-152.

11 Frandsen SK, Vissing M and Gehl J. **A comprehensive review of calcium electroporation - a novel cancer treatment modality.** *Cancers (Basel)* 2020; 12. DOI: 10.3390/cancers12020290.
12 Miller MA, Nelson SL, Turk JR, et al. **Cutaneous neoplasia in 340 cats.** *Vet Pathol* 1991; 28: 389–395.
13 Spugnini EP, Baldi A, Vincenzi B, et al. **Intraoperative versus postoperative electrochemotherapy in soft tissue sarcomas: a preliminary study in a spontaneous feline model.** *Cancer Chemother Pharmacol* 2007; 59: 375–381.
14 Spugnini EP, Fanciulli M, Citro G, et al. **Preclinical models in electrochemotherapy: the role of veterinary patients.** *Future Oncol* 2012; 8: 829–837.
15 Hendel K, Jemec GBE, Haedersdal M, et al. **Electrochemotherapy with bleomycin for basal cell carcinomas: a systematic review.** *J Eur Acad Dermatol Venereol* 2021; 35: 2208–2215.
16 Galant L, Delverdier M, Lucas MN, et al. **Calcium electroporation: the bioelectrochemical treatment of spontaneous equine skin tumors results in a local necrosis.** *Bioelectrochemistry* 2019; 129: 251–258.
17 Spugnini EP, Pizzuto M, Filipponi M, et al. **Electroporation enhances bleomycin efficacy in cats with periocular carcinoma and advanced squamous cell carcinoma of the head.** *J Vet Intern Med* 2015; 29: 1368–1375.
18 LeBlanc AK, Atherton M, Bentley RT, et al. **Veterinary Cooperative Oncology Group—Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2) following investigational therapy in dogs and cats.** *Vet Comp Oncol* 2021; 19: 311–352.