Oral Melanoma in Dogs

Oral melanoma is the most common malignant tumour of the oral cavity in dogs followed by squamous cell carcinoma and fibrosarcoma. Oral melanomas are aggressive tumours with a high rate of metastasis especially to the loco-regional lymph nodes and pulmonary parenchyma. The prognosis for dogs with oral melanoma depends on the histologic features, clinical stage and treatment used. Dogs with Stage I disease treated with surgery, with or without adjuvant radiotherapy, can achieve long term survival or even cure, whereas dogs with stage III and IV disease carry a poor prognosis. For large tumors located in the caudal oral cavity, complete surgical excision is often not possible and radiotherapy may be more appropriate. Response rates for oral melanoma treated with radiotherapy are reported to be around 80-90%. Median survival time for dogs treated with radiotherapy ranges from five to 11 months but may be influenced by both disease stage and the radiotherapy protocol used. Unfortunately, immunotherapy and chemotherapy have not been definitively demonstrated to significantly delay metastatic disease, however some efficacy of the melanoma vaccine has been reported.

Key words: Oral melanoma, melanoma vaccine, radiotherapy

Introduction, comparative and molecular aspects

Canine melanoma is a neoplasm that originates from melanocytes found in the skin, nail bed, footpad, mucous membranes, eyes and, more rarely, respiratory and gastrointestinal tracts (Smith et al. 1999; Hicks and Fidel 2006). Oral melanoma is the most common malignant tumour of the oral cavity in dogs followed by squamous cell carcinoma and fibrosarcoma (Hoyt et al. 2006). Whilst canine dermal melanomas are usually benign and often cured by surgical excision, oral melanomas are primarily aggressive tumours with a high rate of metastasis and a predilection for the loco-regional lymph nodes and pulmonary parenchyma (Bostock 1979; Modiano et al. 1999). Recently a histologically well differentiated oral melanoma with a low mitotic index (<4/10 high power fields (HPFs)) and low Ki67 index has been reported to have a more benign biological behaviour although some oncologists question whether these tumours are truly benign (Esplin et al. 2008; Bergin et al. 2010; Bergman et al. 2013).

Ultraviolet (UV) solar radiation is the most important risk factor for the development of cutaneous melanoma in people (Brozyna et al. 2007). However, as the mucous membranes are not exposed to sunlight, UV radiation is not a risk factor for either canine or human mucosal melanoma. Melanocytes are present in the mucous membranes and, in particular, the mouths of pigmented dogs. Their function in these sites is not well understood, however there is evidence to suggest an immunological role, with potential phagocytic and antigen presenting cell functions (Mackintosh 2001). The risk factors and etiopathogenesis of oral melanoma in dogs are unknown, but a genetic predisposition is possible, given the high prevalence of this disease in some small breeds and breeds with heavily pigmented oral mucous membranes (Ramos-Vara et al. 2000).

Human mucosal melanoma is an uncommon yet aggressive disease with a high rate of regional and distant metastases, high mortality rate and limited treatment options (Gavriel et al. 2001; DelVecchio et al. 2014). Canine mucosal melanoma shares some histological and biological features with the human variant and may thus be considered as a relevant biological model.

Similar oncogenic dysregulation in cell signalling has been found in both human and canine mucosal melanoma (Simpson et al. 2014). In particular, common oncogene mutations in cutaneous melanoma in humans e.g. BRAF and NRAS are uncommon in mucosal melanoma in both humans and dogs (Simpson et al. 2014). Aberrant expression of the oncogene stem cell factor receptor KIT and FAK (focal adhesion kinase) have been found in cutaneous and mucosal melanoma in people (Kahana et al. 2002; Curtin et al. 2006; Beadling et al. 2008; Hess et al. 2008; Satzger et al. 2008).
Aberrant expression of the oncogene KIT is relatively common in certain subtypes of human melanoma (Curtin et al. 2006) however, mucosal melanoma in dogs rarely carries a KIT mutation. In one study KIT mutation was not found in any of 17 samples examined (Murakami et al. 2011) and, in another study, only five of 49 patients had the KIT mutation (Chu et al. 2013). However, both studies only investigated mutations in exon 11 and high immunohistochemical KIT protein expression was identified raising the possibility of the presence of mutations in other exons.

A recent study investigated platelet derived growth factor receptor (PDGFRα/β) expression in oral melanoma and demonstrated that around 50% of oral canine melanomas express PDGFRα and α and β co-expression was shown to correlate with a poorer prognosis (Iussich et al. 2017). PDGFR, in combination with KIT, is a target of the tyrosine kinase inhibitors toceranib and masitinib. It is possible that a poorer prognosis (Iussich et al. 2017). co-expression was shown to correlate with melanomas express PDFGR and α and β co-expression was shown to correlate with a poorer prognosis (Iussich et al. 2017).

**Clinical Presentation and Diagnosis**

Oral melanoma is more common in older dogs and in several breeds including the Golden Retriever, Cocker Spaniel, Miniature Poodle, Gordon Setter, Anatolian Sheepdog and Chow Chow breeds (Ramos-Vara et al. 2000). The Chow-Chow and Shar-Pei breeds are also reported to be at higher risk of developing malignant melanoma of the tongue (Dennis et al. 2006).

Oral tumours are often diagnosed at an advanced stage due to the lack of early clinical signs and difficulties in visualising the mass. Dogs are often presented for investigation of malodorous breath, blood tinged saliva, difficult mastication and/or oral pain. Occasionally, and particularly when in a rostral location, an oral mass is noticed by the owner when the dog pants or yawns. The tumour may originate from the mucosa of the maxilla, mandible, lip, tongue or tonsil. The mass may appear ulcerated, necrotic and/or infected (Figures 1 and 2). Often these tumours are pigmented and dark, but non-pigmented, amelanotic melanomas can occur.

A dark pigmented mass in the mouth carries a high index of suspicion for oral melanoma (Figures 1 and 2). Fine needle aspirate cytology can be useful for the diagnosis of melanoma when typical intracellular melanin granules are present in the neoplastic cells (Figure 3). A definitive diagnosis, however, is better achieved by histopathology. In amelanotic melanoma, achieving a histological diagnosis can be difficult due to the lack of intracellular melanin pigment and the anaplastic appearance of the tumour cells. In these cases an immunohistochemistry panel including PNL2, Melan-A, TRP-1, and TRP-2 has 100% specificity and 93.9% sensitivity for identifying canine oral amelanotic melanoma (Smedley et al. 2011).

**Clinical Staging**

Staging for oral melanoma is important as prognosis and treatment are dependent on the tumor stage. Minimum clinical staging requires haematology, serum biochemistry, three view thoracic radiography and fine needle aspiration of the local lymph nodes. Computed tomography (CT) is however more sensitive for identifying retropharyngeal lymphadenopathy (Figure 4) as well as small pulmonary metastatic nodules that may not be visible radiographically (Nematic et al. 2006). Abdominal ultrasound should also be considered as metastasis to abdominal organs is occasionally reported (Liptack et al. 2013). Clinical stage is based on the TNM system of the World Health Organisation (Table 1).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Tumour &lt; 2cm diameter, no metastases to the lymph nodes</td>
</tr>
<tr>
<td>Stage II</td>
<td>Tumour 2 to 4 cm diameter, no metastases to lymph nodes</td>
</tr>
<tr>
<td>Stage III</td>
<td>Tumour &gt;4 cm or 2-4 cm with metastases to lymph nodes</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Tumour any size with distant metastatic disease to other organs</td>
</tr>
</tbody>
</table>

The metastatic rate for oral melanoma is high with around 50-60% of affected dogs having metastases to the regional lymph node at the time of presentation (Ramos-Vara et al. 2000; Williams et al. 2003). Metastases are reported in the absence of lymph node enlargement in approximately 40% of patients and metastases to the