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Objective—To determine the efficacy (durations of remission and survival) of an alternating-day radiation protocol for incompletely excised histologic grade-III solitary mast cell tumors (MCTs) in dogs.

Design—Retrospective study.

Animals—31 dogs.

Procedure—Radiation (52 Gy in an 18-fraction alternating-day protocol) was delivered to an area bordered by margins ≥ 3 cm around the surgical scar and to the associated local-regional lymph nodes. Dogs were not given chemotherapeutic agents concurrently or after radiation. Information on signalment, duration of remission, and survival time was obtained from medical records.

Results—Median and mean durations of remission were 27.7 and 170 months, respectively (range, 1 to 47 months). Median and mean durations of survival were 28 and 20 months, respectively (range, 3 to 52 months). Dogs with tumors located on the skin of the pinna, perineum, and prepuce had a median duration of remission greater than dogs with tumors located at other sites (27.7 and 14.4 months, respectively). Dogs with tumors ≤ 3 cm in maximum diameter before surgery survived longer than dogs with tumors > 3 cm (31 and 24 months, respectively). The remission rate was 65% and survival rate was 71% at 1 year after treatment. Sixteen dogs that were euthanatized had complications associated with local-regional tumor progression. Systemic metastases to liver, spleen, intestine, and bone marrow were detected in 1 dog.

Conclusions and Clinical Relevance—Without further treatment, incompletely excised grade-III mast cell tumors have high local-regional recurrence; local-regional treatment with radiation may effectively be used to manage many such tumors. (J Am Vet Med Assoc 2004;224:79-82)

Mast cell tumors (MCTs) are the most common cutaneous tumors in dogs, accounting for 7% to 21% of all skin tumors. These tumors are highly variable in regard to location, biological behavior, and treatment response. Factors including histologic grade, World Health Organization stage, duration of disease, argyrophilic nucleolar organizer region count, completeness of excision, DNA ploidy, tumor location, breed, and abnormal expression of p53 tumor suppressor gene have been evaluated as prognostic indicators for MCTs in dogs. Tumor location affects prognosis for dogs with incompletely resected MCTs treated with radiation therapy. Tumors of the limbs are associated with lower metastatic rate, longer duration of remission, and longer duration of survival than tumors located on the trunk. There have been reports that dogs with a tumor of high grade or in a particular body location (ie, perineum, pinna, prepuce) have poor response to local-regional radiation therapy. The purpose of the study reported here was to analyze retrospectively the efficacy of local-regional radiation therapy with an alternating-day protocol in dogs with incompletely excised histologic grade-III solitary MCTs without regional lymph node involvement (stage 0).

Criteria for Selection of Cases

The medical records for all dogs admitted to our hospital for irradiation of localized, incompletely resected, histologically confirmed MCTs of the skin (any grade or location) between 1987 and 1998 were reviewed. Medical records of those dogs with histologic grade-III tumors (stage 0) and prior excision of the localized tumor without prior chemotherapy were included in the study. To appropriately evaluate the radiotherapy protocol, records of dogs that received concurrent or post-irradiation chemotherapy (including the use of prednisone) were excluded from analyses.

Procedures

Medical records were reviewed for signalment, laboratory data (including CBC, serum biochemical profile, urinalysis, buffy coat smear, and regional lymph node aspiration or biopsy), clinical staging (2-view survey radiographs of the thoracic and abdominal cavities, and abdominal ultrasonography), growth characteristics of the tumor, changes in regional lymph nodes, concurrent diseases, treatment methods and associated complications, and outcome. Regional lymph node metastasis was defined as a large population of mast cells that infiltrated the lymph node, poorly differentiated mast cells in the lymph node, or both. For all cases, biopsy specimens were reviewed to confirm the diagnosis, grade, and stage of the tumors. Tumors were staged according to a modified version of the classification system developed by the World Health Organization. Tumors were graded according to the system described by Patnaik et al in which grade I has the best prognosis and grade III has the worst prognosis.

Treatment methods—Dogs were treated with radiation therapy via an external-beam megavoltage tech-
nique with a cobalt 60-unit or 4-MeV linear accelerator, with a source-to-skin distance of 80 cm. Two methods were used to calculate the radiation dose for the tumor. Prior to 1993, tumor dose was calculated by use of a single point along the central axis at the base of the surgical scar. Tumor invasion and size were determined by use of survey radiography and physical examination. Starting in 1993, patients received a computed tomography scan, and a 2-dimensional treatment-planning computer was used to calculate the dose-to-tumor volume. Doses to surrounding critical structures were calculated to ensure that the dose to those tissues did not exceed tolerance levels. The radiation field included the region of the excisional scar and regional lymph nodes, with 3-cm margins. The dose to the lymph node was equivalent to the dose to the primary tumor. Dogs were treated with 18 fractions of 2.9 Gy on an alternate-day (Monday, Wednesday, Friday) schedule for a total dose of 52.2 Gy. To establish our protocol, we assumed a biologically effective dose for acute- and late-affected tissues (ie, α/β) of 3 Gy for late-responding tissues. Conventional daily treatment of 2 Gy/fraction (total dose, 50 Gy) has a biologically effective dose (ie, E/α) for late-responding tissues equal to 83 Gy. For an alternate-day protocol with 3 Gy/fraction (total dose, 54 Gy dose), the E/α is 88 Gy. Our alternate-day protocol with 2.9 Gy/fraction (total dose, 52.2 Gy) had a biologically effective dose (E/α) of 86.6 Gy, which was similar to other conventional treatment protocol values.

Data analyses—Follow-up information concerning response to treatment and outcome was obtained through hospital visits or by telephoning the referring veterinarian or the owner. Survival time was calculated as the interval from the start of treatment to death or to the date on which the dog was last known to be alive. Because all dogs had microscopic tumor involvement only within the surgical site (ie, stage 0), duration of remission was calculated as the interval from the start of treatment to time of visible local-regional tumor regrowth (eg, within the surgical scar or draining lymph node) or distant metastasis. Local tumor progression was confirmed cytologically or histologically. Regional or systemic metastasis was confirmed histologically, cytologically, and radiographically. Differences in distribution of dog and tumor characteristics were analyzed by use of a t test for continuous variables and Pearson χ² statistics for categoric variables. Variables examined as indicators of prognosis included sex, age, presurgical tumor size, tumor stage, and tumor location. Survival and local control rates were computed by use of the product-limit method. Actuarial estimates of survival and local control distributions were tested for statistical differences by use of log-rank statistics. Dogs were censored in the survival analysis if they were lost to follow-up, death was not caused by MCT or treatment, or relapse had not occurred before the end of the study period. The Cox proportional hazards regression model was used to determine independent prognostic factors for remission duration and survival time. The relative risk of tumor recurrence was estimated by use of the hazard rate ratio. Differences were considered significant at P < 0.05. Statistical analyses of data were performed with computer software.

Results

Patient characteristics—Medical records of 31 dogs met study inclusion criteria. Twenty-one dogs were purebred; Labrador Retrievers (n = 7), Golden Retrievers (6), and Boxers (6) were most often represented. Fifteen dogs were spayed females, 10 were neutered males, 3 were sexually intact females, and 3 were sexually intact males. Dogs ranged from 3 to 18 years old (mean, 9.4 years; median, 9 years) and from 3 to 99 kg (11 to 129.8 lb) in body weight (mean, 15.2 kg [33.4 lb]; median, 16 kg [35.2 lb]). Median duration from surgical removal to irradiation was 17 days (range, 10 to 42 days; mean, 22 days). Although alopecia was observed in most dogs, treatment delays associated with complications of radiation therapy (edema, moist desquamation, or erythema) were not observed in any dog.

Tumor behavior—Median tumor size prior to excision was 3.9 cm at the widest diameter (range, 1 to 6 cm; mean, 3.1 cm). After radiation therapy, 16 of the 31 dogs had developed enlarged ipsilateral regional lymph nodes caused by metastasis. One dog had antemortem evidence of systemic tumor involvement (hepatosplenomegaly, gastrointestinal metastasis, and tumor cells in bone marrow aspirate but not bulky in coat smear). A correlation was found between small presurgical tumor diameter (≤ 3 cm vs > 3 cm) and increased duration of remission (χ² test; P = 0.034). A correlation was also found between tumor location (high-grade location vs truncal location) and increased duration of survival (χ² test; P = 0.043). None of the dogs had tumor cells in a bulky coat smear or bone marrow core aspiration biopsy specimen when first evaluated.

Prognostic factors—Seventeen dogs died or were euthanized because of clinical signs associated with tumor recurrence or progression (16 from ipsilateral local-regional lymph node enlargement, 1 from systemic metastasis). Three dogs died from unrelated causes (pancreatitis, disk disease, or traumatic injuries). Eleven dogs were alive with no evidence of disease progression at last follow-up (follow-up range, 12 to 52 months; median, 32 months). Median and mean durations of remission were 27.7 and 17.0 months, respectively (range, 1 to 47 months). The product-limit estimates of the 1-year and 2-year tumor remission rates (mean ± SEM) were 65 ± 8% and 26 ± 11%, respectively. Median and mean durations of survival were 28 and 20 months, respectively (range, 3 to 52 months). The product-limit estimates of the 1-year and 2-year survival rates (± SEM) were 71 ± 9% and 39 ± 9%, respectively. Univariate analysis of duration of remission revealed that tumors located at the pinna, perineum, and prepuce (previously reported high-grade locations) had a longer (log-rank analysis, P = 0.045) duration of remission than dogs with tumors located at other sites (Fig 1). Univariate analysis of duration of survival revealed that presurgical tumor size was a significant (log-rank analysis, P = 0.003) prognostic indicator; dogs with maximum tumor diameter ≤ 3 cm lived longer than dogs with larger tumors (Fig 2).
Canine mast cell tumors are histologically graded on a scale of I, II, and III or they are assessed as being well-differentiated, intermediate, or poorly differentiated. There is a correlation between the grade, degree of differentiation, and survival time. In 1 study, 93% of dogs with well-differentiated tumors were alive at 1,500 days, but only 6% of dogs with poorly differentiated tumors were alive at 1,500 days. When complete excision is not obtained or cannot be attempted, radiotherapy is a good treatment option to consider. If possible, surgery should be performed before radiotherapy to reduce the tumor to a microscopic volume. Median durations of remission after local radiation therapy, regardless of grade or completeness of excision, range from 2 to 125 months (median, 60 months). The response of grade-I and -II canine MCTs is regarded as excellent after radiation, but response is poor for grade-III tumors.

Frimberger et al reported that radiation therapy for incompletely excised moderately differentiated cutaneous MCTs in 37 dogs resulted in 3% recurrence at 1 year and 7% recurrence at 3 years after treatment. LaDue et al used a similar protocol and reported that radiation therapy for incompletely excised MCTs in 56 dogs had median duration of remission of 32.7 months (95% confidence interval, 19 to 70 months). In a study by Turrel et al that evaluated 85 dogs, median duration of remission was 17 months. Percentages of dogs that were tumor-free at 1 and 2 years were 78.8% and 77.0%, respectively. Factors significantly associated with duration of remission were clinical stage (P < 0.001) and neoplasm location (P = 0.019). Prognostic factors significantly associated with survival rates were clinical stage (P < 0.001), neoplasm grade (P = 0.006), and neoplasm location (P = 0.034). The prognosis after radiation treatment for grade-III MCTs, with or without regional lymph node metastasis, has been regarded by many as poor, compared with that of dogs with grade-I or grade-II tumors. However, few studies have reported the response to radiation therapy in dogs with grade-III MCTs treated with a uniform radiotherapy protocol. In a study of 18 dogs with and without grossly evident tumors, total tumor-delivered radiotherapy doses ranging from 36 to 48 Gy in 9 to 12 equal fractions were given over 19 to 27 days. In some instances, local-regional nodes were not irradiated. The 1- and 2-year survival rates for all dogs regardless of grade (n = 85) were 78.8% and 77.0%, respectively, and were comparable to the results of our study. The 1-year tumor-free rate was 55%, lower than the dogs of our study.

Our study confirmed the predictive value of presurgical tumor size of MCTs for duration of remission. Dogs with tumors ≤3 cm in maximum diameter before surgery survived longer than dogs with tumors >3 cm (31 and 24 months, respectively). Staging is not the same as grading. Grade is the assessment of the degree of cellular anaplasia and potential for growth. Staging is the determination of actual metastasis or lack thereof. In addition, the growth rate of the tumor but not the size may be an important prognostic indicator. Dogs with MCTs that grow >1 cm/wk have a 25% chance of living an additional 30 weeks.

In our study, duration of survival was associated with tumor location. Dogs with MCTs located in high-grade locations had median times to recurrences that were longer than dogs with tumors in other locations (27.7 and 14.4 months, respectively). Canine MCTs in high-grade regions are considered by many investigators to be a negative prognostic feature and associated commonly with metastasis to local and deep lymph nodes. The inconsistency between the findings of others and those of our study is not unexpected. Analysis of other predictive factors in dogs with MCTs, such as chromosome nucleolar organizer regions stained with silver, matrix metalloproteinase activities, and c-kit tandem duplication mutations, has been evaluated and correlates well with histologic grade but fails to substantially improve prognostic accuracy for treatment response or metastatic potential.
location may represent another inconsistent prognostic factor for dogs.

Results of our study support the value of evaluating tumor location, presurgical tumor size, and tumor grade when considering radiation in the management of grade-III MCTs. Our results confirm that grade-III MCTs are biologically aggressive tumors with high local-regional metastatic rates. However, many of these tumors may be effectively managed with the local-regional alternating-day radiation therapy protocol described in this report. One year after radiation therapy, the remission rate was 65% and the survival rate was 71%.

References