

Canine tonsillar Squamous cell carcinoma

Isabelle Desmas, DVM, MRCVS, Senior Clinical Training scholar in Oncology, Queen Mother Hospital, Royal Veterinary College, Hawkshead Lane, AL97TA, Hatfield, UK

ABSTRACT

Canine tonsillar squamous cell carcinoma is an uncommon disease, characterised by rapid growth and aggressive infiltration of the underlying tissues. Primary tonsillar cancer is called TSCC¹. Whatever the treatment used, it is generally regarded to carry a poor prognosis. The metastatic rate is around 73%, the disease generally spreads to the regional lymph nodes and to the lungs. Treatment approach includes surgery, radiation therapy, chemotherapy and symptomatic treatment, or any combination of these approaches. Multimodality approach is indicated given the high aggressiveness of this type of cancer. All treatment confounded but keeping a multimodality treatment approach, the median survival time is around six months. Without any treatment, an absence of control of the primary disease will lead to euthanasia in one or two months.

INTRODUCTION

Squamous cell carcinoma (SCC) is a cancer arising from squamous epithelium, which may occur in a variety of location in the oral cavity. Tonsillar squamous cell carcinomas (TSCC) account for 9% of canine oral neoplasms in dogs². TSCCs are very aggressive locally; they can invade the bone with subsequent osteolysis. In contrast to non-tonsillar SCC, TSCC have a high metastatic rate: 73% of the patients have lymph nodes metastasis at diagnosis and 42 to 63 per cent of dogs have more widespread metastasis (most commonly pulmonary involvement)³.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

Urban pollutants are considered as carcinogens that may contribute to the development of tonsillar SCC². Viral aetiologies (papillomavirus) have also been suspected for SCC in various locations⁴, as well as chronic inflammation. The animals generally present middle-aged to old, with a median age around 10 years old. TSCC may be more common in male dogs⁵. German Shepherds have been previously reported as predisposed to oral tumours and it was the most represented breed in one study on TSCC⁶. Clinical signs include ptialism, pain, inappetence and weight loss, lethargy, dysphagia, and halitosis. Lymphadenopathy was the most common clinical sign in one study⁶ (picture 1). The blood results usually do not reveal any abnormalities, except in case of a concomitant disease. A neutrophilia, secondary to infection of ulcerated masses may be present on the haematology.

DIAGNOSIS

As the disease is locally aggressive, the sooner the diagnosis is made, the better a long-term local control can be achieved. Cytology is a rapid, non-invasive way to achieve the diagnosis of SCC. Therefore it is advised as the first diagnostic technique. TSCC are usually accessible during examination of the mouth under general anaesthesia or sedation (picture 2). SCCs are tumours that do exfoliate well and generally good quality cellular samples are obtained by fine needle aspirate (picture 3). A non-diagnostic or equivocal sample may be due to necrosis in the tumour or to a too superficial sampling, where only inflammatory cells are observed. Biopsy may be required to obtain a definitive diagnosis in case cytology is non-diagnostic or equivocal. Sampling of the contralateral tonsil is recommended. In one study⁶, 7% of the population was affected by bilateral disease, and this number may have been underestimated due to absence of sampling of the contralateral tonsil in most of the patients.

A staging should be performed to detect any distant spread in order to plan properly the therapeutic plan. Staging include routine haematology, biochemistry, and urinalysis in order to define the general state of the patient prior to any treatments. Additionally, sampling of the regional lymph nodes (ipsilateral and contralateral), as well as imaging of the chest are recommended. The lymph nodes should be sampled even if they are normal-sized as they could still be infiltrated by the tumour⁶. Three-view radiographs of the chest may be performed but a CT scan would ideally be preferred as it is more sensitive to detect



Picture 1: lymphadenopathy of the right submandibular lymph node in a Cavalier King Charles with a right-sided tonsillar squamous cell carcinoma.

pulmonary lesions. Also, CT scan would further define the extension of the tumour infiltration, as well as show if there is any enlargement of internal lymph nodes such as the retropharyngeal lymph nodes. Advanced imaging is essential for planning of surgery or radiation therapy treatment.

TREATMENT

Surgery

Success of the surgical treatment depends on size and invasiveness of the tumour. One study gave a reported median survival time of two months in eight dogs when surgery was used as a sole option. All dogs had tumour recurrence, with distant metastases being present in all five dogs where a post mortem examination was performed⁷. Another study gave a slightly longer median survival time of 137 days when surgery was used as the only treatment modality⁶. Surgery is indicated whenever possible but may not be recommended when the disease is extensive. For example, it may lead to too many complications when the retropharyngeal lymph nodes are metastatic and need to be removed as they are the bed of many essential arteries and nerves.

Radiation therapy

RT is generally recommended as an adjuvant treatment when the tumour excision is incomplete or as a first-line treatment for tumours that are not amenable for surgery. A study describes the median survival time of eight dogs with tonsillar SCC treated with surgery plus definitive RT as 110 days⁸. Radiation protocols are usually hyperfractionated, meaning that they involve low-dose fractions given daily or every other day over a three-to-four-week period. When advanced or local disease is present and the goal of radiation is to reduce the pain and delay the growth of the tumour, a hypofractionated protocol, with higher fractions at a lower frequency may be used.

Chemotherapy

TSCC are not chemosensitive tumours. In 16 dogs with TSCC, treated with multidrug chemotherapy, there was no appreciable reduction in tumour volume, and 62% of the dogs were euthanized because of progressive disease⁹. When used with another treatment modality, however, chemotherapy has shown good results: two studies reported a median survival time of 211 and 355 days when chemotherapy was used in combination with radiation^{3,6}. The most common chemotherapy drug used for TSCC is carboplatin^{3,10}. Alternative drugs are gemcitabine¹⁰, mitoxantrone, epirubicin¹⁰, or doxorubicin⁹.

Nsaids

Increased expression of COX-2 has been reported in SCC in various locations¹¹. COX-2 is responsible for the production of inflammatory prostaglandins but has also been implicated in cancer progression when overexpressed. Therefore the use of anti-COX2 in SCC would have anti-inflammatory and anticancer properties



Picture 2: Right-sided tonsillar squamous cell carcinoma.

and is advised in their management. A study carried on dogs with unresectable oral SCC revealed that when used a single agent, piroxicam led to 18% remission rate, and 29% of stable disease¹². Additionally, NSAIDs have an analgesic activity that may prove useful in improving the quality of life of patients. Anti-inflammatories are well tolerated and relatively inexpensive, side effects include gastro-intestinal ulceration and renal toxicity.



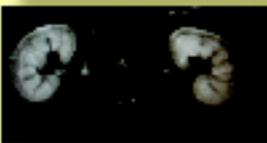
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Picture 3: Fine needle aspirate of a tonsillar squamous cell carcinoma by direct visualisation under general anaesthesia..

Carboplatin

Carboplatin is the drug of choice for treating head and neck cancer in human beings. It is generally well tolerated and is the first line treatment in pets with TSCC as well. A multi-modal approach is advised, with the combination of a local treatment (surgery and radiation therapy) and chemotherapy. With this approach, a study a mean survival time of 211 days was reported in five dogs with tonsillar SCC when carboplatin was used as chemotherapy³. In this study, carboplatin was used in two dogs with measurable

disease that were treated initially with this drug alone. Both showed a clinical partial response, demonstrating that carboplatin alone may also have some efficacy. Carboplatin may also be used as a radiosensitizer prior to radiation therapy. Another study performed in six dogs⁹ reported a median survival time of 240 days when doxorubicin and cisplatin were used as chemotherapy treatments.

Tyrosine kinase inhibitors

Recently, tyrosine kinase inhibitors (TKIs), such as toceranib (Palladia), have been licensed for the use in dogs. These drugs exhibit potent inhibitory activity against Kit and other tyrosine kinase receptors, and toceranib has shown both antiangiogenic and direct antitumour activity. Tyrosine kinase inhibitors have shown some efficacy against diverse types of carcinoma. Unfortunately, no large studies have been conducted in this field, but we think this type of therapy is likely to delay the progression of the tumour. Tyrosine kinase inhibitors are generally well tolerated, however some dogs may develop gastrointestinal toxicity (vomiting, diarrhoea, weight loss), moderate neutropenia, protein losing nephropathy, muscle cramping, epistaxis, hypertension and gastro-intestinal bleeding.

Prognostic Factors

So far, size of the primary tumour, lung metastases or metastatic spread to the lymph nodes have not been reported as negative prognostic factors, however study with larger population may be required. One study revealed that anorexia and lethargy had a significant negative impact on survival time⁶.

CONCLUSION

TSCC is a rare disease with a higher metastatic rate than its other canine counterparts. Complete staging with CT scan of the head, neck and chest is recommended to assess the extension of the disease and plan further treatment. Multi-modal therapy with surgical debulking, coarse fractionated radiotherapy and carboplatin therapy may confer clinical benefits in the treatment of TSCC. Whatever the treatment used, median survival time is around six months.

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Reader Questions and Answers

1. **WHAT IS THE METASTATIC RATE OF TONSILLAR SQUAMOUS CELL CARCINOMA?**
 - a) 58%
 - b) 10%
 - c) 73%
 - d) 35%
2. **WHICH IS THE MOST COMMON SITE OF METASTASIS OF TONSILLAR SQUAMOUS CELL CARCINOMA?**
 - a) liver
 - b) regional lymph nodes
 - c) spleen
 - d) nasal bone
3. **WHICH OF THE FOLLOWING CHEMOTHERAPY HAS BEEN MOST COMMONLY USED IN TONSILLAR SQUAMOUS CELL CARCINOMA?**
 - a) vincristine
 - b) cyclophosphamide
 - c) lomustine
 - d) carboplatin
4. **WHAT IS THE MEDIAN SURVIVAL TIME FOR DOGS WITH TONSILLAR SQUAMOUS CELL CARCINOMA, WHATEVER TREATMENT IS USED?**
 - a) two months
 - b) 18 months
 - c) 6 months
 - d) 12 months
5. **WHICH OF THE FOLLOWING FINDING HAS BEEN PROVEN TO BE PROGNOSTIC FACTOR IN DOGS WITH TONSILLAR SQUAMOUS CELL CARCINOMA?**
 - a) size of the primary tumour > 3cm
 - b) anorexia and lethargy
 - c) metastatic spread to the retropharyngeal lymph node
 - d) ulceration of the primary mass

ANSWERS: 1. C, 2. B, 3. D, 4. C, 5. B