PAPER

Canine tonsillar squamous cell carcinoma – a multi-centre retrospective review of 44 clinical cases

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Objectives: To review the presenting clinical signs, treatment and survival of dogs with tonsillar squamous cell carcinoma and, if possible, to identify useful prognostic indicators.

Methods: Medical records of 44 dogs were reviewed retrospectively. Clinical signs, clinical stage, time of diagnosis, treatment and outcome were recorded. Data were analysed using the Kaplan-Meier, log-rank, Student's *t* test, Kruskal-Wallis test and Chi-square/Fisher Exact test as appropriate.

Results: The most frequent clinical signs were cough (12 dogs, 27%), enlarged lymph nodes (11 dogs, 25%) and dysphagia (11 dogs, 25%). Anorexia and lethargy were less common but were significantly associated with a poor outcome. No matter what treatment modalities were used, survival times were short and median survival time for all the dogs in the study was 179 days. However, there were a small number of long-term survivors.

Clinical Significance: Dogs with tonsillar squamous cell carcinoma that suffered anorexia and lethargy had shorter survival times than patients without these clinical signs. Although surgery, chemotherapy and radiotherapy seem to increase the median survival time of dogs diagnosed with tonsillar squamous cell carcinoma, there is no highly effective treatment for canine tonsillar squamous cell carcinoma.

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INTRODUCTION

Canine tonsillar squamous cell carcinoma (TSCC) is an uncommon disease, representing 9% of canine oral tumours in a UK survey (Bostock and Curtis 1984), and there is relatively limited information regarding presentation, treatment and outcome in the current literature. In contrast to non-tonsillar SCC, TSCC is characterised by rapid growth, infiltration of underlying tissues and high metastatic potential (Brodey 1970, Todoroff and Brodey 1979, White and others 1985), and is generally regarded to carry a poor prognosis (Brodey 1970, MacMillan and others 1982, Brooks and others 1988).

Treatment options for TSCC include surgery, chemotherapy, radiotherapy, symptomatic treatment, or any combination of these approaches. Multi-modality approaches may be appropriate given the high metastatic potential of these tumours and the high incidence of recurrence at the primary site (MacMillan and others 1982, Brooks and others 1988). However, there are very limited data on outcome after therapy. The best reported survival times were achieved in six dogs treated with surgery followed

by radiotherapy and chemotherapy, with a median survival time (MST) of 270 days (Brooks and others 1988). In another small-number study, five dogs receiving multi-modality therapy achieved a MST of 211 days (Murphy and others 2006). The primary objectives of this study were to review the presenting clinical signs, treatment and survival of dogs with TSCC and, if possible, to identify useful prognostic indicators.

MATERIALS AND METHODS

Clinical records of 44 dogs with cytological or histological confirmation of TSCC treated at 10 different institutions from June 1992 to December 2008 were reviewed: site 1 (Davies Veterinary Specialists, Herts, UK; n=20), site 2 (Animal Health Trust, Suffolk, UK; n=9), including 5 patients from a previous study (Murphy and others 2006), site 3 (Dipartimento di Patologia Animale, School of Veterinary Medicine, Grugliasco, Italy; n=3), site 4 (Veterinary Medical Center, Michigan State University, USA; n=3), site 5 (Vet Clinic Korte Akkeren, Gouda, the Netherlands; n=2), site 6 (Small Animal Teaching Hospital, University of Liverpool, Leahurst, UK; n=2), site 7 (De Ottenhorst Clinic for Companion Animal Medicine, the Netherlands; n=2), site 8 (Dier and Johnston Veterinary Surgeons, East Sussex, UK; n=1), site 9 (Clinic for Companion Animal Medicine, Emmeloord, the Netherlands; n=1) and site 10 (Animal Hospital De Visdonk, the Netherlands; n=1). A questionnaire was completed by participating centres for each eligible case (Fig 1). Animals were excluded if the questionnaire was not completed sufficiently to allow data analysis.

Survival times were calculated from the date of histological or cytological diagnosis until the date of death.

Complete remission was defined as resolution of clinical signs together with complete regression of the primary tumour and any lymphadenopathy. An objective response was reported if there was reduction in tumour size and lymphadenopathy without complete regression.

Signalment:

Breed:
Sex:
Date of birth:

Clinical signs at presentation:

Incidental ☐ Ptyalism ☐ Cough ☐ Pain ☐
Anorexia ☐ Lethargy ☐ Retching ☐ Dysphagia ☐
Enlarged lymph nodes ☐ Other ☐

If other, which were the clinical signs?

Tumour:

Location: Right ☐ Left ☐ Both ☐ Unknown ☐

Date of histological diagnosis:

Other diagnostic tests performed:

Chest X-ray ☐ Lymph node histology ☐ Unknown ☐

If performed, what was the result of the above test?

Treatment:

No treatment ☐ Surgery ☐ Chemotherapy ☐
Radiotherapy ☐ Others ☐ Unknown ☐

If chemotherapy, what chemotherapy agent did you use?

If radiotherapy, what protocol did you use?

If other, what treatment did the dog receive?

Follow up:

Is the animal still alive?
Yes ☐ No ☐ Unknown ☐

If yes or unknown, what date did you last see the animal?

If no, was the animal euthanased?
Yes ☐ No ☐ Unknown ☐

What was the date of dead?

In your opinion was the cause of death/euthanasia related to the TSCC?
Yes ☐ No ☐ Unknown ☐

FIG 1. Tonsillar squamous cell carcinoma (TSCC) questionnaire sent to the participating centers

STATISTICS

Data were entered into an Excel spreadsheet (Microsoft Corporation, 2007, USA) and were analysed using Minitab 15 (Minitab Inc., State College, PA, USA) and Stata 10 (Statacorp, College Station, TX, USA).

Basic descriptive statistics were performed and univariate associations were examined using Student's *t* test, the Kruskal-Wallis test and the Chi-square/Fisher Exact test as appropriate. Survival time was calculated in days from the date of diagnosis to the date of death. Dogs that were lost to follow-up were considered to be dead from the disease at the time of last contact. Dogs that were deemed to have died of causes unrelated to the TSCC or were still alive at the end of the study were censored at the time of last contact. Survival times according to presenting clinical signs and treatment received were examined using the Kaplan-Meier method. Differences between groups were tested with the log-rank and Wilcoxon tests. A P value of less than 0·05 was deemed to be statistically significant.

RESULTS

Population data

Forty-five questionnaires were returned but one dog was excluded from the study because of insufficient information. Of the 44 remaining dogs, 26 were male (59%) and 18 were female (41%). The breeds included: German shepherd dog (GSD) (seven), crossbreed (five), cavalier King Charles spaniel (four), springer spaniel (four), border collie (four), West Highland white terrier (three), cocker spaniel (two), rough collie (two), Labrador retriever (two), golden retriever (two) and one each of the following: Dalmatian, Rottweiler, Staffordshire bull terrier, Yorkshire

terrier, schnauzer, Rhodesian ridgeback, greyhound, miniature poodle and Pyrenean mountain dog.

Age at diagnosis ranged from 4 to 13 years and the median age was 10 years. Animals which were younger than or equal to 10 years (25 of 44) survived for a median of 212 days [interquartile range (IQR)=99 to 353 days] compared with older animals (19 of 44) whose survival time was 139 days (IQR=83 to 222 days), P=0·054.

Presenting signs

The most frequent clinical signs were cough (12 dogs, 27%), enlarged lymph nodes (11 dogs, 25%) and dysphagia (11 dogs, 25%). Pain was reported in nine cases (20%), and ptyalism and retching in eight cases each (18%). Interestingly, the TSCC was an incidental finding in 11 cases (25%).

Anorexia was seen in seven dogs and lethargy in four dogs, and these clinical signs were significantly associated with a poor outcome on univariate analysis. These signs were also strongly associated with each other (P=0·01, Fisher's Exact test). Median survival time for dogs with anorexia was 103 days with an IQR of 37 to 116 days (P=0·02), and for dogs with lethargy was 22 days (IQR=20 to 95 days, P=0·015).

Clinical findings and tumour staging

Twenty-three of the 44 dogs (52%) had only the right tonsil affected, 18 (41%) had only the left tonsil affected and in 3 dogs (7%) the disease was considered to be bilateral after cytological assessment. However, cytological or histological assessment of the contralateral tonsil was reported in only five cases. Distribution of the tumour was not significantly associated with outcome (P=0·19). Advanced imaging was not routinely used to evaluate the primary tumours: one dog had a computed tomography scan of the neck and one dog had magnetic resonance imaging for investigation of an unrelated neurological problem, and the TSCC was an incidental finding.

Only 22 animals had the size of the primary tumour reported and maximum diameter ranged from 5 to 60 mm. According to WHO classification for oropharyngeal tumours, dogs were classified as T1 (n=3, 0·13%), T2 (n=13, 59%), T3 (n=4, 18%), and in two cases the tumour was considered to be diffuse.

Eleven dogs (25%) presented with enlarged lymph nodes, in 31 dogs (70%) the lymph nodes were reported to be of normal size and in two dogs (5%) the size of the lymph nodes was not reported. All dogs with enlarged lymph nodes had fine needle aspirates or biopsy performed, and in 9 of 11, metastasis was confirmed, while the other 2 dogs were considered to have reactive nodes. Of the 31 dogs with normal size lymph nodes, 20 had aspirates or biopsy performed, and in 9 of 20 cases, metastatic spread was confirmed. Of the two dogs with unknown lymph node size, one had confirmed metastatic spread to the lymph node on fine needle aspirate.

Forty dogs (91%) had thoracic radiographs performed. In two dogs, (5%) metastatic spread of the tumour to the lungs was suspected but histology or cytology of the pulmonary lesions was not performed for confirmation.

No correlation was found between clinical stage and presenting clinical signs.

Table 1. Treatments received by the 44 dogs of the study

	Number of dogs
No treatment	8
NSAIDs	4
Surgery + NSAIDs	10
Surgery + chemotherapy + NSAIDs	7
Surgery + chemotherapy + radiotherapy + NSAIDs	5
Chemotherapy + radiotherapy + NSAIDs	5
Chemotherapy + NSAIDs	4
Radiotherapy + NSAIDs	1

NSAIDs non-steroidal anti-inflammatory drugs

Treatment

Of the 44 dogs in the study, 12 animals (27%) received no treatment after the diagnosis was made, and only in 4 of those dogs, non-steroidal anti-inflammatory drugs (NSAIDs) were used. Twenty-two dogs had debulking surgery performed, of which seven animals received adjuvant chemotherapy and five received chemotherapy and radiotherapy. Five dogs received chemotherapy and radiotherapy but no surgery, four dogs were only treated with chemotherapy and one dog received only radiotherapy (Table 1).

The chemotherapy protocols consisted of carboplatin as a single agent (seven dogs) or in combination with mitoxantrone (one dog), gemcitabine (two dogs) or epirubicin (nine dogs). Cisplatin and gemcitabine were used as single chemotherapy agents in two more cases. Nine dogs received weekly hypofractionated radiotherapy (four fractions of 9 Gy in eight cases and 8 Gy in one) and two dogs received daily Monday-through-Friday definitive protocols (22 fractions of 2·4 Gy in one case and 16 fractions of 3 Gy in the other). All patients were treated with photons (4 or 6 MeV).

Thirty-eight of the patients (82%) received treatment with NSAIDs. In 10 cases, the NSAID used was carprofen (Rimadyl; Pfizer), 22 cases received meloxicam (Metacam, Boehringer Ingelheim) and 6 cases received piroxicam (Feldene, Pfizer and Pharmachemie, Haarlem).

Summary survival data and outcome

Of the 44 dogs in the study, 1 dog was lost to follow-up (137 days after the diagnosis, this dog had surgery as the only treatment) and 1 dog was still alive at the end of the study (896 days after diagnosis). Forty-two dogs died during the study period, of which eight (19%) died of causes unrelated to the TSCC.

Size of the primary tumour, lung metastases or metastatic spread to the lymph nodes was not significantly associated with outcome.

Median survival time for all dogs in the study was 179 days (IQR=95 to 336 days) and ranged from 6 to 1657 days. For patients that had neither surgery, nor radiotherapy or chemotherapy (n=12), the MST was 65 days (IQR=22 to 109 days) compared with animals that received any treatment (n=32, including

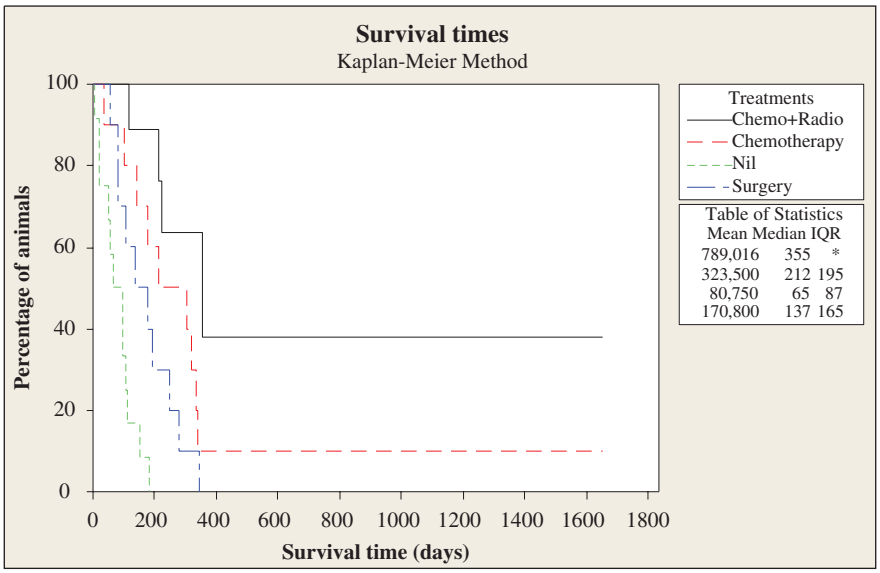

FIG 2. Kaplan-Meier survival curves of the 44 dogs with tonsillar squamous cell carcinoma (TSCC) that received chemotherapy and radiotherapy and/or surgery (Chemo+Radio), chemotherapy and/or surgery (Chemotherapy), no treatment (Nil) or surgery only (Surgery)

surgery, chemotherapy or radiotherapy) for which the MST was 222 days (IQR=137 to 344 days, P<0·01).

For dogs that underwent surgery as the only treatment modality (n=10), the MST was 137 days (IQR=83 to 248 days). Longer survival times were obtained in animals that received chemotherapy (n=11, MST=212 days, IQR=141 to 336 days, P=0·017) or chemotherapy and radiotherapy (n=10, MST=355 days, IQR=222 to >355 days, P<0·01). Interestingly, surgery did not apparently prolong the survival in these groups of dogs (P=0·09) (Fig 2).

For the 22 animals that received chemotherapy and/or radiotherapy, complete remission was achieved in 12 dogs, objective response was reported in 5 dogs and for the other 5 dogs this information was not available.

One- and two-year survival rate was 11·4% (n=5). All surviving dogs received NSAIDs. Two of those dogs were treated with surgery, chemotherapy and radiotherapy, one dog received chemotherapy and radiotherapy, one dog was treated with surgery and chemotherapy and the fifth dog received only radiotherapy. This dog survived 788 days and died from causes unrelated to TSCC. Three-year survival rate was 6% (n=3): one dog received radiotherapy and chemotherapy, one dog had surgery, chemotherapy and radiotherapy and the third dog had surgery and chemotherapy.

DISCUSSION

The signalment for the dogs in this study is similar to previous data on canine TSCC, with middle-aged males being over-represented (Cohen and others 1964, Brodey 1970, Todoroff and Brodey 1979). German shepherd dogs (GSDs) have previously been reported as a breed at high risk of developing oropharyngeal cancer (Cohen and others 1964). GSD was the most frequent breed represented in the current study, but population data were not available to confirm that the breed was over-represented.

In this study, anorexia (16%) and lethargy (9%) were the only clinical signs that had a significant negative impact on survival time. This finding might represent cases that presented with advanced disease, but no correlation was found between these clinical signs and clinical stage. It is also possible that the presence of clinical signs that can be associated with poor quality of life influences an owner or veterinarian's willingness to consider therapy following the diagnosis of an aggressive disease. Strategies to improve the quality of life of dogs with TSCC could have an impact on survival.

Previous reports suggest a high percentage of bilateral disease in cases of TSCC (Brodey 1970, Liptak and Withrow 2007). In our study, the disease was considered to be bilateral in three cases but as the contralateral tonsil was only assessed in five cases the true frequency of bilateral involvement may have been higher.

The high percentage of animals with metastatic spread to the regional lymph node (59%) at presentation is in keeping with the high metastatic potential of this type of tumour (Todoroff and Brodey 1979). However, neither lung metastases nor metastatic spread to the regional lymph nodes had a significant impact on outcome in our study. This most likely reflects the fact that clinical signs due to failure to control the primary disease are a more frequent cause of euthanasia than metastatic disease, but in this study that was difficult to assess given that only 50% of the dogs had tumour size reported. In addition, this is a retrospective study and tumour measurement was not standardised.

Nineteen of the dogs had metastatic spread to the lymph nodes, but only nine of these dogs had enlarged lymph nodes and nine had reportedly palpable normal nodes. This confirms the observation that finding normal-sized lymph nodes does not exclude metastatic spread (Langenbach and others 2001, Williams and Packer 2003, Williams and others 2005). It is,

therefore, possible that some of the 12 dogs that did not have cytological evaluation of nodes had undiagnosed metastatic disease, and failure to recognise this may have masked prognostic relevance of clinical stage.

Surgical treatment of TSCC is generally associated with poor survival times, and a positive impact on survival has not been proven. A previous study reported a MST of less than two months in eight dogs, with all dogs having tumour recurrence (Todoroff and Brodey 1979). In our study, MST for dogs that were treated only with surgery was 137 days. This apparent improvement in surgical outcome compared with the previous published data could be explained by factors such as differences in tumour stage amongst the study population or improved surgical technique. It may also reflect better palliative care compared to the 1970s or the use of NSAIDs in many patients. In our study, surgery exerted a lesser impact on outcome in dogs that received chemotherapy with or without radiotherapy. In most of the dogs presented with TSCC, complete tumour resection will not be achieved because of the infiltrative nature of this tumour, and surgery is considered palliative. More radical surgeries would be necessary in order to improve the survival time of dogs with TSCC but are not generally accepted as they may be associated with a higher morbidity.

In our study, longer survivals were obtained in animals that received treatment with chemotherapy or chemotherapy and radiotherapy, with objective responses or complete remission in most of the cases and a MST of 212 and 355 days, respectively.

The main chemotherapy agent used for the dogs in our study was carboplatin, as a single agent or in combination with other chemotherapy agents. Platinum-derived drugs are one of the main classes of chemotherapeutic drugs used to treat head and neck cancer (which is mainly SCC) in humans (Browman and others 2001). A previous study suggested that the combination of piroxicam and carboplatin is a useful treatment option for oral non-tonsillar SCC in dogs (de Vos and others 2005) with a 57% response rate and all patients alive at a median follow-up of 534 days. This median follow-up time was not achieved for most of the dogs in our study but TSCC is a much more aggressive tumour and it is associated with a poorer prognosis (Brodey 1970, MacMillan and others 1982, Brooks and others 1988). In another study, a combination of piroxicam and cisplatin was used to treat nine dogs with oral SCC, three of which were TSCC: two of them achieved partial remissions (Boria and others 2004).

Overall, outcomes after chemotherapy for TSCC remain disappointing, though there appears to be a beneficial role effect compared to no treatment in the current study. In a previous published study with 22 dogs, 16 dogs were treated with one of three different chemotherapy protocols after surgery (Brooks and others 1988) and achieved MSTs of between 90 and 120 days. Two small studies including six and five dogs treated with chemotherapy and radiotherapy after surgery (Brooks and others 1988, Murphy and others 2006) reported MSTs of 270 and 211 days from pathological diagnosis till death, similar to the current study. Neither study reports an untreated control group.

Previous case series have described an improved outcome in dogs receiving radiotherapy for TSCC (MacMillan and others 1982, White and others 1985, Brooks and others 1988, Murphy and others 2006) although results have not necessarily been substantiated statistically by comparison to untreated controls. The small number of animals and the variety in treatment protocols make it difficult to assess the benefit of radiotherapy in this cohort of animals.

Although the data in this study suggest an increased survival time in dogs receiving any form of treatment, owners who elect to pursue these treatments may be inherently more likely to elect to delay euthanasia compared to owners who do not wish to pursue palliative therapies. There may be a selection bias with patients with more advanced disease being less likely to be treated because of clinicians' or owners' reluctance. Although the data do not support this, the absence of uniform staging may have masked this possibility. In addition, the variation in treatment protocols amongst dogs in our study and between studies, and the small numbers of patients enrolled in each group make it impossible to draw firm conclusions regarding the best treatment protocol for dogs with TSCC.

NSAIDs were used in 38 of the 44 dogs in this study. It has been shown previously that NSAIDs have antitumour effects in dogs and humans (Breau and others 1989, Knapp and others 1992, 1994). In one study, two of four dogs with non-tonsillar oral SCC achieved partial remission following treatment with piroxicam (Knapp and others 1992). In another study, one of five dogs with TSCC treated with piroxicam achieved partial remission and two had stable disease (Schmidt and others 2001).

This is a retrospective multi-institutional study and as such the treatment protocols are not standardised. Clearly there is inherent bias on the part of the owner and of the clinician in selection of a particular therapy based on anecdotal evidence, preconceived notions about anticancer therapies, costs and duration of therapy and timing of euthanasia. Also, the small number of cases in each treatment subgroup limits the power of the study.

CONCLUSIONS

The management of TSCC is challenging, and even with multimodality therapy survival times are poor with almost all patients being euthanased within a year of diagnosis. However, a small percentage of dogs achieve long-term survival (6% alive at three years in the current study). Anorexia and lethargy are negative prognostic indicators in dogs with TSCC. Metastatic spread to the lymph nodes can be expected in a high percentage of dogs at the time of diagnosis but is not always accompanied by lymph node enlargement. Any treatment (surgery, chemotherapy, radiotherapy) apparently prolongs survival compared to no treatment, but further work is required to determine the true roles of surgery, chemotherapy and radiotherapy in dogs diagnosed with TSCC and the most appropriate protocols.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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