

Canine oral melanoma

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ABSTRACT

Oral canine malignant melanoma is a spontaneous, locally aggressive, and highly metastatic tumour. A full clinical staging is required prior to plan a proper treatment, which will combine an aggressive local treatment with systemic therapy (chemotherapy or immunotherapy). This article aims at guiding the practitioners in the first steps of diagnosis and staging and also at providing data regarding prognosis so that they will be able to guide the clients in the decision-making process for their pet.

INTRODUCTION

Primary melanoma arises from melanocytes, which are epidermal cells that generate melanin pigment. It is the most common oral tumour in dogs. Other common differentials for oral tumours include squamous cell carcinoma, fibrosarcoma, and benign tumours (epulides/odontogenic tumours). Oral melanomas are generally discovered secondary to halitosis and this may occur quite late in the development of the tumour (**Figure 1**).



Figure 1: Oral Melanoma.
Credit: Oncology Service, QMHA, Royal Veterinary College.

SIGNALMENT OF DOGS AFFECTED BY THE DISEASE

Oral melanoma is most commonly seen in the following breeds: Scottish terriers, Golden retrievers, Poodles, and Dachshunds¹. Only one study has shown that breed has a prognostic impact in dogs with both cutaneous and oral melanomas included: in that study, 75% of melanocytic neoplasms exhibited a benign behaviour in some breeds (Doberman Pinscher and Miniature Schnauzer), whereas more than 85% of melanocytic neoplasms were malignant in other breeds (Miniature Poodle)². Oral melanoma is primarily a disease of older dogs with no gender predilection reported.

DIAGNOSIS AND CLINICAL STAGING

Diagnosis

Melanomas can be a challenge to diagnose due to the pleomorphism of melanocytic cells. Indeed they can be confounded with carcinomas (epithelioid or polygonal cells), sarcomas (spindle cells), and round cell neoplasms, which

differ in prognosis and treatment. Furthermore, most melanomas are pigmented but amelanotic melanomas have been reported³ (**Figure 2**). A fine needle aspirate of an oral mass may be sufficient enough to diagnose the tumour. If not, an incisional biopsy is recommended in order to proceed to immunohistochemical staining on the tissue. This will help to define the nature of the cells from which the tumour originates. The biopsy should be incisional in order to leave the burden of the disease for appropriate surgical planning and definition of the margins later on. Melan-A, PNL2, TRP-1, and TRP-2 are highly sensitive and 100% specific immunohistochemical markers for the diagnosis of canine oral melanomas and can be requested to the lab when there is any doubt regarding the origin of the submitted tissue³.

Staging

Canine oral melanomas are highly malignant tumours with a high degree of local invasiveness and frequent metastasis to the regional lymph nodes and the lungs. The metastatic rate has been reported to be up to 80% (**Figure 3**). The staging for dogs with oral melanomas first comprises a minimum database which should include a thorough history and physical examination, complete blood count biochemical profile, and urinalysis. Chest imaging (with three-view chest films or a CT scan), and local lymph node aspiration should thereafter complete the assessment of the patient in order to evaluate where the disease is present. A lymphadenomegaly (**Figure 4**) is not necessarily present when the lymph nodes are infiltrated by the tumour⁴, therefore it is recommended to fine needle aspirate the lymph nodes no matter the size they have. Also, due to variability in draining patterns, ipsilateral and contralateral nodes should be sampled. Ideally a CT scan of the head should be



Figure 2: Amelanotic oral melanoma. Credit: the oncology department of the QMHA, RVC

performed as the retropharyngeal lymph nodes are normally non palpable on physical examination and can be a draining site of the oral cavity. Therefore 3D imaging of the head is advised to assess if they are involved.

PROGNOSTIC FACTORS

The biologic behaviour of canine oral malignant melanoma depends on a variety of factors and there are unfortunately no universally accepted criteria to prognosticate this tumour. A combination of different factors has to be evaluated in each patient's neoplasm. The prognostic factors known for canine oral melanomas are summarized in **Table 1**.

SITE

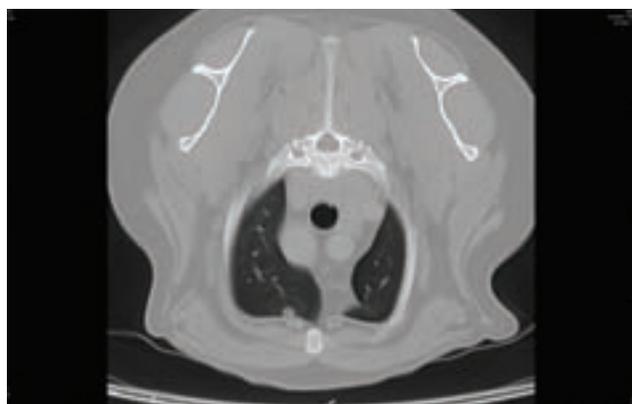


Figure 3: CT showing pulmonary metastasis in a patient that presented with oral melanoma. *Credit: QMHA, RVC*

The melanoma site can predict its invasiveness and its tendency to spread to distant organs. Melanomas involving the haired skin behave in a more benign manner than the one involving the mucosa. Oral melanomas are considered extremely malignant compared to their cutaneous counterparts that are likely to be cured after surgical removal. The location inside the oral cavity has also been found to be prognostic; indeed melanomas in the caudal mandibular and rostral maxillary parts seem to have a worse prognosis. A subset of oral and lip melanocytic neoplasms has been identified with having a more favourable prognosis⁵. In one study, the mean survival time for dogs with oral or lip melanocytic neoplasms was 22.7 months, but this study included only histologically well differentiated melanocytic neoplasms⁶. Another study

Location	Oral/lip
distant metastasis	poor prognosis
lymphatic invasion	poor prognosis
mitotic index	≥4/ 10 hpf poor prognosis
nuclear atypia	≥30% poor prognosis
degree of pigmentation	<50% uncertain prognosis
presence of ulceration	no prognostic significance
level of infiltration/invasion	deep with possible bone lysis poor prognosis
KI=i67	≥19,5 poor prognosis

Table 1: prognostic factors for canine oral melanomas (Adapted from 12)



Figure 4: Lymphadenomegaly of the left submandibular lymph node. *Credit: the oncology department of the QMHA, RVC*

showed that oral melanoma had the shortest median survival time (147 days) when compared with those of the feet and lips (676 days) and to those from the skin(725 days)⁷. The limiting factor of these studies is that they do not differentiate between lip melanomas that arise from the haired skin and those that arise from the mucosa on the lip. Therefore differences in survival times result from the type of lip neoplasms (haired skin vs mucosa) as melanomas arising from haired skin are known to have a better prognosis.

Size

Classification of canine oral melanoma is called the world health organization (WHO) staging scheme and is based on the size and the spreading of the tumour (**Table 2**). It has the following repartition: stage I <2-cm-diameter, stage II ≥ 2-cm- to < 4-cm-diameter, stage III ≥ 4 cm and/or lymph node metastasis, and stage IV = distant metastasis. One study reported median survival times for dogs with oral melanoma treated with surgery to be approximately 17 to 18, 5 to 6, and 3 months with stage I, II, and III disease, respectively⁸. Stage I melanoma have been reported to have median survival times ranging from 12 to 19 months after surgery, and/or radiation and/or chemotherapy⁹⁻¹¹. The big limitation of this classification is that it does not account the size of the dogs. Therefore we do not know if a 2 cm mass in a giant dog has a similar prognosis than a mass of the same size in a miniature breed.

T: Primary tumor
T1 Tumor ≤2 cm in diameter
T2 Tumor 2-4 cm in diameter
T3 Tumor >4 cm in diameter
N: Regionallymph nodes
N0 No evidence of regional node involvement
N1 Histologic/cytologic evidence of regional node involvement
N2 Fixed nodes
M: Distant metastasis
M0 No evidence of distant metastasis
M1 Evidence of distant metastasis
Stage I = T1 N0 M0
Stage II = T2 N0 M0
Stage III = T2 N1 M0 or T3 N0 M0
Stage IV = Any T, any N and M1

Table 2: Traditional World Health Organization TNM-based staging scheme for dogs with oral melanoma

Histological features

The histologic appearance of melanoma as well as histologic criteria are not accounted in the WHO classification but still have an impact on the prognosis of dogs affected by oral melanomas. The histologic grade may help to define the degree of aggressiveness of the tumour, although no classification has been defined yet with a good correlation to prognosis. The morphologic evaluation can rely on evaluation of cell size and shape, nuclear size and shape, chromatin pattern, prominence of nucleoli, and lack of pigment⁵. The most commonly evaluated histologic factor for prognostic utility is the mitotic index (number of mitotic figures per 10 consecutive non-overlapping high power field)¹². Other factors such as nuclear atypia, tumour score, presence of deep inflammation, intralesional necrosis, and junctional activity have also been reported to have a prognostic significance⁷. The mitotic index is the only histological parameter to which a numerical value is assigned with a known cut-off for malignant melanoma. Oral and lip melanocytic neoplasms with ≥ 4 mitoses/10 hpf have been associated with an increased risk of patient death within 1 year of diagnosis, this threshold value had a sensitivity of 90% and a specificity of 84%¹³. Another study showed that none of highly pigmented lip and oral melanocytic neoplasms with a favourable outcome had a MI > 3 per 10 hpf⁶. Additionally, Ki67 is a proliferation marker (tumour growth fraction) determined via immunohistochemistry that can be used for oral melanomas prognostication¹³, with a threshold value of 19.5 positive nuclei per grid reticle.

TREATMENT MODALITIES

Studies have shown that median survival time for untreated dogs with oral melanoma may be as short as 2 months. There are several options for treatment with the best survival times expected with multimodality therapy. With oral malignant melanomas, it is necessary to think about both local disease and distant metastasis, therefore combination of a local and systemic treatment is advised.

Local treatment

SURGERY

The treatment of choice for melanoma without distant metastasis is a wide surgical excision with at least 2 to 3 cm margins. The surgery plan must be prepared according to the diagnostic images to define the borders that need to be achieved. The surgery is usually aimed at being aggressive in order to increase the curative intent. The location of the disease will dictate the type of surgery that is required (e.g., unilateral, rostral, central maxillectomy or mandibulectomy)¹. Even if this type of surgery carries a high morbidity in the short term, dogs cope well and generally the owners are very satisfied. The median survival time for dogs treated only with surgery ranges from 150 to 318 days¹.

RADIATION

Radiotherapy is a good option for control of local disease to prevent recurrence in oral malignant melanoma, as tumoral

melanocytes are radiosensitive. Radiation therapy can play a role in the treatment of oral melanoma when the tumour is not surgically resectable or when the excision is incomplete. In case of microscopic disease, small fraction given daily can be administered; this is called a curative-intent protocol. The lymph nodes can be included in the treatment field in case they are involved. Bigger fractions given weekly may be used when the tumour is treated as a gross disease, without any surgical attempt prior to the radiation exposure. Radiotherapy represents a desirable option for local tumour control, however adverse effects such as inflammation (mucositis) and therefore subsequent discomfort at the treatment site can occur. Those adverse effects are acute and disappear generally in a couple of weeks. The median survival time for dogs treated with radiation therapy ranges from 5.3 to 11.9 months¹.

Systemic treatment

CHEMOTHERAPY

Oral melanomas have a high tendency to spread. Therefore a systemic treatment is indicated. Unfortunately melanoma is not highly responsive to systemic chemotherapy, although carboplatin has been used, with response rates of around 30% in the gross disease setting¹⁴. When carboplatin was combined with radiation therapy a median survival time of 286 d was found in one study¹⁵. On its own (i.e. with no local treatment), carboplatin has been shown to generate mainly partial response and for a very limited time. A further treatment option is the use of metronomic chemotherapy. This therapy consists of administering low doses of a chemotherapeutic agent (cyclophosphamide or chlorambucil) in combination with a COX2 inhibitor (firocoxib or meloxicam). This treatment modality has been documented to be antiangiogenic and effective in some canine neoplasias such as haemangiosarcomas and incompletely resected soft tissue sarcomas. No studies have been performed on oral melanomas, however there is some evidence it may be effective in slowing down the progression of the metastatic disease. This approach has minimal side effects and is generally well tolerated. It is unlikely that it will have good efficacy on its own but can complete a local treatment.

IMMUNOTHERAPY

Oral melanomas are also immunogenic tumours and encouraging preliminary results have been documented with the use of immunotherapy (i.e. canine melanoma vaccine) in combination with either surgery or radiation therapy. Immunotherapy for oral melanoma consists in the administration of a xenogenic vaccine given transdermally once every other week for four times.

The vaccine is a human tyrosinase DNA vaccine (tyrosinase is a melanosomal glycoprotein, essential in melanin synthesis) and aims to stimulate a systemic immune response against the dog's melanoma. The vaccine is licensed to treat dogs with stage II or III oral melanoma where the local disease has been controlled locally with surgery or radiation therapy. There is limited information in the literature currently, but in a study of 9 dogs¹⁶, use

of the vaccine showed a median survival time of 1 year when combined with local treatment. Another study based on a larger group of dogs report a benefit in term of using the vaccine but no survival time has been calculated. This treatment is safe and quite convenient for the owner as it consists of 4 injections every other week (and boosters every 6 months thereafter if the dog is doing well). The vaccine is quite expensive and has to be administered by a specialist holding a license.

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Reader Questions and Answers

1. WHICH OF THE FOLLOWING TUMOUR IS NOT A COMMON DIFFERENTIAL FOR ORAL TUMOUR?

- squamous cell carcinoma
- hemangiosarcoma
- fibrosarcoma
- epulis

2. WHICH OF THE FOLLOWING BREED HAS BEEN SHOWN TO BE AFFECTED BY MORE AGGRESSIVE MELANOMAS?

- Bernese Mountain
- Miniature Poodle
- German Shepherd
- French Bulldog

3. WHICH OF THE FOLLOWING CRITERIA IS CORRELATED WITH A WORSE PROGNOSIS IN CANINE ORAL MELANOMA?

- a size of 4 cm
- a mitotic index of 1/10 hpf

- the presence of prescapular lymphadenopathy
- location of the mass in the rostral mandible

4. WHICH OF THE FOLLOWING LOCATION IS USUALLY ASSOCIATED WITH A GOOD PROGNOSIS AFTER SURGICAL REMOVAL?

- oral cavity
- mucosal part of the lip
- nail bed
- haired skin

5. WHAT IS THE MINIMUM SIZE OF THE SURGICAL MARGINS ATTEMPTED WHEN REMOVING AN ORAL MELANOMA FROM THE ORAL CAVITY?

- 0.5 cm
- 1.5 cm
- 0.2 cm
- 2 cm

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