Clinical response and survival time of cats with carcinoma of the nasal cavity treated with palliative hypo-fractioned radiotherapy

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Abstract

Objective: Carcinoma is the second most common tumour of the nasal cavity in cats. Few studies have been published assessing response and survival of cats with carcinoma of the nasal cavity treated with palliative coarse fractioned radiotherapy.

Objective: Twenty-eight cats were diagnosed with histologically confirmed carcinoma of the nasal cavity. All patients treated with hypo-fractioned radiotherapy protocol were retrospectively reviewed.

Results: Improvement of the clinical signs were reported in 24 cases, median survival time was 342 days and cats with Adam modified stage IV and facial deformity had a significant reduced MST, 152 (p=0.0004) and 67 days (p=0.0002) respectively. Severe radiotherapy related clinical signs were not reported and alopecia and leukotrichia were the most common side effects reported in 9 cases.

Conclusions and relevance: Hypo-fractioned radiotherapy treatment for carcinoma of the nasal cavity in cats is effective in relieving clinical signs. Long survival times can be achieved in particular in cases with less advanced stage of the tumour.

Keywords: Coarse fractioned radiotherapy, nasal carcinoma, feline, radiotherapy

Introduction

Carcinoma is the second most common tumour of the nasal cavity in cats (1) 1Mukaratirwa S. As is the case in dogs, nasal tumours in cats often present with dyspnoea, chronic nasal discharge, sneezing and epistaxis (2). Palliative coarse fractioned and definitive fractioned radiotherapy have been used in nasal tumours in dogs and cats (3)(4)(5).The advantage of palliative coarse fractioned radiotherapy compared to definitive fractioned protocol are less acute side effects, reduced cost of the treatment and reduced number of general anaesthesia, less stress for the patients and less commitment for the owner that often need to travel long distance to reach the referral radiotherapy centre. However coarse fractioned radiotherapy is more likely to cause severe late radiotherapy side effects. The difference in term of efficacy for nasal carcinoma in cats has not been well established. Numerous studies have, even recently, extensively investigated radiotherapy and chemotherapy treatment for the more common feline nasal lymphoma (6)(7). However for nasal carcinoma large studies investigating treatment outcome and prognostic factors have not been published. Radiotherapy treatment for feline nasal carcinoma have been investigated in few and now dated small studies (3)(6). Survival time have been reported between 2 and 36 months for fractioned radiotherapy (3) and between 382 days and 450 days with coarse fractioned radiotherapy protocols (4)(5).

Adam staging of nasal carcinoma in dogs have been reported to be of prognostic significance (8). However large studies investigating the importance of the staging in cats are lacking and even in the more common feline nasal lymphoma, invasion of the cribriform plate as a

prognostic factor, is still controversial (6)(9). The outcome and adverse effects of palliative hypo-fractioned radiotherapy in a population of cats from Japan suffering of nasal tumours of different histology types was recently published. In this study the Adam staging system was reported to be not prognostically significant (5). The aim of the present study was to retrospectively investigate the outcome of feline nasal carcinoma treated in UK with hypofractioned radiotherapy and correlate survival/outcome with the modified Adam staging system.

Materials and methods

Medical records of cats with histologically confirmed carcinomas of the nasal cavity (all different carcinoma subtypes or any malignant epithelial neoplasia without further specification), treated with palliative hypo fractioned radiation therapy in a single referral centre during a period from 2008 to 2019, were evaluated retrospectively. Tumours of the nasal planum were excluded. Age, breed, sex, weight, acute and late side effects, and response to the treatment were evaluated for each patient. Tumour staging was based on advanced imaging MRI or CT scan of the head. Adam modified staging was applied to the feline patient as previously published in dogs (table n.1) (8). Cats with stage T4 nasal carcinoma were compared with all the other stages. Patients with facial deformity with any Adam stages were also separately allocated for outcome investigation. All cats with intent to treat with palliative coarse fractioned radiotherapy were included whether or not they completed their radiotherapy treatment, but the latter were not included in the survival analysis.

The radiotherapy treatment consisted of four weekly 8.5 Gy fractions course of radiotherapy or six, twice a week, 6 Gy protocol. All cats except two, that did not finish their treatment, received the four or six scheduled treatment with a 6 MV photons (34 Gy in total) delivered by a Varian Clinac 2100 IX DMX (Varian, Palo Alto, CA, USA). Treatment plans were done

105 manually with square field and lead blocks used in a subset of patients to block surrounding
106 critical normal tissues (brain or eyes) if necessary or possible. Treatments were delivered in
107 one single beam, with the aim of achieving around 90-99% of the applied dose to all the tumour
108 tissue with 0.2-0.5 cm margins around the tumour when possible. Source-surface distance was
109 always 100 cm and 1 cm tissue-equivalent bolus material was used in the treatment to achieve
110 adequate dose at tumour surface.

111 All the patient were anaesthetised and positioned on sternal recumbence. The head was
112 elevated with cushions and the maxilla with a mouth gag so to achieve a more even surface
113 between the nose and the frontal sinus reducing also the dose to the tongue. This angle also
114 often allowed an easier inclusion of the soft palate and rhino-pharynx in the treatment field
115 when needed, slightly reducing the radiotherapy field length caudally, so to spare, when
116 possible, as much as of the olfactory lobe of the brain. Tumour extension was assessed at the
117 start of RT based on clinical exam, CT scan or MRI. Response to RT was documented during
118 the course of treatment and when available 2 and 6 weeks post radiotherapy treatment or by
119 phone with the referring veterinary surgeon and it was based on the improvement of clinical
120 signs. Assessment of clinical improvement was based on a combination finding including:
121 reduced frequency of sneezing and nasal discharge, increase nasal air flow, owner's perception
122 of increased quality of life. Treatment-related toxicity was assessed by reviewing the patient's
123 medical record. Subsequent follow up data was not standardized due to the retrospective nature
124 of the study.

125 Statistical analysis was performed with a Log-rank (Mantel-Cox) test to analyses the difference
126 in median survival time between groups and Kaplan-Meier survival curves were generated,
127 results with a p value of less than 0.05 were considered significant. Cats that were lost of follow
128 up, alive or died for other cause unrelated to the nasal tumour were censored. GraphPadPrism
129 8.1.2 version program was used for the statistical analysis.

Results

Twenty eight cats were diagnosed with carcinoma of the nasal cavity, fifteen adenocarcinoma, one squamous cell carcinoma, one poorly differentiated carcinoma and eleven unspecified carcinomas. Nineteen cats were neutered male and 9 spayed female, 22 domestic short hair, one Main Coon, 2 British short hair and four domestic long hair. Age ranged from 8 to 15 years, mean 11.8. Three cases did not receive advanced imaging and Adam modified stage of the tumour could not be assessed. The remaining 25 cases were staged based on MRI or CT scan, of these 5 were stage II, 12 stage III, and 8 stage IV. Four cats had also facial deformity, of these, 3 were stage IV and in one case advanced imaging was not performed.

Twenty six cats completed the treatment protocol, two patients received only 1 fraction. The treatment was interrupted due to deterioration of the clinical signs in one case and in the other case due to asthma related respiratory deterioration during the long journey before reaching the radiotherapy treatment centre. Of the 26 cases that completed the radiotherapy 23 received 4 fractions and 3 received 6 fractions. Twenty-four cases (92%) were reported to show a significantly improvement in their clinical signs, in only one case there was no improvement and in one other case there was a deterioration of the clinical signs despite radiotherapy. Three of the four cats with facial deformity also responded with significant reduction of the tumour and improvement of the facial deformity.

Twenty-three cases that finished the radiotherapy treatment had follow up available, median and mean follow up were respectively 240 and 325 days. Of the twenty-three cats with available follow up 13 were censored, 6 were lost at follow up, 5 were still alive and 2 died of unrelated causes, 10 died or were euthanized due to the recurrence of the disease. Median survival time for all the 23 cases with different stages of the disease was 342 days (fig.1). Survival time for stage IV tumour was 152 days compared to 823 days of all the other stages taken together and

this difference was statistically significant (p =0.0004, 95%CI = 1.528 to 19.9)(Fig.2). Cats with facial deformity also had a significant shorter survival time compared to all the other patients, 67 days versus 823 days, p=0.0002, 95% CI 3.56 to 41.65), however most of them were also stage IV, so the significance of this finding is uncertain. Side effects were reported in 10 cases and were alopecia and leukotrichia, not affecting the patient's quality of life. Conjunctivitis, keratitis and ocular discharge was reported in only one case and these complications responded to symptomatic treatment. One case developed a fistula in the nose 3 months post radiotherapy. However, this was most likely the result of the tumour progression rather than a radiotherapy side effect (Summary table n.2).

Discussion

This study investigated the response and outcome of feline nasal carcinomas treated with coarse fractioned radiotherapy. Large recent studies investigating treatment outcome for feline nasal carcinoma in UK are lacking. The prognostic significance of Adam stage applied to nasal carcinoma in a UK cat's population have also not been previously published.

Clinical response to treatment and survival time reported in our study were similar to previously reported. Theon et al.,1994 reported a survival range between 2 and 36 months with fractioned radiotherapy. Mellanby et al.,2002 and Fujiware-igarashi et al.,2014 used hypo fractioned radiotherapy protocols and reported 382 and 450 days respectively. In our study, cats with advanced disease, (stage IV) had a significant reduced survival time compared to stage II and III (152 days for stage IV, versus 823 days for stage II and III). This is different from the finding in the Fujiware study where the stage of the disease did not affect the survival time. However in the latter study from Japan included a high percentage of stage IV cats (62% in Fujiware study compared to 30% in our study) that could be responsible for the close, but not statistically significant difference found in Fujiware study (p value of survival difference

between stage IV versus all the other stages was 0.059). Other possibilities are the different population of cats present in Japan compared to UK or different radiotherapy planning between the two institutions, with a more conservative approach and less margins applied to the tumour in our institution to reduce the dose to the brain compared to Fujiware study. The manual planning could also have caused a geographical miss of the tumour extending in to the brain.

In our study cat with facial deformity had also a very short survival time of only 67 days. However most of the cats with facial deformity were also stage IV making the correlation with survival difficult. This finding will need to be confirmed in a larger cohort of patients. Studies assessing survival time for untreated cats with nasal carcinoma have not been published. However, the prognosis for untreated dogs with nasal tumours, it considered to be poor (around 3 months) (10) and this is likely to be case in cats as well. In our study, the survival of cats with stage II and III of the disease was more than 2 years with a range between (30-1092 days), similar to previously reported (3). However in our study due to the high percentage of cats that were censored, this result need to be taken with caution. This is the first study to prove that Adam stage IV cat with nasal carcinoma and possibly cats with facial deformity have a poor prognosis compared to lower stage when treated with coarse fractioned radiotherapy, however a larger study is need to confirm this finding.

Radiotherapy side effects were mild and often not clinically significant or impacting the quality of life, similar to previously reported (4mellaby)(f5ugi) Late side effects are a well-known major concerns in patient treated with coarse fractioned radiotherapy protocol with radio-necrosis of the bone and brain, oro-nasal fistula, eye cataract KCS and corneal ulceration and second malignancy been the most likely to cause significant morbidity (4)(11). However the incidence of these side effects for cats treated with coarse fractioned radiotherapy is largely unknown. In the largest recent series of cats treated with coarse fractioned radiotherapy for nasal tumours of various histology treated in Japan, the late side effects were reported to be

rare, with only 2 cases of 67 developing severe late site effects and 20% of cases developing cataract (5). In our study, severe late side effects were not reported, however this could be underestimate due to the retrospective nature of the study. It is also possible that severe late effects could not have enough time to develop, especially in the cases that had a short survival time, so to underestimate the real incidence. Compared to the study in Japan cataract was not reported in any of the patients, however this could be due to under reporting due to lack of scheduled ophthalmology examination, so that mild cataract could have been missed on routine clinical examination. It is also possible that compared to the |Japan study a more conservative approach was used shielding more often the eye when in the radiotherapy treatment field.

Although unlikely, the cats with stage IV disease could have had reduced survival time caused by radiotherapy side effects to the brain, however neurological signs were reported only in one case. Even in this case the neurological signs (depression and circling) were most likely due to the tumour progression rather than the radiotherapy, considering the short time frame of manifestation (45 days post treatment). However the local extension in to the brain could not be confirmed due to the lack of post mortem examination. Other limitations of the study were the histopathology diagnosis of carcinoma was not reviewed, post mortem examination were not performed for any of the patients, assessment of the tumour by repeating the CT/MRI scan were rarely performed. For this reason tumour response was assessed by clinical signs, especially nasal airflow, and tumour time to progression could not be accurately estimated. Another limitations of the study is the lack of stage standardization as patients were staged based on CT scan or MRI. Althought not previously investigated in cats, it is possible, as in dogs, that MRI scan could have caused a stage migration compared to the cats that were staged based on CT scan, in particular as meninges enhancement is better visible on MRI(12)(13). This could also have been the reason for the slightly high incidence of stage IV tumours.

However in another study on nasal tumours in dogs CT scan was found of similar value than MRI (14).

In conclusion coarse fractioned radiotherapy treatment for nasal carcinoma in cats is effective in relieving clinical signs. Long survival times can be achieved in particular in cases with less advanced tumour stage. However large scale prospective studies with regimented follow up are needed to better define the role of radiotherapy in the palliation of feline nasal carcinoma. Despite rare, the owner should be informed of the possibility that coarse fractioned radiotherapy could cause severe late side effects.

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Conflict of interests

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Ethical approval

This work involved the use of non-experimental animals only (owned or unowned), and followed established internationally recognised high standards (‘best practice’) of individual veterinary clinical patient care. Ethical Approval from a committee was not necessarily required.

Informed consent

Written Informed consent was obtained from the owner or legal custodian of all animals described in this work for the procedures undertaken.

No animals or humans are identifiable within this publication, and therefore additional Informed Consent for publication was not required.

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