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Evaluation of outcome and prognostic factors for dogs living greater than one year after diagnosis of osteosarcoma: 90 cases (1997–2008)

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Abstract

Objective—To evaluate clinical characteristics, outcome, and prognostic variables in a cohort of dogs surviving > 1 year after an initial diagnosis of osteosarcoma.

Design—Retrospective case series.

Animals—90 client-owned dogs.

Procedures—Medical records for an 11-year period from 1997 through 2008 were reviewed, and patients with appendicular osteosarcoma that lived > 1 year after initial histopathologic diagnosis were studied. Variables including signalment, weight, serum alkaline phosphatase activity, tumor location, surgery, and adjuvant therapies were recorded. Median survival times were calculated by means of a Kaplan-Meier survival function. Univariate analysis was conducted to compare the survival function for categorical variables, and the Cox proportional hazard model was used to evaluate the likelihood of death > 1 year after diagnosis on the basis of the selected risk factors.

Results—90 dogs met the inclusion criteria; clinical laboratory information was not available in all cases. Median age was 8.2 years (range, 2.7 to 13.3 years), and median weight was 38 kg (83.6 lb; range, 21 to 80 kg [46.2 to 176 lb]). Serum alkaline phosphatase activity was high in 29 of 60 (48%) dogs. The most common tumor location was the distal portion of the radius (54/90 [60%]). Eighty-nine of 90 (99%) dogs underwent surgery, and 78 (87%) received chemotherapy. Overall, 49 of 90 (54%) dogs developed metastatic disease. The median survival time beyond 1 year was 243 days (range, 1 to 1,899 days). Dogs that developed a surgical-site infection after limb-sparing surgery had a significantly improved prognosis > 1 year after osteosarcoma diagnosis, compared with dogs that did not develop infections.

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Conclusions and Clinical Relevance—Results of the present study indicated that dogs with an initial diagnosis of osteosarcoma that lived > 1 year had a median survival time beyond the initial year of approximately 8 months. As reported previously, the development of a surgical-site infection in dogs undergoing a limb-sparing surgery significantly affected prognosis and warrants further study.

The prognosis for dogs with appendicular osteosarcoma is considered poor owing to the aggressive biological behavior of this tumor.[1–5] Some factors that have been found to negatively influence prognosis include age (dogs < 5 years old or > 10 years old at the time of diagnosis),[6] elevated serum alkaline phosphatase activity,[7,8] histologic grade,[9] and lymph node metastases.[10] The overall median survival time from the time of diagnosis for dogs undergoing amputation alone has been reported to be approximately 5 months, but the addition of chemotherapy increases the overall median survival time to approximately 1 year.[1,2,11,12]

Osteosarcoma is the most common primary canine bone tumor,[13] which underscores the importance of providing owners with prognostic information for various clinical scenarios (eg, dogs living longer than the historically reported median survival times). Median survival times from the time of osteosarcoma diagnosis have been established for dogs with appendicular osteosarcoma undergoing various treatments; however, little is known about the clinical characteristics and outcome for those patients that survive > 1 year. Thus, the purpose of the study reported here was to estimate survival time in a population of dogs that were still alive at least 1 year after the diagnosis of appendicular osteosarcoma and to evaluate factors that may be of prognostic utility in this patient population.

Materials and Methods

Criteria for selection of cases

Medical records from the Colorado State University Animal Cancer Center were obtained for patients with osteosarcoma identified from 1997 through 2008. Dogs were included in the study if they had appendicular osteosarcoma (defined as osteosarcoma occurring in the scapula or distal in the forelimb or in the femur or distal in the hind limb) and lived > 1 year after initial histopathologic diagnosis of osteosarcoma.

Procedures

Age, breed, sex, body weight, and alkaline phosphatase activities were recorded at the time of diagnosis. Additionally, data regarding anatomic location of osteosarcoma, surgical technique pursued, and type of adjuvant therapy (chemotherapy, radiation therapy, and pamidronate treatment) were obtained for each patient that met the inclusion criteria to determine the influence these variables had on survival time > 1 year from the time of initial diagnosis.

Statistical analysis

Median survival times and 95% confidence intervals were calculated by means of a Kaplan-Meier survival function. Univariate analysis was conducted with the log-rank test to

compare the survival function for categorical variables (breed, sex and neuter status, anatomic location of osteosarcoma, surgical technique pursued, and type of adjuvant therapy [chemotherapy, radiation therapy, and pamidronate]). For continuous variables (age, weight, and serum alkaline phosphatase activity), the Cox proportional hazard model was used to evaluate the risk of death > 1 year after diagnosis on the basis of the selected risk factors in this study. Serum alkaline phosphatase activity was dichotomized as within reference range (20 to 142 U/L) or greater than reference range (> 142 U/L). Statistical software[a] was used for all analyses.

Results

Ninety dogs met the inclusion criteria for the study. Median age of the dogs at the time of diagnosis was 8.2 years (range, 2.7 to 13.3 years), and there were 58 castrated males, 4 sexually intact males, and 28 spayed females. The median weight was 38 kg (83.6 lb; range, 21 to 80 kg [46.2 to 176 lb]) at the time of diagnosis. Mixed-breed dogs (n = 17) and Labrador Retrievers (13) predominated. Other breeds represented included Golden Retriever (n = 8), Rottweiler (8), Great Pyrenees (5), Australian Shepherd (3), German Shepherd Dog (3), Greyhound (3), Mastiff (3), Newfoundland (3), Saint Bernard (3), Akita (2), Bernese Mountain Dog (2), Doberman Pinscher (2), Great Dane (2), Irish Setter (2), Leonberger (2), and 1 each of American Bulldog, Bouvier des Flandres, German Shorthaired Pointer, Husky, Old English Sheepdog, Soft Coated Wheaten Terrier, Staffordshire Terrier, Swiss Mountain Dog, and Weimaraner.

The median total alkaline phosphatase activity was 72 U/L (range, 23 to 1,070 U/L) at the time of diagnosis, and 29 of 60 (49%) dogs for which bloodwork values were available had total alkaline phosphatase activity greater than the upper reference limit of 142 U/L.

Distribution of tumor locations and surgical procedures performed in the cases of this study were summarized (Tables 1 and 2). Of the 90 tumors, 88 (98%) affected long bones, and osteosarcoma was localized to the metaphyseal region in all 88 cases. Eighty-nine of the 90 (99%) dogs underwent surgery. In the 1 dog that did not have surgery, chemotherapy alone was administered. Of the 29 patients undergoing limb-sparing surgery, 20 (69%) developed a postoperative surgical-site infection; all surgical-site infections occurred in dogs that underwent limb-sparing surgeries.

Seventy-eight of 90 (87%) dogs received chemotherapy within 2 weeks after diagnosis of osteosarcoma; 12 (13%) did not receive adjuvant chemotherapy. Seven chemotherapy protocols were used, including carboplatin-doxorubicin (n = 40), carboplatin (23), doxorubicin (9), cisplatin-doxorubicin (3), cisplatin (1), carboplatin-cisplatin-doxorubicin (1), and daily low-dose chemotherapy with cyclophospamide-doxycycline-piroxicam (1). Pamidronate was administered in 11 cases; of these dogs, 8 also received chemotherapy.

Local recurrence was suspected in 6 of 90 (7%) patients, with a median time to recurrence of 171 days after initial diagnosis (range, 65 to 801 days); histopathologic confirmation of

[a]Stata, release 10, StataCorp, College Station, Tex.

recurrence was achieved in 4 of 6 cases. Forelimb-sparing surgery was performed in all 6 patients that had a local recurrence, and 5 of 6 dogs developed a surgical-site infection. After recurrence, no dogs underwent surgery, but 2 dogs received chemotherapy: carboplatin and doxorubicin in both cases.

Overall, 49 of 90 (54%) dogs developed known or suspected metastatic disease (on the basis of radiographic findings). The median time from initial diagnosis until the development of metastatic disease in this population of dogs was 323 days (range, 0 to 1,083 days). The locations of the first known metastatic lesions included pulmonary parenchyma (n = 27), bone (14), both pulmonary parenchyma and bone (3), spleen (3), lymph node (1), and both pulmonary parenchyma and liver (1). Chemotherapy was administered after diagnosis of the first known metastatic lesion or lesions in 21 dogs; 18 (86%) of these dogs had previously received chemotherapy. Eleven chemotherapy protocols were initiated after metastatic disease was noted: carboplatin (n = 4), carboplatin-doxorubicin (4), cyclophosphamide (3), cyclophosphamide-doxorubicin (2), doxorubicin (2), and 1 each of carboplatin-mitoxantrone, cisplatin-doxorubicin, cisplatin, cyclophosphamide-carboplatin-doxorubicin, carboplatin-gemcitabine, and continuous low-dose oral chemotherapy with cyclophosphamide-doxycycline-piroxicam. Fourteen patients underwent surgery to remove the metastatic lesion: lung (n = 6), bone (5), spleen (2), and lymph node (1). Six dogs received palliative radiation therapy alone to treat the metastatic lesion: bone (n = 5) and lung (1).

Of the 90 dogs, 14 (16%) were still alive (median follow-up time, 159 days after 1 year from diagnosis; range, 103 to 557 days) at the time of study completion (right-censored observations). Of the remaining 76 patients, 62 (82%) were euthanized for suspected progression (based on known or suspected metastasis [n = 49], recurrence [6], or owner follow-up discussion [7]) of disease related to osteosarcoma and 14 were lost to follow-up.

The median survival time beyond 1 year of the dogs in this study was 243 days (range, 1 to 1,899 days). Nineteen of 90 (21%) dogs in the present study survived > 2 years after initial diagnosis of osteosarcoma, and 5 (6%) dogs survived > 3 years after initial diagnosis. Of the 19 dogs surviving > 2 years after initial diagnosis, 10 developed metastatic disease. Of the 10 dogs that developed metastatic disease, 3 had metastasis diagnosed prior to 1 year after the initial diagnosis and 7 developed metastatic disease > 2 years after the initial diagnosis; no dogs developed metastasis between years 1 and 2. Two of the 3 dogs that survived > 2 years after initial diagnosis and that developed metastasis prior to 1 year after the initial diagnosis underwent pulmonary metastatectomy and received chemotherapy. For the 7 dogs that survived > 2 years after initial diagnosis and did not develop metastatic disease prior to 1 year, median survival time after 1 year from diagnosis was 521 days (range, 388 to 820 days).

The development of a surgical-site infection in dogs undergoing limb-sparing surgery was shown to be associated with significantly ($P = 0.002$) increased survival time, compared with survival time in dogs undergoing limb-sparing surgery that did not develop infection. The 20 dogs that developed surgical-site infection after limb-sparing surgery survived significantly longer after 1 year (median, 180 days; range, 25 to 1,899 days) than the 9 dogs

that did not develop surgical-site infection after limb-sparing surgery (median, 28 days; range, 8 to 282 days; Figure 1; Table 3).

No significant differences were noted during the univariate analysis of the following variables with respect to survival times: age ($P = 0.40$), sex ($P = 0.35$), weight ($P = 0.45$), serum alkaline phosphatase activity ($P = 0.65$), anatomic location ($P = 0.99$), chemotherapy administration ($P = 0.54$), chemotherapy administration after metastasis ($P = 0.07$), radiation therapy administered to treat a meta-static lesion ($P = 0.10$), and pamidronate administration ($P = 0.52$). The development of metastatic disease during the life of the dog ($P = 0.44$) and metastatectomy ($P = 0.50$) did not significantly affect survival time.

The 6 dogs that developed local recurrence survived significantly ($P = 0.029$) longer after 1 year (median, 441 days; range, 25 to 1,899 days) than dogs that did not develop local recurrence (172 days; range, 1 to 816 days; Figure 2; Table 3).

Discussion

In the present retrospective study of 90 dogs with appendicular osteosarcoma that lived > 1 year after initial histopathologic diagnosis, median survival time after the first year was approximately 8 months, (243 days; range, 1 to 1,899 days). Eighty-nine of 90 (99%) patients underwent a surgical procedure as part of the initial treatment. Dogs that developed a surgical-site infection after limb-sparing surgery (n = 20) had a significantly improved prognosis > 1 year after osteosarcoma diagnosis, compared with dogs that did not develop infections, which warrants further investigation.

Historically, the treatment of appendicular osteosarcoma in dogs has focused on local control of the tumor with surgery or radiotherapy followed by adjuvant chemotherapy.[2,8,12–15] Amputation of the affected limb is generally recommended in those patients in which orthopedic and neurologic disease in other limbs does not prevent the use of this procedure.[12,15] Alternatively, a wide variety of limb-sparing surgical techniques have been described.[12,15–20] Additionally, radiation therapy in the form of stereotactic radiosurgery has been attempted with curative intent,[14] and palliative radiation therapy has been found to be effective in decreasing pain and inflammation in up to 92% of cases.[21] Multiple studies[1,2,12,22,23] have reported that adjuvant chemotherapy may prolong survival times in dogs with osteosarcoma.

The majority (78/90 [87%]) of dogs in this study received chemotherapy. Previous studies[1,2,12] support the use of chemotherapy to prolong survival time to approximately 1 year; however, the use of chemotherapy (initiated at the time of diagnosis) did not significantly influence survival time after 1 year in this study. We suggest that this may be because the population of dogs surviving at least 1 year is a more uniform population than all dogs with osteosarcoma. In effect, there is a selection bias toward dogs with disease that is either more responsive to chemotherapy or less aggressive from the outset. Chemotherapy after the development of pulmonary metastases has been previously shown to be ineffective in prolonging survival times,[24] and a similar finding was noted in the dogs in this study.

A single dog in the present study did not undergo surgical treatment but did receive chemotherapy. Even though this dog would be considered to have a prolonged survival time (ie, > 1 year after diagnosis), this is not typical of what would be expected in a dog with appendicular osteosarcoma. Additionally, 12 of the 90 (13%) dogs in this study did not receive chemotherapy and still would be considered to have a prolonged survival time having lived > 1 year after the diagnosis of osteosarcoma.

Metastatic disease at the time of death has been documented in approximately 90% of dogs within a year when undergoing amputation alone.[6] The cohort of dogs in this study include many that received adjuvant therapies, which may partially account for the lower overall metastatic rate (49/90 [54%]). Additionally, the population of dogs in this study was different from the overall population of dogs with osteosarcoma because this study selected for those dogs that tended to live longer (ie, > 1 year after initial diagnosis). Evaluating only this group of dogs eliminated those patients that would generally fall in the lower half of a survival curve (approx), which would include many dogs that already had metastatic disease.

Metastatic disease at the time of initial diagnosis has been shown be a negative prognostic indicator for survival time in several studies,[4,10] although the use of surgery and radiation to treat metastatic lesions may allow for an improved quality of life in some animals. The development of metastatic disease in the dogs described in the present report did not significantly ($P = 0.44$) affect median survival time. This finding may be helpful for clinicians when providing clients with important information about the prognosis for their dog.

Pulmonary metastatectomy did not prolong the survival time of patients beyond 1 year after initial diagnosis of osteosarcoma in this study population. However, metastatectomy may prolong disease-free interval when performed in appropriate cases, such as when metastatic disease develops > 300 days after diagnosis of osteosarcoma (128 vs 58 days in dogs with the development of pulmonary metastases < 300 days after diagnosis) or when < 3 metastatic nodules are present (95 vs 53 days in dogs with 3 nodules).[25]

Radiotherapy was used to treat bone metastases in 5 patients in this study. Radiotherapy is commonly used as a treatment for metastatic bone disease, especially in patients that have a previous amputation, and approximately 75% to 92% of dogs with appendicular osteosarcoma will have apparent pain relief from palliative radiotherapy to bone lesions.[21,26] In the present study, palliative radiotherapy of metastatic bone lesions did not prolong survival times after > 1 year. Information concerning pain relief provided by the radiotherapy was not able to be obtained from the medical records.

The development of local recurrence of a tumor is generally considered a negative event. Recurrence requires treatment of the local disease to prevent pain associated with the growth of the mass, and further treatment after the initial surgery is generally undesirable and more difficult. Interestingly, in the present study, the 6 dogs that developed local recurrence (median survival time, 441 days; range, 25 to 1,899 days) lived significantly ($P = 0.029$) longer after the first year than did those that did not develop recurrence (median survival

time, 172 days; range, 1 to 816 days). Although this was an unexpected finding, 5 of 6 dogs also had a surgical-site infection, which may have influenced the outcome. Future studies should focus on the impact that these multiple variables may have on survival time.

The development of a surgical-site infection has been reported to prolong survival times in dogs undergoing limb-sparing surgery in 2 prior studies.[19,27] The 20 dogs that developed a surgical-site infection in the present study had significantly longer survival times after 1 year. The median survival time of this group after 1 year was 180 days (range 25 to 1,899 days), which was significantly ($P = 0.002$) longer than the median survival time for the dogs without a surgical-site infection (28 days; range, 8 to 282 days). This warrants further investigation.

The median age of the dogs in this study at the time of diagnosis was 8.2 years (range, 2.7 to 13.3 years), which is consistent with previous reports,[2,3,6,22] with most diagnoses made when patients are between 7 and 9 years of age. Nearly all dogs were either large or giant breeds, and more than two-thirds (62/90) of the patients were male. Although males appear to be slightly overrepresented in comparison to females, the reported sex distributions in previous reports[6,28] are not as skewed as noted among the dogs of this study.

Compared with previous reports,[28] similarities can be seen among the dogs of this study with regard to the most common tumor location. The distal aspect of the radius (54/90) and proximal aspect of the humerus (10) were the most common sites affected among the dogs of this study, and location was not found to impact prognosis. In the dogs with osteosarcoma of a long bone (88/90), the tumor was localized to the metaphyseal region in all cases.

A few previous studies[7,8] have identified increased total (or serum) alkaline phosphatase activity as a negative prognostic factor. However, in the cohort of dogs in the present study, an increased total alkaline phosphatase activity was not identified as affecting survival time beyond 1 year, a finding supported in another study.[29] However, that study[29] did not specifically evaluate a subgroup of patients surviving > 1 year after diagnosis. We suggest that ongoing monitoring of total alkaline phosphatase activity is important in this patient population, as supported by the results of a recent meta-analysis[11] evaluating prognostic factors in dogs with appendicular osteosarcoma that identified increased serum alkaline phosphatase activity as a significant negative prognostic factor for both disease-free interval and survival time.

In the present study, the type of surgical procedure performed did not affect prognosis for survival in the period beyond 1 year after the initial diagnosis of osteosarcoma. This was an expected finding, considering that survival time is not generally altered according to the technique used to treat the local disease or primary tumor. Median survival times among dogs with osteosarcoma, in general, are influenced by the addition of chemotherapy and not whether the patient underwent amputation, limb-sparing surgery, or curative-intent radiotherapy.[15,30]

On the basis of the results of this study, we suggest that if a dog with appendicular osteosarcoma survives to 1 year, the median survival time is approximately 8 months beyond that point. This may be important information to share with owners whose dogs have

survived at least 1 year after the diagnosis of osteosarcoma. Additionally, 19 of the 90 (21.1%) dogs in this study lived > 2 years after initial diagnosis, and 5 (6%) lived > 3 years after initial diagnosis. Interestingly, dogs living > 2 years after osteosarcoma diagnosis had a similar metastastic rate (10/19) versus the overall patient population of the study (49/90 [54%]).

Several limitations of this study can be identified and should be acknowledged. Because the main inclusion criteria selected for patients living > 1 year after the diagnosis of osteosarcoma, the dogs in this study did not receive standardized treatments; this decreases the ability to comment on the value of any particular treatment. A variety of prognostic factors for appendicular osteosarcoma have been identified previously; however, this study did not evaluate all previous known factors (eg, tumor grade) because of the retrospective study design and the lack of uniformity in data entry. Additionally, all histologic samples were not reviewed by a single pathologist, which prevents uniformity in the assessment of the samples and the diagnosis of osteosarcoma. Furthermore, although metastatic disease was not identified in 41 of 90 dogs, all dogs did not have necropsy results available, preventing a true prediction of the metastatic rate in this cohort of dogs. The lack of complete data for all 90 patients for all selected variables prevented a multivariable analysis to account for the combined effect of multiple factors on the survival time of these dogs. However, despite this limitation, our analysis identified factors impacting the prognosis of dogs that lived for > 1 year after the original diagnosis of osteosarcoma. Ideally, prospective studies that follow preestablished treatment protocols and obtain complete data on potential confounding factors at multiple institutions will allow for more comprehensive analysis on the population of dogs that survive at least 1 year following the diagnosis of osteosarcoma.

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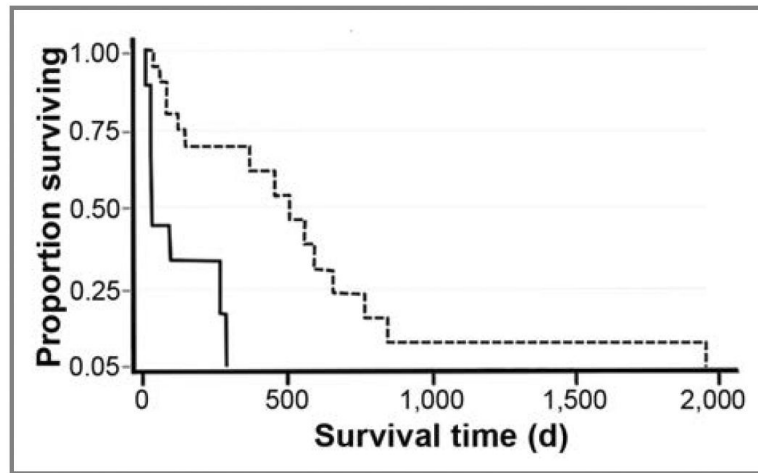
Figure 1.

Kaplan-Meier curves of survival time after the first year for 29 dogs with osteosarcoma that underwent a limb-sparing procedure and survived > 1 year after the initial diagnosis. Dogs (n = 20) that developed a surgical-site infection after limb-sparing surgery (dashed line) survived significantly (log-rank test *P* = 0.002) longer after 1 year (median, 180 days; range, 25 to 1,899 days) than did the 9 dogs that did not develop surgical-site infection after limb-sparing surgery (solid line; median, 28 days; range, 8 to 282 days).
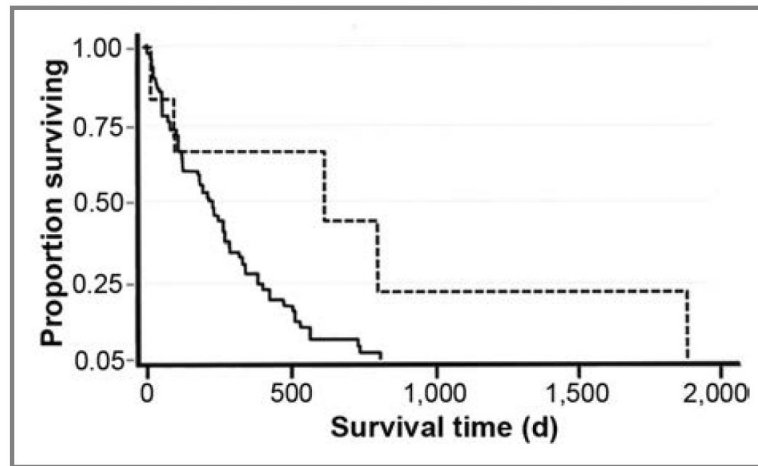
Figure 2.
Kaplan-Meier curves of survival time after the first year for 90 dogs with osteosarcoma that survived > 1 year after the initial diagnosis. The 6 dogs that developed local recurrence (dashed line) survived significantly (log-rank test $P = 0.029$) longer after 1 year (median, 441 days; range, 25 to 1,899 days) than did the 84 dogs that did not develop local recurrence (solid line; median, 172 days; range 1 to 816 days).

Table 1

Tumor location in 90 dogs surviving > 1 year after an initial diagnosis of appendicular osteosarcoma.

Tumor location	No. of dogs
Distal aspect of the radius	54
Proximal aspect of the humerus	10
Proximal aspect of the tibia	8
Distal aspect of the tibia	6
Distal aspect of the femur	5
Proximal aspect of the radius	2
Distal aspect of the ulna	2
Proximal aspect of the femur	1
Scapula	1
Metacarpus	1

Table 2

Surgical procedures performed in 89 dogs with osteosarcoma (1 dog did not undergo surgery).

Surgical procedure	No. of cases
Forelimb amputation	39
Forelimb-sparing surgery	23
Hind limb amputation	19
Limb-sparing surgery with intraoperative radiation therapy for osteosarcoma of the distal aspect of the radius	4
Hind limb–sparing surgery	2
Midshaft femur amputation	1
Fourth metacarpal removal	1
Total	**89**

Table 3

Prognostic factors in dogs surviving > 1 year after initial diagnosis of osteosarcoma.

	Survival time > 1 year after diagnosis (d)		
Variable	Median (range)	Interquartile range	Log-rank test *P* value
Infection with limb sparing			0.002
Infection (n = 20)	180 (25–1,899)	110–558	
No infection (n = 9)	28 (8–282)	22–246	
Local recurrence			0.029
Yes (n = 6)	441 (25–1,899)	110–820	
No (n = 84)	172 (1–816)	82–303	