Outcomes of dogs undergoing radiotherapy for treatment of oral malignant melanoma: 111 cases (2006–2012)

Mifumi Kawabe, DVM, PhD; Takashi Mori, DVM, PhD; Yusuke Ito, DVM; Mami Murakami, DVM, PhD; Hiroki Sakai, DVM, PhD; Tokuma Yanai, DVM, PhD; Kohji Maruo, DVM, PhD

Objective—To evaluate the characteristics and outcomes of dogs with stage I, II, III, or IV oral malignant melanoma treated by various types of radiotherapy.

Design—Retrospective case series.

Animals—111 dogs.

Procedures—Medical records of dogs with oral malignant melanoma treated by radiotherapy (with or without adjunctive treatments) at a veterinary medical center between July 2006 and December 2012 were reviewed. Information regarding signalment, tumor location, disease stage, treatment protocols, adverse effects, and survival time were obtained from medical records and by telephone follow-up. Associations between variables of interest and outcome were analyzed.

Results—Dogs received orthovoltage x-ray (n = 68), megavoltage x-ray (39), or electron beam (4) radiotherapy. Adjunctive treatments included debulking surgery (n = 18), chemotherapy (39), or both (27). Median survival times for dogs with stage I, II, III, and IV melanoma were 758 days (n = 19), 278 days (24), 163 days (37), and 80 days (31), respectively, and differed significantly between dogs with stage I disease and those with all other disease stages. Among dogs with stage III melanoma, risk of death was significantly higher in those that received orthovoltage x-ray treatment than in those that received megavoltage x-ray treatment. Severe (primary or secondary) adverse effects were identified in 9 dogs.

Conclusions and Clinical Relevance—Median survival time was significantly longer for dogs with stage I oral malignant melanoma than for dogs with more advanced disease at the time of staging. The staging system used may be a useful tool for prognosis prediction in dogs undergoing similar treatment protocols for oral malignant melanomas. (*J Am Vet Med Assoc* 2015;247:1146–1153)

Malignant melanoma is one of the most common and aggressive tumors in the oral cavity of dogs.[1–3] Dogs with oral malignant melanoma have poor prognosis because this type of tumor rapidly invades the surrounding tissue and has a high likelihood of regional and distant metastases early in the course of the disease.[4,5]

Surgery and radiation treatment are the most common methods used to locally control oral tumors. The reported MST for untreated dogs with oral malignant melanoma is 65 days.[5] In comparison, the MST for dogs treated by surgery ranges from 9.1 to 9.9 months,[6–8] and in dogs treated by radiotherapy alone or in combination with surgery, the MST ranges from 7.0 to 7.9 months.[9,10] Owing to these reports of extended survival times, aggressive surgery is the first choice for local treatment of oral malignant melanoma.[11] However, a variety of complications such as difficulty eating or aesthetic changes may occur after surgery.[12]

Oral melanoma responds to hypofractionated radiotherapy in humans and in dogs.[9,13–15] Additionally, several prognostic factors that affect radiotherapy outcomes have been identified. Proulx et al[10] reported that the overall survival time was longer in dogs without radiographic evidence of bone destruction than in dogs with radiographically evident bone changes. Blackwood and Dobson[16] also found that dogs with tumors < 5 cm^3 in volume were more likely to achieve a complete response, and they found an association between tumor volume and MST; the MST was 86 weeks in dogs with tumors < 5 cm^3, 16 weeks in dogs with tumors between 5 and 15 cm^3, and 20.5 weeks in dogs with tumors > 15 cm^3 at the time of first treatment. Although Bateman et al[9] did not find any association between the clinical stage of cancer and the response to radiotherapy or survival time, that study lacked sufficient case numbers to make a definitive determination.

The purpose of the study reported here was to evaluate the clinical outcomes of dogs with oral malignant melanoma treated by radiotherapy with or without cytoreductive surgery or other adjunctive treatments. We also sought to identify differences in outcomes for

Abbreviations

MST	Median survival time
MVX	Megavoltage x-ray
OVX	Orthovoltage x-ray
RECIST	Response evaluation criteria in solid tumors

From the Faculty of Applied Biological Sciences, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan.
Address correspondence to Dr. Kawabe (myama@gifu-u.ac.jp).

dogs that received MVX versus OVX radiotherapy and for dogs with different stages of melanoma according to World Health Organization staging guidelines.

Materials and Methods

Case selection—Electronic and hard copy medical charts of the animal medical center at Gifu University were searched to identify dogs with a diagnosis of oral malignant melanoma treated by radiotherapy between July 1, 2006, and December 31, 2012. Dogs that underwent radiotherapy with or without cytoreductive surgery or chemotherapy were included. To appropriately evaluate the efficacy and tolerability of radiotherapy and to compare outcomes of these patients with those of dogs that underwent extensive surgery in other studies, the records of dogs that underwent extensive surgery (eg, mandibulectomy or maxillectomy) were excluded from the analysis. Case records that did not include the date of death were excluded.

Medical records review—Information recorded included signalment, results of diagnostic imaging, biopsy results, tumor stage at the time of first radiation treatment, treatments administered, reasons for changes in the treatment protocols, adverse effects attributed to treatment, and follow-up information including survival time (defined as the time between the first radiation treatment and the date of death). Patient biopsy specimens and slides were not examined for this study. Long-term outcomes were obtained from the medical records or by telephone call with the owners.

Procedures—General anesthesia was induced according to protocols determined by the clinician responsible for each patient. All dogs underwent CT[a] to stage the tumor and plan treatment just prior to the first radiation treatment. The mandibular lymph nodes, retropharyngeal lymph nodes, and entire thorax were imaged. Biopsy specimens were collected by core biopsy or excisional biopsy after the CT. Any enlarged local lymph nodes were also biopsied; subjectively normal-sized lymph nodes were not evaluated. All tumor specimens were evaluated by board-certified veterinary pathologists who had ≥ 10 years of experience. Tumors were classified as stage I, II, III, or IV according to World Health Organization staging guidelines as previously described.[11] Tumors with no evidence of distant metastasis were categorized as stage I (primary tumor of < 2 cm diameter with no evidence of regional lymph node involvement), II (primary tumor of 2 to 4 cm diameter without evidence of regional lymph node involvement) or III (primary tumor of 2 to 4 cm diameter with regional lymph node involvement or > 4 cm diameter without evidence of lymph node involvement).[11] Tumors with evidence of distant metastasis were categorized as stage IV, regardless of size or lymph node involvement.[11]

All dogs underwent radiotherapy. Treatments were delivered with an OVX unit[b] that had an x-ray energy output of 300 kV or with a linear accelerator[c] that had an x-ray energy output of 4 MV. The radiation equipment provided OVX, MVX, or electron beam radiotherapy.

For OVX treatment, the treatment position varied according to the location of the tumor. The exposure field was positioned such that the entire gross tumor volume was contained within the irradiation range. Planning target volume margins were contoured > 0.5 cm around the gross tumor volume limits to include regions at risk for microscopic disease extension. Treatment beams were delivered from 1 or 2 directions while avoiding organs at risk for injury when feasible, such as the eyes and brain. The rated output was 300 kV; the dose prescription was 6.3 to 10.0 Gy/fraction in 4 to 6 fractions, for a total dose of 37.8 to 40 Gy; and irradiations were carried out at 7- to 10-day intervals. For MVX treatment, planning CT scans were performed for each patient in the treatment position (sternal recumbency) with a bite block system. Individualized treatment plans were constructed with a 3-D CT-based computer-generated treatment planning system.[d] Planning target volume margins were contoured to include regions at risk for microscopic disease extension and ranged from 0.3 to 1.0 cm around the gross tumor volume limits. In dogs that underwent debulking surgery before radiotherapy, the clinical target volume was contoured according to the location and extent of the tumor. The planning target volume margins were contoured from 0.3 to 1.0 cm around the clinical target volume limits. Adjacent critical tissues or organs that were deemed healthy and at risk for radiation damage were also contoured on the CT images. A multileaf collimator was used on the linear accelerator to shape the fields exposing the target volume and block the surrounding normal tissues. The isocenter and beam arrangements for each plan were determined by the location of the tumor and adjacent critical normal structures. Treatments were delivered in 5 to 9 unequally weighted fields in multiple oblique beam arrangements. The energy output of the x-ray beam was 4 MV. The dose prescription was 6.0 to 10.0 Gy/fraction in 4 to 8 fractions, for a total dose of 40 to 50 Gy, and irradiations were carried out at 7- to 10-day intervals. Portal imaging was performed during the initial setup to ensure accurate patient positioning. Port films and orthogonal port films were acquired before the first treatment to assist in the setup. For electron beam radiotherapy, the treatment position varied with the location of the tumor. The exposure field was positioned such that the entire gross tumor volume was contained within the radiation treatment field. The planning target volume margins were contoured > 0.5 cm around the gross tumor volume limits. Treatment beams were delivered from 1 direction, and the electron energy was 3 MeV. The treatment dose was 6.0 Gy/fraction in 6 fractions, for a total dose of 36 Gy, with treatments carried out at 7-day intervals.

Treatment response was evaluated ≤ 1 month after the final radiotherapy treatment. Primary tumor measurements were performed through appropriate methods (ie, CT, palpation, and visual examination). Treatment response was classified according to the Veterinary Cooperative Oncology Group RECIST guidelines for dogs.[17] A complete response was defined as the disappearance of all targeted lesions. A partial response was defined as a ≥ 30% reduction in the sum of diameters of the targeted lesions, compared with the baseline sum. Stable disease was defined as a < 30% reduction or < 20% increase in the sum of diameters of the targeted lesions, with the smallest sum of the diameters during the study designated as the reference value. Progressive disease was defined as the appearance of ≥ 1 new lesion or a ≥ 20% increase in the sum of diameters of the target lesions, with the smallest sum during the study designated as the reference; the sum must have also increased by ≥ 5 mm.

Radiation-induced tissue damage was assessed and characterized according to the radiation morbidity scoring scheme described by the Veterinary Radiation Therapy Oncology Group.[18] Serial physical examinations were

performed for all dogs during weekly treatments and at follow-up visits to assess tissue damage attributable to radiation, and the scores (ranging from 0 [no change over baseline] to 3 [most severe] for acute damage and 0 [none] to 3 [most severe] for late damage)[18] were assigned retrospectively on the basis of findings in the medical records. Different types or sites of injury were assessed separately for each dog. The highest score recorded for each injury during the first 6 months after the start of radiation treatment was used in analysis.

Statistical analysis—Kaplan-Meier survival curves were generated for all the dogs; dogs still surviving at the end of the investigation period were censored. The effects of clinical stage on survival time were examined via log rank tests to detect any significant differences between the curves. Differences in survival time between dogs grouped according to tumor stage (eg, stage I vs stage II) and between dogs grouped according to tumor anatomic site were then evaluated with a Tukey multiple comparisons test. The difference in survival time between OVX and MVX treatment groups was evaluated by means of a log rank test. The difference in the median total dose of radiation received by dogs that underwent OVX and MVX treatments was evaluated with the Mann-Whitney test, and χ^2 tests were used to examine differences in sex, therapeutic response, and adverse effects between proportions of dogs in the study population. Analyses were performed with computer software.[e] Values of $P < 0.05$ were considered significant.

The interaction of treatment and survival was evaluated with the Cox proportional hazards model. Breed, weight, sex, age, clinical stage, radiation technique (MVX or OVX), and total radiation dose were included in the multivariable analysis. These analyses were performed with another computer program.[f] Values of $P < 0.05$ were considered significant.

Results

A total of 157 dogs underwent radiotherapy during the study period. Of these, 111 dogs were included in the study; 45 dogs with an unknown date of death and 1 dog that underwent extensive surgery were excluded. Twenty-four breeds were represented. Mixed-breed dogs (22 [19.8%]), Miniature Dachshunds (17 [15.3%]), and Labrador Retrievers (10 [9.0%]) were most commonly affected. Other represented breeds were as follows: Shih Tzu (n = 8), Shiba Inu (8), Beagle (7), Golden Retriever (6), Yorkshire Terrier (6), Toy Poodle (4), Pomeranian (3), German Shepherd Dog (2), Chihuahua (2), Pug (2), Flat-Coated Retriever (2), Miniature Schnauzer (2), American Cocker Spaniel (2), Shetland Sheepdog (1), Scottish Terrier (1), Dalmatian (1), Bernese Mountain Dog (1), Basset Hound (1), Papillion (1), Miniature Pinscher (1), and Akita (1). Median weight of the dogs was 9.8 kg (21.6 lb; range, 2.5 to 52 kg [5.5 to 114.4 lb]), and median age at first visit was 12.2 years (range, 3 to 17 years). There were 36 sexually intact females, 16 spayed females, 45 sexually intact males, and 14 castrated males in the study population. There was no significant (P = 0.64) difference observed between the numbers of female and male dogs, but a significant ($P < 0.001$) difference was observed between sexually intact and neutered (spayed and castrated) dogs. There were 19, 24, 37, and 31 dogs with stage I, II, III, and IV melanoma, respectively. There were no significant differences in weight, age, or sex of dogs grouped according to the clinical stage of disease (**Table 1**). Metastasis to the mandibular lymph node was confirmed in 39 dogs by histologic evaluation of a biopsy sample, and pulmonary metastasis was confirmed in 31 dogs by results of diagnostic imaging.

Radiotherapeutic treatments included OVX (n = 68 dogs), MVX (39), and electron beam irradiation (4). Five of 39 dogs that underwent MVX treatment had first received OVX, but only for 1 treatment. These 5 dogs were switched from OVX to MVX treatment for the following reasons: insufficient time to plan MVX for the first treatment (n = 3 dogs), mechanical problems during the first treatment (1), and owner request (1). Irradiation treatment was discontinued in midcourse for 31 of 111 dogs because of death (n = 8 dogs), deterioration of clinical condition (8 dogs), or owner

Table 1—Demographic characteristics for and anatomic locations of oral malignant melanomas in 111 dogs that underwent radiotherapy (OVX [n = 68], MVX [39], or electron beam irradiation [4]) with or without adjunctive treatments at a veterinary teaching hospital between July 1, 2006, and December 31, 2012.

	Stage			
Variable	**I (n = 19)**	**II (n = 24)**	**III (n = 37)**	**IV (n = 31)**
Median body weight (kg)	6.0	9.7	10.2	11.7
Age (y)				
Median	10.2	12.3	12.6	12.4
Mean ± SD	10.6 ± 2.3	12.2 ± 1.4	12.3 ± 2.8	12.2 ± 2.5
Sex				
Male	15 (78.9)	14 (58.3)	16 (43.2)	14 (45.2)
Female	4 (21.1)	10 (41.7)	21 (56.8)	17 (54.8)
Tumor location				
Maxilla	9 (47.4)	8 (33.3)	9 (24.3)	14 (45.2)
Mandible	5 (26.3)	9 (37.5)	17 (46.0)	7 (22.6)
Lip	3 (15.8)	3 (12.5)	2 (5.4)	3 (9.7)
Tongue	0 (0)	2 (8.3)	1 (2.7)	0 (0)
Buccal mucosa	0 (0)	1 (4.2)	5 (13.5)	5 (16.1)
Hard palate	2 (10.5)	1 (4.2)	1 (2.7)	0 (0)
Soft palate	0 (0)	0 (0)	2 (5.4)	2 (6.5)

Values are number (%) unless otherwise indicated.

request (15 dogs). Seven of these 31 dogs had stage I (n = 2) or stage II (5) melanoma, and treatment was discontinued at the owner's request for all 7. The therapeutic response for 4 of these dogs was complete, but this variable was unknown for the remaining 3 dogs. In contrast, for dogs with stage III (n = 8) or IV (16) melanoma, the most common reason for discontinuing radiotherapy was deteriorating clinical condition or death (16/24 [67%]). The median total radiation dose was 37.8 Gy (range, 6.3 to 74.3 Gy). One geriatric dog (age, 15 years) had lymph node metastasis confirmed at the initial physical examination; the patient was not expected to survive long term and was thus administered > 70 Gy of radiation. A significant ($P < 0.001$) difference was observed between the median total radiation doses for dogs that received OVX (31.50 Gy) versus MVX (49.00 Gy) treatment.

Ninety-nine of 111 dogs had ≥ 1 adjunctive treatment. This included debulking surgery (n = 18 dogs), chemotherapy (39), or both (27). Of the 66 dogs that received chemotherapeutic agents, 26 had local treatment only, 26 had systemic treatment only, and 14 had both. Other treatments (given to 65 dogs) included firocoxib (5.0 mg/kg [2.27 mg/lb], PO, q 24 h; n = 46 dogs), prednisolone (0.5 to 1.0 mg/kg, [0.23 to 0.45 mg/lb], PO, q 24 h; 29), mebendazole (5.0 mg/kg, PO, q 24 h; 5), and hyperthermia (2). In 7 of 45 dogs that underwent debulking surgery, there were no macroscopically measureable tumor lesions at the time of radiation treatment planning; all 7 dogs were classified as having stage I tumors prior to resection. Cisplatin[g] (0.5 mg [1 mL]/dog/treatment, q 1 to 2 wk) injected directly into the tumor was used for local chemotherapy, and carboplatin (180 to 250 mg/m^2, IV, q 3 wk) was used for systemic chemotherapy. The number of dogs that underwent chemotherapy according to clinical stage was as follows: stage I, 11 dogs (local only, 3 dogs; systemic only, 4 dogs; local and systemic, 4 dogs); stage II, 19 dogs (local only, 9 dogs; systemic only, 5 dogs; local and systemic, 5 dogs); stage III, 20 dogs (local only, 9 dogs; systemic only, 8 dogs; local and systemic, 3 dogs); and stage IV, 16 dogs (local only, 5 dogs; systemic only, 9 dogs, local and systemic, 2 dogs). Local chemotherapy was used concurrently with radiotherapy for 2 dogs and was performed after radiotherapy was complete in 38 dogs. Systemic chemotherapy was used concurrently with radiotherapy in 32 dogs and administered after radiotherapy was complete in 8 dogs. Anatomic locations of oral melanomas included maxilla (n = 40), mandible (38), lip (11), buccal mucosa (11), hard palate (4), soft palate (4), and tongue (3). The survival curves did not vary significantly (P = 0.16) among dogs grouped by tumor sites (**Figure 1**). The survival curves also did not vary significantly between dogs with rostral (n = 29) and caudal (9) maxillary tumors (P = 0.20) or between those with rostral (29) and caudal (5) mandibular tumors (P = 0.51). Six dogs were excluded from the analysis because their tumors were too large to classify as rostral or caudal.

The MST for all 111 dogs was 171 days (range, 3 to 1,620 days). The MST for dogs with stage I, II, III, and IV melanoma were 758, 278, 163, and 80 days, respectively. The survival curves for dogs with each stage of disease are indicated (**Figure 2**). Although survival times differed significantly ($P < 0.001$) among stages by the log rank test, the Tukey test revealed significant differences in MST between stages I and II ($P < 0.05$), stages I and III ($P < 0.001$), and stages I and IV ($P < 0.01$) only, with no significant differences observed between stages II and III (P = 0.83), stages II and IV ($P = 0.90$), and stages III and IV ($P = 1.0$).

Fifteen dogs were still alive at study completion (8 dogs with stage I [surviving 1,620, 1,159, 675, 598, 577, 468, 402, and 339 days], 3 with stage II [surviving 966, 769, and 479 days], 2 with stage III [surviving 424 and 392 days], and 2 with stage IV melanoma [surviving 343 and 312 days]). Of the 96 dogs that died, 3 were euthanized, 66 died of melanoma, and 11 died of other conditions (ie, other tumors or unrelated disease); cause of death was unknown in 16 dogs. The cause of death was confirmed as melanoma in 69 dogs, including the 3 dogs euthanized because of the disease;

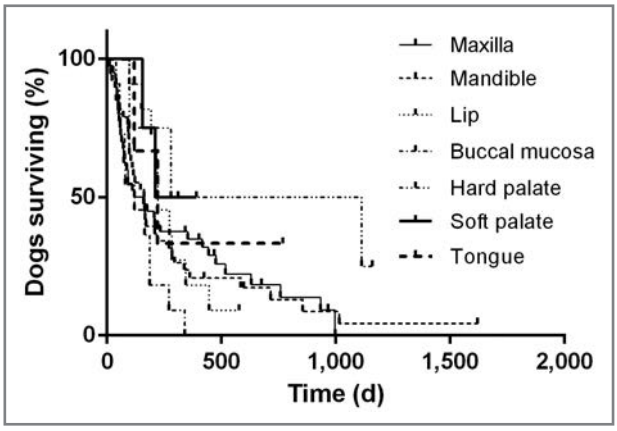

Figure 1—Kaplan-Meier survival curves of 111 dogs with oral malignant melanoma evaluated according to tumor location (maxilla [n = 40], mandible [38], lip [11] buccal mucosa [11], hard palate [4], soft palate [4], or tongue [3]. The survival curves did not vary significantly ($P = 0.16$) according to tumor site.

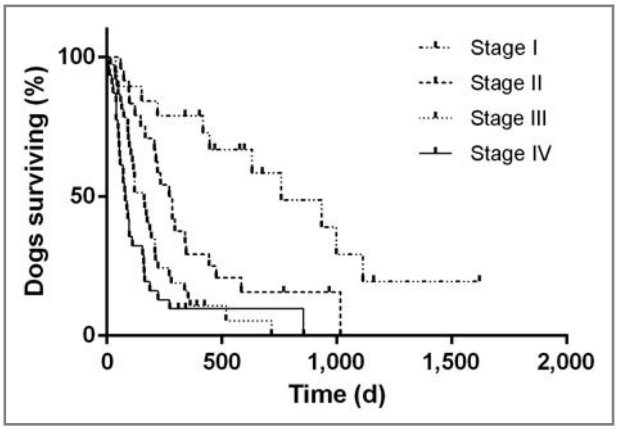

Figure 2—Kaplan-Meier survival curves of the same dogs as in Figure 1, evaluated on the basis of World Health Organization tumor stage[11] (I [n = 19], II [24], III [37], or IV [31]). Significant differences in MST were found between stages I and II ($P < 0.05$), stages I and III ($P < 0.001$), and stages I and IV ($P < 0.01$). There was no significant difference observed between stages II and III ($P = 0.83$), stages II and IV ($P = 0.90$), or stages III and IV ($P = 1.0$).

the mechanisms of death included pulmonary metastasis, brain metastasis, anemia resulting from tumor hemorrhage, and respiratory failure caused by physical obstruction. Unfortunately, exact numbers could not be determined because many case records did not include detailed information on the cause of death.

The MST of the 107 dogs that received OVX (68 dogs) and MVX (39 dogs) treatments was 121.5 days (range, 11 to 1,620 days) and 233 days (range, 3 to 966 days), respectively, and a significant ($P < 0.05$) difference was observed between the 2 treatment groups (**Figure 3**). When survival times of dogs that underwent OVX and MVX treatments were compared according to disease stage, there was no significant difference observed between groups with stage I (997 days [n = 12 dogs] vs 934 days [6], respectively), stage II (246 days [12] vs 258.5 days [10], respectively), or stage IV melanoma (78.5 days [24] vs 97 days [7], respectively). However, the MST differed significantly ($P < 0.01$) between groups with stage III disease (OVX, 98.5 days [n = 20 dogs] vs MVX, 209.5 days [16]). The 6-month survival rate was 50 of 107 (46.7%), and the 1-year survival rate was 25 of 107 (23.4%). When the influence of clinical stage, signalment factors, radiation technique (OVX vs MVX), and total radiation dose on death within a year was evaluated in multivariate analysis, clinical stage ($P < 0.001$) and age ($P < 0.05$) were each significantly associated with this outcome, but weight ($P = 0.23$), sex ($P = 0.79$), radiation technique ($P = 0.26$), and radiation dose ($P = 0.35$) were not. In dogs with stage III melanoma, the risk of death within a year was not significantly ($P = 0.46$) associated with the total radiation dose, but the risk of death (hazard ratio, 5.05) was significantly ($P < 0.01$) greater for dogs that received OVX treatments, compared with those that received MVX radiotherapy. When the 5 dogs that underwent OVX radiotherapy for 1 treatment followed by MVX radiotherapy were excluded from the analysis, the MSTs for dogs that received OVX (n = 68) and MVX (34) radiotherapy were 121.5 and 214.5 days, respectively ($P < 0.05$), but risk of death within a year was not significantly ($P = 0.27$) associated with radiation technique. The MSTs for dogs in each treatment group categorized according to stage were as follows: stage I (OVX, 997 days [n = 12 dogs] vs MVX, 934 days [5]), stage II (OVX, 246 days [12] vs MVX, 233 days [9]), stage III (OVX, 98.5 days [20] vs MVX, 187 days [13]; $P < 0.01$), and stage IV (OVX, 78.5 days [24] vs MVX, 97 days [7]).

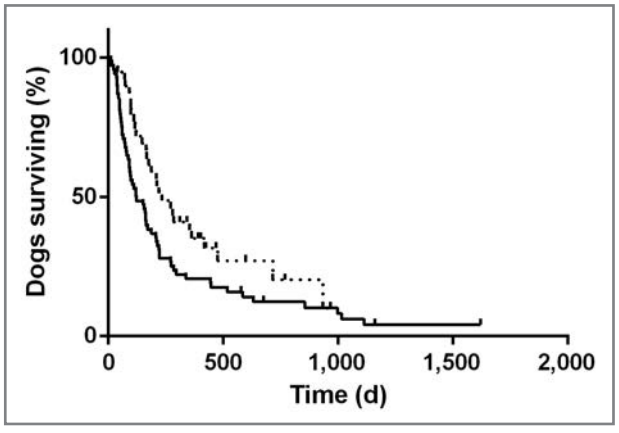

Figure 3—Kaplan-Meier survival curves of 107 dogs with oral malignant melanoma that underwent OVX (solid line; n = 68) or MVX (dashed line; 39) radiotherapy. The survival times differed significantly ($P = 0.032$) between treatment types.

Therapeutic response information was evaluated for 87 dogs. A complete response was observed for 38 (44%) dogs, and a partial response was observed for 36 (41%). The disease was assessed as stable for 7 (8%) dogs and progressive for 6 (7%). Significantly ($P < 0.001$) fewer dogs had stable or progressive disease than had partial or complete responses. Unfortunately, the response data could not be evaluated in all 111 dogs because some did not visit the hospital after radiotherapy (n = 15) or underwent partial resection during radiotherapy (9).

Acute radiation damage was indicated in the medical records of 49 dogs, and the 62 remaining dogs did not have sufficient information in the records to assign a score. More than 1 sign of radiation damage was indicated for 29 of 49 dogs. Acute radiation damage noted in the medical records was retrospectively scored as follows: 31 dogs had ≥ 1 sign of damage with a score of 1, for a total of 50 observations (hair loss, 21; dermatitis, 11; changes in skin pigmentation, 10; and conjunctivitis, 8); 26 dogs had ≥ 1 sign with a score of 2, for a total of 36 observations (stomatitis, 23; keratoconjunctivitis, 9; corneal ulcer, 2; epidermal hypertrophy, 1; and keratoconjunctivitis sicca, 1); and 9 dogs each had 1 sign with a score of 3 (cutaneous necrosis, 4 [OVX group, 2; MVX group, 2]; cutaneous edema, 2 [OVX group, 1; MVX group, 1]; necrosis of the oral mucosa, 2 [OVX group, 1; MVX group, 1]; and cutaneous ulcer, 1 [in the MVX group]). Twenty dogs in the OVX group and 27 dogs in the MVX group had ≥ 1 sign of radiation damage. When acute damage scores were compared according to radiation type, scores of 1, 2, and 3 were observed in 18, 14, and 4 dogs that underwent OVX treatment, respectively. Acute damage was scored as 1, 2, and 3 in 31, 21, and 5 dogs that underwent MVX treatment, respectively. The acute radiation damage was scored as 1 and 2 in 2 dogs that underwent electron beam radiotherapy. When classified according to the affected site, the skin, oral cavity, and eye were involved in 19, 12, and 5 dogs that underwent OVX treatment, respectively, and in 30, 12, and 15 dogs that underwent MVX treatment, respectively. In the 2 affected dogs that underwent electron beam radiotherapy, acute damage developed in the skin and oral cavity. Late radiation-induced damage, which is scored as 2 or 3, was not determined to have developed in any dogs.

The following serious adverse effects resulted directly or indirectly from tumor reduction in dogs with large tumors: oronasal fistula (6/111 [5.4%] dogs), mandibular fracture (2 [1.8%]), and trismus (1 [0.9%]). In all 6 dogs with oronasal fistula, the lesion occurred in the hard or soft palate region surrounding the tumor. In the 2 dogs with mandibular fracture, the fracture site had CT evidence of osteolysis before radiotherapy. In the dog with trismus, the tumor encompassed a large area of the left cheek (including masseter, zygomaticus,

and buccinator muscles), and the volume of muscle in the area was markedly decreased after radiotherapy. Globe rupture occurred in 1 dog that had a tumor invading the orbital cavity and had radiation-induced conjunctivitis in the same eye. Thirty-four of 66 (52%) dogs that received chemotherapy as adjunctive treatment developed adverse effects (local chemotherapy only, 10/26 dogs; systemic only, 14/26 dogs; local and systemic, 10/14 dogs; total, 34/66 dogs). Adverse effects were observed in 15 of 45 (33%) dogs that did not receive chemotherapy. The proportion with adverse effects was not significantly ($P = 0.73$) different between dogs that did and did not receive chemotherapy.

Discussion

In the present study, oral malignant melanomas were nearly equally distributed according to sex, with 52 (46.8%) females and 59 (53.2%) males in the study population. This result is consistent with findings in some reports, but contradicts other reports regarding oral melanoma in dogs, which indicate that males are significantly overrepresented.[1,19–23] The present study also included a large number of sexually intact dogs (female, 36/52 [69%]; male, 45/59 [76%]), which may reflect the low rate of spaying and neutering of dogs in Japan.

Bergman[11] stated that established therapeutic approaches such as surgery, chemotherapy, and fractionated radiation therapy are not curative after metastasis in canine malignant melanoma. In our study, we were unable to make this determination because information on causes of death and the number of dogs with death attributable to metastasis was insufficient.

Radiotherapy was discontinued in midcourse for 31 of 111 dogs in the present study. In dogs with stage I or II melanoma (n = 7), the treatment was discontinued by choice of the owner. Some owners may have believed that their dogs were cured, considering that most (4/7) of these patients had complete or partial response to treatment. In dogs with stage III or IV disease (n = 24), radiotherapy may have been initiated as a means of improving the quality of life despite the serious illness, to avoid or delay need for euthanasia. Deteriorating condition or death was the most common cause for noncompletion of treatment (16/24 dogs) in this group.

In 1 report,[7] dogs with stage I oral melanoma treated with surgery had an MST of 559 days (n = 21 dogs), whereas those with stage II or III disease had an MST of 121 days (26). In another report,[24] the MSTs of dogs treated with surgery for stage I, II, and III oral melanoma were 943 (n = 10), 193 (5), and 161 days (5), respectively. In our study, the MSTs following radiotherapy (with various adjunctive treatments in most cases) for dogs with stage II or III disease were similar to or slightly longer than these previously reported values, suggesting that the radiotherapy regimens described may be as effective as surgery for dogs with stage II and III disease.

Bateman et al[9] reported the MST in dogs with oral malignant melanoma treated by radiotherapy was 7.0 months, and that reported by Proulx et al[10] was 7.9 months. In our study, the MST for all 111 dogs was 5.7 months, which was shorter than in previous reports. However, the MST of dogs with stage I melanoma was significantly longer than that of dogs with other of the disease, and the present study included fewer dogs with stage I or II than with stage III or IV disease. The study by Bateman et al[9] included 6 dogs each with melanoma of stages I, II, and III, and in the study by Proulx et al,[10] the staging was unknown. Thus, disease stage distribution may have contributed to the apparent differences in MSTs. Additionally, differences in radiation protocols or adjunctive treatments may also have influenced these results. Dogs in the study by Bateman et al[9] received radiation (800 cGy) on days 0, 7, and 21, for a total dose of 2,400 cGy in 3 weeks, and those evaluated by Proulx[10] et al underwent 1 of 3 radiation therapy protocols (36 Gy [9 Gy × 4 fractions], 30 Gy [10 Gy × 3 fractions], or > 45 Gy [2 to 4 Gy × 12 to 19 fractions]) with or without chemotherapy.

In a study of dogs that underwent surgical treatment for oral malignant melanoma, Hahn et al[24] reported that dogs with tumors in rostral mandibular or caudal maxillary locations had significantly longer survival times, compared with dogs that had tumors in other locations. In our study, a difference was not detected in the MST of dogs grouped by tumor site (including comparisons between rostral and caudal mandibular or maxillary regions). Complete surgical excision may be difficult or may create problematic changes in facial configuration, depending on the primary region. In addition, cases judged unsuitable for surgical treatment were not included in the aforementioned study.[24] Because radiation can be delivered to all locations, MST was not expected to be influenced by the primary tumor site in patients that received radiotherapy.

Of 87 dogs that were evaluated through the use of RECIST guidelines in the present study, therapeutic response was complete in 38 (44%) and partial in 36 (41%), with 7 (8%) and 6 (7%) having stable and progressive disease, respectively. In other reports, complete response rates of 44 of 86 (51%) to 25 of 36 (69%) and partial response rates of 9 of 36 (25%) to 27 of 86 (31%) were achieved, yielding overall response rates of 82% to 94%.[9,10,16,25] The overall response rate for dogs evaluated in our study was similar to those observed in earlier reports. However, the RECIST criteria were not available at the time of those earlier studies,[9,10,16,25] and thus the complete and partial response rates reported may have been different if evaluated by those criteria.

We found a significant difference in the MST of dogs receiving OVX versus MVX treatment, with dogs in the MVX group having longer MST. When the MSTs of these dogs were compared according to disease stage, the data suggested that this difference primarily resulted from differences in dogs with stage III disease and was likely attributable to differences in radiation energy. In dogs with stage I and II melanoma, because the tumor is small, a sufficient dose can be delivered by an OVX unit. By contrast, in stage III melanoma, the tumor is large or has lymph node involvement; for large tumors, a uniform dose distribution cannot be delivered by an OVX unit. In addition, it is difficult to increase the total radiation dose because of the potential for radiation injury in surrounding normal soft tissue as well as the increased irradiation of bone, compared

with soft tissue, when OVX treatment is used. In contrast, MVX treatment can deliver a sufficient dose to a large tumor because the dose distribution is more easily adjusted through computerized planning. This may have resulted in the observed difference in clinical outcome for dogs with stage III disease that underwent these 2 radiotherapy techniques. In dogs with stage IV disease, we hypothesized that the difference in local radiation did not significantly affect the therapeutic outcome because the MST was influenced by metastatic lesions rather than the primary tumor, but this could not be evaluated in the present study because the cause of death was unclear for many dogs.

Radiation toxicosis can impact a patient's quality of life. A standardized scoring system for acute and late radiation effects on oral mucosa and bone in veterinary patients has been published by the Veterinary Radiation Therapy Oncology Group.[18] The hair loss, dermatitis, skin pigmentation, and conjunctivitis observed in the present study each received a score of 1 on the scale of 0 to 3. Cutaneous necrosis, cutaneous edema, necrosis of the oral mucosa, and cutaneous ulcers were given scores of 3; these adverse effects were considered the most critical, with the potential to decrease quality of life. Acute radiation damage was noted in the medical records of 49 of 111 (44%) dogs, and 29 of these had multiple signs present; however, the records did not contain sufficient information for scoring radiation effects in the 62 remaining dogs. Most signs had severity scores of 1 (50 observations in 31 dogs) or 2 (36 observations in 26 dogs). Nine (8%) dogs each had 1 finding assigned a score of 3, and this severity of damage was clearly indicated in the medical records of those dogs, given that it was critical in nature.

When acute radiation damage was compared between dogs grouped according to the radiotherapy type, we found that MVX treatment more commonly resulted in damage than did OVX treatment, especially to the eyes, although frequencies were not compared statistically. The ocular damage was considered attributable to the following mechanisms. During OVX treatment, the eye at risk of radiation exposure is protected by a lead shield, and radiation is directed away from the eyes, which is relatively simple because the radiation beam is only delivered from 1 or 2 directions. By contrast, exposure to the eyes may be far greater during MVX treatment, compared with OVX treatment, because a lead shield is not used and the larger or deeper tumors that are typically targeted with MVX require irradiation from many directions, although effort was made to reduce the radiation exposure to the eyes during treatment planning.

In addition to direct radiation damage, injuries that were considered secondary were also observed in dogs undergoing treatment. Oral malignant melanomas are locally aggressive and may invade adjacent tissue and bone.[26] Two dogs in the present study had mandibular fractures, which were not considered related to the radiotherapy but were instead attributed to bone lysis caused by the tumor beforehand; the fractures developed in areas of bone lysis identified through CT before treatment. Similarly, an oronasal fistula was detected in a region of normal tissue that was invaded by the tumor before radiotherapy in 6 dogs. In 1 dog that had a tumor invading the orbital cavity, the globe ruptured when the dog rubbed the eye forcefully; notably, the eye was initially affected by radiation-induced conjunctivitis. This dog was a Shih Tzu and had a history of a descemetocele in the same eye. However, despite these considerations, the possibility existed that both the fractures and the globe rupture resulted from radiation damage. The fractures occurred 233 and 463 days after the start of radiotherapy, which are times when late adverse effects of radiation may develop. Osteonecrosis is considered a type of late radiation injury and may have occurred at the fracture site. Assessment of the relationship between the globe rupture and radiation was difficult owing to preexisting conjunctivitis that had not resolved despite treatment (ie, the eye was protected physically and treated with ointment), as well as the possible effects of breed and clinical history of the patient. The risk of potential injuries as observed in these patients can be subjectively assessed by evaluating the position and size of the tumor before beginning radiotherapy. Before beginning treatment, owners should be thoroughly educated in regard to potential complications.

One weakness of this study was its retrospective nature, particularly in the retrospective application of the radiation scoring system. The findings would have been more complete and reliable had the adverse radiation effects been scored in real time. A prospective study evaluating acute and late radiation effects in dogs undergoing radiotherapy is necessary. Another weakness was the inability to assess the influence of different types of adjunctive treatments on the outcomes because treatments in the study were reflective of typical clinical practices.

The results of this study supported that OVX and MVX radiotherapy with various adjunctive treatments can result in MSTs similar to those previously reported for dogs undergoing surgery. However, severe complications occurred in some dogs. Radiotherapy should be commenced only after performing a thorough examination and after considering the potential advantages and drawbacks of the treatment.

a. Asteion Super4 Edition, Toshiba Medical Systems, Tokyo, Japan.
b. Radioflex 300EMG, Rigaku Corp, Tokyo, Japan.
c. PRIMUS Mid Energy, Tokyo, Japan.
d. XiO, version 4.6, Elekta AB, Stockholm, Sweden.
e. Prism, version 6.01, GraphPad Software Inc, La Jolla, Calif.
f. JMP, version 10.0.0, SAS Institute Inc, Cary, NC.
g. Randa Inj, 50 mg/100 mL, Nippon Kayaku Co Ltd, Tokyo, Japan.

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