Ulnar osteosarcoma in dogs: 30 cases (1992–2008)

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Objective—To examine the biological behavior of ulnar osteosarcoma and evaluate predictors of survival time in dogs.

Design—Retrospective case series.

Animals—30 dogs with primary ulnar osteosarcoma.

Procedures—Medical records were reviewed. Variables recorded and examined to identify predictors of survival time were signalment, tumor location in the ulna, tumor length, serum alkaline phosphatase activity, surgery type, completeness of excision, tumor stage, tumor grade, histologic subtype, development of metastases, and use of chemotherapy.

Results—30 cases were identified from 9 institutions. Eleven dogs were treated with partial ulnar ostectomy and 14 with amputation; in 5 dogs, a resection was not performed. Twenty-two dogs received chemotherapy. Median disease-free interval and survival time were 437 and 463 days, respectively. Negative prognostic factors for survival time determined via univariate analyses were histologic subtype and development of lung metastases. Telangiectatic or telangiectatic-mixed subtype (n = 5) was the only negative prognostic factor identified via multivariate analysis (median survival time, 208 days). Dogs with telangiectatic subtype were 6.99 times as likely to die of the disease.

Conclusions and Clinical Relevance—The prognosis for ulnar osteosarcoma in this population was no worse and may have been better than the prognosis for dogs with osteosarcoma involving other appendicular sites. Partial ulnar ostectomy was associated with a low complication rate and good to excellent function and did not compromise survival time. Telangiectatic or telangiectatic-mixed histologic subtype was a negative prognostic factor for survival time. The efficacy of chemotherapy requires further evaluation. (J Am Vet Med Assoc 2013;243:96–101)

Osteosarcoma is the most common primary bone tumor in dogs and has aggressive behavior.1 Many negative prognostic factors have been associated with osteosarcoma in dogs, including older age,2 high serum ALP activity, high serum ALP activity that does not resolve within 40 days following amputation,3–5 evidence of gross metastases,5,6 higher body weight,7 high tumor grade,8 high tumor microvascular density,9 and percentage of tumor necrosis induced by neoadjuvant doxorubicin treatment.10 Location of the primary tumor may also be of prognostic importance. Rib or scapular locations have been associated with shorter survival times for osteosarcoma of the axial skeleton,8,6 and proximal locations in the humerus have been associated with shorter survival times for osteosarcoma of the appendicular skeleton.8,11 Osteosarcoma of the ulna is rare. To the authors’ knowledge, the only veterinary report12 (12 cases) spe...
ifically addressing primary osteosarcoma of the ulna was published 1991. That study found a high metastatic rate for ulnar osteosarcoma and an MST of 8.5 months. A high local recurrence rate was associated with partial ulnar ostectomy; 5 of 8 dogs had local recurrence. Little is known about the biological behavior, treatment, and prognostic factors associated with ulnar osteosarcoma. The purpose of the study reported here was to evaluate the biological behavior and prognostic factors associated with ulnar osteosarcoma in dogs.

Materials and Methods

Case selection criteria—Cases of canine ulnar osteosarcoma evaluated between 1992 and 2008 were identified retrospectively from 9 institutions. Cases were included if osteosarcoma was identified histologically or cytologically by use of ALP staining in the ulna of a dog. Cases were excluded if no follow-up information was available.

Medical records review—Factors that were evaluated from the medical records included tumor location, tumor length, pre- and postoperative total serum ALP activities, surgery type (amputation vs partial ulnar ostectomy), completeness of excision, local recurrence, tumor stage, tumor grade, histologic subtype, development of bone or lung metastases, and use of chemotherapy.

Tumor location was classified as involving the proximal, middle, or distal third of the ulna. If the proximal and middle thirds were affected, the tumor was classified in the proximal third group. If the middle and distal thirds were affected, the tumor was included with the distal third group. If all thirds were affected, the tumor was classified in the proximal third group because of elbow joint involvement. Tumor length was defined as the longest measurement of the tumor in any radiographic projection. Complete resection was defined as the absence of tumor cells at the surgical margin. Tumor stage was determined according to the method of Kirpensteijn et al. Histologic subtypes were classified as osteoblastic, chondroblastic, fibroblastic, telangiectatic, mixed, or giant cell subtypes. After evaluating these groups separately, telangiectatic and telangiectatic-mixed subtypes were grouped together and evaluated against all other subtypes grouped together. All available histologic slides were evaluated by a single pathologist (TAD).

Statistical analysis—Kaplan-Meier analysis and the Cox PHR were used for univariate analysis of categorical variables, and the Cox PHR was used for multivariate analysis of continuous variables. A stepwise Cox PHR model was used for multivariate analysis of categorical and continuous variables that achieved \( P \leq 0.2 \) via univariate analysis. For all final comparisons, values of \( P \leq 0.05 \) were considered significant.

Results

Thirty cases with follow-up information were identified from the Animal Medical Center (n = 4), University of Pennsylvania (9), Tufts University (3), University of Georgia (4), Red Bank Veterinary Hospital (2), Hôpital Vétérinaire Rive-Sud (2), East Bay Veterinary Specialists and Emergency (2), Veterinary Specialists of South Florida (1), and Northwest Veterinary Specialists (1).

Twenty-three dogs were male and 7 were female. Twenty-seven cases were in large-breed dogs, with breeds represented being Rottweiler (n = 9), Labrador Retriever (5), Great Dane (2), Golden Retriever (2), large crossbreed (4), Dalmatian (1), Doberman Pinscher (1), Munsterlander (1), American Staffordshire Terrier (1), Belgian Malinois (1), and 1 case each of Boston Terrier, Basset Hound, and small crossbreed. There were 2 sexually intact male dogs. All other dogs were spayed (n = 7) or castrated (21). Patient age at evaluation ranged from 5 to 12 years (median, 8 years). Body weights ranged from 12.0 to 74.0 kg (26.4 to 162.8 lb), with a median weight of 38.0 kg (83.6 lb).

Six dogs had involvement of the proximal third of the ulna, including 1 dog that had involvement of all thirds of the ulna. Six dogs had the tumor confined to the central third of the ulna. Seventeen dogs had involvement of the distal third of the ulna (with or without involvement of the middle third). The portion of ulna involved was not recorded in 1 dog. Radiographic involvement of the adjacent radius was not reported in any case. Tumor length ranged from 2.0 to 10.0 cm (median, 6.1 cm); tumor length was not reported for 4 cases. Neither tumor location nor tumor length was associated with survival time as determined via univariate analysis.

Total serum ALP activity was measured in 27 dogs before surgery and was greater than reference range in 12 dogs and within reference range in 15 dogs (median, 113 U/L; range, 38 to 816 U/L). Seven diagnostic laboratories provided services to the multiple institutions and veterinary hospitals participating in the study, so 7 reference ranges were used (5 to 131 U/L, 10 to 130 U/L, 13 to 122 U/L, 12 to 127 U/L, 20 to 155 U/L, 24 to 174 U/L, and 23 to 212 U/L). Total serum ALP activity was measured after surgery in 11 dogs, including 1 dog for which a preoperative value was not recorded; activity was increased in 6 dogs and within reference range in 5 dogs (median, 164 U/L; range, 36 to 611 U/L). All but 2 postoperative serum ALP analyses (which both yielded results within reference range) were performed at least 40 days after surgery (median, 88 days; range, 27 to 672 days). Neither preoperative nor postoperative total serum ALP activities were associated with survival times via univariate analysis. Other reasons for increased total serum ALP activity, such as liver disease or corticosteroid administration, were not investigated.

Twenty-nine of the 30 dogs did not have evidence of pulmonary metastasis on thoracic radiographs at the initial evaluation; 1 dog had evidence of pulmonary metastasis. Computed tomography of the forelimb was performed in 4 cases, which included 2 cases for which concurrent thoracic CT was performed. Two of the 4 dogs had a partial ulnar ostectomy, 1 had an amputation, and 1 had only an incisional biopsy. One dog treated via partial ulnar ostectomy had a clean resection; the state of the surgical margins in the other case was not reported. Pulmonary metastasis was not detected via any of the thoracic CT examinations. Scintigraphy was performed in 1 case and revealed uptake at the primary tumor and no evidence of metastatic disease.
In 8 cases, a fine-needle aspirate of the primary tumor was performed; cytologic findings were consistent with a nonspecific diagnosis of sarcoma in 7 cases and were not diagnostic in 1 case. Seven of these 8 cases had subsequent histologic confirmation of osteosarcoma. Alkaline phosphatase staining of the cytologic preparation was used in the remaining case to help support a diagnosis of osteosarcoma. There was no histologic confirmation of the diagnosis in that case.

The tumor in 1 dog was classified as stage IA, in 1 as stage IB, in 23 as stage II, in 1 as stage III A, and in 1 as stage IV B. Tumor stage was not determined in 3 dogs. In 25 dogs, a surgical procedure was performed. Fourteen of those dogs were treated with an amputation, and 11 were treated with a partial ulnar ostectomy. Three dogs only had incisional biopsies performed at the time of surgery, and 2 dogs had no surgery performed (in one dog, ulnar osteosarcoma was diagnosed with the assistance of ALP staining, and in the other dog, it was diagnosed via histologic examination following necropsy). Tumor stage was not associated with survival time.

Of 11 dogs with a partial ulnar ostectomy, 5 had a histologically incomplete resection and 3 had complete resection with narrow margins (< 2 mm); for 3 dogs, results were not reported. The tumor involved the distal third of the ulna in 8 of these dogs and was confined to the diaphysis in 3 dogs. Complete resection was achieved in 3 dogs: 2 with involvement of the distal third of the ulna and the other with diaphyseal involvement only. In one of the dogs with a complete resection involving the distal third of the ulna, the styloïd process was not removed. The styloïd process was removed in 3 cases (1 complete resection, 1 incomplete resection, and 1 not reported). Stabilization of the carpus was not performed in any dog. Lameness was not observed in 2 dogs that had removal of the styloïd process at reevaluation 2 to 3 months after surgery. Presence or absence of lameness was not recorded for the third dog. Local recurrence was identified in 1 dog, in which resection was incomplete, at 210 days. The median follow-up time specifically for dogs treated with partial ulnar ostectomy was 307 days (range, 108 to 1,077 days). Partial ulnar ostectomy was not a prognostic factor.

Of the dogs treated with partial ulnar ostectomy and in which lameness was recorded, including the 2 dogs treated with removal of the styloïd process with lameness information, 9 dogs had presence and severity of lameness recorded at various times. At 10 to 14 days after surgery, 1 dog was not lame, 3 had mild lameness and were consistently weight bearing, and 2 had obvious lameness and were consistently weight bearing. At 2 to 3 months after surgery, 5 dogs were not lame, 3 had mild lameness, and 1 was obviously lame with consistent weight bearing. At the final evaluation (range, 161 to 656 days), 4 dogs were not lame, 2 had mild lameness and were consistently weight bearing, 1 was intermittently weight bearing, and 1 was non–weight bearing. The latter 2 dogs had late-occurring fractures (157 and 283 days after surgery, respectively) of the adjacent radius at the surgical site. One dog had been treated with stabilization of the proximal portion of the ulna to the radius by use of a cortical screw. No other report of damage to the radius at the time of surgery was found. In 4 dogs, evaluation of the axillary lymph node was performed; in 1 dog, there was evidence of metastasis and survival time was 109 days.

Twenty-two dogs received chemotherapy, including carboplatin plus doxorubicin (n = 10 [6 alternating protocols and 4 sequential protocols]); carboplatin alone (5); doxorubicin alone (4); cisplatin plus doxorubicin (2 with alternating protocols); doxorubicin, carboplatin, and cisplatin (1 with a sequential protocol). Eight dogs did not receive chemotherapy. The median number of chemotherapy treatments was 5 (range, 2 to 11). Two dogs received local radiation after having a partial ulnar ostectomy. One of those dogs had an incomplete resection, and margins were not reported for the other. Neither dog developed evidence of local recurrence. Use of chemotherapy, type of chemotherapy, and use of radiation were not associated with survival times. Chemotherapy intent (preplanned vs administered for incomplete resection) was not investigated.

There were 22 cases with slides available for histologic review. Two dogs were classified with grade I tumors (survival time, 307 and 1,077 days), 13 dogs with grade II tumors (survival time, 14 to 937 days), and 7 dogs with grade III tumors (survival time, 84 to 527 days). Tumor grade was not associated with survival time.

Histologic subtypes identified were osteoblastic (n = 16), chondroblastic (2), telangiectatic (3), mixed osteoblastic-chondroblastic (2), mixed osteoblastic-telangiectatic (2), and giant cell (1). A fibroblastic subtype was not identified. Histologic subtype was not reported and slide review was not available for 3 cases. Histologic examination was not performed in 1 case, which was diagnosed on the basis of radiographic changes, cytologic findings, and ALP staining of the tumor. Histologic subtype was not associated with survival time when each subtype was compared to others individually. On univariate analysis, histologic subtype was significantly (P = 0.035) associated with survival time when telangiectatic and telangiectatic-mixed subtypes were compared with all other subtypes grouped together (Cox PHR, 5.814; 95% CI, 1.133 to 29.412). On multivariate analysis, histologic subtype (telangiectatic or telangiectatic-mixed) was the only significant (P = 0.047) prognostic factor associated with survival time (Cox PHR 6.993; 95% CI, 1.025 to 47.619). Median survival time for dogs with the telangiectatic or telangiectatic-mixed subtypes was 208 days. Median survival time for dogs with all other subtypes was 463 days (Figure 1).

Fifteen (50%) dogs had or developed evidence of distant metastases, including 1 dog with lung metastases at initial evaluation that was euthanized and 1 dog that did not have surgery performed. Eleven dogs had or developed evidence of gross lung metastases (DFI range, 52 to 437 days, not including 2 dogs that were never disease free). Five dogs developed radiographic evidence and 1 dog developed scintigraphic evidence of bone metastases (DFI range, 109 to 903 days). Two of these 6 dogs also had evidence of gross lung metastases (DFI, 411 and 437 days). Evidence of bone metastases were seen in the ilium (1 dog), distal portion of the tibia (1 dog), proximal portion of the femur (1 dog), humerus (1 dog), scapula and humerus (1 dog), both femurs, and 4 ribs (1 dog). Metastases were not histologically or cytologically confirmed.
Twelve dogs died because of their disease, 13 were alive at the last follow-up, including 2 dogs lost to follow-up, and 5 died from apparently unrelated causes. The Kaplan-Meier median DFI was 437 days. Eleven dogs were censored from analysis because they were disease free (Figure 2). The Kaplan-Meier MST was 463 days (Figure 3). The overall median follow-up time was 221.5 days. Five dogs were classified as dying from other causes, including bacterial sepsis (this dog did not receive chemotherapy and had a survival time of 89 days), pericardial effusion (survival time, 192 days), gastric dilatation-volvulus (survival time, 527 days), aspiration pneumonia (survival time, 583 days), and hind limb weakness-ataxia without evidence of bone pain (survival time, 656 days). None of these 5 dogs had a telangiectatic or telangiectatic-mixed subtype. Although it could not be ruled out that the hind limb weakness was caused by late metastasis, the lack of signs of bone pain raised the possibility of spinal cord disease rather than vertebral metastasis.

Negative prognostic factors for DFI determined on the basis of univariate analyses were histologic subtype (telangiectatic or telangiectatic-mixed; Cox PHR 4.464; 95% CI, 1.085 to 18.182; \( P = 0.038 \)) and development of lung metastases (Cox PHR 7.692; 95% CI, 2.321 to 25.641; \( P < 0.001 \)), but not development of bone metastases. No significant prognostic factors for DFI were identified via multivariate analysis.

Factors associated with a shorter survival time via univariate analyses were histologic subtype (telangiectatic or telangiectatic-mixed subtype; Cox PHR 5.814; 95% CI, 1.133 to 29.412; \( P = 0.035 \)), development of metastases (Cox PHR 6.494; 95% CI, 1.406 to 28.241; \( P = 0.016 \)), and development of lung metastases (Cox PHR 3.226; 95% CI, 1.011 to 10.309; \( P = 0.048 \)), but not development of bone metastases. The only significant (\( P = 0.047 \)) factor associated with survival time detected via multivariate analysis was histologic subtype (telangiectatic or telangiectatic-mixed patterns). Dogs with these tumor subtypes were 6.993 times as likely to die from their disease as dogs with other tumor subtypes (Cox PHR 6.993; 95% CI, 1.025 to 47.619).

Discussion

Results indicated that telangiectatic and telangiectatic-mixed subtypes were negative prognostic factors for both DFI and survival time. These tumor subtypes were grouped together because of the low numbers of affected dogs, the low power of the study, and the fact that there is some evidence in the veterinary literature that dogs with telangiectatic subtypes may have a worse prognosis.6 In a study6 of 45 dogs with osteosarcoma of the axial skeleton, 4 dogs had a telangiectatic subtype and all developed metastases. The overall metastatic rate in that study6 was 35%. Statistical analysis was not performed with regard to prognosis of the dogs with the telangiectatic subtype. Telangiectatic subtype is a vascular subtype, which could be misdiagnosed as hemangiosarcoma.1 Hemangiosarcoma of bone has a worse prognosis than primary osteosarcoma in dogs.1 For 4 of the 5 dogs with telangiectatic osteosarcoma in the present study, histologic slides were available for review. In these cases, there was evidence of neoplastic osteoid production, consistent with a diagnosis of osteosarcoma. It was deemed that immunohistochemical staining was not necessary to make the diagnosis, because of the histologic appearance of the tumors and presence of neoplastic osteoid production. Human patients with telangiectatic osteosarcoma
have been considered to have a poorer prognosis, compared with patients with other subtypes of osteosarcoma, but results of a recent study indicate comparable survival times for humans with telangiectatic and other subtypes of osteosarcoma. The nonosteoblastic subtype has been identified in the literature as a negative prognostic factor for survival time. Rates of response to chemotherapy in human osteosarcoma have been found to differ by subtype, although the telangiectatic subtype was not associated with a worse prognosis in that study. Vascular endothelial growth factor expression is negatively associated with DFI in dogs. Vascular endothelial growth factor expression is predictive of pulmonary metastasis and poor prognosis in the human literature, and correlation between expression of vascular endothelial growth factor and histologic subtype has not been found. Although telangiectatic osteosarcoma is a vascular subtype, it is unclear whether it has high expression of vascular endothelial growth factor in dogs with osteosarcoma.

In the present study, most primary ulnar osteosarcomas occurred in middle-aged large-breed male dogs; only 7 of 30 dogs were female. This was consistent with a previous report. Seventeen dogs had involvement of the distal third of the ulna, 6 dogs had involvement of the middle third (diaphysis), and 6 dogs had involvement of the proximal third. On the basis of these findings and depending on the extent of soft tissue involvement, partial ulnar ostectomy may be an option for a large proportion of dogs with ulnar osteosarcoma.

With regard to survival time, dogs that had a partial ulnar ostectomy did no worse than dogs that were treated via amputation. In the 11 dogs that had a partial ulnar ostectomy, only 1 dog had evidence of local recurrence (at 210 days). This was despite the fact that only 3 of 8 dogs for which margins were reported had complete resections. This was in contrast to a previous study in which 5 of 8 dogs treated with a partial ulnar ostectomy had evidence of local recurrence, including 3 of 4 dogs that had concurrent local radiation therapy. This difference may have been attributable to undetected local recurrence in the cases in the present study or because local recurrence did not occur until a prolonged period had passed. The median follow-up time specifically for dogs treated with partial ulnar ostectomy was 307 days.

In 3 dogs in which a partial ulnar ostectomy was performed, the styloid process was also removed. In none of these dogs was stabilization of the carpus performed subsequently. There are no continuous collateral ligaments for the 3 main joints of the carpus. Two sleeves of collagenous tissue confer stability to the carpus. These sleeves fuse, in part, to form the short collateral ligaments, and long collateral ligaments are lacking. The styloid process may be removed by splitting the longitudinal fibers of the short ulnar collateral ligament and use of sharp dissection directly around the process. Although a cadaveric study revealed an increase in carpal extension following transaction of the lateral collateral ligament, stability conferred to the carpus by muscles and tendons was not accounted for because of the in vitro nature of that study. Dogs in the present study that had the styloid process removed did not have surgical stabilization of the carpus performed and appeared to have had adequate function after surgery.

In the present study, most dogs in which a partial ulnar ostectomy was performed had good to excellent function after surgery, which was consistent with another report. Two dogs had either non-weight bearing or intermittent weight bearing lameness associated with late-occurring fractures of the radius adjacent to the surgical site. The fractures occurred at 157 and 283 days after surgery. In one of these dogs, a cortical screw was placed from the ulna to the radius during the initial procedure, and in the other, radiation therapy was performed after surgery. Although the small number of late fractures precluded meaningful interpretation, it is prudent to protect the radius at the time of ostectomy to avoid any cortical damage to the radius and decrease the risk of a late fracture occurring. A cortical screw used to stabilize the ulna to the radius limits the motion between the radius and ulna and may cause a stress-riser in the radius.

The fact that the development of metastases and development of lung metastases were negative prognostic factors for survival time was not surprising. It is interesting to note that development of distant bone metastases was not an independent negative prognostic factor. Evidence of bone metastases only developed in 6 dogs in this study, which included 2 dogs that developed both lung and bone metastases. Eleven dogs developed lung metastases. One dog had lymph node metastasis at initial evaluation and later developed evidence of bone metastasis. Metastases were not recognized in other locations. In humans, metastases to bone (stage IVB) and other organs have been associated with a worse prognosis than metastases to the lungs (stage IVA). In the present study, this analysis was not possible because only 1 dog each was affected with these stages of tumor. Dogs that developed bone metastases had an MST of 388 days, whereas those with lung metastases had an MST of 463 days. Conversely, in another study of dogs with metastatic disease, dogs with bone metastases at initial evaluation had a longer MST than dogs with soft tissue metastases. All dogs in that study underwent some form of treatment, and dogs that were treated palliatively with radiation and chemotherapy had longer survival times.

It should be noted that chemotherapy did not provide a survival advantage in the present study. Twenty-two dogs received chemotherapy in the form of a platinum compound, doxorubicin, or both. Because of the many chemotherapy protocols used, we also compared use of any chemotherapy protocol versus no chemotherapy, and there was no statistically survival advantage. It is possible that this occurred because 13 of 30 dogs were still alive at the end of the study, so a relatively large number of dogs were censored. Fifty percent of dogs in this study developed evidence of metastases, and it is likely that more would do so. A previous study revealed ulnar osteosarcoma to be highly metastatic, with all 8 dogs that underwent a necropsy having evidence of metastasis. Use of chemotherapy for osteosarcoma of the axial skeleton is controversial, with lower metastatic rates suggested for mandibular osteosarcoma and other calvarial locations. Osteosarcoma of the canine scapula may have a worse prognosis even when treated with surgery and chemotherapy. The role of chemotherapy for ulnar osteosarcoma remains to be defined.

The MST in this study was 463 days. Although direct comparisons cannot be made between studies, this was
far better than the MST of 8.5 months reported for dogs with canine ulnar osteosarcoma.23 Only 6 of 11 dogs in that study24 received chemotherapy, compared with 22 of 30 in the present study. The MST was similar to23 or better than what has been reported for canine appendicular osteosarcoma.25 The short overall median follow-up time (221.5 days) and the large number of dogs still alive at the end of the study (13 dogs) may have increased the MST.

Limitations of the present study included its retrospective nature and the inherent problems associated with this study design. The cases were from multiple institutions, with various medical and surgical management protocols, different follow-up times, and incomplete records. Only 22 cases had histologic slides available for review. The overall median follow-up time was only 221.5 days, with 13 of 30 dogs still alive at the close of the study. Postmortem examinations were not performed in most cases, so metastatic rates and organs affected may have been underestimated.

The prognosis for ulnar osteosarcoma appeared no worse than that for radial osteosarcoma and was possibly better. The distal third of ulna was most commonly affected, and many cases may be suitable for a partial ulnar osteotomy. Partial ulnar osteotomy was associated with good to excellent function in most cases and a low complication rate and was not associated with shorter survival times. It is prudent to protect the radius during osteotomy to minimize the risk of iatrogenic damage. The telangiectatic subtype was associated with a shorter survival time than other tumor subtypes. Further studies are required to determine how carpal stability is affected by removal of the styloid process and the role of chemotherapy in ulnar osteosarcoma.

References