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Original Article

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A pilot study evaluating stereotactic body radiation therapy for feline facial squamous cell carcinomas

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SAGE

Michaela B Swan, Deanna M Morrow and David M Lurie

Abstract

Objectives The use of stereotactic body radiation therapy (SBRT) has not been assessed in advanced-stage feline solar-induced facial squamous cell carcinomas (SCC). The objective of this study was to provide preliminary data on the use and safety profile of coarse fractions administered with an SBRT regime to manage advanced-stage feline solar-induced facial SCCs.

Methods This retrospective study assessed five cats diagnosed with advanced-stage solar-induced facial SCCs that received SBRT as their primary treatment or, in one cat, following failed surgical intervention. Tumour sites received three fractions totalling 26.25–27 Gy over a 3–5 day period.

Results All patients developed acute effects following SBRT including alopecia, epilation and erythema. Late effects were mild and included alopecia, variable pigmentation and leukotrichia within radiation fields. All patients are currently alive at the time of submission, with overall survival times ranging from 118 to 991 days.

Conclusions and relevance The results suggest that coarse fractionation administered with an SBRT technique is a safe and effective treatment tool for the management of advanced-stage feline solar-induced facial SCCs. These data provide preliminary evidence to support larger, prospective studies evaluating the management of feline facial SCCs with SBRT.

Keywords: UV-induced tumour; cutaneous SCC; radiation therapy, SBRT

Accepted: 21 January 2021

Introduction

Squamous cell carcinomas (SCCs) are relatively common tumours, accounting for approximately 15% of all feline cutaneous tumours.[1] Chronic ultraviolet exposure and subsequent photo-carcinogenesis is strongly associated with their development. Thus, these tumours are generally diagnosed on the heads of lightly coloured and hypopigmented geriatric cats (median age 10–12 years at diagnosis).[1,2] The most common sites affected include the external nares/nasal plane, pinnae, eyelids and lips.[1,2] Treatment is mostly successful for small, superficial lesions, which can be controlled for >1 year in most cats. Long-term control (2–7 years) is achieved in 10–60% of cats.[2] However for larger and more invasive tumours, control times are generally <2 years with current treatment modalities.[2] Metastasis is generally rare and late to progress, occurring mostly within the regional lymph nodes (RLNs) and lungs.[3]

Numerous treatment modalities are available for the management of feline facial SCCs, including comprehensive surgical excision (including nosectomy), cryotherapy, strontium-90 plesiotherapy (Sr-90), photodynamic therapy, topical immunotherapy with imiquimod cream, electrochemotherapy, intralesional chemotherapy and external beam radiation.[4–11] Treatment of early facial, cutaneous SCCs is primarily surgical if feasible.[12] However, surgery for facial cutaneous SCCs, in most cases, is significantly disfiguring, especially for advanced-stage tumours. Additionally, given the

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anatomical location of most facial solar-induced SCCs, achieving clean margins is rare.

Given radiation treatment (RT) does not cause significant disfiguration and is relatively non-invasive, it is our experience that owners of cats with advanced-stage facial SCCs generally prefer this treatment option. For cases with advanced facial SCCs (stage T3–T4), many of the previously mentioned treatments have limited efficacy.[13] Proton irradiation for feline nasal plane SCCs has been evaluated, achieving a favourable median survival time (MST) of 946 days for disease stage T1–T2.[14] High-dose brachytherapy with a total dose of 30 Gy delivered over 4–5 fractions for nasal plane SCCs has also been assessed, yielding a median progression-free survival and MST of 316 and 835 days, respectively.[15] Flash RT, which is a novel irradiation modality where large doses of irradiation are delivered in single fractions, was assessed as part of a dose-escalation study in six cats with nasal planum SCCs.[16] Patients in this study had stage T2–T3 disease, and received 25–41 Gy in a single fraction of treatment. All cats had a complete response by 3 months, and this was maintained until at least 16 months post-RT, except for one patient who had a local recurrence at 6 months and was euthanased at 8 months. All patients developed a mild mucositis and epilation; however, acute and late effects were minimal.[16] A hypofractionated, accelerated radiation protocol has also been described for various stages of feline cutaneous SCCs, where patients received 7.6–10 Gy per fraction once weekly for four treatments.[17] Complete, partial and no responses were achieved by 40%, 12% and 48% of patients, respectively. Mean overall survival time (OST) was 224 days and mean disease-free interval was 271 days.[17] An accelerated protocol where 44 cats with stage T1–T2 nasal plane SCCs has been published. Patients received 10 fractions of 4.8 Gy over a 1 week period. All patients had a complete response to treatment.[18] Acute and late effects were self-limiting and were similar to those previously reported.[17,18]

Stereotactic body radiation therapy (SBRT), is a recent advancement in RT, where large doses of radiation are delivered to a defined target, in a small number of fractions (3–5).[19] Specialised positioning equipment and image-guided treatment delivery are used to ensure that radiation is delivered accurately to the target volume, while limiting radiation exposure to organs at risk (OARs) as a result of rapid dose fall off gradients and inverse planning.[19,20]

To our knowledge, SBRT has not been assessed in feline facial SCCs. The aim of this retrospective study was to provide preliminary data on tumour response, as well as acute and late tissue toxicity associated with a SBRT regimen for the management of advanced-stage feline solar-induced facial SCCs. These data can be used in the planning of larger prospective studies.

Materials and methods

Case selection

Feline patients with a cytological or histological diagnosis of solar-induced facial SCC treated with SBRT were identified via a retrospective analysis of the Animal Referral Hospital, Homebush, NSW veterinary database from April 2017 to July 2020.

Inclusion criteria included cytological or histopathological diagnosis of a facial SCC for which SBRT was utilised as the primary treatment or following failed surgical intervention. Patients were excluded from the study if they received prior treatments, including Sr-90, cryotherapy, chemotherapy or toceranib kinase inhibitors. All patients required full staging with physical examination, complete blood count, biochemistry and thoracic imaging (radiographs or thoracic CT). Lesions were measured and photographs were taken on initial presentation and throughout the treatment course. RLNs were measured and sampled if enlarged for cytological assessment. Distant metastasis was either confirmed via fine-needle aspirate (FNA) and cytology if possible, or suspected, based on diagnostic imaging findings (radiographs or CT). Patients were staged according to previously published guidelines and only those patients with stage T3 and T4 were included within the study.[13] Verbal or written owner consent was obtained prior to inclusion of patients within this study.

Treatment

The initial SBRT planning involved a CT simulation where patients were placed under general anaesthetic. Patients were placed in sternal recumbency in a VacBag/cushion (SecureVac Vacuum Cushion; Bionix), which was moulded to the patient's body contour. The VacBag was indexed to the treatment couch with a lock bar (Radiotherapy Indexing Lokbar; Civco) and box adaptor (T firm SecureVac Box Adaptor; Bionix). The same moulded VacBag was used for each subsequent RT. Patients were positioned in either a bite block (Radfix Perspex Biteblock; Abbott Plastics) within an individualised dental mould (Mouthpiece Lab Putty Base and Activator; Coltene), or in a modified human maxillary fixation device (Elekta Fraxion Stereotactic Frame; Elekta) within an individualised dental wax (Hoffmann's Impression Compound; Henry Schein Halas). Cats either had exaskin (Exaskin High Density Bolus; Anatomical Geometry SL) or superflab bolus (Superflab Skinless Bolus; Action Products) placed over their dorsal skull covering the irradiated field and the patients' eyes. Tissue-equivalent bolus material (Solidifying Powder; TX Products) was also used within air gaps between the patient and the exaskin resulting from facial tissue erosion by the tumour. Bolus material was utilised over the affected region to increase the skin surface dose and

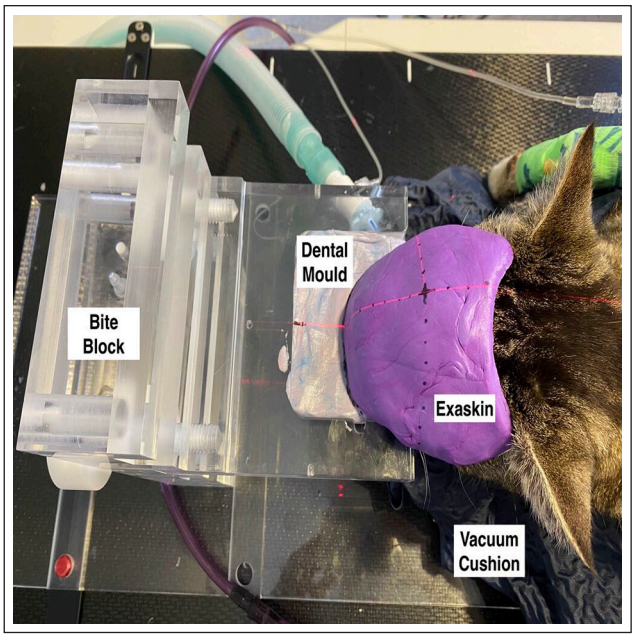

Figure 1 Patient positioning for stereotactic body radiation therapy in bite block and dental mould

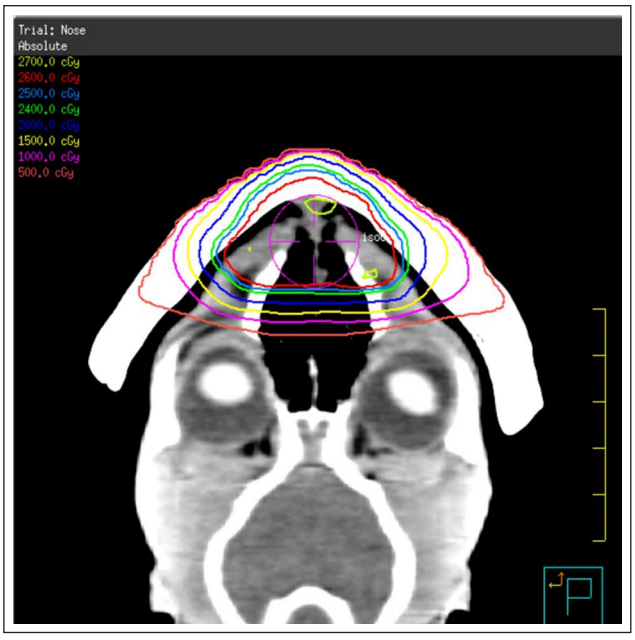

Figure 2 Dose distribution for cat number 4 with a nasal planum squamous cell carcinoma

ensure adequate dosing to the superficial planning target volume (PTV).

Marks were made over the dorsal skull or exaskin with a permanent marker at the intersection of the CT lasers (CT Lasers; A2J Healthcare) mounted on the external walls (lateral) and ceiling (sagittal), to assist alignment and positioning. CT simulation was performed with 0.7–1 mm slices (SOMATOM Force; Siemens) to enable treatment planning. Refer to Figure 1 for an example image of patient positioning. Gross tumour volume (GTV) was defined for the primary tumour by an American College of Veterinary Radiology (ACVR)-certified radiation oncologist (RO).

After contouring the GTV, a 2–5 mm isotropic expansion was used around the GTV to create the PTV. A clinical target volume was not utilised in this study. OARs included the skin, left and right eyes, left and right lens, and palate. Dose constraints were closely adhered to during the development of the protocol, ensuring all OARs within the PTV received their respective maximum tolerable doses.[20] Data and figures detailing treatment volumes, absorbed doses within targets and OARs are summarised in Figure 2 and Tables 1–4.

The treatment system's planning software (Pinnacle 3 9.1; Phillips) was used to calculate the volumetric modulated arc therapy or 'SmartArc' utilising either two partial or two full arcs and the collapsed cone convolution algorithm. Heterogeneity correction was used for couch and added bolus material. Treatment plans were revised and included a review of the isodose distribution and dose volume histogram. Single isodose centres were used. Plan

Table 1 Target treatment volumes

Tumour volume (cm^3)		
	Gross tumour volume	Planning target volume
Minimum	2.9	9.0
Maximum	9.6	19.7
Median	5.3	11.5
Mean	5.6	13.5
SD	2.6	4.9

coverage was achieved with the 95% isodose line covering 98% of the PTV.

Quality assurance of the beams was performed prior to treatment. This was done by delivering the beams to the Electronic Portal Imaging Device (EPID). This information was sent to the Per Fraction Software (Sun Nuclear), which compared the calculated beams from the treatment planning software to those delivered to the EPID.

Patients underwent general anaesthesia and were repositioned as per CT simulation for SBRT treatments. Volumetric images were attained via on-board kV cone beam CT (CBCT) immediately prior to each treatment. These images were matched with those from the planning CT using soft-tissue structures, bone anatomy and automatic registration using an imaging program (XVI; Elekta). Translational direction errors (left/right, dorsal/ventral and cranial/caudal) were corrected to match the CT simulation images and, accordingly, the couch

Table 2. Planning target volume (PTV) within tumour

PTV within tumour (Gy)							
	Minimum	Maximum	Median	Mean	D2%	D98%	D95%
Minimum	19.2	27.3	23.6	26.7	27.2	25.7	24.4
Maximum	25.8	28.6	27.1	27.5	28.2	26.3	26.8
Median	24.6	27.9	25.9	27.0	27.6	26.1	26.3
Mean	22.9	28.0	25.5	27.0	27.7	26.1	26.0
SD	3.0	0.5	1.5	0.3	0.4	0.2	0.9

Dx refers to the radiation dose (Gy) delivered to DX% of the treatment volume

Table 3 Planned absorbed doses (planning target volume) within organs at risk – skin and palate

	Skin	Palate
Dose maximum (Gy)		
Mean	28.0	25.4
Median	27.3	25.7
SD	0.5	2.5
Dose minimum (Gy)		
Mean	0.3	9.8
Median	0	8.9
SD	0.4	9.9
% Volume receiving >27 Gy		
Mean	9.6	0
Median	2.2	0
SD	14.2	0
% Volume receiving >26 Gy		
Mean	16.2	15.5
Median	19.1	0
SD	16.4	4.7

Dose maximum and minimum is the dose in Gy received by specific organ at risk. Percentage (%) of organ at risk receiving dose

carrying the patient was moved as per the calculated translational displacements, to ensure the CBCT isocentre matched that from the CT simulation. Imaging analysis occurred prior to each treatment by an ACVR-certified RO and/or an Australian board-certified radiation therapist. Automatic registration was used for image matching; however, manual manipulation was also employed to ensure optimal results. Treatment was delivered using 6 MV photons from a linear accelerator (Versa HD Elekta), which operated with 160 leaf multileaf collimator. Patients received 8.75–9 Gy per fraction, and received a total of 26.25–27 Gy to the primary site over a 3–5 day period. Arcs moved in a clockwise and counter-clockwise direction to facilitate treatment. Beam weighting ranged from 41.4% to 58.1% clockwise and from 41.9% to 58.1% counter clockwise, depending on whether partial or complete arcs were utilised.

Table 4 Planned absorbed doses (planning target volume) within organs at risk – eyes and lens

	Left eye	Right eye	Left lens	Right lens
Dose maximum (Gy)				
Mean	7.7	7.3	2.6	2.5
Median	4.7	6.6	1.3	2.2
SD	6.0	7.1	2.1	2.2
Dose minimum (Gy)				
Mean	0.4	0.4	0.6	0.6
Median	0.6	0.3	0.6	0.5
SD	0.1	0.1	0.2	0.2

Dose maximum and minimum is the dose in Gy received by specific organ at risk

Assessment of response/data analysis

Follow-up Re-check examinations were recommended at 2 weeks post-SBRT. Depending on patient response, acute effects and client cooperation, further rechecks were performed at 2–4 week intervals. Re-checks and re-staging (thoracic radiographs ± RLN [AQ: 1] FNA) were advised to occur every month for 3 months, then every 3 months for 12 months, then every 6 months ongoing.

Response to SBRT The RECIST (response evaluation criteria in solid tumours) criteria was utilised to report tumour control following SBRT.[21] Complete response was regarded as achieved when the primary tumour was no longer visible or palpable. Partial response was defined as when the primary tumour was reduced in size by 50%. Response status was determined by an ACVR-certified RO at the re-checks as outlined above.

Radiation therapy toxicity Each cat's acute and late effects were evaluated and allocated a grade based on the toxicity criteria of the veterinary radiation therapy oncology guidelines by an ACVR-certified RO.[22] Acute effects were defined as those occurring during or within the first 2 weeks of treatment. Acute delayed effects were those occurring 2 weeks–4 months post-treatment. Late

effects were defined as those developing >4 months post-treatment. A retrospective review of veterinary records was undertaken to evaluate history findings provided by clients and examination findings, in order to ensure all acute and late effects were documented.

Results

Patient characteristics and treatment regimens

Following retrospective analysis, a total of five cases met the inclusion criteria. A diagnosis of SCC was made via cytology in two cases and histopathology in three cases. Three cats were male and two were female; all were neutered. All patients had disease affecting the nasal plane and cat 2 also had a lesion on the inter-ocular nasal bridge. Cats 2, 3 and 4 had stage T3 disease and cats 1 and 5 had stage T4 disease. No patient had obvious RLN metastasis based on either lymph node palpation or abnormal appearance on CT imaging at the time of treatment planning. However, this was only confirmed cytologically in cat 1. Cat 5 had suspected pulmonary metastasis based on thoracic radiographs at diagnosis.

Cat 1 had a partial nosectomy with incomplete margins performed 45 days prior to starting SBRT. At the time of presentation to our service, this patient had significant regrowth of the tumour and was deemed to be a poor surgical candidate and SBRT was pursued. The remaining patients received no other treatments prior to SBRT. Cats 2 and 3 had incisional biopsies performed only for histopathology diagnosis. Refer to Table 5 for a summary of patient data.

All patients were treated on three consecutive days, except for cat 5, who had a 3 day break between its second and third treatments due to client constraints. All cats received three fractions of 9 Gy, totalling 27 Gy, to the tumour site, except for cat 4, which received a mild dose reduction owing to client concerns. This cat received three fractions of 8.75 Gy, totalling 26.25 Gy, to the tumour site as the client specifically requested a lower dose than what previous patients had received, owing to concerns over the novelty of the treatment and potential side effects. Cats 2, 3, 4 and 5 were positioned in a bite block (Radfix Perspex Biteblock; Abbott Plastics) within an individualised dental mould (Mouthpiece Lab Putty Base and Activator; Coltene) and had exaskin (Exaskin High Density Bolus; Anatomical Geometry SL) placed over their dorsal skulls. Cat 1 was instead positioned in a modified human maxillary fixation device (Elekta Fraxion Stereotactic Frame; Elekta) within an individualised dental wax (Hoffmann's Impression Compound; Henry Schein Halas) and had superflab bolus (Superflab Skinless Bolus; Action Products) placed over their dorsal skull owing to equipment availability. In addition, cat 5 had tissue-equivalent bolus material (Solidifying Powder; TX Products) placed between the exaskin and the skin to fill an air gap between the exaskin and the patient's face due to the erosive nature of the disease.

Patient outcomes

All patients had a minimum of 3.5 months' follow-up following the conclusion of SBRT, ranging from 118 to 991 days.

Response status was assessed in all patients. All patients achieved a complete local response within 22–50 days. Please refer to Table 5 for individual patient time to complete response and OSTs. Refer to Figure 3 for images of cats 1 and 2 pretreatment, 3 and 6 weeks post-SBRT. At the time of publication, there was no progression of the suspected pulmonary metastasis for cat 5 based on thoracic radiograph findings.

Cat 1 developed a new lesion within the irradiated field 260 days after completion of SBRT. The lesion was small, approximately 5 mm in diameter, over the right dorsolateral nasal bridge. The mass was surgically removed with complete margins and there has been no recurrence or disease progression since. This patient was still alive at the time of publication, over 991 days after completion of SBRT.

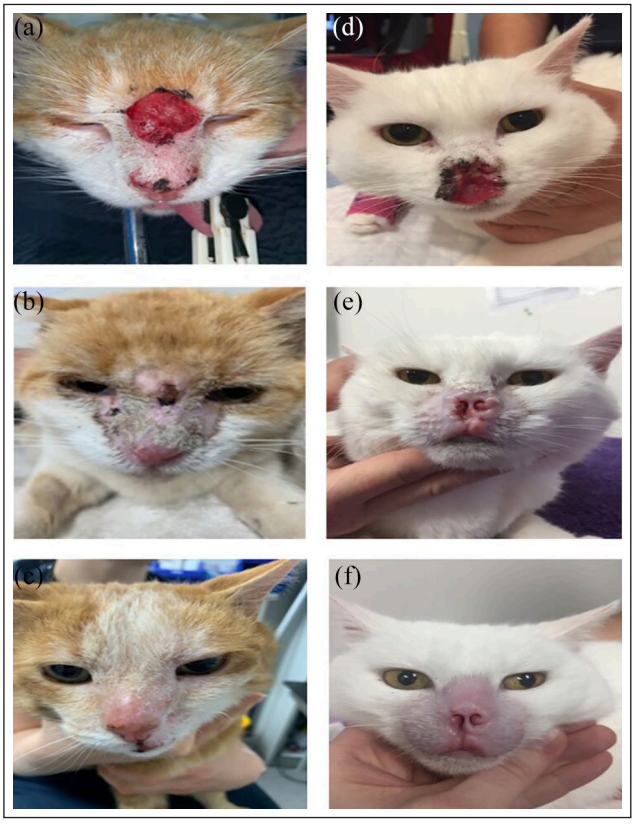

Figure 3 Patient images pre- and post-SBRT. (a) Cat 2 with inter-ocular nasal bridge and nasal planum squamous cell carcinoma (SCC) prior to treatment. (b) Cat 2 three weeks post-stereotactic body radiation therapy (SBRT). (c) Cat 2 six weeks post-SBRT. (d) Cat 1 with nasal planum SCC prior to treatment. (e) Cat 1 three weeks post-SBRT. (f) Cat 1 six weeks post-SBRT

Table 5 Summary of patient data

Cat	1	2	3	4	5
Diagnosis method	Excisional biopsy	Incisional biopsy	Incisional biopsy	Cytology	Cytology
TNM staging	T4, N0, M0	T3, N0, M0	T3, N0, M0	T3, N0, M0	T4, N0, M1
Lesion location	NP	NP	NP and inter-ocular nasal bridge	NP	NP
Days to CR	22	36	42	50	22†
Progressive disease	LR	NED	NED	NED	NED‡
PFS	260	NED	NED	NED	NED‡
OS days	991*	515*	459*	382*	118*

*Alive at time of analysis
†CR for local disease only
‡NED for local disease and unknown for suspected pulmonary metastasis
NP = nasal plane; CR = complete response; LR = local recurrence; NED = no evidence of disease; PFS = progression-free survival (days); OS = overall survival (days)

The other four patients, at the time of publication, showed no evidence of local, regional or distant disease progression. At the time of publishing, no patients had died.

Radiation toxicity

Overall, toxicities were mild. Acute skin effects occurred in all patients and included alopecia, erythema and epilation, and were apparent at initial re-check appointments, at 2–3 weeks post-SBRT. All acute effects were managed with anti-inflammatories (meloxicam 0.05 mg/kg PO q24h). Cat 4 was transitioned to an alternate opioid medication (buprenorphine 0.01 mg/kg PO q12h) due to inappetence and suspected gastrointestinal upset secondary to anti-inflammatory administration. Anti-inflammatories and pain-relief medications were utilised for 3–6 weeks after the conclusion of SBRT pending individual patient acute effects. Cats 2 and 5 required a course of antibiotics to manage suspected secondary infections due to self-trauma (cefovecin 8 mg/kg SC or amoxicillin/clavulanic acid 15–22 mg/kg PO q12h). Late effects were common and mild. All patients developed alopecia, variable dermal pigmentation and eventual leukotrichia over the irradiated primary tumour site. No oral or ocular acute or late effects were observed within the study. No patients required hospitalisation to manage radiation toxicity effects.

Discussion

Incorporation of SBRT into a treatment protocol for the management of advanced-stage feline solar-induced facial SCCs was well tolerated and effective within this study population. Although the sample population was small, SBRT lead to a complete response in all patients.

These preliminary results show SBRT to be a reasonable treatment alternative in the management of advanced feline facial SCCs. In comparison to surgery, RT does not cause significant facial deformity. Nosectomy or nasal planectomy surgeries, in particular, depending on the extent of nose and nasal plane removed, can lead to an increased occurrence of upper respiratory tract infections and incessant sneezing. The appearance of patients postsurgery can also be quite alarming and difficult for clients to comprehend, and in many instances may still not achieve local tumour control. The major advantage of SBRT, in comparison to conventional radiation treatment protocols, is a reduction in overall treatment time and significantly fewer anaesthetic and hospital visits. In addition, for many tumour types such as nasal carcinomas, brain meningiomas and osteosarcomas, similar or superior patient outcomes have been achieved with SBRT in comparison to conventional fractionation regimens with significantly diminished acute effects and limited late effects.[23–25] Whereas recent studies have started to evaluate hypofractionated and FLASH radiation regimens for the treatment of SCCs, SBRT has not been evaluated for the management of this disease. This is owing to a lack of preliminary data on efficacy, as well as concern for severe and intolerable late effects associated with coarse fraction facial irradiation. With appropriate treatment planning, we hypothesised that the increased convenience of a SBRT regimen could be achieved without significant detrimental effects and with comparative efficacy to conventional radiation regimens.

Within this study, only one patient developed local recurrence within the irradiated field during the follow-up time. This lesion was surgically removed with complete margins, and the patient remained in clinical remission at the time of publishing. In addition, no wound healing complications were observed in this patient. The remaining patients have had no evidence of disease progression at this time. Follow-up times were variable, given the retrospective nature of this study. This study has served as a proof-of-principle analysis showing that, within the sample population, SBRT was effective in achieving complete local responses of advanced-stage feline solar-induced facial SCCs.

Within this study, acute and late radiation toxicoses were mild and responsive to conservative medical

management. Given the small sample size and variable follow-up times (only 4/5 cats finished SBRT >4 months ago, thus late effects could not be established in all patients), these data should be considered as preliminary only. All patients were positioned within a Vacbag and bite block or modified human maxillary fixation device with a dental mould/wax contoured to the patient's dentition, as per previous study recommendations.[26] In using such positioning tools, combined with image-guided CBCT treatment setups, radiation was accurately and precisely delivered to the PTV, with limited acute and late effects. Our experience suggests that feline skin has superior tolerance to RT than canine skin. As per the guidelines, 24 Gy is the maximum dose suggested for skin.[20] However, given minimal acute and late skin effects in this feline cohort, cats may be able to tolerate a higher skin dose.[20]

Given its retrospective nature and the small patient population, limitations were present in this study. Potential patients were excluded from this study owing to prior treatments, thus reducing the study population. One patient had suspected metastatic disease; however, this was unable to be confirmed. One patient also had a 3 day break between its second and third treatments. The first patient in this study was positioned using alternative equipment, owing to lack of equipment availability. Some clients declined some recommended follow-up re-checks and re-staging diagnostics, and follow-up times varied. OSTs were calculated from the conclusion of SBRT, rather than from diagnosis date, which may have negatively affected the MSTs in this study.

Conclusions

This study should be considered as preliminary data for the use of coarse fractionation delivered with an SBRT regime for the management of advanced-stage feline solar-induced facial SCCs. Given the limited effective treatment modalities for these tumours and significant disfigurements incurred if surgery is possible, SBRT is an alternative treatment option. Radiotoxicity is mild and medically manageable, provided the appropriate techniques and measures are taken to ensure correct positioning. Further large-scale prospective controlled studies are warranted to assess the use and efficacy of SBRT for feline solar-induced facial SCCs, using the method described herein.

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Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). For any animals or humans individually identifiable within this publication, informed consent (either verbal or written) for their use in the publication was obtained from the people involved.

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