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ONCOLOGY

Diagnosis and Treatment of Canine Oral Melanoma

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Malignant melanoma is the most common oral tumor in dogs. Overrepresented breeds include miniature poodle, dachshund, Scottish terrier, cocker spaniel, chow chow, and golden retriever.[1-3] Most dogs that develop oral malignant melanoma (OMM) are older; there is no gender predilection.[4] OMM must be differentiated from other malignant tumors of the oral cavity (e.g., squamous cell carcinoma, fibrosarcoma) as well as benign oral tumors and inflammatory and hyperplastic lesions, which are more prevalent than oral malignancies.[5,6]

PRESENTATION AND CLINICAL SIGNS

Affected dogs may be asymptomatic. In these cases, an oral mass is often discovered by the owner or during a routine physical examination or dental prophylactic procedure. Clinical signs of OMM include halitosis, excessive drooling, bleeding from the oral cavity, dysphagia, facial swelling, and pain on mouth manipulation.[4,7,8] OMMs are often pigmented (**FIGURE 1**), but up to 38% can be amelanotic.[9] The most common locations are the gingiva, lips, tongue, and hard palate.[3,4,10]

HIDDEN DANGER
In asymptomatic cases of oral malignant melanoma, an oral mass is often discovered by the owner or during a routine dental examination.

DIAGNOSIS

In some cases, especially if a tumor is pigmented, the diagnosis of OMM may be confirmed with cytology of a fine-needle aspirate. An incisional

FIGURE 1. A pigmented oral malignant melanoma on the left rostral maxillary gingiva of a dog.

punch or a wedge biopsy, often in conjunction with immunohistochemistry (IHC), is needed for most nonpigmented oral tumors, as amelanotic melanoma can histologically mimic a poorly differentiated sarcoma or epithelial tumor. Application of IHC antibodies such as Melan-A, S-100, PNL2, TRP-1, and TRP-2 may be recommended by a pathologist to help reach a definitive diagnosis.[11-13]

Excisional biopsies result in incomplete margins and should be avoided when possible. If a tumor is small and an excisional biopsy is unavoidable, accurate documentation of tumor size and location, including photographs, is important for planning further treatment. Biopsy should always be performed from within the oral cavity. Special care should be taken to avoid contaminating normal tissue.

STAGING

Staging for OMM (**TABLE 1**) should include blood work (complete blood count and serum biochemistry profile), urinalysis, assessment of regional lymph nodes, and imaging of the thoracic cavity. Submandibular lymph nodes are the only palpable regional lymph nodes. Both ipsilateral and contralateral nodes should be aspirated regardless of size. Up to 40% of normal-sized lymph nodes may contain metastatic disease.[15]

Three-view thoracic radiography or thoracic computed tomography (CT) should be used to screen for pulmonary metastasis. Abdominal ultrasonography, although not routinely performed, should be considered to rule out metastasis to the liver and other intra-abdominal organs as well as comorbidities unrelated to melanoma.

Preoperative cross-sectional imaging of the head and neck is imperative for surgical planning, especially for tumors arising from the hard palate, caudal maxilla, or caudal mandible (**FIGURE 2**). Both CT and magnetic resonance imaging (MRI) are more sensitive than radiography for assessing the extent of invasion into the surrounding tissues, including bone. CT scans provide better bone detail than MRI. Cross-sectional imaging also allows assessment of the nonpalpable parotid and medial retropharyngeal lymph nodes.

TREATMENT

Surgery

Surgery is the best means of achieving locoregional tumor control.[16] When OMMs are excised, margins of at least 2 cm of normal tissue should be taken in all directions if possible.[7] Margins must include bone when the tumor is located on the maxilla or mandible, necessitating a partial or full maxillectomy or mandibulectomy (**FIGURE 3**).

Removal of locoregional lymph nodes with suspected or confirmed metastatic disease may be beneficial.[17] Removal of normal locoregional lymph nodes is not routinely performed.[18] Sentinel lymph node mapping is being investigated in veterinary medicine and may prove to be useful in identifying target nodes for lymphadenectomy.[19,20]

TABLE 1 The World Health Organization Staging Scheme for Canine Oral Malignant Melanoma[14]

	STAGE I	STAGE II	STAGE III	STAGE IV
Primary tumor size	T1 (≤2 cm in diameter)	T2 (2–4 cm in diameter)	T2 *or* T3 (>4 cm in diameter)	Any T
Regional lymph nodes	N0 (no regional lymph node involvement)	N0	N1 (presence of regional lymph node metastasis) *or* N0	Any N, including N2 (fixed nodes)
Distant metastasis	M0 (no evidence of distant metastasis)	M0	M0	M1 (presence of distant metastasis)

Dogs that undergo oral surgery, including maxillectomy and mandibulectomy, have good cosmetic and functional outcomes (**FIGURE 3**). They enjoy a great quality of life, and many dogs adapt to their new jaw conformation and learn how to eat as early as 3 days after surgery.[16] Ptyalism that reduces over time is the most commonly noted long-term side effect, especially after mandibulectomy.[7]

Radiation

Radiation therapy is another option for treatment of locoregional disease. Melanomas are considered to be relatively radioresistant tumors that may respond better to higher doses of radiation per fraction.[21] A variety of radiation protocols have been described in veterinary literature.[16] They typically consist of 3 to 6 treatments delivered either daily or weekly.[22-24] Total doses of more than 30 Gy are associated with better tumor response.[22-24] In the authors' institution, a protocol of 4 weekly fractions of 8 Gy is preferred for both microscopic and gross OMM.

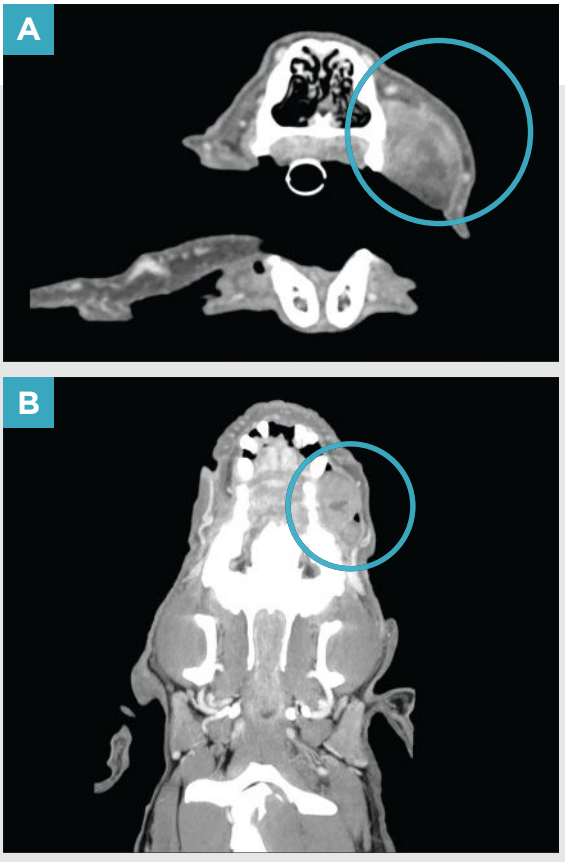

FIGURE 2. (A) Transverse and **(B)** sagittal computed tomographic image of oral malignant melanoma in the same dog as Figure 1. There is a lobular, soft tissue–attenuating, mildly heterogeneously contrast-enhancing mass with ill-defined margins associated with the buccal aspect of the gingiva of the left rostral maxilla **(circled)**. This mass extends from the caudal aspect of the canine tooth to the rostral aspect of the fourth premolar and measures approximately 2.3 (W) x 1.8 (H) x 3.3 (L) cm. The central portion of this mass is non–contrast enhancing, with peripheral rim enhancement.

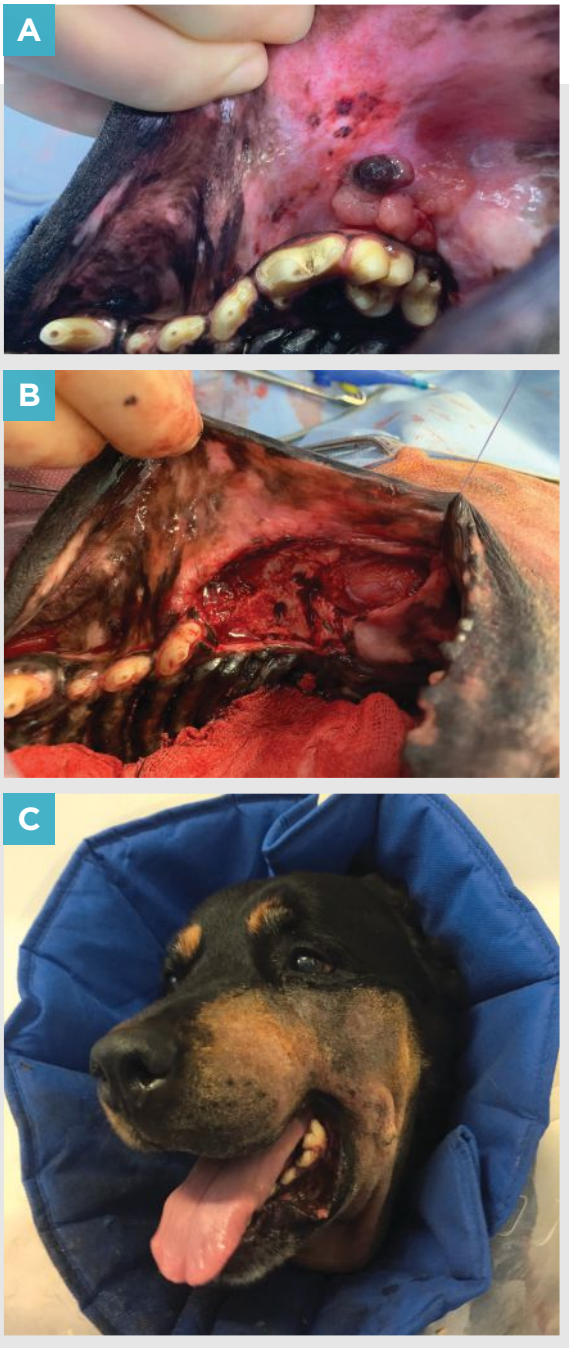

FIGURE 3. (A) Preoperative, **(B)** intraoperative, and **(C)** postoperative images of a dog with oral malignant melanoma of the left labial mucosa located dorsal to the first molar. The tumor was excised with 2-cm margins via a rim maxillectomy.

Clockwise from top right: Courtesy of Josep Aisa, DVM, DECVS, University of Tennessee (3)

Chemotherapy and Immunotherapy

Chemotherapy has a limited role in management of canine OMM. The overall response rates in dogs with gross disease have been low, with the most promising rates being 18% for cisplatin and piroxicam[25] and 28% for carboplatin.[26] Moreover, multiple studies have failed to identify a survival benefit with addition of chemotherapy to surgery and radiation.[24-26]

Systemic immunotherapy for adjuvant treatment of canine melanoma may be more promising than chemotherapy. A xenogeneic DNA vaccine, Oncept (Boehringer Ingelheim, petcancervaccine.com), has made headway as the first conditionally approved immunotherapy for the treatment of canine OMM. Initial literature described promising activity against OMM: dogs with stage II and III OMM treated with Oncept after surgical resection (with or without radiation therapy) had longer median survival times (MSTs) than dogs in the control group.[27] Subsequent studies failed to show similar significant differences in survival.[28-30] However, these studies were retrospective, with small numbers of patients in vaccinated and nonvaccinated groups, among other weaknesses inherent to retrospective studies, and should be interpreted with caution. Other retrospective studies have shown evidence of complete responses to Oncept alone in dogs with gross disease.[28,29]

Based on the current body of research, Oncept melanoma vaccine is safe and easy to administer and may be an effective adjuvant systemic therapy for dogs with OMM.[27,30] The authors believe that Oncept's pitfalls and potential benefits should be discussed with owners on a case-by-case basis.

PROGNOSIS

The overall prognosis for OMM remains guarded. Most dogs die of metastatic disease. Dogs that undergo radical surgery that includes 2- to 3-cm bone and 1-cm soft tissue margins, or surgery and radiation therapy, have longer MSTs than dogs that receive no treatment.[23,31] Overall, MSTs after complete excision are 1 to 2 years for stage I disease, 6 months to 2 years for stage II, and 5 to 8 months for stage III.[31]

TABLE 2 Prognostic Indicators for Canine Oral Malignant Melanoma

PROGNOSTIC FACTORS	CHARACTERISTICS	AVERAGE SURVIVAL TIME
Age[22,32]	▪ Older dogs are more likely to experience complications related to anesthesia and surgery	Dogs ≤11 years old: 7 months Dogs >11 years old: 7 months
Stage[16,23]	▪ Higher WHO stage is directly linked to decreased survival times and is more likely to have metastasis	Stage I: 2 years Stage II: 1 year Stage III: 6 months Stage IV: 2.5 months
Tumor size[22,31]	▪ Every 1-cm increase in size was associated with a 32% increase in local recurrence[31] ▪ Increased size can lead to tumor heterogeneity and increased radioresistance ▪ The effect of size is similar to stage, as WHO stages include size of the tumor	Small tumors <4 cm (stage I/II): 27 months Large tumor ≥4 cm (stage III/IV): 4 months
Bone lysis[22,28]	▪ Greater degree of bony lysis has been associated with quicker time to recurrence after radiation and immunotherapy	**Radiation:** Absence of lysis: 9.5 months Presence of lysis: 4 months **Immunotherapy:** Absence of lysis: >1 year Presence of lysis: <1 year
Histology[28]	▪ Histologic markers, specifically mitotic index (MI) and degree of differentiation, are linked to prognosis	MI <5 and well-differentiated cells: 1–2 years MI >5 and undifferentiated cells: <1 year
Immunohistochemistry[32]	▪ High levels of Ki67, a marker for tumor growth, are highly correlated to more aggressive and higher-stage tumors	Ki67 index ≥19.5: <1 year Ki67 index <19.5: 1–2 years
Location[7,22]	▪ Tumors caudal to the 4th premolar present more difficult margins and are identified at later stages	Rostral tumors: 7.5–11 months Caudal tumors: 4.5–7 months

WHO=World Health Organization

Dogs with nonresectable tumors have shorter progression-free survival and MSTs. In a report looking at radiation as a sole treatment for dogs with macroscopic OMM, MSTs were highly variable.[22] Dogs showing no negative prognostic indicators had an MST of up to 21 months; MST for dogs with 1, 2, or 3 negative prognostic indicators was 11, 5, and 3 months, respectively. **TABLE 2** lists prognostic factors for canine OMM. **TVP**

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