
Kim P. Freeman, Kevin A. Hahn, F. Dee Harris, and Glen K. King

This retrospective study in 39 dogs with incompletely resected oral melanoma examined the efficacy of hypofractionated radiation therapy and platinum-containing chemotherapy. All dogs were completely staged, with the majority of dogs classified as stage I. Dogs received 6 weekly fractions of 6-gray (Gy) megavoltage irradiation with a cobalt-60 unit or a 4-MeV (megaelectron volts) linear accelerator. Dogs received cisplatin (10–30 mg/m² IV) or carboplatin (90 mg/m² IV) chemotherapy 60 minutes before radiation delivery. Durations of local control, metastasis-free survival time, and overall survival time were recorded. By the Kaplan-Meier method, 15% of the dogs had local recurrence within a median time of 139 days. Fifty-one percent of the dogs developed metastatic disease within a median time of 311 days (range, 24–2,163 days). Median survival time for all 39 dogs was 363 days. The combined use of chemotherapy and radiation therapy in this protocol provided local control consistent with previous studies. Low-dose chemotherapy was used with the intent of enhancing radiation therapy for the local control of an incompletely excised tumor. Survival times were longer than previously reported for dogs with oral malignant melanoma. Additional studies are required to determine whether these results were due to the effects of chemotherapy on microscopic disease or the enhanced local control provided by chemoradiation therapy.

Key words: Canine; Chemoradiation; Melanosarcoma.

Oral malignant melanoma in dogs is an aggressive invasive neoplasm that causes signs of oral discomfort, inappetence, and dysphagia. Surgical attempts at complete excision rarely are successful, and local recurrence is common. Complications from distant metastatic lesions in the lung, liver, regional lymph nodes, and other sites commonly occur. Different single-modality approaches (eg, surgery and radiation) and multimodality approaches (eg, chemotherapy, surgery, and adjuvant radiation therapy) have been evaluated in an attempt to improve the survival time for dogs with oral melanoma. Melanomas are radiation-responsive neoplasms, and radiation therapy may reduce local recurrence rates. Chemotherapy may enhance the effect of radiation therapy.

The objective of this study was to evaluate a protocol with chemotherapy and radiation therapy as adjuncts to incomplete surgical excision in dogs with stage I and II disease in an attempt to provide long-lasting local tumor control. The intent of surgery was to reduce the tumor volume and prevent facial deformity. Chemotherapy was administered at a dosage below what is considered standard so that it could be used safely on a weekly basis to enhance the biological effects of radiation. Chemotherapy was not given with the expectation that such a low dosage would prolong the time to onset of metastasis or extend the survival time.

Materials and Methods

Criteria for Selection of Dogs

The medical records of dogs presented for treatment to Gulf Coast Veterinary Oncology with histologically confirmed oral melanoma from September 1987 to July 1997 were reviewed.

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Table 1. Modified staging scheme for oral melanoma in dogs.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Tumor</th>
<th>Regional Lymph Nodes</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T₁, any T₂</td>
<td>N₀</td>
<td>M₀</td>
</tr>
<tr>
<td>II</td>
<td>T₁, any T₂,</td>
<td>N₀</td>
<td>M₀</td>
</tr>
<tr>
<td></td>
<td>T₃</td>
<td>N₁</td>
<td>M₀</td>
</tr>
<tr>
<td>III</td>
<td>T₁, any T₂,</td>
<td>N₀</td>
<td>M₀</td>
</tr>
<tr>
<td></td>
<td>T₃</td>
<td>Any T</td>
<td>N₀</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M₀</td>
</tr>
</tbody>
</table>

* T₁, tumor in situ or ≤2 cm in maximal diameter (volume ≤8 cm³); T₂, tumor 2–4 cm in maximal diameter (volume 8–64 cm³); T₃, tumor >4 cm in maximal diameter (volume >64 cm³)
* Mitotic index: (a) ≤3 per high-power field; (b) >3 per high-power field. Oral cavity or oropharyngeal location: (1) rostral mandible/caudal maxilla; (2) other.
* N₀, no evidence of regional node involvement; N₁, histologic evidence of regional node involvement; N₂, fixed nodes.
* M₀, no evidence of distant metastasis; M₁, distant metastasis (including distant nodes).

Table 2. Patient characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Total (n)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breed</td>
<td>Purebread</td>
<td>35</td>
<td>89.7</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>4</td>
<td>10.3</td>
</tr>
<tr>
<td>Gender</td>
<td>Intact males</td>
<td>9</td>
<td>23.1</td>
</tr>
<tr>
<td></td>
<td>Castrated</td>
<td>10</td>
<td>25.6</td>
</tr>
<tr>
<td></td>
<td>Intact females</td>
<td>2</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>Spayed</td>
<td>18</td>
<td>46.1</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0–6</td>
<td>2</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>7–10</td>
<td>16</td>
<td>41.0</td>
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<tr>
<td></td>
<td>11–14</td>
<td>16</td>
<td>41.0</td>
</tr>
<tr>
<td></td>
<td>≥15</td>
<td>5</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0–10</td>
<td>10</td>
<td>25.6</td>
</tr>
<tr>
<td></td>
<td>11–20</td>
<td>10</td>
<td>25.6</td>
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<td>20–30</td>
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<td></td>
<td>≥30</td>
<td>5</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>18.3</td>
<td></td>
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<tr>
<td>Stage</td>
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<td>22</td>
<td>56.4</td>
</tr>
<tr>
<td></td>
<td>T₂aN₀M₀</td>
<td>3</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>T₂bN₀M₀</td>
<td>11</td>
<td>28.2</td>
</tr>
<tr>
<td></td>
<td>T₃bN₀M₀</td>
<td>3</td>
<td>7.7</td>
</tr>
<tr>
<td>Location</td>
<td>Rostral mandible</td>
<td>7</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>Caudal mandible</td>
<td>8</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>Rostral maxilla</td>
<td>11</td>
<td>28.2</td>
</tr>
<tr>
<td></td>
<td>Caudal maxilla</td>
<td>9</td>
<td>23.1</td>
</tr>
<tr>
<td></td>
<td>Soft palate or tongue</td>
<td>4</td>
<td>10.2</td>
</tr>
</tbody>
</table>

* See Table 1 for stage explanation.

Results

Thirty-nine dogs were included in the study (Table 2). The mean age was 11.2 years (median, 11.0 years; range, 5–18 years). The mean body weight was 19.2 kg (median, 18.3 kg; range, 6.0–38.6 kg). Tumors were small in size before surgery (T₁, 0–2 cm in diameter, n = 22 or 56.4%; T₂, 2–4 cm in diameter, n = 14 or 35.9%) but highly invasive to surrounding bone (ie, substage b [T₁or₂b], n = 36 or 92%).

At the time of analysis, 71.7% of the studied population (28 of 39) had died or were euthanized. Eleven dogs were lost to follow-up (median duration of follow-up, 350 days; range, 35–1,657 days).

Differences in local control duration, disease-free interval, and survival time among dogs grouped by patient characteristics (breed, age, gender, body weight, tumor stage, and tumor location) were not observed.

Six of the 39 dogs (15%) had local recurrence (median time to recurrence, 139 days; range, 20–1,077 days) after treatment completion (Fig 1). Nine of the 11 dogs lost to follow-up had unrecorded times to local recurrence. On the basis of the Kaplan-Meier product limit method, >50% of the dogs with an incompletely excised oral melanoma did not have local recurrence by this protocol.

Metastases were observed in 20 dogs. The median time to metastasis was 311 days (range, 20–1,416 days) (Fig 2). Only 1 dog lost to follow-up had metastatic disease before becoming lost to follow-up.
Aggressive surgical excision (eg, rostral mandibulectomy and caudal maxillectomy) may achieve complete tumor resection and decrease the likelihood of local recurrence, but metastatic disease still develops in dogs with oral melanoma and limits survival time. In one study of dogs with oral melanoma, conservative local excision (ie, tumor-positive microscopic surgical borders) resulted in a median survival time of 14 weeks and a high local recurrence rate (34 of 40 dogs). The median survival time of other dogs after partial maxillectomy was 7.3 months, with 1 of 5 dogs having local recurrence. The majority of dogs that have local excision procedures performed develop metastatic disease. In other studies, aggressive surgical excision (ie, tumor-negative microscopic surgical borders) resulted in median survival times of 7.3–9.1 months, with the onset of metastatic disease detected 1.2–6.5 months after excision. One-year survival time after aggressive surgery has been reported to be 27%. Local recurrence rate has been reported to be 38–48% after partial maxillectomy with 1-cm margins beyond grossly evident disease.

Malignant melanomas have been shown to be radioreponsive tumors. In humans, high individual radiotherapy fraction size, rather than high total radiotherapy dosage, appears to be the critical factor in successful local control. Previous studies of melanoma response to radiation therapy in humans and rats showed that cell survival curves had a large shoulder before becoming exponential. These curves indicated that tumor cells had a large capacity to accumulate and possibly repair sublethal damage. This finding led to the initial belief that melanomas were radioresistant. In 1978, it was reported that humans with melanoma skin metastases would not respond to fractionation schemes with individual doses smaller than 5 Gy, regardless of total dose. In addition, the 1978 study showed that the response of the primary tumors and of metastases in lymph nodes was better after treatment regimes with large doses per fraction and fewer fractions. Another study in 1986 demonstrated that total dose, treatment time, and various modifications of the nominal standard dose concept did not show any correlation with response in humans with malignant melanoma. This study showed a marked correlation between dose per fraction and response, with a higher dose per fraction (≥4 Gy) yielding a markedly better response than doses <4 Gy. The radiation therapy fraction protocol used in the current study is consistent with that reported for use in humans in whom the responsive fraction dose of melamomas is >4 Gy. A minimum fraction size of 4 Gy appears to be effective in providing durable local control in people. The limiting factor for total tumor dose is based on the tolerance of normal tissue to the effects of radiation.

To establish our protocol for oral melamomas in dogs, we assumed an alpha-to-beta ratio (α:β) of 3 Gy for late-responding tissues. Conventional therapy of 2 Gy per fraction with a 60-Gy total dose has a biologically effective dose (E:α) for late-responding tissues equal to 100 Gy. For a protocol that uses 4 Gy per fraction with a 36-Gy total dose, the E:α ratio is 83.9 Gy. For a protocol that uses 6 Gy per fraction with a 36-Gy total dose, the E:α ratio is 98 Gy. For 8 Gy per fraction with a 24-Gy total dose, the E:α ratio is 88 Gy. Our protocol of 6 Gy per fraction with a
36-Gy total dose satisfied the high dose per fraction deemed necessary to treat melanomas (>4 Gy) and was biologically the most effective dose that was closest to conventional therapy.13

In dogs with oral melanoma in which radiation therapy is the sole modality of treatment, median survival ranges from 5 to 8 months.4,14 In one study of dogs with oral melanoma in which a total radiation dose of 36 Gy (4-Gy fractions) was applied to nonresectable tumors, tumors with positive surgical margins, or recurrent tumors, median survival time was 21 weeks. Clinical signs related to the onset of metastatic disease were the primary reason for euthanasia in 25 of 36 dogs in that study.3 When a total radiation dose of 24 Gy (8-Gy fractions), with or without surgery, was used in another study, median survival time was 7.9 months.3 These 2 studies did not evaluate fraction size when evaluating survival times. It is likely, however, on the basis of data acquired from affected humans, that the longer reported survival time in the 2nd study was based on the higher fraction size used in that study.

Platixil is thought to produce partial response or stable disease in dogs with oral melanoma.29,30 Melphanal also has been used to treat melanoma in dogs anecdotally.31 Cisplatin and carboplatin are cell cycle nonspecific chemotherapeutics. They interrupt cell replication by creating DNA cross-linkage. Chemotherapy is thought to interact in a number of ways with radiation to enhance tumor cell death. Chemotherapy and radiation act against different tumor subpopulations on the basis of hypoxia, cell cycle specificity, and pH. Cells in the G2-M phase of the cell cycle are very sensitive to the effects of radiation. Chemotherapy that acts on cells in G0-G1, or that affects the ability of cells to repair damage creates an additive effect with radiation therapy. After fractionated radiation therapy, decreased tumor cell repopulation occurs as a result of chemotherapy. Increased tumor cell recruitment occurs from G0 into a therapy-responsive cell cycle phase. After radiation, increased tumor cell oxygenation occurs, thus improving drug or radiation activity. Improved drug delivery with a shrinkage of the tumor also may occur. Early eradication of tumor cells may prevent emergence of drug- and radiation-resistant cells. Cells resistant to one treatment modality can be eradicated by another modality. Cell cycles can be synchronized, and radiation and chemotherapy combined can inhibit repair of sublethal radiation damage or inhibit recovery from potentially lethal radiation damage.32 On the basis of these premises, chemotherapy is used concomitantly with radiation therapy.

Although their use is controversial, immunotherapeutic agents such as Corynebacterium parvum, liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE), and granulocyte macrophage colony-stimulating factor (GM-CSF) have been studied as adjuvant therapies in treating oral melanoma in dogs.9 L-MTP-PE and GM-CSF have shown benefit in dogs with stage I disease (ie, melanomas <2 cm in maximal diameter). C parvum combined with surgery in 89 dogs in all stages of disease resulted in a median survival time of 370 days; by contrast, dogs that had surgery alone had a median survival time of 228 days.10 The above alternative protocols may offer potentially beneficial roles to delay the onset of metastatic disease when combined with surgery or radiation therapy.9,10,12,29–31

The protocol as described in this report resulted in a low rate of local recurrence, prolonged control of metastatic disease, and a survival time comparable to previous reports for dogs with incompletely resected oral malignant melanoma. This protocol was well tolerated by the dogs, and no treatment delays due to radiation therapy effects or chemotherapy occurred. Acute grade I radiation adverse effects on oral mucosa were noted during weeks 3 or 4 of therapy but resolved after completion of therapy. Chronic radiation reactions included alopecia and dermal thinning from 1 to 12 months after completion of the radiation protocol. Chemotherapy was given well below the maximum tolerated dose, and no adverse effects were observed.

By Kaplan-Meier analysis, it was predicted that >50% of the 39 dogs in this study would not have local recurrence of disease. Local disease recurrence was observed in 6 of the 39 dogs (15%) of the studied population (Fig 1). In these 6 dogs, local disease recurrence was noted to occur within the 1st year after treatment. At the time of death in 24 dogs, no local recurrence of disease was observed. Nine of the 11 dogs lost to follow-up have unrecorded times to local recurrence. Either these patients never had local recurrence, or recurrence occurred after they were lost to follow-up. Low recurrence rates may be due to radiation, chemotherapy, or a combination of the 2 treatment modalities. Radiation has been shown to be highly effective in controlling local disease or regrowth after oral melanoma surgery.3,5 Radiation alone has been associated with local recurrence rates of 12–32%.3,5,6 A 48% recurrence rate has been observed in dogs after hemimaxillectomy (the majority of dogs were stages I–III), and a 38% recurrence rate has been observed in dogs after partial maxillectomy with 1-cm surgical margins.4,15 Our results are consistent with those previously reported for the use of radiation after surgical resection.5

In principle, low-dose chemotherapy should not prevent local tumor progression and development of metastasis. The intent of chemotherapy is to maintain stable disease rather than achieve remission. In a recent study of oral melanoma, dogs were treated with 300–350 mg/m2 of carboplatin every 21 days until no further response to therapy was noted.33 This protocol resulted in an overall response rate of 28%. Thirty-six percent of the dogs had stable disease, and 36% had progressive disease. The majority of dogs had stage III disease, and some also may have had previous surgical or radiation therapy, all of which likely influenced the study’s outcome. Response to treatment was markedly associated with carboplatin dose on a milligram per kilogram basis. This finding supports the idea that carboplatin may have some role in controlling the growth of oral melanomas. However, the milligram dose and dose interval of chemotherapy, as well as the stage of disease, were dramatically different and thus form a poor basis for comparison to our study. In our study, it is difficult to assess the contribution of chemotherapy to the effects of radiation therapy in preventing local recurrence and controlling metastatic disease. Previous studies have indicated an 80% metastatic rate for oral melanoma in dogs.19 The lower rate of metastasis in this study may be due to the employment of
chemotherapy (20 of 39 dogs or 51%). Alternatively, the inclusion of regional lymph nodes in the radiation therapy protocol may have played a role in delaying the onset of metastasis by eliminating clinically undetected microscopic nests of neoplastic cells. The median time to detection of metastatic disease was 311 days (range, 20–1,416 days) (Fig 2). This rate is lower than previously reported metastatic rates for oral melanoma in dogs.\(^1,2\) Such an effect with a low dose of chemotherapy was not an anticipated outcome when initiating this protocol. However, it is difficult to explain the improved metastatic rate when comparing this combination protocol with the metastatic rate of radiation and surgery without chemotherapy.

There was no endpoint to the data presented in this study, indicating that not all dogs developed metastasis within the time frame of the study. The last point on the Kaplan-Meier analysis was a dog that, at the time of final evaluation, had no evidence of metastatic disease. After surgery alone, the median metastasis-free interval has been reported to be 1.25–6.5 months.\(^3\) This finding suggests that there is some benefit to the use of radiation (local and nodal) and chemotherapy as beneficial therapeutic adjuvants to control or decrease the development of metastatic melanoma.

Kaplan-Meier analysis predicted a 1-year survival rate of 45% for all dogs (Fig 3). Previous reports showed a 1-year survival rate of 27% by surgical resection alone.\(^4\) The median survival time for all dogs (363 days) was substantially longer than the survival times reported for aggressive surgical excision alone or radiation therapy alone. The longest previously reported median survival time in dogs that had been treated by aggressive surgery alone was 9 months, and for dogs that had received radiation therapy (with or without prior surgical resection), survival time was 7.9 months.\(^5,6\)

With a limited population size of 39 dogs, tumor stage, tumor grade, gender, breed, or age were not found to be statistically significant with regard to influence on the rate of local recurrence, metastasis-free survival time, or overall survival time. Our data may be influenced by the fact that the majority of tumors were \(T_1\)\(b, N_0, M_0\), but location likely was not a major prognostic indicator, because 18 tumors were in the rostral oral cavity, and 17 were in the caudal oral cavity.

A multimodality approach to the management of oral malignant melanoma in dogs merits additional investigation. The benefit of low-dose chemotherapy on metastatic disease cannot be explained by these results. One shortcoming of a retrospective study is the lack of a control group that received radiation therapy alone compared to radiation and chemotherapy combined. Sample sizes of patients treated with the linear accelerator versus the cobalt unit and carboplatin versus cisplatin were too small for comparison. Another shortcoming was the large number of dogs with stage I disease. Further investigation is warranted to evaluate the benefit of chemotherapy for dogs in all stages of disease.

The low rate of local recurrence, prolonged time to onset of distant metastasis, and potential for extended survival time appear better than the results reported by other studies.\(^1,3,6\) In addition, because this protocol was associated with a low rate of local recurrence after incomplete tumor excision (ie, excision performed only to reduce the amount of grossly identifiable disease), the surgeon or pet owner can elect a more cosmetic surgery (eg, forego hemimaxillectomy or hemimandibulectomy) apparently without compromising the dog’s prognosis.

### Footnotes

\(^1\) Cisplatin (cis-diammine-dichloroplatinum II), Bristol-Myers-Squibb Oncology, Evansville, IN

\(^2\) Carboplatin (diammine [1,1-cyclobutane-dicarboxylato(2)-0,0'][SP-4-2]), Bristol-Myers-Squibb, Evansville, IN

\(^3\) GraphPad Prism, version 3.02, GraphPad Software, Inc, San Diego, CA

\(^4\) Melphalan (4-[bis(2-chloroethyl)amino-[L-phenylalanine]), GlaxoSmithKline, Research Triangle Park, NC

### Acknowledgments

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### References


