Radiation treatment for incompletely resected soft-tissue sarcomas in dogs

Josephine A. McKnight, DVM; G. Neal Mauldin, DVM, DACVIM, DACVR; Margaret C. McEntee, DVM, DACVIM, DACVR; Karelle A. Meleo, DVM, DACVIM, DACVR; Amiya K. Patnaik, BVSc, MVSc

Objective—To evaluate efficacy of radiation for treatment of incompletely resected soft-tissue sarcomas in dogs.

Design—Prospective serial study.

Animals—48 dogs with soft-tissue sarcomas.

Procedure—Tumors were resected to < 3 cm³ prior to radiation. Tumors were treated on alternate days (three 3-Gy fractions/wk) until 21 fractions had been administered. Cobalt 60 radiation was used for all treatments.

Results—Five-year survival rate was 76%, and survival rate was not different among tumor types or locations. Four (8%) dogs developed metastases. Eight (17%) dogs had tumor recurrence after radiation. Development of metastases and local recurrence were significantly associated with reduced survival rate. Median survival time in dogs that developed metastases was 250 days. Median disease-free interval for all dogs was 1,082 days. Median time to recurrence was 700 days. Dogs that developed recurrence after a prolonged period responded well to a second surgery. Acute radiation toxicosis was minimal; osteosarcoma developed at the radiation site in 1 dog.

Conclusions and Clinical Relevance—An excellent long-term survival rate may be achieved by treating soft-tissue sarcomas in dogs with resection followed by radiation. Amputation is not necessary for long-term control of soft-tissue sarcomas in limbs. Development of metastases and recurrence of local tumors after radiation treatment are associated with decreased survival rate. Acute and delayed radiation toxicosis was minimal with the protocol used in this study. (J Am Vet Med Assoc 2000;217:205–210)

Soft-tissue sarcomas comprise approximately 15% of all canine skin and subcutaneous neoplasms.¹ These tumors have an incidence in dogs of approximately 35/100,000.² Soft tissue sarcomas, which arise from mesenchymal tissues, are histologically distinct but share many common features with respect to their biological behavior. These common features include the fact that these tumors are pseudocapsulated fleshy masses with poorly defined margins and often infiltrate through fascial planes. Local recurrence is common after excision; as many as 25% of these tumors metastasize via hematogenous routes, and response to chemotherapy and radiation treatment is generally poor.³

Soft-tissue sarcomas in dogs include fibrosarcoma, nerve sheath tumors (neurofibrosarcoma, malignant Schwannoma), malignant fibrous histiocytoma, hemangiopericytoma, myxosarcoma, and liposarcoma.⁴ Other tumors that are sometimes included in this group are rhabdomyosarcoma, leiomyosarcoma, mesenchymoma, and synovial cell sarcoma.⁵

There is no standard protocol for treatment of soft-tissue sarcomas in dogs. Neither surgery nor radiation treatment alone is entirely successful, and the efficacy of chemotherapy has yet to be determined.⁶ Prior to the routine availability of radiation treatment, radical and often disfiguring surgery was the mainstay of treatment. This type of surgery, when used as the only method of treatment, results in 1-year control rates ranging from 70 to 80% in dogs with hemangiopericytoma.⁷ Surgeries other than amputations often result in incomplete resection attributable to pseudocapsule formation and the invasive nature of these tumors. Although radical surgeries such as amputation may provide a cure for soft-tissue sarcomas involving the limbs, these surgeries are impossible or unacceptable in many instances. The goals in treating dogs with soft-tissue sarcomas must be to obtain tumor control without loss of function and to preserve quality of life.

In human medicine, the use of radiation treatment as an adjunct to surgery has nearly eliminated the need for ablative or radical resection of soft-tissue sarcomas.⁸ ¹¹ Although these tumors have traditionally been thought to be radiation resistant, results of recent studies indicate that radiation treatment can eliminate or control subclinical tumors located at or beyond the margins of the surgical site and thereby prevent or delay local tumor recurrence after surgery.¹² ¹³ As a result, local control obtained with a combination of marginal resection and radiation treatment often equals that obtained with radical resection alone.⁸ Five-year control rates of 87 to 93% have been reported for human patients treated with surgery and radiation treatment.¹⁴ ¹⁵

Few studies have been published in the veterinary literature that evaluate the combined use of surgery and radiation treatment in dogs with soft-tissue sarcomas. Results of early studies that used a variety of radiation doses indicate some promise for combination treatment.¹⁶ ¹⁷ The purpose of the study reported here was to prospectively evaluate efficacy of radiation for treatment of incompletely resected soft-tissue sarcomas in dogs.
Materials and Methods

Dogs and tumor resection—Forty-eight client-owned adult dogs with naturally occurring soft-tissue sarcomas (excluding oral tumors) were evaluated at The Animal Medical Center between 1988 and 1996 and were included in the study. Eight (17%) dogs were sexually intact males, 15 (31%) were castrated males, 4 (8%) were sexually intact females, and 21 (44%) were spayed females. Mixed-breed (n = 14), Golden Retriever (11), Labrador Retriever (3), and German Shepherd Dog (3) were the most commonly represented breeds. Other breeds included Boxer, Shetland Sheepdog, Airedale Terrier, Doberman Pinscher, Toy Poodle, Maltese, Miniature Schnauzer, Kerry Blue Terrier, Bloodhound, and Puli. Mean age was 8.5 years (range, 3 to 15 years).

Thirty-three of the dogs had undergone incomplete tumor resection prior to referral to The Animal Medical Center. All dogs underwent physical examination and were evaluated for evidence of metastases or other disease processes by use of CBC, biochemical analyses, and thoracic radiography using 3 views; none of the dogs had evidence of tumor metastasis at time of entry into the study.

Dogs with palpable tumors underwent tumor resection; tumors were reduced to < 3 cm³. Surgical specimens were fixed in neutral-buffered 10% formalin and processed, and sections were cut on a microtome and stained with H&E. Slides were obtained for review on all dogs that had surgery at clinics other than The Animal Medical Center. All histologic slides were examined by one pathologist (AKP) to establish a diagnosis of soft-tissue sarcoma. Thirty-eight tumors were graded on the basis of degree of differentiation (well-differentiated, moderately differentiated, or poorly differentiated), number of mitotic figures per 10 HPF, and amount of necrosis (none, moderate, or extensive), as described.1 Ten dogs were entered into the study prior to publication of this grading scheme, and slides from these dogs were not available for review. Histologic evidence of residual tumor, determined by identifying neoplastic cells extending to at least one surgical margin, was present in all dogs.

Radiation treatment—Dogs began receiving radiation treatment 2 to 3 weeks after surgery. Radiation was performed after surgery, because several dogs had surgery prior to referral, and our study design required that all dogs be treated with the same protocol. Anesthesia was induced by IV administration of thiamylal sodium or propofol and maintained with isoflurane or 100% oxygen. Radiation treatments were performed by use of a cobalt unit. All dogs were treated on alternate days (3 fractions/ wk and 3 Gy/fraction) until 21 fractions had been administered. The target dose was 63 Gy. Two centimeters was selected as a reasonable margin around the identified tumor. Thus, the target volume consisted of the tumor volume (in some instances this had to be estimated from the surgical scar) plus a 2-cm margin, except where precluded by anatomic location. When circumferential radiation was necessary on a limb, a 3-mm strip of skin was spared to preserve lymphatic drainage. Radiation was delivered by parallel opposed beams in all dogs except 1. Dosimetry calculations were performed by use of a proprietary 2-dimensional dosimetry system to ensure that no site within the target volume received > 105% of the prescribed dose. Geometric characteristics of the radiation field were optimized to minimize dose heterogeneity within the treatment field. All target volumes were treated within a dose range of 90 to 105% of the prescribed dose. Tumor volume was always within the 95 to 105% isodose lines (range, 60 to 66 Gy). The periphery of the target volume was allowed to decrease to the 90% isodose line to prevent a tumor volume dose > 105%. Bolus administration was necessary to achieve the defined isodose target in 11 dogs. For one dog, complex geometric configuration required the use of wedged fields and bolus administration to achieve the desired isodose distribution.

Follow-up evaluation—Follow-up evaluation involved physical examinations performed 2 weeks after completion of radiation treatments and every 3 months thereafter for a period of at least 1 year. At each follow-up visit, dogs were evaluated for evidence of tumor regrowth, metastases, and adverse effects of radiation. Thoracic radiographs were taken every 6 months or whenever dogs developed clinical signs associated with respiratory tract disease. Neoplasms that developed at the radiation site or elsewhere were biopsied to confirm regrowth or metastasis of the original tumor. One dog was lost to follow-up after 22 months; this dog did not have evidence of recurrence or metastasis at the time of the last follow-up. Necropsies were not performed.

Statistical analyses—Statistical analyses were performed by use of a commercially available statistical software package. Kaplan-Meier survival analysis was used to compare survival times among dogs according to tumor type, histologic grade, anatomic location, development of recurrence, and development of metastasis. Kaplan-Meier product limit survival analysis was used to calculate 1-, 2-, 3-, 4-, and 5-year survival rates. Post hoc comparisons of survival analyses were performed by use of the Gehan-Wilcoxon test. Variables that failed a Kolmogorov-Smirnov test for normality were evaluated by use of either a Kruskal-Wallis or Mann-Whitney test, as appropriate for the number of groups being tested. Similarly, variables that passed the Kolmogorov-Smirnov test for normality were evaluated by use of either a t-test for dependent samples or a 1-way ANOVA. A value of P < 0.05 was considered significant. A Pearson correlation was used to compare survival times with age and time to recurrence. Regression analysis was used to compare field size with time to recurrence (disease-free interval) and survival. Time to recurrence was calculated from the date of surgery until recurrence; recurrence was confirmed by examination of a biopsy specimen. Survival times were calculated from the date of surgery until the date of death. For the purposes of survival calculations, dogs that died because of their soft tissue sarcoma were considered completed events. Dogs that were lost to follow-up, died of causes other than their soft tissue sarcoma, or were still alive without evidence of tumor recurrence or metastasis were removed from further calculations (censored) at the time of their last follow-up examination.

Results

Significant negative correlation (r = −0.33) was detected between age and survival. Significant correlation was not detected among age of dog and prevalence of tumor type.

Tumors included 14 (29%) fibrosarcomas, 28 (58%) nerve sheath tumors, 4 (8%) liposarcomas, and 2 (4%) malignant fibrous histiocytomas. Significant correlation between survival time and tumor type was not detected (P = 0.65). Twenty-one tumors were grade 1, 17 were grade 2, and none were grade 3. Similarly, histopathologic grade was not a significant predictor of recurrence (P = 0.86) or survival (P = 0.79).

Tumors were located on the extremities in 24 (50%) dogs, on the trunk in 15 (31%) dogs, and on the head or neck in 9 (19%) dogs. Significant correlation between survival and anatomic location of the tumor was not detected (Fig 1).
The mean and median field sizes were 1.91 and 1.71 equivalent squares, respectively. The field sizes ranged from 1.13 to 4.72. Significant correlation between field size and time to recurrence or survival was not detected.

Eight (16%) dogs developed local recurrence of tumor after radiation treatment. Recurrent tumors included 4 nerve sheath tumors, 2 fibrosarcomas, 1 liposarcoma, and 1 malignant fibrous histiocytoma. In dogs that developed recurrence, median time for development of recurrence was 700 days (range, 71 to 1,533 days; Fig 2). All recurrences developed at or beyond the edge of the radiation field. A strong negative correlation ($r = -0.839; r^2 = 0.71$) between development of recurrence and survival was evident. Dogs that did not develop local recurrence had a significant ($P = 0.003$) survival advantage over those that did develop recurrence. However, 4 dogs without local recurrence died soon after radiation treatment because of development of metastases.

Among dogs that developed local recurrence, neoplasia was controlled for many for a substantial period of time after recurrence by performance of a second surgery. Three dogs that developed recurrence at 356, 1,365, and 1,533 days after radiation underwent a second resection and were alive and disease-free at 1,408, 2,987, and 2,220 days, respectively.

Twenty-four dogs remained alive without recurrence (mean, 1,352 days; median, 1,341 days; range, 106 to 2,361 days). Median disease-free interval for all dogs in the study was 1,082 days.

Four (8%) dogs developed metastasis that was confirmed by examination of biopsy specimens. The metastatic tumors included 3 fibrosarcomas and 1 nerve sheath tumor. The site of metastasis was the lung in all 4 dogs; none of these dogs had local tumor recurrence. These dogs had significantly ($P < 0.001$) decreased survival time (median survival, 250 days), compared with dogs that did not develop metastatic disease (median survival, > 3 years). Three of the 4 dogs that developed metastasis died within 1 year.

Median follow-up period was 902 days (range, 71
to 2,987 days). Median survival could not be calculated, because many dogs are still alive. The 1- and 2-year survival rates were 87%, 3- and 4-year survival rates were 81%, and 5-year survival rate was 76% (Fig 3).

Radiation toxicosis was minimal with the protocol used in the study reported here. Acute adverse effects of radiation included mild to moderate radiodermatitis (alopecia, ulceration, hyperpigmentation, and hyperkeratosis), which was controlled in all instances by application of medicated cleansers (0.2% chlorhexidine), antibiotic creams, and oral administration of dexamethasone. Some dogs had no adverse effects other than mild persistent alopecia and hyperpigmentation at the radiation site. One (2.1%) dog developed osteosarcoma at the radiation site 5.32 years after radiation treatment.

Discussion

Sex and breed distribution of dogs in the study reported here were similar to those reported in other studies of soft-tissue sarcomas in dogs. In our study, correlation between sex or breed and tumor presence, tumor type, or survival were not detected. Lack of correlation between soft-tissue sarcoma and sex is consistent with results of other studies, although a predisposition for the development of hemangiopericytoma in female dogs has been reported.

Consistent with other reports, results of our study indicated that soft-tissue sarcomas were common in older dogs. Mean age of dogs at time of diagnosis was 8.5 years, which is similar to that reported for nerve sheath tumors and slightly younger than that reported in several other studies. Although we observed a significant negative correlation between age and survival, this correlation was likely related to factors other than the tumor, because most deaths in our study were not tumor related.

Prevalence of specific tumor types was also similar to that of another report. Survival after radiation was not significantly associated with tumor type.

As reported elsewhere, we did not observe a significant correlation between tumor grade and tumor recurrence. Results of other studies, however, indicate that tumor grade is an important prognostic indicator of metastatic rate and overall survival, with high-grade tumors associated with higher metastatic rate and decreased patient survival time. In our study, lack of a detectable association between tumor grade and overall survival may be attributable to the low number of intermediate-grade tumors, absence of high-grade tumors, or the small number of dogs.

Results of many studies reported in human and veterinary medical literature indicate a survival advantage for patients with tumors of the limbs, compared with those with tumors of the trunk or head and neck. In the study reported here, there was no relationship between survival and tumor location; however, many of the dogs that had tumors of the limbs are still alive, and with time, a substantial survival advantage may be detected in this group. Results of our study (> 60% survival at 2,000 days after diagnosis) indicate that long-term survival can be achieved in patients with soft-tissue sarcoma affecting the extremities by use of surgery and radiation treatment, making this a viable alternative to amputation.

Two factors were found to be significantly associated with survival. One of these factors was the development of local tumor recurrence after radiation treatment. All 8 recurrences developed outside the 90% isodose line and represent tumor foci that were missed by treatment. These recurrences can therefore be attributed to inadequate radiation delivered to the margin of the tumor or inadequate definition of the tumor volume. All dogs with local recurrence had surgery performed at hospitals other than The Animal Medical Center and were treated on the basis of size of surgical scar plus a 2-cm margin. Placement of clips to define the tumor margin at the time of surgery may allow for more accurate radiation treatment and decrease the incidence of tumor recurrence.

Dogs that did not develop local recurrence had a significant survival advantage over dogs that developed recurrence. Recurrence rate in our study (16%) compares favorably with that of previous reports.
et al.\textsuperscript{16} recently reported a recurrence rate of 15% following wide surgical excision alone. In the study reported here, median disease-free interval for all dogs was 1,082 days; disease-free interval was reasonably long, even in dogs that developed recurrence (median time to recurrence, 700 days), and compared favorably to the disease-free interval (343 days) reported by Brewer and Turrell.\textsuperscript{17} Presently, 24 dogs from our study are still alive without recurrence (median disease-free interval, 1,341 days), which we feel indicates that local tumor control was achieved without more aggressive surgery. Similar results have been reported in human literature.\textsuperscript{18}

Although the recurrence rate (16%) for incompletely resected tumors is encouraging, further improvement might be achieved by increasing radiation dose intensity. Dogs can tolerate a higher dose intensity than was used in our study, and provided that the fraction size does not increase, there should not be a substantial increase in serious complications that develop later.

The second factor that was significantly associated with survival was development of metastasis. Rate of metastasis for dogs in our study was 8%, which is slightly lower than that of another report (17%).\textsuperscript{19} It is possible that some instances of metastasis were missed, because abdominal ultrasonography and necropsy examinations were not performed; however, such instances were likely rare, because none of the dogs developed clinical signs associated with intra-abdominal metastasis. As might be expected, those dogs that developed metastatic disease had substantially decreased survival (median survival, 250 days), compared with dogs that did not develop metastatic disease (5-year survival, >75%). None of the dogs in our study developed local tumor recurrence and metastases.

Radiation treatment is often associated with complications. Acute adverse effects of radiation include dermal erythema, ulceration, and mucositis. Late-developing injury to normal tissue includes bone necrosis, infarcts, and development of other tumor types at the radiation site. By use of 3 Gy/fraction, acute radiation toxicosis was limited to mild to moderate radiodermatitis that was easily managed by use of orally administered dexamethasone, topical cleansers, and antibiotic ointments. One (2.1%) dog in our study developed osteosarcoma at the radiation site more than 5 years after radiation treatment.

As reported in human and veterinary medical literature, radiation treatment can be performed before or after surgery. Radiation treatment was performed after surgery in our study; because many of the dogs had surgery prior to referral to The Animal Medical Center, as is common with many referral centers. Postoperative radiation treatment has several advantages over preoperative radiation treatment, including earlier removal of the tumor and avoidance of compromised wound healing that may develop with irradiated tissue.\textsuperscript{3} Preoperative radiation treatment also has advantages. This form of treatment may be used to decrease tumor size, permitting less extensive surgical procedures, and often requires a smaller treatment field, because the tumor and a margin of surrounding tissue are treated rather than treating an entire surgical scar plus a margin of surrounding tissue. Preoperative radiation treatment may also decrease the risk of intraoperative implantation or dissemination of tumor cells at the time of surgery.\textsuperscript{5}

The 5-year survival rate was 76%, which compares favorably with reports of various soft-tissue sarcoma treatments including radiation alone,\textsuperscript{16} radiation and hyperthermia,\textsuperscript{14} and chemotherapy alone.\textsuperscript{17} Although many different treatment modalities have been used for soft-tissue sarcomas in dogs, the greatest survival rates have been achieved in studies involving radical resection. Kuntz et al.\textsuperscript{18} reported median survival of 1,416 days with wide excision alone.\textsuperscript{18} On the basis of data from our study, it appears that survival rates attained by use of conservative surgery and radiation treatment can equal or exceed those attained with wide excision. Thus, veterinary patients for whom radical excision is not possible because of tumor location or concurrent disease, like humans, may have prolonged survival without the necessity of radical surgery.

References


