Efficacy of systemic adjuvant therapies administered to dogs after excision of oral malignant melanomas: 151 cases (2001–2012)

Sarah E. Boston, DVM, DVSc; Xiaomin Lu, MA, PhD; William T. N. Culp, VMD; Vincenzo Montinaro, DVM; Giorgio Romanelli, DVM; Robert M. Dudley, DVM, MS; Julius M. Liptak, DVM, MS; Lisa A. Mestrinho, DVM, MSc; Paolo Buracco, DVM

Objective—To determine prognostic factors for and compare outcome among dogs with oral malignant melanoma following excision with or without various systemic adjuvant therapies.

Design—Retrospective case series.

Animals—151 dogs with naturally occurring oral malignant melanomas treated by excision with or without adjuvant therapies from 2001 to 2012.

Procedures—Case accrual was solicited from Veterinary Society of Surgical Oncology members via an email list service. Information collected from case records included signalment, tumor staging, tumor characteristics, type of surgical excision, histologic diagnosis, adjuvant therapy, and survival time.

Results—The overall median survival time was 346 days. Results of multivariate analysis indicated that tumor size, patient age, and intralesional excision (vs marginal, wide, or radical excision) were considered poor prognostic indicators. All other demographic and clinical variables were not significantly associated with survival time after adjusting for the aforementioned 3 variables. A clear survival benefit was not evident with any systemic adjuvant therapy, including vaccination against melanoma or chemotherapy; however, the number of dogs in each treatment group was small. Ninety-eight dogs received no postoperative adjuvant therapy, and there was no difference in survival time between dogs that did (335 days) and did not (352 days) receive systemic adjuvant therapy.

Conclusions and Clinical Relevance—For dogs with oral malignant melanoma, increasing tumor size and age were negative prognostic factors. Complete excision of all macroscopic tumor burden improved survival time. Long-term survival was possible following surgery alone. Although systemic adjuvant therapy was not found to improve survival time, this could have been due to type II error. (*J Am Vet Med Assoc* 2014;245:401–407)

Malignant melanoma is the most common oral tumor in dogs and can be a devastating disease in both human and canine patients.[1–4] This type of tumor is locally invasive and highly metastatic.[1–4] Current treatment recommendations are local control with curative-intent surgery or radiation therapy (or both) and systemic adjunctive therapy.[1–4] Although local control through wide excision with or without radiation therapy has been fairly successful, death due to metastatic disease remains a major challenge among dogs with melanoma.[3–6] Traditionally, systemic adjunctive therapy administered after surgery has consisted of full-course chemotherapy with a platinum-based compound.[2,5,7] This has led to inconsistent and generally disappointing results.[8,9] Vascular endothelial growth factor has been shown to be a possible target for adjunctive therapy in cases of canine malignant melanoma,[10] and newer adjunctive therapies such as metronomic chemotherapy and treatment with tyrosine kinase inhibitors may have a role in the systemic control of melanoma. Furthermore, a vaccine[a] against melanoma was recently licensed for use in dogs[11–13] and is widely used in cancer centers in North America after affected dogs undergo local treatment with surgery or radiation. Early results with this treatment were encouraging[12]; however, authors of a recent retrospective study[14] involving a small number of dogs with oral melanoma concluded that the additional use of the melanoma vaccine did not improve survival time.

Abbreviations

CI	Confidence interval
MST	Median survival time

From the Department of Small Animal Clinical Sciences, College of Veterinary Medicine (Boston), and the Department of Biostatistics and Children's Oncology Group, College of Public Health and Health Professions and Medicine (Lu), University of Florida, Gainesville, FL 32608; the Department of Veterinary Surgical and Radiological Sciences, School of Veterinary Medicine, University of California-Davis, Davis, CA 95616 (Culp); Clinica Veterinaria Nerviano, Via Giulio Cesare Lampugnani, Nerviano, MI 320014, Italy (Montinaro, Romanelli); MedVet Columbus, Medical and Cancer Centers for Pets, 300 E Wilson Bridge Rd, Worthington, OH 43085 (Dudley); Alta Vista Animal Hospital, 2616 Bank St, Ottawa, ON K1T 1M9, Canada (Liptak); Center for Research in Veterinary Sciences, Faculty of Veterinary Medicine, Lusofona University, Lisbon, Portugal (Mestrinho); and the Dipartimento di Scienze Veterinarie, University of Turin, Torino, 10095, Italy (Buracco).

Supported by the Veterinary Society of Surgical Oncology Research Committee.

Address correspondence to Dr. Boston (sboston@ufl.edu).

Unauthenticated | Downloaded 12/17/25 12:05 PM UTC

Recommendations for postoperative adjuvant therapy for canine oral malignant melanoma vary among clinicians and institutions. There is no consensus regarding which treatment options should be recommended as first-line adjunctive therapy after surgery. Furthermore, many systemic adjuvant therapy recommendations are opinion based, rather than evidence based, and can generate vigorous discussion among specialists.[b] An objective evaluation of the usefulness of the available adjunctive treatments is needed.

The objectives of the study reported here were to determine prognostic factors for and compare outcome among dogs with oral malignant melanoma following excision with or without various systemic adjuvant therapies, and to provide a basis for a randomized, prospective study to evaluate the treatment protocols that show the most promise for successful treatment of oral malignant melanomas in dogs. We hypothesized that following excision of the melanoma, administration of systemic adjuvant therapy would prolong the overall survival time among dogs, compared with that among dogs that received no systemic adjuvant therapy; that the size of the oral melanoma would be a prognostic factor for survival time; and that wide and radical excision would be more effective for local control and result in longer survival times, compared with findings following marginal or intralesional excision. The null hypothesis was that there would be no difference in overall survival time among the groups of dogs receiving various systemic adjuvant therapies.

Materials and Methods

Case accrual was solicited from Veterinary Society of Surgical Oncology members via email.[b] Inclusion criteria for the study were that dogs had histologically confirmed oral malignant melanoma and were treated by tumor excision in the period from 2001 to 2012. Dogs that underwent incisional biopsy only were excluded from the study. Information collected from the medical record for each case included signalment (age, breed, and sex), tumor size (based on maximum dimension), tumor location, preoperative tumor staging (local and systemic), type of excision (intralesional, marginal, wide, or radical), histologic diagnosis and margin evaluation, adjuvant radiation therapy, systemic adjuvant therapy, evidence of local recurrence, overall survival time, and cause of death. An intralesional excision was defined as an excision within the tumor with cytoreductive intent, where some macroscopically tumor-bearing tissue was not removed. A marginal excision was defined as the apparent removal of all macroscopically tumor-bearing tissue, but where the excision margins would not be anticipated to completely remove all microscopically diseased tissue and were within the tumor reactive zone. A wide excision was defined as the attempt to remove of all macroscopic and microscopic tumor-bearing tissue by excision of the tumor with a margin of unaffected tissue around the tumor that was outside the tumor reactive zone. A radical excision was defined as the removal of an anatomic segment as an attempt to achieve the same goals as intended with a wide excision. Survival time was the primary outcome measure in the study and was defined as the period from the date of surgery until the date of death or last follow-up contact. As has been reported for another study[12] of dogs with oral malignant melanoma, progression-free interval was not specifically evaluated because of the typical rapid progression from evidence of gross metastasis and death with this neoplastic condition. The retrospective nature of the present study and the lack of consistent time points of evaluation of the dogs further compounded this issue.

Statistical analysis—Descriptive statistics, including median and range for continuous variables and population size and proportion for categorical variables, were used for summarizing the data. The overall survival time was compared among treatment groups by means of the log rank test. The corresponding hazard ratio and its 95% CI were estimated through the Cox proportional hazard regression model.

Both univariate and multivariate analyses were performed to assess the association of demographic and clinical variables with overall survival time. A forward selection method was used to select the most significant prognostic factors that were highly associated with survival time. When performing survival analyses, the continuous variables age and tumor size were classified into groups to assess the corresponding group effect on the overall survival time. To be specific, for tumor size, the dogs were categorized into 3 groups on the basis of whether the maximum dimension of the tumor was < 2, 2 to 4, or > 4 cm. A receiver operating characteristic curve analysis of age effect on mortality rate suggested that 12 years of age was an appropriate cutoff for assessing the age effect on survival time with dichotomized data. For age, dogs were categorized into 2 groups on the basis of whether they were < 12 or ≥ 12 years old. The sensitivity, specificity, and positive and negative predictive values of lymph node palpation and cytologic evaluation findings for detection of metastatic disease were evaluated, with histopathologic findings for lymph nodes as the gold standard.

The association of demographic and clinical variables with whether systemic adjuvant therapy was used was tested by an exact χ^2 test. As well, the association between patient age and the categorical variables (including whether adjuvant treatments were administered) was assessed by means of the Kruskal-Wallis test. For all analyses, a value of $P < 0.05$ was considered significant.

Results

Dogs—One hundred fifty-one cases were submitted and met the inclusion criteria. Cases were contributed from 8 institutions and 4 countries. The cases were accrued from the University of Turin, Italy (n = 45), University of California-Davis (36), Clinica Veterinaria Nerviano, Milan, Italy (27), MedVet, Columbus, Ohio (17), Lusofona University, Lisbon, Portugal (11), Ontario Veterinary College (9), and Alta Vista Animal Hospital, Ottawa (6). The median age and weight of dogs at the time of surgery were 12.0 years (range, 4.7 to 17.8 years) and 22.3 kg (49.1 lb [range, 2.3 to 69.0 kg {5.1 to 151.8 lb}]), respectively. Among the dogs, mixed breeds were most common (n = 48 [32%]), and

Unauthenticated | Downloaded 12/17/25 12:05 PM UTC

Cocker Spaniels (16 [11%]), Labrador Retrievers (13 [9%]), and Golden Retrievers (8 [5%]) were the most common breeds. There were 62 female (54 spayed) and 89 male (33 castrated) dogs included in the study.

Tumor size and location—Among the 151 dogs, the tumor location was primarily the mandible (n = 58 [38%]), followed by the maxilla (41 [27%]) and lip (34 [23%]), with the palate (8 [5%]) and other sites within the oral cavity also affected (9 [6%]). For 1 case, the location was not noted. In the records of 102 dogs, the tumor location was additionally described as a left (51 [50%]), right (40 [39%]), or central position (11 [11%]); in the records of 83 dogs, the tumor location was additionally described as a rostral (53 [64%]) or caudal (30 [36%]) position. The maximum dimension of the tumor was noted in the records of 135 dogs. The median maximum tumor dimension was 2.6 cm (range, 0.4 to 7.0 cm). Maximum tumor dimension was < 2, 2 to 4, and > 4 cm in 39 (29%), 71 (53%), and 25 (19%) of the 135 dogs, respectively.

Tumor staging—The mandibular lymph nodes were evaluated by palpation, cytologic evaluation, and histologic evaluation. The type of lymph node evaluation and whether this was unilateral or bilateral were not consistent or standardized among the dogs included in the study. Draining mandibular lymph node characteristics determined via palpation, cytologic evaluation, and histologic evaluation were summarized (**Table 1**). The sensitivity, specificity, positive predictive value, and negative predictive value of lymph node palpation, compared with histologic evaluation, for detection of metastatic disease were 65.6%, 77.8%, 84.0%, and 56.0%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of lymph node cytologic evaluation, compared with histologic evaluation, for detection of metastatic disease were 78.1%, 64.3%, 83.3%, and 56.3%, respectively.

Thoracic radiography was performed before surgery in 127 cases; with regard to radiographic evidence of gross metastatic disease, findings were considered negative for 122 dogs, positive for 2 dogs, and equivocal for 3 dogs. Thoracic CT was performed before surgery in 18 cases; with regard to CT evidence of gross metastatic disease, findings were considered negative for 14 dogs, positive for 3 dogs, and equivocal for 1 dog. Among the 3 dogs for which CT findings were considered positive, radiographic findings were considered equivocal for 2 and negative for 1. Thoracic radiographic views were not available in the case for which CT findings were considered equivocal.

Type of surgery and margins—The type of surgery was recorded or inferred from the surgery report for 150 cases. The excision was considered intralesional in 7 dogs, marginal in 29 dogs, and wide or radical in 114 dogs. Histologic margin information was available for 122 dogs. A complete excision was noted in the records of 77 dogs, and an incomplete excision was noted in the records of 45 dogs. Among the 92 dogs treated with wide or radical excision and for which margin information was available, the tumor removal was considered complete for 73 and considered incomplete for 19.

Adjuvant therapy—Following surgery, 12 dogs received radiation therapy. The radiation therapy protocol varied but was most often a hypofractionated protocol. Chemotherapy was used as adjunctive treatment following surgery in 32 cases. The chemotherapy protocols varied, but 26 dogs received a platinum-based treatment; 21 of those dogs received carboplatin. Other chemotherapeutic agents administered included lomustine, dacarbazine, and doxorubicin. Metronomic chemotherapy was used in 4 cases. Immunotherapy with the melanoma vaccine was used in 24 cases; 14 dogs were treated with a commercial vaccine[a] against melanoma, and 10 dogs were treated with an investigative vaccine against melanoma developed at the University of Wisconsin. No dogs were treated with tyrosine kinase inhibitors. Ninety-eight dogs received no systemic adjuvant therapy after surgery.

The systemic adjuvant therapy groups evaluated included dogs that were treated with chemotherapy, metronomic chemotherapy, or vaccination. The vaccinated dogs were considered as a group and as 2 subgroups on the basis of the type of vaccination (University of Wisconsin vaccine or the commercial melanoma vaccine). There were no differences in survival times detected between the 2 vaccine subgroups. None of the systemic

Table 1—Mandibular lymph node characteristics (determined via palpation, cytologic evaluation, and histologic evaluation) in 151 dogs with naturally occurring oral malignant melanoma that underwent tumor excision and were or were not given a form of systemic adjuvant therapy in the period 2001 to 2012.

Variable	Proportion of dogs	Proportion positive for presence of metastatic disease	Percentage positive for presence of metastatic disease
Palpation characteristics recorded	95/151	—	—
Node enlargement detected via palpation	40/95	—	42
Node considered normal via palpation; cytologic evaluation performed	19/55	3/19	16
Node considered normal via palpation; histologic evaluation performed	25/55	11/25	44
Node enlargement detected via palpation; cytologic evaluation performed	28/40	13/28	46
Node enlargement detected via palpation; histologic evaluation performed	25/40	21/25	84
Cytologic evaluation performed	62/151	—	—
Metastasis detected via cytologic evaluation	28/62	—	45
Cytologic findings considered normal; histologic evaluation performed	16/34	7/16	44
Cytologic findings indicative of metastasis; histologic evaluation performed	25/28	24/25	96
Histologic evaluation performed	95/151	56/95	59

— = Not applicable.

Unauthenticated | Downloaded 12/17/25 12:05 PM UTC

adjuvant treatments had a significant impact on survival time among the study dogs. Comparison of data for dogs that underwent surgery and were given a form of systemic adjuvant therapy (n = 53) and data for dogs that underwent surgery and were not given a form of systemic adjuvant therapy (98) revealed no difference in survival times between the 2 groups. The MST was 335 and 352 days for dogs that received systemic adjuvant therapy and those that did not, respectively (**Figure 1**). A post hoc power calculation was performed for comparison of survival time between dogs that received systemic adjuvant therapy and those that did not. Assuming a proportional hazard relationship between the 2 groups with the observed hazard ratio of 0.856 and 3-year survival rate of 12.7%, the post hoc power to detect the observed difference at the significance level of $P = 0.05$ was 13.5%. To detect a difference between these 2 groups with a power of 80%, the required sample size would be 1,615 dogs if the allocation ratio between the 2 groups remained the same as observed or 1,530 dogs if equal allocation was considered.

Cause of death—The date of last follow-up contact was known in 148 cases, with 90 confirmed deaths and 58 dogs still alive at that time. Of the 90 deaths, the cause was known for 82; for 58 dogs, the cause of death was melanoma related. Among the dogs that were alive, overall median follow-up interval from the date of surgery to the date of last data collection was 175 days. Local tumor recurrence was noted for 24 dogs. In these 24 cases, margin status was considered incomplete in 13 and complete in 6; margin status was not recorded in 5 cases. Pulmonary metastases developed in 35 dogs. Lymph node metastases developed in 28 dogs, of which 12 had documented cytologic or histologic evidence of lymph node metastasis at the initial evaluation.

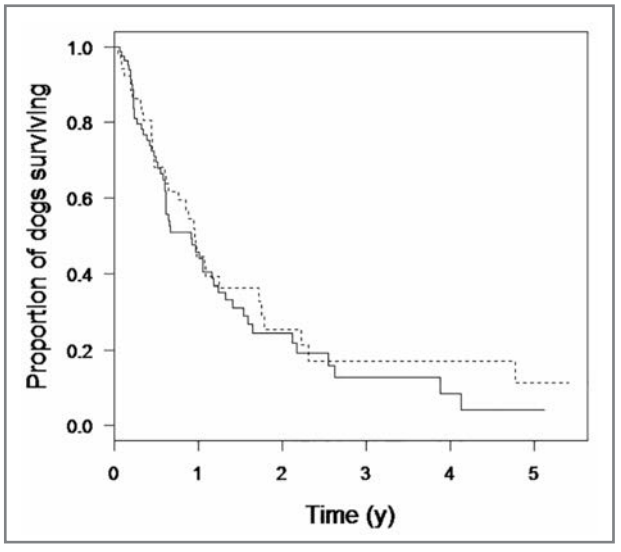


Figure 1—Kaplan-Meier survival curves for 151 dogs with naturally occurring oral malignant melanoma that underwent tumor excision and were (n = 53 [dashed line]) or were not (98 [solid line]) given a form of systemic adjuvant therapy in the period from 2001 to 2012. There was no significant ($P = 0.472$) difference in survival times between the 2 groups; the MST was 335 and 352 days for dogs that received systemic adjuvant therapy and those that did not, respectively.

Univariate survival analysis—In univariate analysis, age ≥ 12 years (vs < 12 years) was significantly ($P = 0.002$) associated with limited survival time (hazard ratio, 2.26; 95% CI, 1.461 to 3.483; **Figure 2**). Other significant ($P < 0.001$) variables included greater maximum tumor dimension (2 to 4 cm vs < 2 cm; hazard ratio, 2.23; 95% CI, 1.295 to 3.831; > 4 cm vs < 2 cm; hazard ratio, 5.201; 95% CI, 2.646 to 10.225; **Figure 3**). Metronomic chemotherapy (hazard ratio, 7.82; 95% CI, 2.36 to 25.93; $P = 0.001$) and intralesional surgery (marginal vs intralesional excision [hazard ratio, 0.29; 95% CI,

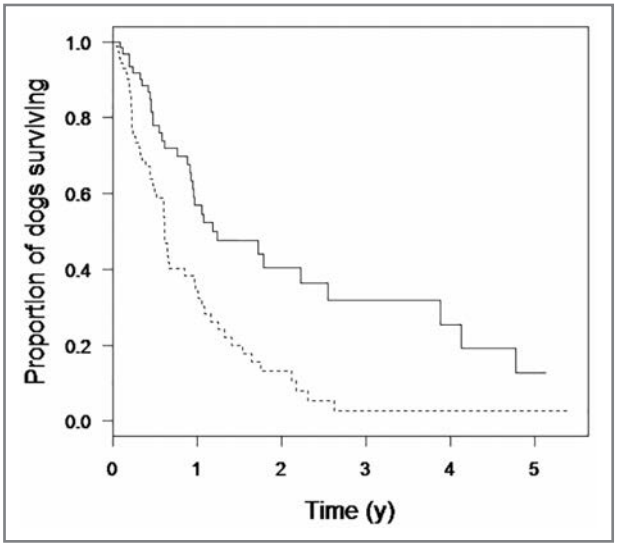


Figure 2—Kaplan-Meier survival curves for the dogs in Figure 1 that were < 12 years old (n = 68 [solid line]) or ≥ 12 years old (76 [dashed line]) at the time of tumor excision. In univariate analysis, age ≥ 12 years (vs < 12 years) was significantly ($P < 0.001$) associated with reduced survival time (hazard ratio, 2.26; 95% CI, 1.461 to 3.483).

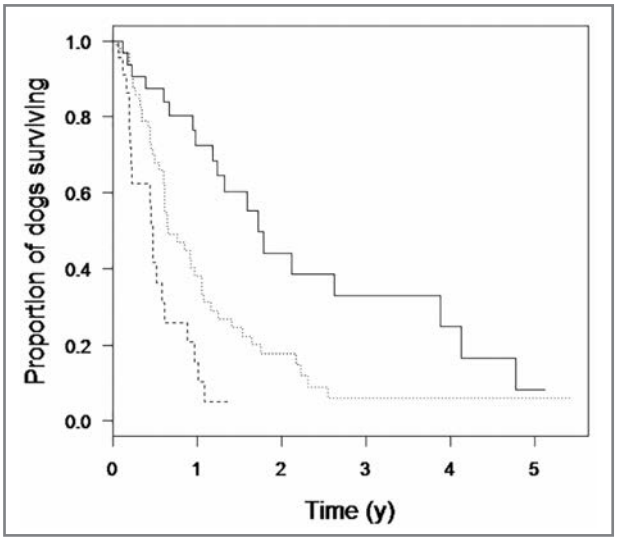


Figure 3—Kaplan-Meier survival curves for the dogs in Figure 1 for which the maximum tumor dimension was < 2 cm (n = 37 [solid line]), 2 to 4 cm (70 [dotted line]), or > 4 cm (25 [dashed line]). A significant ($P < 0.001$) variable was higher maximum tumor dimension (2 to 4 vs < 2 cm: hazard ratio, 2.23 [95% CI, 1.295 to 3.831]; > 4 vs < 2 cm: hazard ratio, 5.201 [95% CI, 2.646 to 10.225]).

Unauthenticated | Downloaded 12/17/25 12:05 PM UTC

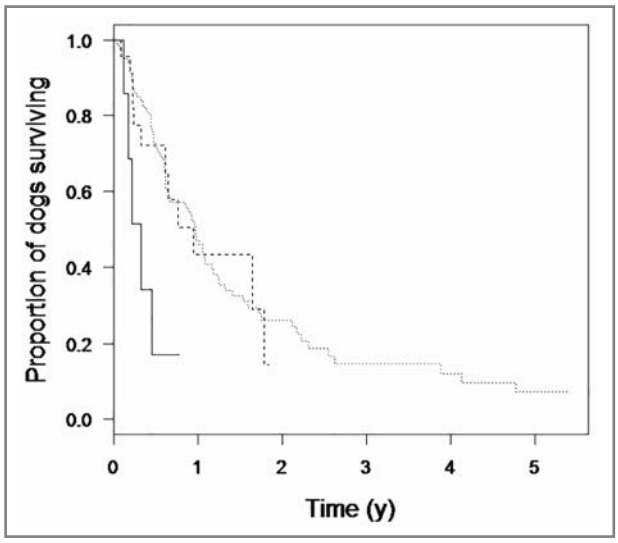


Figure 4—Kaplan-Meier survival curves for the dogs in Figure 1 that underwent intralesional excision (n = 7 [solid line]), marginal excision (29 [dashed line]), or wide or radical excision (111 [dotted line]). An intralesional excision was defined as an excision within the tumor with cytoreductive intent, where some macroscopically tumor-bearing tissue was not removed. A marginal excision was defined as the apparent removal of all macroscopically tumor-bearing tissue but where the excision margins would not be anticipated to completely remove all microscopically diseased tissue and were within the tumor reactive zone. A wide excision was defined as the attempt to remove of all macroscopic and microscopic tumor-bearing tissue by excision of the tumor with a margin of unaffected tissue around the tumor that was outside of the tumor reactive zone. A radical excision was defined as the removal of an anatomic segment as an attempt to achieve the same goals as intended with a wide excision. Intralesional surgery was significantly (P = 0.011) associated with reduced survival time (marginal vs intralesional excision, hazard ratio, 0.29 [95% CI, 0.10 to 0.83]; wide or radical vs intralesional excision, hazard ratio, 0.26 [95% CI, 0.10 to 0.67]).

0.10 to 0.83] and wide or radical excision vs intralesional excision [hazard ratio, 0.26; 95% CI, 0.10 to 0.67]; P = 0.011) were significantly associated with shorter survival time (**Figure 4**). The addition of radiation therapy was significantly (P = 0.013) associated with longer survival time (hazard ratio, 0.20; 95% CI, 0.05 to 0.82). However, among dogs that received this treatment, the effect of radiation therapy was confounded by age. Dogs that had radiation therapy were younger than those that did not; therefore, the association of radiation therapy and increased survival time was not significant in multivariate analysis. Patient weight, location of the tumor (lateral and rostral locations vs caudal location), adjuvant cytotoxic chemotherapy, treatment with the vaccine against melanoma, and lymph node involvement were not associated with survival time.

Dogs that received systemic adjuvant chemotherapy were more likely to receive concurrent postoperative radiation therapy (P = 0.026). No other significant differences with regard to age, weight, tumor size, type of surgery, or tumor location were detected. Older dogs were significantly less likely to receive both radiation therapy (P = 0.010) and the vaccine against melanoma (P = 0.016) after surgery, with no differences detected in tumor size or location, type of surgery, adjuvant chemotherapy, or metronomic chemotherapy based on age.

Table 2—Prognostic variables that were identified as significant via univariate and multivariate analysis and MSTs for the 151 dogs in Table 1 (overall MST, 346 days).

Variable	No. of dogs	MST (d)
Age (y)*†		
< 12	70	433
≥ 12	77	224
Maximum tumor dimension (cm)*†		
< 2	39	630
2–4	71	240
> 4	25	173
Type of surgery*†		
Intralesional excision	7	116
Marginal excision	29	346
Wide or radical excision	114	354
Postoperative radiation therapy*	12	1,747
Systemic treatment		
Metronomic chemotherapy*	4	53
Chemotherapy	32	352
Vaccine against melanoma	24	352
Systemic adjuvant therapy	53	352
No systemic adjuvant therapy	98	335

*Variable assessed via univariate analysis. †Variable assessed via multivariate analysis.

Multivariate survival analysis—In multivariate analyses, age ≥ 12 years (vs < 12 years) at the time of surgery had a significant (P = 0.005) negative effect on survival time (hazard ratio, 1.99; 95% CI, 1.224 to 3.228). Maximum tumor dimension had a significant (P = 0.007) effect on survival time; for a maximum tumor dimension of 2 to 4 cm versus < 2 cm, the hazard ratio was 1.709 (95% CI, 0.962 to 3.036), and for > 4 cm versus < 2 cm, the hazard ratio was 3.87 (95% CI, 1.92 to 7.80). Intralesional excision had a negative (P = 0.015) impact on survival time, compared with marginal excision (hazard ratio, 0.26; 95% CI, 0.07 to 0.97) and with wide or radical (hazard ratio, 0.17; 95% CI, 0.05 to 0.60) excision. Other factors were not significantly associated with survival time after controlling for these 3 variables. The prognostic factors that were significant in univariate and multivariate analysis were summarized (**Table 2**). The significant increase in likelihood of receiving postoperative radiation therapy in dogs that had received systemic adjuvant therapy was not significant in multivariate analysis after adjusting for the covariates such as age, tumor size, type of surgery, and tumor location.

The overall MST among the study dogs was 346 days (range, 1 to 1,716 days). Dogs that were < 12 years of age had an MST of 630 days, compared with an MST of 224 for dogs that were ≥ 12 years of age. For dogs with tumors for which the maximum dimension was < 2, 2 to 4, or > 4 cm, the MST was 630, 240, and 173 days, respectively. Dogs that underwent intralesional excision had an MST of 117 days, which was less than that of dogs that underwent marginal (346 days) and wide or radical excision (354 days).

Discussion

The present retrospective study involved a large number of dogs with oral malignant melanoma that were surgically treated with or without adjuvant therapy. Our aims were to evaluate prognostic factors in this group of

Unauthenticated | Downloaded 12/17/25 12:05 PM UTC

dogs and specifically to evaluate the outcome associated with postoperative systemic adjunctive therapy.

Age was determined to be a prognostic factor in the present study, with significantly shorter survival time in dogs ≥ 12 years old, compared with dogs < 12 years old. This association maintained significance when only cases of melanoma-related death were considered. This may be due to selection bias, wherein older patients were treated with less aggressive surgical and medical interventions. Older dogs were significantly less likely to receive both radiation therapy and the vaccine against melanoma as postoperative adjuvant therapies. It is also possible that the older dogs in the study may have had a more aggressive form of melanoma. Previous studies[15] have not shown that age is a prognostic factor for dogs with oral malignant melanoma.

Given the low sensitivity and specificity of both lymph node palpation and cytologic evaluation for detection of metastatic disease in dogs with oral malignant melanoma in the present study, routine biopsy of lymph nodes is recommended for lymph node staging. Williams and Packer[16] previously reported that lymph node palpation alone is an insensitive method for determining whether oral malignant melanoma has metastasized to the draining lymph nodes. Furthermore, it is our opinion that dissection of both the ipsilateral and contralateral mandibular and retropharyngeal lymph nodes should be performed to determine whether metastatic disease is present. To our knowledge, no studies have evaluated the incidence of contralateral lymph node metastasis in dogs with oral melanoma; however, contralateral lymph node metastasis in humans with oral melanoma has been reported.[17] Lymph node metastasis was not found to be of prognostic value among the dogs in the present study. This was similar to the findings of 2 previous studies,[15] which did not show regional lymph node involvement to be prognostic. The apparent lack of prognostic value may be because lymph node assessment had not been standardized in those retrospective studies.[15] Lymph node status has prognostic importance in human cases of oral malignant melanoma, suggesting that lymph node staging in similarly affected dogs may be worthwhile.[18,19]

In the present study, larger tumor size was a negative prognostic indicator. Tumor size and WHO stage have not been definitively shown to be prognostic for dogs with oral melanoma.[15,20] However, it is intuitive that a large oral malignant tumor would be associated with a poorer prognosis for several potential reasons: unlike a small tumor, it has a more aggressive growth pattern, it has likely been present longer and therefore has an increased risk of distant metastasis, or local control is more difficult to achieve with surgery.

The dogs in the present study that underwent intralesional excision had a significantly shorter survival time, compared with dogs that underwent marginal excision or wide or radical excision. This is expected, considering that a decision to perform intralesional surgery was likely based on palliative intent. Interestingly, dogs treated with marginal excision did not have a shorter survival time than dogs treated with wide or radical excision. It is possible that removal of the primary tumor via a marginal or wide excision may eliminate tumor-mediated immunosuppression and allow a dog's immune system to react to the remaining microscopic tumor burden.[21] Having said that, until there are more compelling data to the contrary, we still believe that the goal of surgery should be complete removal of both macroscopically and microscopically diseased tissue via wide or radical excision. When this is not possible, a marginal excision can be considered. Intralesional resection does not appear to offer a survival advantage but may improve patient comfort in a palliative setting.

In the present study, the overall survival time was 346 days, with 29% of the dogs living > 1 year before death or loss to follow-up. This survival time is comparable to those reported recently for dogs with oral melanoma.[8,9] These results are encouraging and should support a shift in prognostication and treatment of this disease. An overly negative prognosis has the potential to lead to undertreatment of this disease because of the perceptions of the client and attending clinician.

One of the study goals was not achieved in the present study: determining which systemic adjunctive therapy or therapies had the most promise for treatment of canine oral malignant melanoma. This was due to a combination of factors. It is possible that these adjunctive therapies do not actually make a difference in the course of this disease, as has been suggested from results of recent studies in which carboplatin[8,9] or the vaccine against melanoma[14] were not associated with improved survival time in cases of canine oral malignant melanoma. It is also possible that the low number of dogs in each treatment group in the present study (combined with the inherent study limitations including lack of randomization and treatment protocol standardization) made it impossible to detect any differences in survival times provided by the various systemic adjuvant therapies. This could be due to a type II error, or it may be that there was no difference in survival times between the treatment groups. Post hoc power analysis revealed an exceedingly low statistical power (13.5%) to detect the observed difference based on the sample size. To detect the same difference with 80% power, inclusion of at least 1,530 dogs would have been required, depending on the allocation ratio between the 2 groups. However, post hoc power analysis should be interpreted with caution. It is also possible that we did not detect a difference in survival time between dogs that did and did not receive systemic adjuvant therapy because of unmeasured confounding factors in this retrospective study. This highlights the need for a randomized prospective study to assess the impact of commonly used adjuvant therapies on survival time among dogs with oral malignant melanoma. It also indicates that a large number of cases will be required and that a multi-institutional study would be appropriate to have an adequately powered study.

One large study[13] in dogs compared adjuvant treatment with the commercial xenogeneic human tyrosinase DNA vaccine with historical controls. Interestingly, the historical controls also had a long survival time of 324 days.[13] The vaccinates had a significantly longer survival time, and the median for this group was not reached.[13] Although these findings are promising, the comparison of the treatment group to historical

Unauthenticated | Downloaded 12/17/25 12:05 PM UTC

controls was suboptimal and the long survival time in that historical control group and in the dogs that were treated with surgery alone in the present study suggests that a prospective study with placebo versus treatment is both ethical and warranted.

The major limitations of the present study reflected the limitations that exist in current knowledge of this disease, which is fraught with bias in how treatments are selected for patients. A wide range of clinical approaches were used in the cases included in the present study. Study dogs did not receive standardized treatment for this disease, and both selection bias and confirmation bias likely played a role in treatment decisions. Another major limitation was that we were not able to conduct a histologic review for these cases. This may have helped to stratify the cases and determine prognosis. It is known that mitotic index, nuclear atypia, and growth fraction are important factors in the prognosis for dogs with melanocytic neoplasia.[15] It is possible that the histopathologic characteristics are the ultimate determinants of the biological behavior of this disease and determine prognosis, regardless of clinical efforts.

One unexpected finding in the present study was the large number of dogs that did not receive any form of systemic therapy after local tumor treatment. Why these dogs were not treated with adjuvant therapy is not clear. Possibly, the histopathologic features of the tumor were not highly aggressive in these cases and hence adjuvant therapy was not recommended. However, this was considered unlikely because all cases in the present study had a definitive diagnosis of malignant melanoma. More likely, these dogs did not have further treatment because of factors that were related to the owners' or the attending clinicians' opinions about adjuvant therapy rather than to features of the tumor itself, but this is difficult to prove or disprove. Following surgery, 98 dogs in the present study had no additional treatment with no apparent effect on the survival time, compared with dogs that were treated with either vaccination or chemotherapy. Looking at this group as a stand-alone population is interesting because there are no reports of such a large group of dogs that have undergone surgery for oral melanoma with no additional treatment. Most dogs in the present study had wide or radical excision of the tumor. The results suggested that systemic adjunctive therapy may not provide additional benefits to wide or radical excision alone. The similar outcome in dogs that underwent surgery but were not treated with adjuvant therapy underscores the suggestion that local control and biological behavior of the tumor may be the most important factors in determining outcome for affected dogs.

Results of the present study indicated that surgical treatment of oral malignant melanoma in dogs can result in an MST of 346 days, with long-term survival in 29% of cases. Dogs that were treated with surgery alone had an MST of 352 days, and we were not able to detect a survival advantage with any form of postoperative adjuvant therapy. Surgery should continue to be a cornerstone in the treatment of this disease. No definitive recommendations for adjunctive therapy could be made on the basis of the findings of the present study. As mentioned in reports of other retrospective studies[8,9,15] of this disease, it is evident that a randomized, prospective clinical trial that compares postoperative adjuvant therapies for oral melanoma in dogs is needed.

a. Oncept Canine Melanoma Vaccine, DNA, Merial, Duluth, Ga.
b. VSSO email list service, Veterinary Society of Surgical Oncology, Fort Collins, Colo.

References

1. González-García R, Naval-Gías L, Martos PL. Melanoma of the oral mucosa. Clinical cases and review of the literature. *Med Oral Patol Oral Cir Bucal* 2005;10:264–271.
2. Tanaka N, Mimura M, Ogi K, et al. Primary malignant melanoma of the oral cavity: assessment of outcome from the clinical records of 35 patients. *Int J Oral Maxillofac Surg* 2004;33:761–765.
3. Liptak JM, Withrow SJ. Cancer of the gastrointestinal tract. In: *Small animal clinical oncology*. St Louis: Saunders, 2007;455–475.
4. Liptak JM, Lascelles BX. Oral tumors. In: Kudnig ST, Séguin B, eds. *Veterinary surgical oncology*. Ames, Iowa: Wiley Blackwell, 2012;119–178.
5. Murphy S, Hayes AM, Blackwood L, et al. Oral malignant melanoma—the effect of coarse fractionation radiotherapy alone or with adjuvant carboplatin therapy. *Vet Comp Oncol* 2005;3:222–229.
6. Blackwood L, Dobson JM. Radiotherapy of oral malignant melanomas in dogs. *J Am Vet Med Assoc* 1996;209:98–102.
7. Proulx DR, Ruslander DM, Dodge RK, et al. A retrospective analysis of 140 dogs with oral melanoma treated with external beam radiation. *Vet Radiol Ultrasound* 2003;44:352–359.
8. Brockley LK, Cooper MA, Bennett PF. Malignant melanoma in 63 dogs (2001–2011): the effect of carboplatin chemotherapy on survival. *N Z Vet J* 2013;61:25–31.
9. Dank G, Rassnick KM, Sokolovsky Y, et al. Use of adjuvant carboplatin for treatment of dogs with oral malignant melanoma following surgical excision. *Vet Comp Oncol* 2014;12:78–84.
10. Taylor KH, Smith AN, Higginbotham M, et al. Expression of vascular endothelial growth factor in canine oral malignant melanoma. *Vet Comp Oncol* 2007;5:208–218.
11. USDA licenses DNA vaccine for treatment of melanoma in dogs. *J Am Vet Med Assoc* 2010;236:495.
12. Bergman PJ, McKnight J, Novosad A, et al. Long-term survival of dogs with advanced malignant melanoma after DNA vaccination with xenogeneic human tyrosinase: a phase I trial. *Clin Cancer Res* 2003;9:1284–1290.
13. Grosenbaugh DA, Leard AT, Bergman PJ, et al. Safety and efficacy of a xenogeneic DNA vaccine encoding for human tyrosinase as adjunctive treatment for oral malignant melanoma in dogs following surgical excision of the primary tumor. *Am J Vet Res* 2011;72:1631–1638.
14. Ottnod JM, Smedley RC, Walshaw R, et al. A retrospective analysis of the efficacy of Oncept vaccine for the adjunct treatment of canine oral malignant melanoma. *Vet Comp Oncol* 2013;11:219–229.
15. Smedley RC, Spangler WL, Esplin DG, et al. Prognostic markers for canine melanocytic neoplasms: a comparative review of the literature and goals for future investigation. *Vet Pathol* 2011;48:54–72.
16. Williams LE, Packer RA. Association between lymph node size and metastasis in dogs with oral malignant melanoma: 100 cases (1987–2001). *J Am Vet Med Assoc* 2003;222:1234–1236.
17. Suton P, Lukšić I, Müller D, et al. Lymphatic drainage patterns of head and neck cutaneous melanoma: does primary melanoma site correlate with anatomic distribution of pathologically involved lymph nodes? *Int J Oral Maxillofac Surg* 2012;41:413–420.
18. Sun CZ, Chen YF, Jiang YE, et al. Treatment and prognosis of oral mucosal melanoma. *Oral Oncol* 2012;48:647–652.
19. Bodem JP, Gülicher D, Engel M, et al. Role of neck dissection in the treatment of melanoma of the head and neck. *J Craniofac Surg* 2013;24:483–487.
20. Hahn KA, DeNicola DB, Richardson RC, et al. Canine oral malignant melanoma: prognostic utility of an alternative staging system. *J Small Anim Pract* 1994;35:251–256.
21. Bast RC, Kufe DW, Pollock RE, et al. Principles of surgical oncology. In: Holland JC, Frei E, eds. *Cancer medicine*. 5th ed. Hamilton, ON, Canada: BC Decker, 2000.

Unauthenticated | Downloaded 12/17/25 12:05 PM UTC