Liposarcomas in dogs: 56 cases (1989–2000)

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Objective—To determine the biological behavior of liposarcomas in dogs and identify clinical signs, the effect of treatment on survival time, and potential prognostic factors.

Design—Retrospective study.

Animals—56 dogs with histologically confirmed liposarcoma.

Procedure—Information was obtained on signalment, tumor size, location of the tumor, stage of disease, remission duration, overall survival time, cause of death, type of surgery (incisional biopsy, marginal excision, or wide excision), and any additional treatments given.

Results—Surgery consisted of incisional biopsy in 6 dogs, marginal excision in 34, and wide excision in 16. Twenty-five dogs had histologic evidence of tumor cells at the surgical margins and 28 did not (status of the margins was unknown in 3 dogs). Twelve of 43 dogs had local recurrence. Median survival time was 694 days, and the only factor significantly associated with survival time was type of surgery performed. Median survival times were 1,188, 649, and 183 days, respectively, for dogs that underwent wide excision, marginal excision, and incisional biopsy. Factors that were not found to be significantly associated with survival time included tumor size, status of the margins, tumor location, and histologic subtype.

Conclusions and Clinical Relevance—Results suggest that in dogs, liposarcomas are locally invasive neoplasms that rarely metastasize and occur primarily in appendicular or axial locations and that wide excision is preferred to marginal excision when feasible. (*J Am Vet Med Assoc* 2004;224:887–891)

Liposarcomas are uncommon neoplasms of dogs that consist of malignant lipoblasts and mesenchymal tissue.[1-4] In most affected dogs, liposarcomas are cutaneous, but they can also develop in the abdominal cavity and other extracutaneous sites.[2,5-7] No specific breed or sex predilection has been identified.[1] As with other soft tissue sarcomas, liposarcomas tend to be locally invasive, and although the true incidence of metastasis is unknown,[8] metastasis has generally been considered to be a rare occurrence for liposarcomas. On the other hand, metastasis to liver, lung, and bone has been reported,[7,9,10] and these tumors have been reported to have variable growth rates and variable degrees of histologic differentiation.[11,12] Because liposarcomas and lipomas are often indistinguishable grossly, histologic examination is required for a definitive diagnosis. Liposarcomas have been classified histologically into subtypes,[3,11] and in humans, these subtypes have been associated with differences in biological behavior.[12] However, the biological behavior of liposarcomas in dogs has not been fully characterized, and the optimal treatment is therefore unknown. Surgery remains the treatment of choice for soft tissue sarcomas in general, and the usefulness of chemotherapy and radiation therapy has not been evaluated.[13,14]

The purposes of the study reported here were to identify clinical signs in dogs with liposarcomas, determine the biological behavior of liposarcomas and the effect of treatment on survival time, and identify potential prognostic factors.

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Criteria for Selection of Cases

Records of the Biopsy Service at the University of Pennsylvania School of Veterinary Medicine for January 1989 through March 2000 were searched to identify biopsy specimens histologically identified as liposarcomas, and information was obtained for dogs from which these biopsy specimens had been obtained. For dogs treated at the Veterinary Hospital of the University of Pennsylvania, information was obtained from the medical records. For dogs treated at other hospitals, surveys were sent to the referring veterinarians. If necessary, follow-up telephone calls were made to referring veterinarians to clarify responses to survey questions. Dogs were included in the study only if histologic samples were available for review.

Procedures

Information was obtained on signalment, tumor size, location of the tumor, stage of disease, remission duration, overall survival time, cause of death, type of surgery (incisional biopsy, marginal excision, or wide excision), and any additional treatments given. Potential prognostic factors that were evaluated included the type of surgery performed, the size of the tumor, histologic classification of tumor subtype, tumor location, and histologic appearance of the biopsy margins.

A single pathologist (MJH) reviewed all available sections of the biopsy specimens and classified each tumor according to the liposarcoma subtype classification system recognized by the World Health Organization panel on soft tissue tumors of domestic animals.[3] Subtypes that were used included well-differentiated, pleomorphic, and myxoid.

Statistical analyses—Categorical data were summarized as frequencies and percentages, and continuous data were summarized as means and ranges. Survival times of dogs stratified on the basis of surgery type, tumor subtype, and tumor size were estimated by means of the Kaplan-Meier product limit method.

Statistical differences in survival times among surgery types, tumor subtypes, and tumor sizes were assessed by use of the log rank test. To determine whether covariates were distributed equally across surgery types, χ^2 or Fisher exact tests were used for categorical data and ANOVA was used for continuous data (ie, tumor size). To determine whether age was associated with survival time, the proportional hazards model was used. When applicable, bivariate analysis with the Kaplan-Meier product limit method was used. All analyses were performed with commercially available software[a]; values of $P < 0.05$ were considered significant.

Results

During the study period, 109 biopsy specimens were identified histologically as liposarcomas, of which 18 had been submitted from dogs examined at the Veterinary Hospital of the University of Pennsylvania and 91 had been submitted from dogs examined at other hospitals. Fifty-three of the 91 dogs examined at other hospitals were excluded from the study because of a lack of adequate follow-up information or a change in the final diagnosis on the basis of histologic review of biopsy specimens. The remaining 38 dogs examined at other hospitals and all 18 dogs examined at the Veterinary Hospital of the University of Pennsylvania were included in the study.

Of the 56 dogs included in the study, 21 (38%) were spayed females, 17 (30%) were neutered males, 14 (25%) were sexually intact males, and 4 (7%) were sexually intact females. Twenty-seven dogs were of mixed breeding. The remaining dogs consisted of 5 Golden Retrievers, 5 Shetland Sheepdogs, 3 Labrador Retrievers, 2 Miniature Poodles, 2 Maltese, 2 Doberman Pinschers, 2 Beagles, and 1 of each of the following breeds: Bloodhound, Cocker Spaniel, Cardigan Welsh Corgi, Dalmatian, German Shepherd Dog, German Shorthaired Pointer, Keeshond, and Standard Poodle. Age of the dogs at the time of diagnosis ranged from 2 to 16 years (mean, 10 years). Information on body weight was available for 18 dogs. Mean weight was 23 kg (51 lb; 6.2 to 55 kg [13.6 to 121 lb]), with 5 of the 18 dogs weighing < 15 kg (33 lb).

Liposarcomas were located in the axial region (shoulder region, thorax, axilla, tail base, or hip region) in 26 dogs, the appendicular region in 23 dogs, and within the viscera in 6 dogs. In the remaining dog, the tumor appeared to arise from the bone marrow of the femoral head. Tumors ranged from 0.5 cm to 20 cm in diameter (mean, 6.8 cm). Three dogs had well-differentiated liposarcomas, 7 had myxoid liposarcomas, and 34 had pleomorphic liposarcomas. In the remaining 12 dogs, tumor subtype was not determined as biopsy specimens were not available for examination. Type of surgery consisted of incisional biopsy in 6 dogs, marginal excision in 34 dogs, and wide excision in 16 dogs. Twenty-five dogs had histologic evidence of tumor cells at or near the surgical margins and 28 did not; status of the surgical margins was unknown in the remaining 3 dogs. Follow-up information regarding recurrence was available for 43 dogs, of which 12 (28%) had local recurrence. Seven of the 12 dogs in which the tumor recurred locally had had histologic evidence of tumor cells at or near the surgical margins, including 6 dogs that had undergone marginal excision and 1 that had undergone an incisional biopsy. The remaining 5 dogs in which the tumor recurred locally did not have histologic evidence of tumor cells at or near the surgical margins, including 3 dogs that had undergone marginal excision and 2 that had undergone wide excision.

Median survival time for all dogs included in the study was 694 days (range, 1 to 1,782 days). The only factor significantly ($P = 0.02$) associated with survival time that was identified was type of surgery performed (**Fig 1**). Dogs that underwent wide excision had a median survival time of 1,188 days (range, 5 to 1,746 days), whereas dogs that underwent marginal excision had a median survival time of 649 days (range, 1 to 1,782 days), and dogs that underwent incisional biopsy had a median survival time of 183 days (2 to 733 days). The median size of tumors in this study was determined to be 4 cm. Although median survival time for dogs with tumors < 4 cm in diameter (961 days) was greater than median survival time for dogs with tumors ≥ 4 cm in diameter (612 days), this difference was not significant ($P = 0.11$; **Fig 2**). Finally, median survival time was not significantly different between

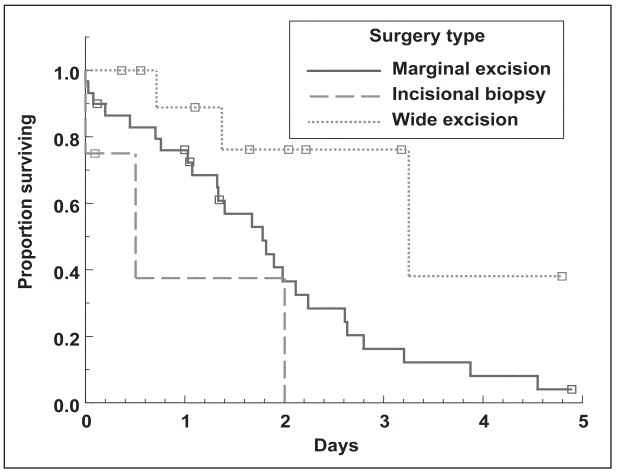

Figure 1—Kaplan-Meier survival curves for 56 dogs with liposarcomas grouped on the basis of surgery type.

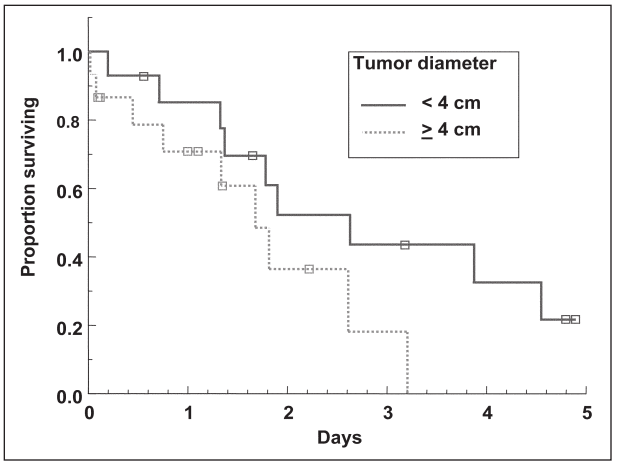

Figure 2—Kaplan-Meier survival curves for 56 dogs with liposarcomas grouped on the basis of tumor diameter.

groups when dogs were grouped on the basis of tumor location (axial vs appendicular), status of the surgical margins, or tumor subtype. Median survival time for dogs with appendicular tumors was 500 days, compared with a median survival time of 693 days for dogs with axial tumors ($P = 0.61$; because of the small number of dogs with tumors involving the viscera, median survival time was not calculated for these dogs). Median survival time for dogs without evidence of tumor cells at or near the surgical margins (693 days) was not significantly ($P = 0.19$) different from median survival time for dogs with such evidence (649 days). Dogs with myxoid liposarcomas and dogs with pleomorphic liposarcomas had median survival times of 649 days and 512 days, respectively; the difference between these 2 groups was not significant ($P = 0.74$). Median survival time was not generated for dogs with well-differentiated liposarcomas because of the small number of cases and limited follow-up information.

The χ^2 test was used to examine whether tumor subtype was associated with surgery type; no relationship was found ($P > 0.05$). Dogs that underwent wide excision were significantly ($P = 0.006$) more likely to not have histologic evidence of tumor cells at or near the surgical margins (14/16 [87%]) than were dogs that underwent marginal excision (14/31 [45%]). χ^2 Analysis did not show a relationship between the type of surgery performed and the status of the surgical margins ($P = 0.85$).

Cox's proportional hazard model was used to determine whether age of the dog at the time of diagnosis was associated with survival time; no association was found ($P = 0.3$). Mean tumor diameter for dogs undergoing marginal excision (8.5 cm) was significantly ($P = 0.03$) greater than mean tumor diameter for dogs that underwent wide excision (2.7 cm). The log rank test was used to test for differences in survival time among dogs grouped on the basis of tumor size and type of surgery. A longer median survival time was found for dogs that had tumors < 4 cm in diameter and underwent wide excision (1,188 days) than for dogs with tumors < 4 cm in diameter or ≥ 4 cm in diameter that underwent marginal excision (698 and 612 days, respectively), but this difference was not significant ($P = 0.08$).

Forty-five of the 56 dogs were reported to be dead, and a cause of death was reported for 25 of these dogs. Fifteen dogs died or were euthanatized for causes unrelated to the tumor, and 10 dogs died or were euthanatized for causes directly related to the tumor. Seven of these 10 dogs were euthanatized because of local tumor recurrence (1 also had evidence of splenic and hepatic metastases), and 1 was euthanatized because of radiographic evidence of pulmonary metastases (but did not have evidence of local tumor recurrence). The remaining 2 dogs did not have evidence of local tumor recurrence, but although the cause of death was reported to be tumor related, specific information on cause of death was not available.

Thirty-two dogs underwent thoracic radiography at the time of surgery as part of the initial staging process, and only 1 had radiographic evidence of pulmonary metastases. Nine dogs underwent abdominal ultrasonography at the time of surgery, and 3 had evidence of splenic and hepatic metastases.

Discussion

Results of the present study suggest that in dogs, liposarcomas are locally invasive neoplasms that rarely metastasize and occur primarily in appendicular or axial locations. We did not identify differences in survival times among dogs grouped on the basis of histologic tumor subtype; therefore, the clinical importance of these subtypes in veterinary medicine is still not clear. On the other hand, median survival time for dogs that underwent wide excision was significantly longer than times for dogs that underwent marginal excision or incisional biopsy. Prolonged survival times (median, 3.3 years) are possible following wide surgical excision or radical surgery such as amputation.

Mean age of dogs in the present study was consistent with the suggestion in previous reports[1,2] that liposarcomas are more common in older dogs; however, at least 1 dog in the present study was relatively young (2 years old). Subjectively, no obvious breed or sex predilection was apparent; however, we did not compare breed and sex distributions of these dogs with distributions for a control population. Dogs in this study ranged from small-breed dogs such as Miniature Poodles and a Cardigan Welsh Corgi to large-breed dogs such as Doberman Pinschers and a German Shepherd Dog, indicating that the tumor is not limited to dogs of a particular body size. Previous reports[2,8,15] have documented liposarcomas in small-breed dogs such as Dachshunds, Poodles, and Terriers.

In humans, the most common sites for liposarcomas are the thigh and the retroperitoneal region.[11,16] Liposarcomas have been documented in various locations in dogs, with subcutaneous masses in the axial region most commonly reported.[1,2,6] However, reports[1,2,7-9,15] of liposarcomas in the appendicular region, as well as in the abdomen or involving the viscera, do exist.In the present study, liposarcomas were fairly evenly divided between axial and appendicular regions, with only 6 dogs having primary liposarcoma of the viscera and 1 dog having liposarcoma of the bone marrow. Primary liposarcoma arising from the bone marrow in a dog has been reported previously.[7]

The metastatic rate for liposarcomas in dogs is unknown, although in the present study, metastasis to the pulmonary parenchyma was apparently rare. Evidence of visceral metastasis was seen in 3 of 9 dogs that underwent abdominal ultrasonography, including 1 dog with primary splenic liposarcoma that appeared to have metastasized to the liver and 2 dogs with tumors in an axial (dorsal to the tail base) or appendicular (distal portion of the radius) location that had evidence of metastasis to the spleen or liver. However, abdominal ultrasonography was not performed in most dogs in this study, and the diagnosis of splenic or hepatic metastasis was not confirmed histologically in the 3 dogs with ultrasonographic evidence of visceral metastasis.

In humans, the biological behavior of liposarcomas is related to the histologic subtype, with well-differentiated liposarcomas considered unlikely to metastasize, pleomorphic liposarcomas considered to be highly malignant,[16] and myxoid liposarcomas involving the extremities considered likely to metastasize to

extrapulmonary soft tissue locations rather than to the lungs.[17,18] These distinctions have not been identified in dogs as of yet, and more information is needed to determine whether histologic subtype is associated with biological behavior of liposarcomas in dogs. However, 3 of the 4 dogs with evidence of metastatic disease at the time of surgery in the present study did have pleomorphic liposarcomas.

In the present study, median survival time of dogs with tumors ≥ 4 cm in diameter was not significantly different from median survival time for dogs with tumors < 4 cm in diameter. In contrast, in people with soft tissue sarcomas in general, size of the tumor is associated with disease-free interval.[16,18] In addition, surgery is the mainstay of treatment for humans and dogs with soft tissue sarcomas,[13,14] and it seems intuitive that smaller tumors would be easier to remove completely. Although status of the surgical margins was not associated with survival time in the present study (ie, median survival time for dogs with histologic evidence of tumor cells at or near the surgical margins was not significantly different from median survival time of dogs without such evidence), previous studies[14,16,19] in the human and veterinary literature have shown that complete surgical resection of soft tissue sarcomas is associated with prolonged disease-free intervals. The present study was retrospective, and the incidence of local recurrence and distant metastasis may have been underreported because many of these dogs likely were not monitored closely for recurrence or metastases. Thus, it is difficult to draw strong conclusions about the lack of an association between tumor size and survival time and between surgical margin status and survival time in the present study.

An unexpected finding of the present study was that mean diameter of tumors in dogs that underwent marginal excision was significantly greater than mean diameter of tumors in dogs that underwent wide excision. A possible explanation for this would be that it could be more difficult to obtain wide margins for a larger size tumor, depending on its location. Even after adjusting for tumor size, dogs that underwent wide excisions had significantly longer survival times than dogs that underwent marginal excisions. On the basis of these findings, surgeons should make an effort to obtain the widest margins possible when removing liposarcomas.

Local recurrence of the tumor in 5 dogs in the present study that did not have histologic evidence of tumor cells at or near the surgical margins was unexpected; the possibility of skip metastases or field recurrences in these dogs cannot be discounted. However, most dogs with local tumor recurrence had undergone only marginal excision, with only 2 of 12 having undergone wide excision. In addition, the pathologists who examined these tumors histologically were able to evaluate only a few selected areas of the surgical margins, and it is possible that tumor cells at or near the margins would have been found if more extensive review of the surgical margins had been possible. This may be particularly important with liposarcomas because of the invasive nature of sarcomas. In addition, light microscopy may not be as sensitive a method of assessing surgical margins as is thought, and in human oncology, molecular staging techniques are being used to evaluate the completeness of surgical margins.[20]

In human patients with soft tissue sarcomas, adjunctive treatment (ie, radiation therapy or chemotherapy) is administered on the basis of tumor size and grade.[16] In general, however, chemotherapy is not routinely used in human patients with liposarcomas because most liposarcomas are only moderately sensitive to chemotherapy at best,[21] and further study is needed to determine whether chemotherapy has a role in the treatment of dogs with liposarcomas. Similarly, although radiation therapy is considered to be an appropriate treatment option for dogs and cats with incompletely excised soft tissue sarcomas and is the standard of care for humans with soft tissue sarcomas,[13,22-24] only limited information is available on radiation therapy in dogs with liposarcomas,[25,26] and more study is needed to determine whether it has a role.

[a]SAS, version 8.0, SAS Institute Inc, Cary, NC.

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