# Outcome following curative-intent surgery for oral melanoma in dogs: 70 cases (1998–2011)

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**Objective**—To evaluate the outcome in terms of progression-free interval (PFI) and overall survival time (ST) after curative-intent resection of oral melanoma in dogs.

**Design**—Retrospective case series.

**Animals**—70 client-owned dogs.

**Procedures**—An electronic medical record search and review was performed for dogs that underwent curative-intent resection of oral melanoma (May 1, 1998, to December 31, 2011). Information gathered included signalment, oral location of tumor, staging results, type of surgery, type of adjuvant therapy, findings on histologic evaluation, and outcome.

**Results**—36 (51.4%), 16 (22.9%), 13 (18.6%), and 1 (1.4%) of 70 dogs had tumors classified as stage I, II, III, and IV, respectively; tumor stage could not be determined for 4 (5.7%) dogs because of the lack of tumor size information. Fifty-one (72.9%) dogs had tumors completely excised. Twenty-nine (41.4%) dogs received adjuvant therapy. Median PFI and ST were 508 and 723 days, respectively. Thirty-two (45.7%) dogs had disease progression. Significant associations with PFI or ST were found for administration of adjuvant therapy, presence of metastatic disease at the time of diagnosis, higher tumor stage (III or IV), increased tumor size (> 3 cm), and sexually intact female dogs. Administration of adjuvant treatment was associated with a 130% increased hazard (hazard ratio, 2.3; 95% confidence interval [CI], 1.0 to 5.0) of disease progression; the presence of metastases at the time of diagnosis was associated with a 281% increased hazard (hazard ratio, 3.8; 95% CI, 1.5 to 9.6) of death.

**Conclusions and Clinical Relevance**—Results indicated that dogs with oral melanoma can have a long PFI and ST after resection with wide margins. (*J Am Vet Med Assoc* 2014;245:1266–1273)

Melanoma is the most common oral malignancy in dogs[1,2] and is most frequently located in the gingiva but can be found in any location, including the lip, tongue, and palate.[1–3] The appearance of oral melanomas can vary from heavily pigmented to amelanotic, and they can appear ulcerated and necrotic. Oral melanoma is an aggressive malignant tumor that is both locally invasive and highly metastatic.[4,5] The most common sites of metastasis include regional lymph nodes and lungs, with the CNS and bone being less common sites.[1–3,6] At diagnosis, staging tests are often performed in an effort to detect metastatic spread. Oral melanoma in dogs is staged according to the World Health Organization staging scheme, and patient stage has been shown to be prognostic.[7,8]

The reported STs for oral melanoma vary widely, depending on factors such as stage and type of treatment received.[1,7–10] Wide resection is the most effective modality for eradication of the primary tumor.[11,12] Given the aggressive biological behavior, adjuvant therapies have been recommended for oral melanoma, including chemotherapy,[9,13–15] radiation therapy,[16,17] and a xenogeneic DNA vaccine.[18–21] Equivocal data exist regarding the efficacy of chemotherapy,[14,15] and most recently, Brockley et al[9] failed to demonstrate improved ST in dogs with oral melanoma with the use of adjuvant carboplatin following excision. The efficacy of the DNA vaccine is similarly equivocal, on the basis of 2 clinical reports[20,21]; Ottnod et al[21] failed to show any survival advantage with vaccine use. Other adjuvant modalities that have been explored include liposome encapsulated muramyl tripeptide phosphatidylethanolamine (L-MTP-PE),[22] in vivo transfections of immunostimulatory genes,[23] intralesional cisplatin implants,[24] and local hyperthermia combined with intralesional cisplatin.[25]

**Abbreviations**

| | |
|---|---|
| CI | Confidence interval |
| HR | Hazard ratio |
| MTD | Maximum tolerated dose |
| PFI | Progression-free interval |
| ST | Survival time |

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Several prognostic factors for dogs with melanoma have been reported, including tumor size, tumor stage, histologic features such as mitotic index and nuclear atypia, and the Ki67 index.[26] Many studies[1,3–5,27] identifying prognostic factors and evaluating the efficacy of adjuvant therapy included a diverse patient population ranging from patients with all oral neoplasms to patients with melanomas in differing anatomic (oral, digital, and cutaneous) locations, and many of these patients underwent various treatment modalities. Limited studies have assessed outcome in a homogenous patient population with oral melanoma.

The purpose of the study reported here was to evaluate treatment outcomes and prognostic indicators of PFI and ST following curative-intent surgery for oral melanoma in dogs. We hypothesized that location of the lesion within the oral cavity and type of resection (soft tissue alone vs bone) would influence PFI and ST. Specifically, we hypothesized that maxillary or mandibular lesions that were located more rostrally and melanomas confined within soft tissues alone and not involving bone would be associated with a longer PFI and ST. Second, we hypothesized that the presence of metastasis at time of diagnosis, higher disease stage, incomplete surgical margins, large tumor size, and lack of use of adjuvant therapy would be associated with a shorter PFI and ST.

## Materials and Methods

**Case selection**—An electronic medical record search was performed at Colorado State University Veterinary Teaching Hospital for dogs that had curative-intent surgery for oral melanoma between May 1, 1998, and December 31, 2011. To be included in this study, the diagnosis of oral melanoma had to be confirmed histologically and a report available for review. Curative-intent surgery was defined as a resection with wide (ie, 2- to 3-cm bone margins and 1-cm soft tissue margins or widest margins appropriate relative to size of dog) margins, with a view to achieving histologically complete resection. Cases were excluded if only marginal tumor excision was planned, if no surgery was performed, or if there was a complete lack of follow-up information.

**Medical records review and follow-up data**—Historical data from medical records and follow-up information gathered from referring veterinarians and owners included signalment, body weight, oral location of tumor, staging results (ie, findings on thoracic radiography and cytologic and histologic evaluation of regional lymph nodes), date of surgery, and type of surgical procedure performed (ie, maxillectomies, mandibulectomies, glossectomies, and full-thickness lip resections). The use of adjuvant therapy (ie, chemotherapy, radiation, melanoma vaccine, and interferon treatment), histologic evaluation including margin quality, development of local recurrence or metastasis, location of metastasis, and date and cause of euthanasia or death (or the date of last follow-up if alive) were obtained as well.

The oral location of the tumor was categorized as mandibular gingiva, maxillary gingiva, buccal and labial mucosa, lip, tongue, tonsils, hard palate, or soft palate. Cases of cutaneous melanoma involving the cutaneous surface of the lip or cheek were excluded from the analysis because cutaneous melanomas have historically had a more favorable prognosis than melanomas of the oral mucosa and cavity.[26] Caudal was defined as caudal to the fourth premolar, and rostral was defined as rostral to the fourth premolar. Tumors of the mandibular and maxillary gingiva and hard palate that dictated a bony deep surgical margin because of their adjacent location to bone were classified as resections involving bone. Tumors of the lip, tongue, and tonsil were categorized as resections involving soft tissue only because their surgical planning did not involve bony resection.

Clinical stage was assigned retrospectively from information in the medical record at the time of definitive intervention on the basis of World Health Organization criteria.[28] The longest reported diameter of the tumor based on physical examination or imaging (radiography or CT when available) was used for analysis. Margin quality was obtained from the histopathologic report and was characterized as complete or incomplete. Margins were categorized as complete if no tumor cells abutted the edges of the resection and categorized as incomplete if any tumor cell contacted the edges of the resection.

**Statistical analysis**—Continuous baseline, tumor, and treatment characteristics were evaluated graphically for normality and described as mean ± SD if normally distributed or median and interquartile range if nonnormally distributed. Categorical variables were described with frequencies and percentages.

Kaplan-Meier survival analysis was used to estimate median PFI and median ST for the study population and subgroups. Progression-free interval was calculated as the time from definitive surgery to local recurrence, development, or progression of detectable metastases. Local recurrence was defined as development of an oral melanoma at the original surgical site after removal of the primary tumor, and evidence of melanoma on cytologic evaluation or biopsy of lymph nodes or radiographic evidence of pulmonary nodules was taken as indicative of detectable metastases. Dogs were censored from the PFI analysis if no detectable recurrence or metastasis was present at the last follow-up or at death. Survival time was calculated as the time from definitive surgery to death attributed to disease or, if the dog was alive, last follow-up. Death of the dog was determined to be attributed to disease if metastasis or local tumor recurrence was the cause. Dogs with an unknown cause of death were presumed to have died from disease. Dogs were censored from the survival analysis if alive at last follow-up or if the dog died of causes other than disease. A univariable analysis was performed to assess for associations between different variables and PFI or ST by means of Cox proportional hazards models with the Breslow method for ties. Variables assessed included age, sex and neuter status, breed, tumor stage, presence of metastases at diagnosis, tumor size, resection involving bone or soft tissue, tongue tumor location, rostral versus caudal tumor location, administration of adjuvant treatment, and incomplete surgical margins. The results were presented as HRs and 95% CIs. As a result of the



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relatively low number of events for both PFI and ST, the multivariable analysis was restricted to a 3-variable model and adjusted HRs and 95% CIs were calculated for tumor size, presence of metastases at diagnosis, and use of adjuvant therapy. Significance was set at $\alpha = 0.05$, and the statistical analysis was performed with the aid of commercially available statistical software.[a]

## Results

Seventy dogs met study inclusion criteria and underwent curative-intent surgery for removal of oral melanoma, which was confirmed via histologic evaluation. The mean ± SD age at time of diagnosis was 10.4 ± 2.2 years. The mean ± SD body weight at diagnosis was 27.2 ± 11.8 kg (59.8 ± 26.0 lb). Fifty-one (72.9%) dogs were purebred, and 19 (27.1%) dogs were of mixed breeding. The most common breeds were Labrador Retrievers (10 [14.3%]), Golden Retrievers (8 [11.4%]), Cocker Spaniels (5 [7.1%]), and German Shepherd Dogs (3 [4.3%]). There were 29 (41.4%) spayed females, 27 (38.6%) castrated males, 2 (2.9%) sexually intact females, and 12 (17.1%) sexually intact males. The follow-up period ranged from 413 to 1,975 days (median, 821.5 days).

Twenty (28.6%) tumors occurred on the mandibular gingiva, 17 (24.3%) on the maxillary gingiva, 17 (24.3%) on the lip, 10 (14.3%) on the tongue, 4 (5.7%) on the buccal or labial mucosa, 1 (1.4%) on the tonsils, and 1 (1.4%) on the hard palate. Considering mandibular and maxillary tumors together, 23 (32.9%) were located rostrally and 14 (20.0%) were located caudally. Information on tumor size was available for 66 tumors, with a median diameter of 2.3 cm (range, 0.3 to 5.7 cm).

Nine of 70 (12.9%) dogs had metastatic disease at time of diagnosis: 8 (11.4%) had lymph node metastasis and 1 (1.4%) had pulmonary nodules visualized on radiographs. Thirty-six (51.4%) dogs had tumors classified as stage I, 16 (22.9%) as stage II, 13 (18.6%) as stage III, and 1 (1.4%) as stage IV. Tumor stage could not be determined for 4 (5.7%) dogs because of the lack of tumor size information.

Overall, there were 38 of 70 (54.3%) tumors where resection involved excision of bone and 32 (45.7%) tumors where excision involved soft tissue only. Twenty (28.6%) mandibulectomies, 17 (24.3%) maxillectomies, 17 (24.3%) full-thickness lip resections, 10 (14.3%) partial glossectomies, 5 (7.1%) wide (≥ 2-cm margins) excisions of soft tissue masses, and 1 (1.4%) hard palate resection were performed. Fifty-one (72.9%) tumors were completely ex-

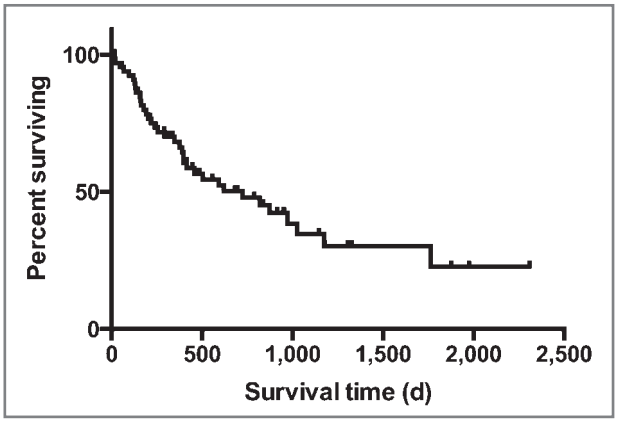



Figure 1—Kaplan-Meier survival curve for 70 dogs that underwent curative-intent resection of an oral melanoma. The overall median ST was 723 days (95% CI, 396 to 1,025 days). Seven dogs were lost to follow-up, 36 died of their disease, 19 died of apparently unrelated causes, and 8 were alive at final follow-up a median of 15.8 months after surgery (range, 4.3 to 77 months). Only 5 owners consented to a postmortem examination.

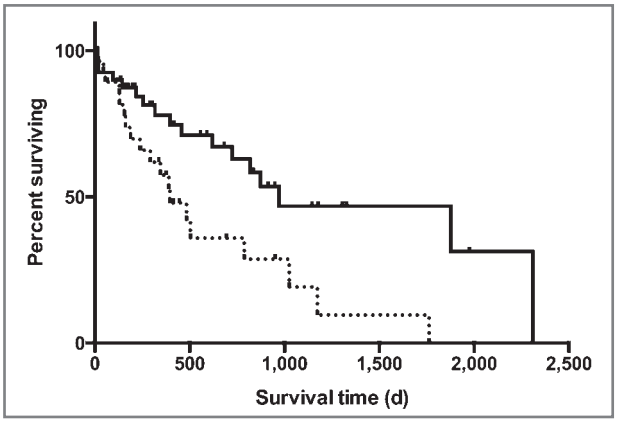



Figure 2—Kaplan-Meier survival curve for dogs in Figure 1 that had surgery as sole treatment (solid line; PFI > 567 days [median not reached]; median ST, 874 days) versus those that had surgery plus adjuvant therapy (dotted line; median PFI, 241 days; median ST, 396 days).

Table 1—Types and combinations of adjuvant therapy administered, stage of disease, and margin completeness for 29 dogs after curative-intent resection of oral melanoma.

| | | Stage | | | | Margins | |
|---|---|---|---|---|---|---|---|
| **Adjuvant therapy type** | **No. of dogs** | **I** | **II** | **III** | **IV** | **Complete** | **Incomplete** |
| MTD chemotherapy alone* | 7 | 3 | — | 3 | — | 5 | 2 |
| Radiation alone | 0 | | | | | | |
| MTD chemotherapy and radiation | 2 | 0 | 0 | 2 | 0 | 0 | 2 |
| MTD chemotherapy, radiation, metronomic chemotherapy, and vaccine | 1 | 1 | 0 | 0 | 0 | 0 | 1 |
| Radiation and metronomic chemotherapy | 4 | 0 | 2 | 2 | 0 | 1 | 3 |
| MTD chemotherapy and metronomic chemotherapy | 3 | 1 | 1 | 1 | 0 | 3 | 0 |
| MTD chemotherapy and vaccine | 1 | 0 | 1 | 0 | 0 | 1 | 0 |
| MTD chemotherapy and interferon-α* | 1 | — | — | — | — | 1 | 0 |
| Metronomic chemotherapy and vaccine | 1 | 0 | 0 | 1 | 0 | 0 | 1 |
| Metronomic chemotherapy alone* | 8 | 3 | 3 | — | 1 | 6 | 2 |
| Vaccine alone | 1 | 0 | 1 | 0 | 0 | 1 | 0 |

*One dog with unknown disease stage in this category.
— = Not applicable.



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cised and 19 (27.1%) tumors were incompletely excised on histologic evaluation. Two of the 19 tumors resected with incomplete margins were histologically well-differentiated oral melanomas. Eight dogs in the study had a histopathologic diagnosis of well-differentiated melanomas; 5 of these dogs did not receive any adjuvant therapy, 1 dog received the xenogeneic melanoma vaccine, 1 dog was administered MTD chemotherapy, and 1 dog was lost to follow-up. Four of these dogs were alive at the end of the study, 3 had died of unrelated causes, and 1 was lost to follow-up. The rest of the tumors were histologically aggressive malignant melanomas that ranged from being undifferentiated to moderately differentiated.

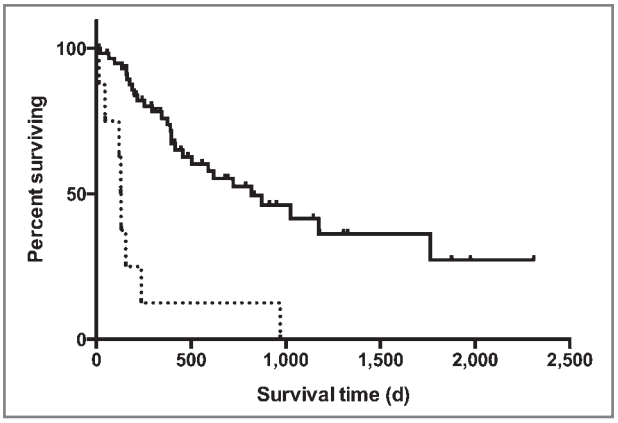



Figure 3—Kaplan-Meier survival curve for dogs in Figure 1 that had metastasis at the time of diagnosis (dotted line; median PFI, 187 days; median ST, 131 days) versus those that did not have metastasis (solid line; median PFI, 567 days; median ST, 818 days).

Twenty-nine (41.4%) dogs received adjuvant therapy: 7 (10.0%) received MTD chemotherapy only, 7 (10.0%) received metronomic chemotherapy only, 1 (1.4%) received a xenogeneic canine melanoma vaccine[b] only, and 14 (20.0%) received a combination of adjuvant therapy that included MTD chemotherapy, radiation therapy, metronomic chemotherapy, interferon treatment, and the xenogeneic canine melanoma vaccine.[b] The chemotherapy protocol used in dogs receiving MTD chemotherapy was carboplatin (300 mg/m$^2$, IV, q 21 d, for 4 to 6 cycles). Metronomic chemotherapy included combinations of doxycycline (5 to 10 mg/kg [2.3 to 4.5 mg/lb], PO, q 24 h), an NSAID such as piroxicam or carprofen at standard labeled dosages, and cyclophosphamide at a low dosage (15 to 17 mg/m$^2$, PO, q 24 h). The stage of disease, margin quality, and type of treatment administered to the 29 dogs receiving adjuvant therapy were summarized (**Table 1**). Three of these dogs with stage III disease also had tumors resected with incomplete margins.

The overall median PFI was 508 days (95% CI, 245 to 2,310 days), and the overall median ST was 723 days (95% CI, 396 to 1,025 days; **Figure 1**). Seven dogs were lost to follow-up, 36 died of their disease, 19 died of apparently unrelated causes, and 8 were alive at the final follow-up a median of 15.8 months after surgery (range, 4.3 to 77 months). Only 5 owners consented to a postmortem examination of their deceased dog.

Table 2—Univariable analysis of variables assessed for significant associations with PFI and ST after curative-intent resection of oral melanoma in 70 dogs.

| Variable | Median PFI (d) | HR (95% CI) | *P* value | Median ST (d) | HR (95% CI) | *P* value |
|---|---|---|---|---|---|---|
| Treatment | | | | | | |
| Surgery and adjuvant therapy (n = 29) | 241 | 2.9 (1.4–6.0) | 0.003 | 396 | 2.1 (1.1–4.1) | 0.024 |
| Surgery only (n = 39) | > 567 (NR) | — | — | 874 | — | — |
| Metastases present at diagnosis | | | | | | |
| Yes (n = 10) | 187 | 3.9 (1.6–9.6) | 0.002 | 131 | 5.1 (2.3–11.0) | < 0.001 |
| No (n = 59) | 567 | — | — | 818 | — | — |
| Stage | | | | | | |
| I (n = 36) | > 567 (NR) | — | — | 874 | — | — |
| II (n = 16) | > 187 (NR) | 1.2 (0.5–3.1) | 0.72 | 818 | 1.3 (0.5–3.0) | 0.60 |
| III (n = 13) | 245 | 2.9 (1.2–7.1) | 0.017 | 207 | 3.9 (1.7–8.9) | 0.001 |
| IV (n = 1)* | — | 46.5 (4.0–536.3) | 0.002 | — | 18.6 (2.1–166.6) | 0.009 |
| Tumor size | | | | | | |
| > 3 cm (n = 47) | 245 | 2.0 (1.0–4.2) | 0.046 | 396 | 1.7 (0.9–3.3) | 0.115 |
| < 3 cm (n = 23) | > 567 (NR) | — | — | 874 | — | — |
| Sex and neuter status | | | | | | |
| Sexually intact female (n = 2) | 80 | 8.8 (1.8–42.3) | 0.007 | 157 | 6.0 (1.2–28.9) | 0.026 |
| Spayed female (n = 29) | > 372 (NR) | — | — | 504 | — | — |
| Sexually intact male (n = 12) | 360 | 1.3 (0.5–3.4) | 0.54 | 818 | 1.0 (0.4–2.3) | 0.98 |
| Castrated male (n = 27) | > 567 (NR) | 0.9 (0.4–2.0) | 0.76 | > 619 (NR) | 0.7 (0.3–1.5) | 0.35 |
| Type of resection | | | | | | |
| Resection involving bone only (n = 38) | 360 | 1.4 (0.7–2.9) | 0.32 | 416 | 1.8 (0.9–3.7) | 0.076 |
| Resection involving soft tissue only (n = 32) | 567 | — | — | 971 | — | — |
| Location of tumor | | | | | | |
| Rostral (n = 23) | 360 | — | — | 375 | — | — |
| Caudal (n = 14) | 358 | 0.9 (0.3–2.2) | 0.74 | 416 | 1.2 (0.5–3.0) | 0.63 |
| Margin completeness | | | | | | |
| Complete (n = 51) | > 2,310 (NR) | — | — | 619 | — | — |
| Incomplete (n = 19) | 446 | 1.6 (0.8–3.4) | 0.19 | 723 | 0.8 (0.4–1.8) | 0.70 |
| Adjuvant therapy | | | | | | |
| Yes (n = 29) | 241 | 2.9 (1.4–6.0) | 0.005 | 396 | 2.1 (1.1–4.1) | 0.03 |
| No (n = 41) | > 2,310 (NR) | — | — | 874 | — | — |

*Median PFI and ST were not applicable for stage IV disease because there was only 1 dog.
— = Not applicable. NR = Median not reached.



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Table 3—Multivariable analysis of variables identified to have significant associations with PFI and ST after curative-intent resection of oral melanoma in 70 dogs

| | PFI | | ST | |
|---|---|---|---|---|
| **Variable** | **Adjusted HR (95% CI)** | ***P* value** | **Adjusted HR (95% CI)** | ***P* value** |
| Tumor size | 1.1 (0.8–1.5) | 0.43 | 1.1 (0.1–1.4) | 0.62 |
| Surgery and adjuvant therapy | 2.3 (1.0–5.0) | 0.045 | 1.8 (0.9–3.8) | 0.11 |
| Metastases present at diagnosis | 2.7 (1.0–7.7) | 0.57 | 3.8 (1.5–9.6) | 0.005 |

Dogs that had surgery as the sole treatment had a PFI > 567 days (median not reached) and a median ST of 874 days, compared with those that had surgery plus adjuvant therapy, in which median PFI was 241 days and median ST was 396 days (**Figure 2**). Patients that had metastasis at the time of diagnosis had a median PFI of 187 days and median ST of 131 days, compared with those that did not have metastasis, in which median PFI and median ST were 567 and 818 days, respectively (**Figure 3**).

Thirty-two of 70 (45.7%) dogs developed metastasis or local tumor recurrence: 20 (28.6%) of these dogs had metastatic disease only, 7 (10.0%) developed local tumor recurrence alone, and 5 (7.1%) dogs had both local recurrence and metastasis. Six (8.6%) dogs developed lymph node metastasis, 12 (17.1%) dogs developed pulmonary metastasis, 4 (5.7%) dogs developed both nodal and pulmonary metastases, 1 (1.4%) dog developed pulmonary and subcutaneous metastases, 1 (1.4%) dog developed pulmonary and dermal metastases, and 1 (1.4%) dog developed tonsillar metastasis. All metastases with the exception of pulmonary metastases were confirmed on the basis of findings on cytologic or histologic evaluation.

On univariable analysis, administration of adjuvant therapy, presence of metastatic disease at the time of diagnosis, higher disease stage (III or IV), increased tumor size (> 3 cm), and being a sexually intact female were factors identified as having significant associations with PFI or ST (**Table 2**). Every 1-cm increase in tumor size was associated with a 32% increased hazard of local recurrence or metastasis (HR, 1.32; 95% CI, 1.03 to 1.68; $P = 0.026$) and a 29% increased hazard of death (HR, 1.29; 95% CI, 1.021 to 1.63; $P = 0.033$). Following adjustment for the presence of metastatic disease at diagnosis and administration of adjuvant therapy, these associations were not significant (**Table 3**). Following adjustment for tumor size and the presence of metastases at diagnosis, administration of adjuvant treatment was associated with a 130% increased hazard of developing local recurrence or metastatic disease (HR, 2.3; 95% CI, 1.0 to 5.0; $P = 0.045$). Following adjustment for tumor size and administration of adjuvant therapy, the presence of metastases at diagnosis was associated with a 281% increased hazard of death (HR, 3.8; 95% CI, 1.5 to 9.6; $P = 0.005$).

## Discussion

Curative-intent surgery for treatment of oral melanoma was associated with a long median PFI and ST in this study. Dogs receiving adjuvant therapy had a higher hazard of disease progression but not death, compared with dogs that did not receive adjuvant therapy after adjustment for tumor size and presence of metastases at diagnosis. In addition, the presence of metastatic disease at diagnosis was associated with increased hazard of death but not with disease progression after adjustment for tumor size and administration of adjuvant treatment. Higher disease stage and sex of the dog were also negatively associated with progression or death in the univariable analysis, and when tumor size was treated as a continuous variable, increasing size was associated with an increased hazard of disease progression and death. This study failed to provide evidence to suggest that the type of lesion, location of the lesion within the oral cavity, and incomplete margins were associated with progression or death. To the authors' knowledge, this is the first study to focus on reporting treatment outcomes and factors associated with PFI and ST for dogs with oral melanoma that have undergone curative-intent surgery.

Administration of adjuvant therapy resulted in an increased hazard for disease progression and death in the univariable analysis, but after adjustment for tumor size and presence of metastases at diagnosis in the multivariable analysis, only disease progression remained significant. This observation may have been an artifact of selection bias; generally, the dogs for which adjuvant therapy is recommended are those that have indicators of biological disease aggression such as histologically aggressive features (eg, high mitotic index) and higher stage disease and those with incomplete resections.

In this study, 26 of the 29 dogs that received adjuvant therapy had known disease stages, and 18 of these dogs had stage II to IV disease. In our univariable analysis, higher stage of disease was prognostic for poorer PFI and ST. Also, 11 of the 29 dogs had their tumors resected with incomplete margins. Oral melanoma appears to be responsive to radiation therapy, with reports[13,29,30] of efficacy when used as primary treatment for local tumor control. Radiation therapy has also been used in the adjuvant setting and appears to be efficacious in achieving local tumor control,[13,16] and it continues to be a valid modality in the management and treatment of dogs with oral melanoma. However, the role of chemotherapy in extending ST for animals with oral melanoma is poorly established, and previous studies[13,31] mainly have investigated the use of chemotherapy after definitive radiation. A recent study by Brockley et al[9] evaluated the use of carboplatin after surgical removal of the primary tumor and found no significant increase in ST with the use of chemotherapy. Similarly, the efficacy of the xenogeneic DNA vaccine is undetermined. Grosenbaugh et al[20] reported promising extension of STs (median ST not reached) in dogs that received the vaccine, compared with historical controls, but a more recent case series[21] did not show any benefit of the vaccine in increasing PFI, disease-free interval, or median ST. The study reported here supports the recommendation of curative-intent resection of oral melanoma in



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dogs, but the role of adjuvant therapies such as chemotherapy or the xenogeneic vaccine remains unclear. Randomized controlled clinical studies for individual adjuvant therapies would be required to elucidate their role in managing dogs with oral melanoma.

Higher disease stage, presence of metastatic disease at time of diagnosis (which is related to higher disease stage), and increasing tumor size resulted in lower PFI and ST in the univariable analysis in this study. The presence of metastatic disease at the time of diagnosis maintained its negative association with ST in the multivariable analysis. Several other studies[7,8,26,30] have shown an association between disease stage and treatment outcomes for oral melanoma. MacEwen et al[7] reported a median ST of 160 and 168 days for dogs with stage II and III tumors and a longer median ST of 511 days for dogs with stage I tumors. Theon et al[30] reported longer PFI in dogs with stage I oral melanoma (19 months), compared with those with stage II and III disease (6 and 7 months, respectively). In the present study, dogs with stage III and IV tumors had a higher hazard of developing metastasis or recurrence (HR, 2.9 and 46.5, respectively) and a higher hazard of death (HR, 3.9 and 18.6, respectively), compared with dogs with stage I disease. Although it is likely that stage IV disease leads to a higher hazard of progression and death, in the present study, it must be noted that the estimate of the hazard may be inaccurate given that there was only 1 dog with stage IV disease.

In this study, every 1-cm increase in tumor size was associated with a 32% increased hazard of local recurrence or metastasis and 29% increased hazard of death in the univariable analysis. However, although tumors with measurements > 3 cm resulted in shorter PFIs, in the multivariable analysis following adjustment for metastases at diagnosis and use of adjuvant therapy, it was not a significant factor. On the basis of findings of previous studies,[19,26] this may be the result of selection bias insofar as dogs with bigger tumors were prescribed adjuvant therapy or were directed away from curative intent treatment altogether. In this study, tumor size was not expressed as a ratio to the weight of the dog because this may provide an inaccurate relative tumor size as a result of the prevalence of obesity in dogs. Larger tumor size may make it increasingly difficult to obtain the desired wide margins, in turn increasing the chance of obtaining incomplete margins, which has been previously reported as a negative prognostic indicator. In 2 reports by Schwartz et al,[11,12] dogs that had incomplete margins following mandibulectomies and maxillectomies were 2.4 times and 3.6 times as likely to die of disease, respectively. Interestingly, in our study, there was no evidence to suggest that incomplete margins were associated with decreased PFI or ST, which is consistent with 2 other studies[4,32] that did not find incomplete margins to be a poor prognostic indicator. However, one of these studies[32] determined that wide resection still led to improved remission and ST, compared with conservative resections, where underlying bone was not removed, regardless of whether the margins were complete. This finding in our study could be caused by a bias introduced by the study population, given that these dogs were determined by a surgeon to have tumors amenable to wide resection and received curative-intent surgery that resulted in a high proportion of dogs (72.9%) having complete excision of the tumor, as determined on the basis of histologic evaluation. In addition, 2 of the 19 dogs with incomplete margins had histologically well-differentiated oral melanomas, which could have positively biased their prognosis. With these factors as likely confounders of an association between completeness of resection and treatment outcomes, we continue to recommend wide resection with the goal of obtaining complete surgical margins as the standard of care for dogs with oral melanoma.

We failed to find evidence to suggest soft tissue lesions and rostrally located maxillary or mandibular lesions were associated with increased PFI and ST. Previous studies[13,32] have found there to be improved prognosis with rostral location of lesions; however, in one of these studies,[32] tumors of the caudal portion of the maxilla also were associated with increased disease-free interval and ST. Schwarz et al[11,12] found that dogs with more caudally located oral tumors were at higher risk of death caused by disease and that incomplete margins negatively affected ST. These studies included all oral tumors in dogs, without an individual assessment of oral melanoma. The findings in the present study of a lack of association between tumor location and outcome could be the result of patient selection, with all dogs being assessed to have tumors amenable to curative-intent surgery and receiving surgery regardless of whether the tumors involved resection of soft tissue and bone versus only soft tissue lesions or were rostrally versus caudally located lesions; all were resected with the aim of complete margins. Also, with improvements in surgical techniques, wide resections of tumors are more readily attainable, which can improve outcomes. Another possibility is that the standard of small animal veterinary care has evolved to include more consistent wellness examinations and prophylactic dental cleanings, thus facilitating earlier diagnoses of oral lesions. At this time, there is no supporting evidence to suggest that there are oral cavity location differences in biological behaviors of oral melanoma in dogs. As long as caudally located lesions and maxillary or mandibular tumors were amenable to resection with appropriately wide margins, their prognosis did not differ from rostrally located tumors and soft tissue lesions.

In this study, sexually intact female dogs had an increased hazard of developing metastasis or local recurrence and death. Sex has not been shown to be a prognostic indicator for oral melanoma in the past.[4,26] The observation in this study that sexually intact female dogs have a poorer prognosis is most likely an artifact of a low sample number, given that the study included only 2 sexually intact female dogs, and is most likely a type I error.

The overall median PFI (508 days) and the overall median ST (723 days) in this retrospective series were longer than what have been previously reported. In general, reported overall median ST for dogs with oral melanoma varies greatly, depending on factors such as stage of disease and type of treatment, and range from 147 to 440 days.[5,9,10,33] Overall PFIs similarly vary from 78 to 259 days.[5,14,33] The long PFI and ST in this study



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could potentially be attributed to the difference in patient population between studies, in that this case series was selective for patients that received curative-intent surgery; thus, by default, their lesions may have been less advanced than those of patients with tumors not amenable to curative-intent resection or to any surgery at all. Also, some reports[5,34] suggest that not all oral melanomas behave in a similarly aggressive manner. Oral melanomas with more well-differentiated histologic features may carry a better prognosis, with 61 of 64 dogs either alive or dead from unrelated causes at the end of 1 study.[34] Eight of the dogs in our study had well-differentiated melanomas on histologic evaluation; 5 of these dogs did not receive any adjuvant therapy, 1 received carboplatin, and 1 received the xenogeneic melanoma vaccine.[b] Our findings emphasize that oral melanoma patients with lesions amenable to curative-intent surgery can have an extended PFI and ST with appropriately wide resections. This finding can potentially guide decision making when assessing the need for and type of adjuvant therapy following curative-intent resection of oral melanoma, given that the role of adjuvant therapy remains unclear.

In this study, dogs that had surgery as the sole treatment had a longer-than-expected PFI (> 567 days, with the median not reached) and median ST (874 days). Previous reports indicate an ST of 228 days[7] and 495 days[9] for dogs that only had surgery. The planned extent of surgery was not specified in those reports. We may have observed the improved PFI and ST in dogs that had surgery alone because of the extensiveness of the curative-intent surgery. With improvements in cross-sectional imaging and surgical techniques, assessment of the local extent of disease and wide excision may be more readily achievable. For example, advancement in maxillectomy techniques such as the combined dorsolateral and intraoral approach[35] improves surgical exposure, allowing for wide excision of caudally located tumors that may have otherwise not been amenable to radical resection.

This study demonstrates that curative-intent surgery with wide margins, even as the sole treatment option, for dogs with oral melanoma offers extended PFIs and STs, compared with previous reports.[1,7–10,21] Metastatic disease present at the time of diagnosis carries a poorer prognosis and is negatively associated with ST. The use of adjuvant therapy was negatively associated with disease progression, but this could be the result of selection bias, considering that patients with more advanced and biologically aggressive disease tend to be the ones receiving adjuvant therapy. The role of adjuvant therapies such as chemotherapy and the xenogeneic vaccine remains unclear.

a. SAS, version 9.3, SAS Institute Inc, Cary, NC.
b. Oncept canine melanoma vaccine, Merial, Duluth, Ga.

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