Proceedings of the
World Small Animal Veterinary Association
Sydney, Australia – 2007

Hosted by:

Australian Small Animal Veterinary Association (ASAVA)

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Next WSAVA Congress

ORAL TUMOURS

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INTRODUCTION

Oral malignancies are some of the most common cancers encountered in small animal patients. Prognoses and treatment options vary considerably depending upon tumour type and location. This talk will focus on the most commonly oral malignancies: squamous cell carcinoma (SCC), malignant melanoma (MM) and fibrosarcoma (FSA).

CLINICAL SIGNS

The clinical signs associated with tumours of the oral cavity are similar and will be considered collectively, rather than by tumour type. Animals with tumours located in the rostral oral cavity are often presented for evaluation when the mass is detected by the pet owner. The visibility of this location makes earlier detection likely, which may facilitate complete tumour excision. As such, rostral tumour sites are associated with a better prognosis for malignancies such as SCC. Early detection and diagnosis of oral cancer is less likely when the primary mass is located in a less visible location such as the caudal oral cavity or under the tongue. Lesions with a benign outward appearance may also go unaddressed by pet owners who are unaware of the possibility of oral cancer in dogs and cats. Suspicion of oral cancer may develop during routine dental procedures. A hallmark of oral cancer is the presence of loose teeth in a patient with otherwise good dentition. Veterinarians are advised to obtain biopsy samples of surrounding tissues at the time of tooth extraction for patients with this clinical presentation. This is especially true for feline oral SCC. Typical clinical signs reported for dogs and cats with oral cancer include ptyalism, halitosis, dysphagia, weight loss or decreased oral intake, palpable regional lymph node enlargement, disinterest in chew toys, and blood staining noted on food and water bowls, forepaws, or bedding.

DIAGNOSIS AND STAGING

Tumour location may dictate the procedures used to diagnose and stage oral tumours. Lesions in the rostral oral cavity and masses that are friable may be easily sampled using only sedation. Lesions in more caudal or inaccessible sites and those masses that are likely to bleed when biopsied may necessitate general anaesthesia. If oral cancer is suspected, 3-view chest radiographs are advised in order to detect subclinical metastatic disease prior to beginning an expensive work-up. Radiographic or computed tomography (CT) imaging of the affected site will help to determine tumour extent and will aid in planning for surgery or radiation therapy. For this reason, when malignancy is suspected, it is advisable to plan ahead and discuss performing skull radiographs or CT imaging under the same anaesthesia as the biopsy procedure in order to limit the number of anaesthetic events. Visual inspection of oral masses often greatly underestimates disease extent, especially for feline oral SCC and for maxillary lesions.

Oral mass biopsy should be performed with curative intent if the lesion is small and pedunculated or superficial. Larger, more invasive lesions should be sampled by incisional biopsy, as treatment decisions may depend on the tumour type and stage of

disease. Samples should be large and representative of the mass, with care taken to avoid sampling areas of necrosis. When performing an incisional biopsy, the biopsy site should be located such that it can be easily excised at the time of definitive surgery. In general, this means that oral lesions should be sampled via an oral approach, as opposed to creating a biopsy tract through the overlying skin. Use of electrocautery should be withheld until after the biopsy sample is obtained, as it can distort the histological appearance of tissues. Immunohistochemistry (IHC) may be necessary to determine the diagnosis for poorly differentiated tumours. IHC stains used to differentiate oral masses include cytokeratin for carcinomas, vimentin for sarcomas, and S-100, melanin A, or tyrosinase to identify MM. It is often difficult to differentiate MM from other oral malignancies, because the cells may be round, ovoid, or spindle shaped, mimicking other oral tumours. They may also be amelanotic, thus lacking the granules that distinguish MM from other tumours. It may be helpful to make impression smears of biopsy tissues before placing them in formalin, such that cytological evaluation can be compared with the histological appearance in difficult cases.

Tumour staging should include evaluation of regional lymph nodes. The ipsilateral mandibular lymph node should be aspirated, as should any enlarged regional nodes. CT may be necessary to fully evaluate for nodal metastasis, as the parotid and retropharyngeal nodes also drain the oral cavity, yet may not be palpable on physical examination. If nodal metastasis is suspected based on palpation, tumour type (melanoma), or advanced imaging, it may be wise to biopsy or remove the affected node(s) at the time of surgery. There is no evidence to suggest that lymph node excision facilitates distant metastasis of oral cancer in animals. Furthermore, lymph node biopsy may reveal regional metastasis that was not cytologically evident from fine needle aspirate samples. If nodal or distant metastasis has occurred, therapy that targets only the oral lesion will not suffice. Along with chest radiographs, a serum chemistry profile, CBC and urinalysis are generally advised to detect organ dysfunction that may alter therapy choices, assess for paraneoplastic syndromes (such as hypercalcaemia with feline oral SCC), and detect any concurrent complicating diseases.

TUMOR BIOLOGICAL BEHAVIOR

Malignant melanoma

Malignant melanoma is the most prevalent canine oral cancer, but is uncommon in cats. Canine MM is an aggressive cancer, with metastatic rates exceeding 80%. Tumours that measure <2cm and have not metastasized to the lymph nodes (Stage I) warrant a much better prognosis than large (>4 cm) MM or those with nodal metastasis (Stage III). In one report, the median survival time (MST) for dogs with Stage I tumours (511 days) far exceeded that of dogs with Stage III tumours (164 days).

Squamous cell carcinoma

The most common oral cancer in cats and the second most common in dogs, SCC is a very locally invasive malignancy. Underlying bone lysis may be very extensive by the time of diagnosis. As such, imaging with radiographs or CT is advised to accurately estimate the degree of local invasion. Oral SCC is most often a disease of older animals (average age = 10). Regional lymph node metastasis is uncommon, except

with canine tonsillar or lingual SCC. Both of these SCC sites are accordingly associated with a poor prognosis. Regional lymph node enlargement may actually be the reason for initial presentation for dogs with tonsillar SCC, with gross evidence of the primary tumour appearing later in the disease course. Prognosis varies by tumour location. Rostral tumours may be cured with surgery or radiation therapy. However, tonsillar and sublingual lesions are likely to recur and metastasize. Canine tonsillar SCC often occurs bilaterally, with survival beyond a year unlikely. Similarly, the one-year survival rate for cats with oral SCC rarely exceeds 10% regardless of treatment.

Fibrosarcoma

Oral FSA is a malignant mesenchymal tumour with a propensity for the palate of dogs and the gingiva of cats. Achieving local tumour control is often challenging, as FSA invades bone and surrounding tissues and may be quite large before noted by the pet owner. Some canine FSAs are characterized by a benign or low-grade histological appearance that is contrary to the aggressive biological behaviour of the mass. This scenario has been reported most commonly for golden retrievers and is usually associated with mandibular and maxillary lesions, as opposed to palate lesions. The reported metastatic rate for FSA is less than 25%, with metastasis usually to the lungs.

TREATMENT OPTIONS

Surgery

If metastasis has not yet occurred, complete surgery affords the best chance for cure of any primary oral cancer. Lesions of the rostral oral cavity, including those on the mobile portion of the tongue, should be removed with curative intent. Dogs can still prehend food and drink, even after excision of over half of the mobile portion of the tongue. Cats may not tolerate extensive oral surgery as well and may have a poor hair coat due to an inability to groom normally after partial glossectomy. Two-centimetre surgical margins are advised, although obtaining margins in excess of 2 cm is unlikely to improve outcome. In one study of dogs with oral MM, case outcome was similar, regardless of the extent of surgery (radical vs. limited) beyond complete local tumour excision. Long-term outcome after mandibulectomy or maxillectomy varies by tumour type. In one report, the 1-year survival after maxillectomy or mandibulectomy was 91% with SCC, 50% with FSA, and 21% for dogs with MM. The reported MST for cats undergoing mandibulectomy for SCC is between 2.5 and 6 months. In both species, cryosurgery may be a reasonable technique for small (<2 cm diameter) lesions if bone invasion is minimal. In cases that do not fit these criteria, treatment complications such as oronasal fistula or bone necrosis and fracture may occur after cryosurgery.

Radiation Therapy

Radiation therapy (RTX) is utilized with curative intent for small SCC or for localized tumours with incomplete margins after surgery. Alternatively, radiation can be used to down-stage oral tumours prior to surgery. Response rates are best for SCC, with more moderate responses expected for FSA and MM. For canine oral MM, coarse fractionation (once weekly) provides similar clinical responses to those with standard fractionation, and permits patients to spend more time at home. One report suggests that platinum-based chemotherapy used in conjunction with coarsely fractionated RTX

(six weekly fractions) provides a better outcome (MST = 363 days) than that reported for RTX or chemotherapy alone. Prospective evaluation is needed to confirm this.

The bone-targeting radioisotope, ^{153}Sm-EDTMP, has been used to treat unresectable oral masses that have a minimal soft tissue component. A bone scan is needed prior to treatment to ensure that tumour uptake of the radiopharmaceutical will be adequate. Although the therapy must be performed at sites licensed for its use, it requires less patient hospitalization than standard external beam radiation therapy.

Medical therapy

The cause of death or euthanasia for small animal patients with oral cancer is often local disease progression, rather than metastasis. For this reason, systemic chemotherapy may be less important than localized therapy for improving clinical outcome of dogs and cats with oral cancer. In the case of canine oral MM, metastatic disease is an important cause of treatment failure, but this type of cancer is relatively resistant to standard chemotherapy. Cisplatin, carboplatin, and melphalan are reported to provide clinical responses in dogs with oral MM, but response rates are less than 30% and significant improvement in survival has not yet been demonstrated. The most promising results with chemotherapy against SCC were reported by de Vos, et al. Four of 7 dogs treated with carboplatin and piroxicam experienced remission, with MST not yet reached after a median follow-up time of 534 days. The author and others recently completed a prospective study comparing toxicity and efficacy of piroxicam single-agent therapy to combined mitoxantrone and piroxicam for cats with oral SCC. Data analysis is pending and available results will be provided. Prior to this study, the best responses reported for cats with oral SCC involved combining radiation and mitoxantrone, but MST was still only six months, compared to one to two months with most other protocols.

Photodynamic therapy

Photodynamic therapy (PDT) requires infusion or topical application of a photosensitizing agent, followed by exposure of the tumour to a specific wavelength of light that will activate the photosensitizing agent. McCaw, et al, reported their results obtained with PDT after surgery for dogs with oral SCC in the *British Journal of Cancer*. Eight of 12 dogs were alive and apparently disease-free >17 months after treatment. In contrast, our experience with PDT for feline oral SCC has been disappointing.

Immunotherapy/Gene therapy

Recent areas of investigation of immunotherapy approaches against canine oral MM include tumour vaccines and cytokine therapy such as IL-2 and GM-CSF. The 2007 USDA approval of a vaccine using a DNA plasmid expressing the human tyrosinase gene to treat MM has generated new enthusiasm for such immunological approaches. Dogs with Stage II – IV MM receiving four biweekly injections of the vaccine had a MST of 389 days, compared to historical MST of <5 months for dogs with Stage II oral MM and 2 to 3 months for dogs with Stage III or IV disease treated with surgery. Updates will be provided after commercial release of the vaccine the US this summer.

REFERENCES AVAILABLE UPON REQUEST