



A possible role of coarse fractionated radiotherapy in the management of gingival squamous cell carcinoma in dogs: A retrospective study of 21 cases from two referral centers in the UK

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ABSTRACT. Surgery with or without the addition of radiotherapy is the treatment of choice for canine oral squamous cell carcinoma (SCC). Fractionated radiotherapy alone is also effective in the long-term control of the disease, however coarse fractionated radiotherapy (CF-RT) for gingival SCC has not been extensively reported. The aim of this study was to describe side effects, clinical response, and median survival time (MST) of dogs with gingival SCC treated with CF-RT in the palliative and adjuvant setting. Twenty-one cases from two referral centres in the UK treated with CF-RT for gingival SCC between July 2013 and June 2019 were retrospectively evaluated. Of the 21 dogs, 11 developed mild acute adverse effects. Oral mucositis was the most common radiation induced toxicity. Three dogs developed chronic severe adverse effects (oro-nasal fistula, bone necrosis and gum recession). Overall clinical response rate was 77% in dogs receiving palliative treatment with MST of 365 days (60–1,095 days). MST was not reached for dogs treated in the adjuvant setting with a mean of 466 days (121–730 days). In cases of advanced gross disease CF-RT might have a role in short term palliation of clinical signs. However, it carries a significant risk of late toxicity for cases with unexpectedly long survival times and further investigations are required to identify an optimal CF-RT protocol. Randomized controlled trials are needed to confirm the role of CF-RT as adjuvant treatment of incompletely resected gingival SCC.

KEY WORDS: canine, oral tumor, palliative, radiation therapy, squamous cell carcinoma

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Squamous cell carcinoma (SCC) is the second most frequent tumor of the oral cavity in dogs [14, 20]. Most dogs with oral SCC are presented with an oral mass, especially when the disease is rostral. Whilst, tumors located caudally will present with increased salivation, bloody oral discharge, halitosis, exophthalmos or facial swelling and pain on opening the mouth [20]. Oral gingival SCC are locally aggressive tumors with approximately 10% of dogs developing regional lymph node metastasis and 3–36% distant metastasis to the lungs [16, 29]. In comparison, the probability of metastasizing for dogs with lingual and tonsillar SCC is high [2, 8, 20, 23], and metastatic disease is still a major cause of death in dogs with lingual and tonsillar SCC. Local tumor control for gingival SCC is usually the most important challenge, with local recurrence rate of 10% following mandibulectomy [16] and 29% after maxillectomy [33]. Surgery with or without the addition of radiotherapy (RT) is the treatment of choice with long survival times frequently achievable [10, 18, 20, 28, 33]. RT treatment for oral SCC can be fractionated or coarse fractionated. Most often for oral SCC the dose is fractionated, that is, delivered in multiple smaller doses per treatment [20]. Coarse fractionated radiotherapy (CF-RT) involves larger doses delivered over a few treatments [22]. Veterinary experience of RT as a sole treatment for gingival SCC is limited but has been reported. Mean tumor-free interval for dogs with oral SCC treated with orthovoltage radiation therapy (on a Monday-Wednesday-Friday schedule, for 10 fractions with an average total dose of 38.5 Gy) was 12 months and 3.4 months for dogs with maxillary and mandibular tumors, respectively [10]. An accelerated manually planned radiation therapy protocol using 14 fractions of 3.5 Gy over 9-days, combined with carboplatin chemotherapy as a radiosensitizer has been also evaluated in 3 dogs with oropharyngeal SCC and a complete response and long-term survival (>2-years) was achieved in all patients [27].

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A computer planned RT treatment alone using 12–19 fractions of 3.5–4 Gy over 4 or 5 weeks was also effective in 14 dogs in the long-term control of the disease with survival times between 12–36 months reported [18].

However, it is not always possible to deliver fractionated RT protocols to veterinary patients due to client and patient factors such as anaesthesia risk and financial concerns or owner commitment and the use of CF-RT can be a valid option. CF-RT is a well-tolerated intervention that is crucial for the appropriate delivery of palliative oncology care, aiming to relieve symptoms at the site of primary or metastatic tumors with improvement of patient's quality of life [20]. CF-RT protocols for macroscopic oral SCC can be used in a true palliative setting (e.g. providing pain relief, decreasing bleeding or inflammation and improvement of clinical signs) for elderly patients or patients presenting with serious comorbidities. CF-RT can also be used in the adjuvant setting as a “compromise protocol” for a definitive approach in cases of microscopic gingival SCC where the owner declined more fractionated protocols. CF-RT for gingival SCC in a palliative or adjuvant setting has only been reported in two previous papers to our knowledge. In one large study of solid tumors treated palliatively with CF-RT, only two non-tonsillar SCC were included, with survival reported as 324 and 448 days; no side effects were mentioned [31]. In another study, dogs undergoing adjunctive CF-RT with 4MV photons after incomplete excision of oral SCCs had a significantly longer median survival time (MST) (2,051 days) than dogs with incompletely excised tumors and no RT (MST, 181 days) [28].

Given the lack of reporting of CF-RT for gingival SCC we aim to describe side effects, clinical response, and MST of dogs with gingival SCC treated with CF-RT in the palliative and adjuvant setting.

MATERIALS AND METHODS

Dogs and staging

Medical records from two referral centers (Institute A, The Queen's Veterinary School Hospital, Cambridge, UK; Institute B, Southfields Veterinary Specialists, Basildon, UK) were retrospectively evaluated to identify dogs with gingival SCC treated with CF-RT in the palliative and adjuvant setting between July 2013 and June 2019. Dogs were included if they had a cytological or histological diagnosis of oral non-tonsillar, non-lingual SCC and completed a CF-RT protocol. The goal of palliative intent RT was defined as relief of symptoms at the site of the primary tumor. All the cases selected for palliative intent CF-RT were chosen on the basis of patient related factors (i.e. advanced age, severe comorbid disease), tumor related factors (too advanced to be resected) or the owner declined aggressive surgical intervention. Dogs with recurrence following initial surgical treatment were permitted and received CF-RT with palliative intent on macroscopic disease. The cases selected for adjuvant CF-RT were because the owner declined more fractionated protocols after surgical procedure, so CF-RT was offered as a “compromise protocol” for a definitive approach.

Information from medical records included age, breed, sex, weight, and history of previous treatment. The initial pre-treatment evaluation consisted of physical and oral examination, and combinations of complete blood count, serum biochemistry profile, urinalysis, cytology of the local lymph node, thoracic radiographs or thoracic computed tomography (CT) scan and head and neck CT scan. CT scan was not re-evaluated at the time of writing. Tumor measurements were obtained by calipers in all cases for maintaining consistency in measuring tumor response at follow-up. Lymph node size was documented by CT scan when available and recorded in the clinical notes by the attending clinician during consultation. Other treatments were also recorded. Tumor location was classified by anatomic subsite (maxilla, mandible, or buccal), by intraoral location (rostral or caudal to the second premolar) and lateralization (tumors crossing the midline were called intermandibular or intermaxillary). All tumors were staged at initial presentation according to the World Health Organization (WHO) [25] classification for oral tumors. When tumor relapsed in the same location, this was assumed to be the same tumor type and re-sampling was not performed.

Anesthesia protocol for radiotherapy

Anesthesia protocol varied between institutions. At Institute A, each dog was premedicated with 10 µg/kg intravenous (IV) alfentanil (Rapifen, Piramal Critical Care Ltd., Langford, UK) and 12 µg/kg IV atropine (Atrocare, Animalcare, York, UK), anesthesia was induced with propofol (PropoFlo, Zoetis, Spriengfield, UK) to effect and maintained with sevoflurane (SevoFlo Zoetis). At Institute B, each dog was premedicated with 0.2 mg/kg IV butorphanol (Torbugesic, Zoetis) or 0.2 mg/kg IV methadone (Comfortan, Dechra, Sherewsbury, UK) dependent on patient pain score. Anesthesia was induced with propofol (PropoFlo, Zoetis) to effect and maintained with isoflurane (IsoFlo Zoetis).

Irradiation protocol

The radiation dose was 32–34 Gy given in 4 fractions once weekly (8 Gy to 8.5 Gy/fraction) of 6 MV photons delivered by a Varian Clinac 2100 IX DMX (Varian, Palo Alto, CA, USA) at Institute A and by a Varian Clinac 600x IX DMX (Varian) at Institute B. Treatment plans were manual with square or rectangular fields and lead blocks used in a subset of patients to block surrounding normal tissues at risk (eyes and tongue) if necessary or possible. Blocks were manually positioned using anatomical landmarks or measurements from the diagnostic CT scan and the block tray factor included in the monitor unit calculation. Lymph nodes were irradiated in patients where metastasis was confirmed by cytology. Lymph nodes were irradiated with the same protocol if they could be included in the same radiation field or in a different field (with the same dose) if it was not possible because of tumor location or size.

For dogs with macroscopic disease that received palliative CF-RT, tumor measurements were obtained in three dimensions from the CT and used to establish prescription depth and isocenter position. Gross tumor volume (GTV) was measured on CT scan and

with calipers and 1–2 cm margins (combined CTV/PTV) around the tumor were applied (allowing for natural tissue boundaries) at the decision of the attending oncologist. The prescription aim was to achieve between 90–95% dose to the planned target volume (PTV). For tumors up to 3 cm deep or less, single field source-axis distance (SAD) technique for photon plans with 100% dose was prescribed at Dmax. For tumors extending deeper than 3 cm two parallel opposed beams were used with a SAD technique and 100% dose was prescribed to the isocenter. When necessary 0.5–1 cm tissue-equivalent bolus material was used in the treatment to achieve adequate dose at tumor surface. The direction of the beam and the decision to use single or parallel opposed fields was based on the clinical experience of the radiation oncologist and determined using anatomical landmarks and measurements from the diagnostic CT scan.

For dogs with microscopic disease that received adjuvant CF-RT the radiotherapy field included the surgical scar plus 2–3 cm margins. When necessary 0.5–1 cm tissue-equivalent bolus material was used in the treatment to achieve adequate dose at surgical site surface. The direction of the beam was based on the clinical experience of the Radiation Oncologist and determined using anatomical landmarks and measurements from the diagnostic CT scan.

Data analysis and follow-up

Adverse events were graded according to the Veterinary RT Oncology Group (VROG) [17] morbidity-scoring scheme. Treatment-related toxicity was assessed by reviewing patient medical records, some cases were graded via retrospective assessment. Subsequent follow-up data was not standardized due to the retrospective nature of the study.

The overall clinical response was evaluated only for dogs receiving palliative CF-RT treatment on macroscopic diseases and was calculated as the number of dogs whose gross disease responded to RT (i.e., number of dogs that were classified as having a complete response and partial response) divided by the number of dogs receiving palliative CF-RT treatment for macroscopic disease. Tumor response evaluation was based on the canine RECIST (cRECIST v1.0; 2015) [24] criteria and considering the minimum tumor size achieved. The size of the mass was assessed (longest diameter) at the start of RT by caliper measurement. Clinical improvement from RT treatment was also assessed and took into consideration relief of symptoms at the site of primary tumor.

Response to RT was documented in all dogs at the last RT treatment, after 10–14 days at the referring veterinary practice and in compliant cases at the scheduled 6–8 weeks post RT treatment at the RT center. Response was also documented at various time intervals after RT by re-examination in compliant cases and/or telephone follow-up in all cases. If precise tumor measurements were not available, response was estimated on the basis of clinical signs recorded in the medical record or reported by the owner during a follow-up phone call. The quality of life of the patients was also investigated during follow-up phone calls and where the clinician was in doubt, the case was reassessed at the radiation institution or the client was advised to have a consultation with the primary care veterinarian. Responses were required to last for at least 28 days.

MST was calculated from the date of initiation of RT until date of death. Kaplan-Meier survival curves for MST were generated for dogs receiving CF-RT as palliation on macroscopic disease and as adjuvant treatment on microscopic disease. Dogs were censored in the survival analysis if they were lost to follow-up, died of causes unrelated to the tumor or were alive at time of analysis. GraphPad Prism version 8.1.2 was used for statistical analysis.

RESULTS

Dogs and staging

Twenty-one dogs were included in the study. The study population consisted of 5 entire males, 5 castrated males, and 11 spayed females and had a median age of 9.5 years (range, 6 to 13 years). The breeds most commonly represented were Labrador Retriever (n=5), Staffordshire Bull Terrier (2), and Jack Russell Terrier (2); 12 other breeds were also represented (Springer Spaniel, English Setter, Toy Poodle, German Shepherd Dog, Dachshund, Doberman, Cross Breed, Lhasa Apso, Golden Retriever, Samoyed, Bassett Griffon, Yorkshire Terrier). All dogs were initially presented with an oral mass. Eight cases were presented with oral discomfort or dysphagia, eight cases had oral ulceration and oral hemorrhagic discharge and five of these cases had halitosis, three cases had exophthalmos.

Of the 21 dogs evaluated, 15 (71%) had hematology and serum biochemistry documented as part of the initial investigation, 6 (29%) dogs had hematology and serum biochemistry done at the referring practice and these were not repeated. No hematological or biochemical abnormalities related to gingival SCC were detected and dogs were considered suitable for anesthesia. Twenty (95%) dogs had a histological diagnosis of squamous cell carcinoma, one (5%) dog was diagnosed on the basis of cytology only. Primary tumor extension was evaluated by CT scan in 16 (76%) dogs. Five (24%) dogs did not have primary tumor evaluation by means of any imaging modalities. Distant metastatic spread was assessed with thoracic radiographs in 4 (20%) dogs, and with thoracic CT scan in 15 (71%) dogs. Two (9%) dogs did not have any form of thoracic imaging. Seven (33%) dogs had increase in size of regional lymph node reported from the CT scan. Thirteen (62%) dogs had regional lymph node aspiration performed (Table 1).

Six (28%) tumors were located in the rostral maxilla, eight (38%) were located in the caudal maxilla with two involving the zygomatic bone, four (20%) were located in the rostral mandible and three (14%) in the caudal mandible with one involving the oral commissure and one the buccal mucosa (Table 1). Thirteen tumors were left sided, seven were right sided, one was in the intermandibular region. Three (15%) dogs were stage I, 10 (50%) dogs were stage II and seven (35%) were stage III. One dog was not staged because no head or thoracic imaging was performed, and no fine needle aspirates from the regional lymph nodes were taken. In the 13 cases treated with CF-RT with palliative intent for macroscopic disease only two were stage I, five were stage II and six were stage III.

Table 1. Patient and treatment details, reported acute and late-onset radiation-induced adverse effects (AE), and response for 21 dogs treated with coarse fractionated radiotherapy for confirmed oral squamous cell carcinoma (SCC)

Dog	Sex	Age	Breed	Diagnosis	Staging	SCC location	WHO stage	Treatment	Acute AE	Chronic AE	6–8 weeks follow up	Other follow up	Response	MST (days)	TTP (days)
1	ME	10	Jack Russell Terrier	Histology, LN cytology	Head and thoracic CT scan	Maxilla caudal	III	RT	N/A	Oro-nasal fistula. Bone necrosis	Yes	Yes	SD	182	121
2	MN	7	Springer Spaniel	Histology	Head and thoracic CT scan	Maxilla rostral	II	RT	G III mucositis	N/A	Yes	Yes	PR	182*	182* Alive
3	MN	11	Lhaso Apso	Histology, LN cytology	Head and thoracic CT scan	Maxilla caudal	I	RT on gross recurrence	N/A	N/A	Yes	Yes	SD	365*	365* Alive
6	ME	9	German Shepherd	Histology, LN cytology	Head and thoracic CT scan	Mandible caudal and left buccal mucosa	III	RT on gross recurrence	N/A	N/A	Yes	Yes	PR	60	60
7	MN	12	Dachshund	Histology, LN cytology	Head and thoracic CT scan	Maxilla caudal and zyg bone	II	RT	N/A	N/A	Yes	Yes	PR	547*	547* Alive
8	FN	11	Basset Griffon	Histology	Head and thoracic CT scan	Maxilla caudal and zyg bone	III	RT	N/A	N/A	Yes	Yes	PD	152	121
9	FN	6	Labrador Retriever	Histology, LN cytology	Head and thoracic CT scan	Maxilla caudal	III	RT	GI mucositis	Oro-nasal fistula. Bone necrosis	No	Yes	PR	365	60
10	ME	12	Yorkshire Terrier	Histology, LN cytology	Head and thoracic CT scan	Mandible caudal and oral commissure	II	RT on gross recurrence	N/A	N/A	Yes	No	PR	91	91
12	ME	10	Labrador Retriever	Histology, LN cytology	N/A	Maxilla caudal	III	RT	Alopecia, mucositis grade II	Oro-nasal fistula. Bone necrosis	Yes	Yes	CR	1,095	1,095
17	FN	13	Staffordshire Bull Terrier	Histology, LN cytology	Thoracic radiographs	Mandible rostral	II	RT	N/A	N/A	Yes	No	PR	90*	90* Alive
18	FN	12	Golden Retriever	Histology, LN cytology	Thoracic radiographs	Maxilla rostral	I	RT on gross recurrence	N/A	N/A	Yes	Yes	PR	578	578
19	FN	7	Samoyed	Cytology mass	Head CT scan	Maxilla caudal	II	RT	N/A	N/A	Yes	Yes	PR	182	91
21	FN	6	Labrador Retriever	Histology	Thoracic radiographs	Mandible rostral, sublingual	III	RT	N/A	N/A	Yes	Yes	PR	Lost	Lost
4	MN	9	Labrador Retriever	Histology	Head and thoracic CT scan	Maxilla caudal	II	Adj RT	Grade II mucositis	N/A	Yes	Yes	No recur	547*	547* Alive
5	ME	7	Staffordshire Bull Terrier	Histology	Head and thoracic CT scan	Maxilla rostral	III	Adj RT	Grade II mucositis	N/A	Yes	Yes	Local recur	121	121
11	FN	9	Toy Poodle	Histology, LN cytology	Head and thoracic CT scan	Maxilla rostral	II	Adj RT	Alopecia, grade I skin burn	N/A	No	Yes	No recur	Lost	Lost
13	MN	7	Cross Breed	Histology, LN cytology	Head and thoracic CT scan	Mandible rostral	II	Adj RT	GI mucositis	N/A	No	Yes	No recur	Lost	Lost
14	FN	12	Jack Russell Terrier	Histology	Head and thoracic CT scan	Maxilla rostral	I	Adj RT	GI mucositis	N/A	Yes	No	No recur	Lost	Lost
15	FN	10	English Setter	Histology, LN cytology	Head and thoracic CT scan	Mandible caudal	II	Adj RT	N/A	N/A	Yes	No	No recur	730*	730*
16	FN	7	Labrador Retriever	Histology, LN cytology	Head and thoracic CT scan	Mandible rostral	II	Adj RT	Grade I dermatitis	N/A	Yes	No	No recur	Lost	Lost
20	FN	13	Cross breed	Histology	Thoracic radiographs	Maxilla rostral	N/A	Adj RT	desquamation	N/A	No	Yes	No recur	Lost	Lost

FE, female entire; ME, male entire; FN, female neutered; MN, male neutered; y, year; LN, lymph node; RT, radiotherapy only; Adj RT, adjuvant radiotherapy; G, grade, AE, adverse events; MST, median survival time; TTP, Total time to progression; Lost, lost at follow-up; SD, stable disease; PR, partial response; PD, progressive disease; CR, complete response; No recur, no recurrence; Zyg, zygomatic bone; * dog censored; the number in days is indicative of the last follow up available.

Table 2. Radiotherapy dose details and comparison with other radiotherapy protocols

Dose (Gy)	Fraction	BED3 (Gy)	BED10 (Gy)	Total dose (Gy)
8.0	4	117.33	57.60	32
8.5	4	130.33	62.90	34
6.0	5	90.00	48.00	30
4.0	5	46.60	28.00	20
3.0	19	114.00	74.10	57

Gy, gray (unit); BED3, biologically effective dose ($\alpha/\beta=3.00$); BED10, biologically effective dose ($\alpha/\beta=10.00$).

Treatment and outcome

Biological effective dose (BED) was calculated for our protocol and is described in Table 2. All of the dogs (n=21) completed the planned CF-RT protocol. None of the cases died during treatment. Thirteen dogs (60%) received CF-RT with palliative intent on macroscopic disease, and eight (40%) of these dogs also received long term adjuvant meloxicam treatment. Four cases had cytologically confirmed node metastasis of the ipsilateral submandibular lymph node, and these nodes were irradiated. In two cases the metastatic lymph node was included in the same radiation field used for the primary tumor, in the remaining two cases a different field from the primary tumor was used to irradiate the metastatic lymph node. Eight dogs (40%) received CF-RT as adjuvant treatment after incomplete surgical resection of the tumor for microscopic disease. 6/8 of these dogs had planned curative intent surgery but only one of these dogs had a completely removed SCC with narrow margins, whilst the other five dogs had infiltrated margins. 2/8 dogs had planned marginal resection of the SCC. Radiotherapy was started after the surgical wound was completely healed and ranged from 15 to 22 days post-surgery. All of these 8 cases received meloxicam for 5 days post-surgical resection.

Two weeks follow-up at the referring veterinary practice was available for all dogs and 6–8 weeks follow-up post RT treatment at the RT center was available for 17 dogs. Telephone follow-up was available at various intervals for 16 cases. Six cases were eventually lost to follow-up (median follow up time was 547 days (60–1,460 days)). For the cases lost to follow-up, five had surgery and adjuvant CF-RT. Of these cases, information was available at the rescheduled 6–8 weeks follow-up for two cases, and at various intervals by phone call or visit for 3 cases. Only one dog that received palliative CF-RT was lost at early follow-up, however 6–8 weeks follow-up was still available for this case (Table 1). All cases presented at the referring veterinary surgeon with severe acute or chronic/late side effects were reassessed at the RT hospital.

Following RT initiation, 11 (52%) dogs developed acute adverse effects, including: mucositis (n=9 dogs), alopecia (3), dermatitis (1) and desquamation (1). Oral mucositis was noticed during last dose of CF-RT treatment in 9 cases. This was considered grade I in 5/9 dogs, grade II in 3/9 dogs and grade III in 1/9 dogs. The other acute radiation-induced cutaneous effects were very mild and considered grade I. Dogs that developed grade II or III mucositis received meloxicam or meloxicam and antibiotics, respectively with resolution of mucositis recorded at two weeks follow-up at the referral practice. The other acute radiation-induced cutaneous effects were noticed at two weeks follow-up at the referral practice.

Three dogs (14%) that received CF-RT with palliative intent for macroscopic tumors, developed late radiation toxicity: all had oro-nasal fistula, bone necrosis and gum recession. These developed 3 months after treatment in one case, after 7 months and after 24 months in the other two cases. These dogs lived for 6 months, 1 year and 3 years, respectively; all dogs were WHO clinical stage III, and two had nodal metastasis. All dogs with chronic sides effects received 34 Gy divided into 4 weekly fractions. All dogs that developed oro-nasal fistula received multi-modal analgesia as required (meloxicam, paracetamol and tramadol).

All of the cases with caudal maxillary tumors (n=7) had the eye shielded and none of these developed obvious related ocular acute or chronic side effects.

Of the 13 dogs that received CF-RT with palliative intent on macroscopic disease, 1 (8%) developed progressive disease, 2 (15%) achieved stable disease, 9 (69%) achieved a partial response, 1 (8%) achieved a complete response and had the longest survival in the study (1,095 days). The overall clinical response for those dogs receiving CF-RT with palliative intent was 77% (10/13 dogs). All dogs, but the one with progressive disease, improved clinically after RT treatment. In these cases, owners reported improved oral comfort, reduced halitosis, and reduction of hemorrhagic discharge when present.

Of the 8 dogs that received adjuvant CF-RT after surgery, only 1 dog had recurrence of his tumor and was euthanised 4 months after initial presentation.

MST for all cases was 578 days (60–1,095 days; Fig. 1). MST for dogs that received palliative intent CF-RT for macroscopic disease was 365 days (60–1,095 days; Fig. 2). MST for dogs that received CF-RT as adjuvant treatment for microscopic disease was not reached with a mean of 466 days (121–730 days; Fig. 2). There were 12 dogs that were censored in the Kaplan-Meier analysis. Five of the dogs censored received CF-RT with palliative intent for macroscopic disease and seven received CF-RT as adjuvant treatment for microscopic disease.

Of the dogs treated with palliative intent 7 dogs were euthanised due to progressive disease. One dog was euthanised because of side effects from RT (oro-nasal fistula and bone necrosis). Four dogs were alive at the time of writing (90, 182, 365 and 547 days) and one was lost to follow-up (60 days).

Of the dogs treated with adjuvant CF-RT, one dog died of tumor-unrelated causes (730 days). One dog was euthanised due to

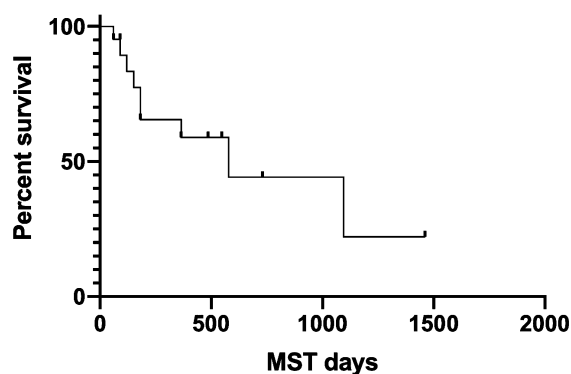


Fig. 1. Kaplan-Meier plot of median survival time (MST) for all cases. There were 12/21 dogs censored in the analysis.

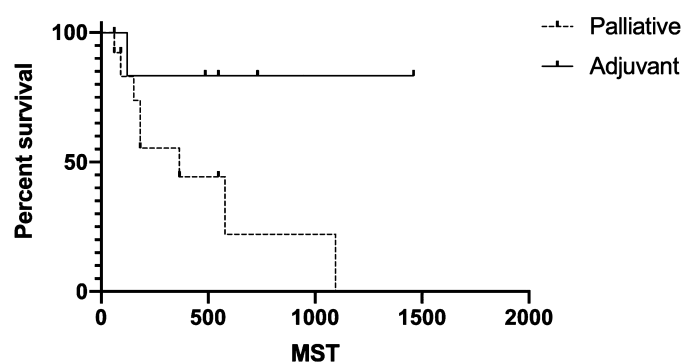


Fig. 2. Kaplan-Meier plot of median survival time (MST) for dogs that received coarse fractionated radiotherapy (CF-RT) on macroscopic disease (palliative) and for dogs that received CF-RT on microscopic disease (adjuvant). There were 5/12 dogs censored in the analysis that received CF-RT for macroscopic disease and 7/12 that received CF-RT for microscopic disease.

tumor regrowth (121 days). One dog was still alive at the time of writing (547 days), and five dogs were lost to follow-up and had a median follow-up time of 547 days (60–1,460 days; Table 1).

DISCUSSION

The aim of this study was to describe clinical response, survival and side effects of dogs treated with CF-RT for gingival SCC in the palliative and adjuvant setting. This is the first study to report a group of dogs (13) treated with CF-RT with palliative intent in the macroscopic setting. Only 1/13 dogs achieved a complete response and was alive for 1095 days after starting RT treatment. The majority of the dogs achieved a partial response (9/13) or stable disease (2/13), whilst 1/13 had progressive disease despite RT treatment. The overall clinical response was 77%. All dogs, but the one with progressive disease, improved clinically and experienced a clinical improvement from RT treatment with owners reporting increase in oral comfort, reduced halitosis, and reduction of hemorrhagic discharge where present leading to an overall improved quality of life. Assessing the effectiveness of palliative intent protocols is difficult. For example, tumor response is assessed by objective measures such as a decrease in tumor size and duration of survival. In contrast, assessment by the owner on the overall clinical improvement is subjective and includes amelioration in clinical signs and quality of life. Tumor size might remain unchanged following radiotherapy, but the patient may have marked clinical improvement in regard to signs of pain.

In our study, the RT dose was standardized; however, dose distribution and dose delivery were not standardized due to the lack of computer based planning and retrospective case selection. MST for dogs that received CF-RT with palliative intent for macroscopic disease was 365 days. This is not dissimilar to that described by Tollett *et al.* (2016), in which the protocol was not standardized, where the 2 dogs with oral non-tonsillar SCC that received palliative RT had similar survival times (12 and 15 months) [31] and to dogs with oral non-tonsillar SCC that underwent curative-intent radiation therapy (MST of 15–16 months and receiving a total dose of 48 to 57 Gy) [10, 18]. Unfortunately, size, location and stage were not reported by Tollett *et al.* (2016), however, it is possible that the longer survival of one of the two cases in this study might have been due to lower stage or better tumor location (less than 2 cm and rostral). The majority of dogs in our population were classified as stage II (50%) or stage III (35%) and 47% were located caudally, which might account for a worse outcome [19].

SCC of head and neck (SCCHN) in people is a radiosensitive neoplasia [4] and more fractionated RT alone results in high tumor control and cure rates for early stage tumors (Stage I or II) [1]. Surgery is usually preferred so that the late toxic effects of radiation can be avoided. Surgery, RT, and chemotherapy are the main means for curative management of locally advanced SCCHN (stage III or IV) and a major advancement in the treatment of this stage of disease has been the introduction of concurrent administration of chemotherapy and RT (chemoradiotherapy) [32]. Chemoradiotherapy for oropharyngeal SCC has been evaluated in 3 dogs with macroscopic disease [23] and a complete response and long-term survival (>2-years) was achieved in all canine patients. In this study two dogs had stage I and II oral non-tonsillar SCC, while one dog had a tonsillar SCC. A manually planned protocol using 14 fractions of 3.5 Gy over 9-days, combined with carboplatin chemotherapy as a radiosensitizer (total dose 300 mg/m²) was used. Carboplatin chemotherapy was not used in our group of dogs, and this might have been of benefit. It is possible that radiochemotherapy would have resulted in an improved outcome in our cases, however more studies are needed as only one single case series has been published [23] in which the two oral non-tonsillar SCC reported were relatively low grade compared to our population.

RT can be used as adjuvant treatment for incompletely resected tumors in cases of canine oral SCC [19]. Historically, fractionated protocol has been showed to be effective in the long-term control of oral non-tonsillar SCC [10, 18]. However, little

is known about the role of CF-RT as adjuvant treatment for microscopic residual disease. Only one recent study [28] described dogs receiving aggressive surgery for oral tumors and adjuvant CF-RT. In Riggs *et al.* the MST after surgery and adjuvant CF-RT for dogs with oral SCC was not reached, however MST for dogs with incompletely excised tumors and no radiotherapy was 181 days and MST for dogs undergoing adjuvant radiotherapy for incomplete excision of oral SCCs was 2,051 days and 1,191.5 days (range, 100 to 2,266 days) for the dogs that were censored. In our study, MST for dogs receiving adjuvant CF-RT for incompletely removed gingival SCC was not reached with a mean of 466 days (121–730 days). This is a promising result, however not dissimilar to previous reported time to recurrence of SCC treated with surgery alone with incomplete margins [1, 18, 19, 28, 33]. Effectiveness on survival of this protocol goes beyond the aim of this paper and new studies comparing the effect of surgery alone versus surgery and adjuvant CF-RT protocols are required.

Dogs treated with CF-RT are at lower risk for the development of acute adverse effects and at higher risk for the development of chronic late adverse effects [22] than dogs receiving more fractionated protocols. In the present study, 11 of 21 (52%) dogs developed acute adverse effects following CF-RT in the palliative and adjuvant setting, the most common of which was mild mucositis, however the dogs were not rechecked at the first week post treatment, so peak acute side effect could have been missed in some cases. One dog that received palliative CF-RT developed severe (grade III) mucositis which is surprising in this setting and may have been difficult to assess accurately and distinguish from ongoing tumor induced inflammation and pre-existing mucositis in this case. Similar to findings in other studies that used CF-RT protocols [12, 13], most of the acute adverse effects in the dogs of the present study were self-limiting and resolved with supportive care (NSAIDs and antibiotics). Dogs that receive palliative RT generally have a short life expectancy; therefore, the likelihood that those dogs will survive long enough to develop chronic/late adverse effects from the CF-RT is reasonably low [30]. Nevertheless, dogs treated with CF-RT are at risk of developing severe complications, and those risks should be discussed with clients before initiation of treatment. In the present study, mild chronic side effects were not consistently documented in all cases due to the retrospective nature of this work and because were probably not considered clinically impacting at the time of follow-up. However, moderate and severe chronic adverse effects were recorded for three dogs that received CF-RT with palliative intent on macroscopic disease. All three of those dogs were ultimately euthanised but all survived over six months and one had the longest survival in the study (35 months). The latter was euthanised due to the presumed RT side effects (oro-nasal fistula and bone necrosis) and the other two dogs because of progressive disease. Interestingly, all three dogs had WHO clinical stage III and two had nodal metastasis. Large tumors that invade the maxilla and the nasal cavity causing extensive destruction of the normal oral soft tissue structures and maxillary and palatine bones appear more likely to develop oro-nasal fistula in the event of complete tumor response. As the tumor regresses, no normal soft tissue and bony structures are left to separate the oral cavity from the nasal cavity, therefore resulting in an oro-nasal fistula, which can also be tumor related in the partial response or stable disease setting. Palliative RT with a 4Gy \times 5 fractions protocol has been used by McDonald *et al.* (2012) in different primary bone tumor types reporting variable overall response rate depending on tumor characteristics (54.5–80%). In these cases, MST was calculated between 3 and 7.9 months. In this population (n=80) only 15% of cases developed mild acute side effects and only 3% developed chronic side effects [21]. It is possible that a 4Gy \times 5 fractions palliative RT protocol might have been better in our cohort of cases reducing risk of acute and chronic side effects and perhaps obtaining similar survival time. Although, none of the cases described in McDonald's work were canine oral SCC, therefore direct comparison is difficult. The incidence of chronic/late RT adverse effect is reported to be low in the adjuvant setting [10, 18, 19, 28], in our study none of the dogs that received adjuvant CF-RT for microscopic gingival SCC developed chronic/late adverse effects.

BED is a way to compare the biologic effects of different RT protocols and predict the expected acute and chronic adverse effect on a particular tissue. BED is calculated from the number of fractions, the dose per fraction and the alpha beta ratio (α/β) of the tissue in question [15]. BED10 is applied to tumour control and fast dividing tissues while BED3 is relevant to effects of radiation seen on the slow dividing tissues.

BED3 of our protocol (Table 2) might have played a role in the high rate of late side effects. In this palliative setting we have accepted a high level of BED3 considering the likely unfavorable prognosis of the patient and the low likelihood that they would have survived long enough to develop significant late radiation toxicity. BED3 is lower with other palliative protocol options in comparison (Table 2). Given that many patients in this population survived longer than six months and some enjoyed longer term survival it would be prudent to consider a CF-RT regimen with similar to slightly higher BED10 for tumor control and lower BED3 for canine patients with macroscopic SCC. For example, a treatment delivered in five fractions of 6 Gy applied twice per week, resulting in an overall treatment time of 2.5 weeks would have decreased BED3 to 90 decreasing also the risk of late side effects. RT induced vascular damage contributing to osteonecrosis may also have played a role in the development of bone changes in this population [3, 9]. Previous studies with this protocol are available for oral soft tissue sarcoma [26], malignant oral melanoma [6] and other tumor types [5, 7, 11], however no studies exist in oral SCC. Palliative intent protocols should be employed on an individual basis and balance the number of visits/anesthesia episodes and financial cost for the client with the likelihood of tumor control and risk of both acute and late toxicity for the patient. All the cases selected for CF-RT were because the tumor was too advanced to be resected or because the owner declined aggressive surgical intervention or more fractionated radiation regimens. Palliative CF-RT in these cases had the purpose to decrease inflammation associated with the tumor, decrease discomfort and decrease tumor volume, while adjuvant CF-RT had the aim of decreasing the number of visits while offering a “compromise” of a more fractionated protocol.

The present study had a number of inherent limitations because of the study's retrospective nature. The total number of patients was small, and a significant proportion was censored from the survival analysis (12/21 [57%]) making survival times difficult to interpret, tumor measurements were not always obtained by the same individual and follow-up of patients was not standardized.

Outcomes were frequently extrapolated from assessments of owners or referring veterinarians in the absence of rigorous diagnostic testing or necropsy. It is possible that due to the lack of consistency in our follow-up we might have missed some acute and chronic side effects. However, we considered this unlikely due to the continuous conversation with the owner or the referring veterinarian (often another specialist). Other limitations are the use of a manual planning for the delivery of RT treatment and poorly detailed records describing prescription points and isodose coverage. Without the use of planning software and imaging guided RT techniques, dose distribution to the tumor and organs at risks can only be approximately estimated based on the clinician experience and knowledge of the body anatomy rather than precisely calculated and delivered by sophisticated computer planning and imaging guided techniques.

In conclusion, this is the first study to describe outcome for a group of dogs receiving and completing CF-RT with palliative intent on macroscopic disease for gingival SCC. Palliative RT offers an alternative for dogs where extensive surgery has been declined or is not possible because of the size or location of the tumor, however compared to more fractionated RT it appears less effective in the long-term local control of the disease. It is well tolerated with improved quality of life reported and mild acute side effects; nevertheless, carries a risk of significant toxicity for that cases that experience unexpected long survival and late side effects need to be seriously discussed with the owner as they can be severe and result in euthanasia. CF-RT may also have a role in the adjuvant treatment of incompletely resected SCC and support the result of a previous study, but larger studies comparing surgery alone versus surgery and adjuvant radiotherapy are needed to confirm these findings.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

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