Biologic Behavior and Clinical Outcome of 25 Dogs with Canine Appendicular Chondrosarcoma Treated by Amputation: A Veterinary Society of Surgical Oncology Retrospective Study

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Objective—To characterize biologic behavior, clinical outcome, and effect of histologic grade on prognosis for dogs with appendicular chondrosarcoma treated by amputation alone.

Study Design—Case series.

Animals—Dogs (n = 25) with appendicular chondrosarcoma.

Methods—Medical records were searched to identify dogs with appendicular chondrosarcoma treated by limb amputation alone. Information recorded included signalment, anatomic location, radiographic appearance, and development of metastasis. Histopathologic diagnosis was confirmed and graded (1, 2, or 3). Survival curves were generated by the Kaplan–Meier method and the association between covariates (gender, age, weight, and tumor grade) and survival were evaluated using the univariate proportional hazards model.

Results—Histopathology slides were available for 25 dogs. Rates of pulmonary metastasis were as follows: grade 1–0%, grade 2–31%, and grade 3–50%. Overall median survival time (MST) was 979 days. Age, weight, and sex were not significantly associated with survival (P = .16; .33; and .31, respectively). Survival was significantly associated with tumor grade (P = .008), with dogs with tumor grade of 1, 2, and 3 having MSTs of 6, 2.7, and 0.9 years, respectively.

Conclusion—Canine appendicular chondrosarcoma can be treated effectively with amputation alone. Low to intermediate grade chondrosarcoma has a good prognosis, whereas high-grade tumors appear to behave aggressively.

Clinical Relevance—The overall prognosis for appendicular chondrosarcoma is better than that of appendicular osteosarcoma treated by amputation alone or in combination with chemotherapy.
INTRODUCTION

Chondrosarcoma is the second most common primary bone tumor in both dogs and humans, and accounts for 5–10% of reported cases.\(^1\)–\(^6\) Reported anatomic locations for chondrosarcoma in dogs include the nasal cavity, axial skeleton (e.g., rib, facial bones), appendicular skeleton and extraskeletal sites such as the mammary gland.\(^4\)–\(^6\),\(^8\) Chondrosarcoma is generally considered moderately metastatic,\(^1\) with rates ranging from 18% to 60% and reported sites including the lungs, pleura, mediastinum, pericardium, lymph nodes, bone, liver, kidney, adrenal gland, and eyes.\(^1\),\(^4\),\(^6\),\(^7\),\(^9\) In 1 study tumor location rather than histologic grade was considered prognostic, with tumors of the facial bones, nasal turbinates and extremities having prolonged survival when compared with those located in the rib.\(^8\) In a more recent study, histologic grade was prognostic for survival.\(^7\) Chemotherapy has not been shown to prolong survival in either dogs or humans and is typically not recommended after surgical excision in either species.\(^7\),\(^10\)

Several reports of skeletal chondrosarcomas have included a number of appendicular cases.\(^6\)–\(^9\) The reported survival times for dogs treated with surgery alone (typically amputation) varied widely: Obradovich et al\(^7\) reported a median survival time (MST) 163 days (n = 7), Popovitch et al\(^6\) reported a MST 540 days (n = 5), and Waltman et al\(^7\) reported a mean survival time of 2618 days (n = 13, 10 of which were treated by amputation and 3 were untreated). Such discrepancies make it difficult to predict survival accurately. Our purpose with a retrospective, multi-institutional study was to identify a prospective, multi-institutional study was to identify a number of dogs with appendicular chondrosarcoma treated with limb amputation alone to characterize biologic behavior, assess clinical outcome and determine effect of histologic grade on prognosis.

MATERIALS AND METHODS

Inclusion Criteria

Medical records (1995–2005) of all contributing institutions were searched to identify dogs with chondrosarcoma of the appendicular skeleton that were treated by limb amputation alone. Dogs that had adjunctive therapy (e.g., chemotherapy or radiation therapy) or did not have 6 weeks of follow-up information were excluded. Only dogs with a confirmed histologic diagnosis of chondrosarcoma on tissue sections collected from the amputated limb were included.

Data Retrieved

Information recorded included: age, weight, sex, breed, bone affected, location within the bone (i.e., proximal, middle, or distal), preoperative serum alkaline phosphates levels, radiographic appearance (i.e., proliferative, lytic, or mixed), details about preoperative biopsy, level of amputation, development of metastasis (anatomic location and number of days detected postamputation) and overall survival.

Histopathology

Hematoxylin and eosin (H&E)-stained slides were evaluated and graded by a single pathologist (M.K.), without having knowledge of the corresponding clinical history, radiologic interpretations, or gross pathologic findings. A grading scale was adapted from a previous human chondrosarcoma grading scale and grade was determined by assessing the following features: matrix production, architecture, degree of pleomorphism, cellularity, necrosis, and mitosis. Each descriptive feature was assigned a numerical value of 0, 1, 2, or 3, with 0 indicating not observed and 1, 2, and 3 indicating increasing presence. Mitosis was assessed by counting the number of mitotic figures/10 high-power fields (HPF). Values for each category were then summed (including the number of mitotic figures/10 HPF) and each case was assigned a grade according to the following scale: Grade I—total histologic score <6 and mitosis 0–1 or total histologic score 7 and mitosis = 0; Grade II—total histologic score 7–10 and mitosis = 1 or 2; and Grade III—total histologic score 11–16 or mitosis = 3.

Data Analysis

Survival time was defined as the interval between amputation and death. Cause of death was classified as chondrosarcoma or nonchondrosarcoma related. Dogs with unknown causes of death were presumed to have died from chondrosarcoma. For the purposes of survival calculations, dogs that died as a result of their chondrosarcoma were considered completed events and dogs that died of other causes other than chondrosarcoma, or were still alive at the time of last contact, were censored. Survival curves were generated by the Kaplan–Meier method. Association between covariates (gender, age, weight, and tumor grade) and survival were evaluated using both univariate and multivariate proportional hazards models. Rate of pulmonary metastasis was compared by Fisher’s exact test. All data were analyzed using statistical software (SAS version 9.1.3 software, SAS Institute, Cary, NC).

RESULTS

Twenty-seven dogs met the inclusion criteria; however, 2 cases previously diagnosed as chondrosarcoma were reclassified as chondroblastic osteosarcomas and were therefore excluded, resulting in a total of 25 cases. Eight cases were previously included in the study by Waltman et al\(^7\) Mean age was 6.58 years (range, 1.8–12 years). Mean weight was 30.5 kg (range, 7–52 kg). There were 14 females (2 intact, 12 spayed) and 11 males (2 intact, 9 neutered). Breeds included 4 mixed breed dogs, 2 Golden Retrievers, 4 Bernese mountain dogs, 2 Doberman Pinschers, 2 Australian cattle dogs and 1 each of Rottweiler,

Serum alkaline phosphatase levels were available for 10 dogs and were normal in 8. Of the 2 outside the reference range, 1 was below normal (3; institution reference interval, 5–131 IU/L) and the other was elevated (142; institution reference interval, 17–86 IU/L). Ten tumors were located in the tibia (6 proximal, 4 distal), 5 in the femur (2 proximal, 3 distal), 4 in the humerus (3 proximal, 1 distal), 2 in the ulna (both distal), 1 in metacarpals II and III, 1 in the carpus, 1 in the proximal aspect of the radius, and 1 in the calcaneus. When radiographs were available for review, pathologic changes were observed osteolytic (7 dogs), osteoproliferative (2 dogs), or a mixed process (6 dogs; Figs 1 and 2).

Information regarding preoperative biopsy was available for 12 of the confirmed chondrosarcomas; however, none of these samples were available for re-evaluation by our pathologist. In 8 of these cases, chondrosarcoma was
initially diagnosed. In the other 4 cases a different diagnosis was initially made (2 as chondroma, 1 focal chondrodysplasia, and 1 bone marrow fibrosis). One of the tumors diagnosed as chondrosarcoma preoperatively was also subjectively graded by the initial pathologist. This case, which was given a low preoperative grade, was considered a grade 2 chondrosarcoma in our study. This dog was alive at the time of this report at 550 days.

The primary tumor was treated by amputation in all dogs. One dog was treated by partial pelvectomy (i.e., acetabulectomy) because of proximity of the tumor to the coxofemoral joint (originated in the greater trochanter of the femur). Eight dogs were still alive at the time of writing. Six dogs died of unknown causes and 5 died from unrelated conditions, including splenic hemangiosarcoma (1), prostatic adenocarcinoma suspected (1), renal failure (1), and 2 euthanatized for other geriatric problems. Pulmonary metastasis was diagnosed radiographically in 7/25 (28%) dogs and 2 of these had confirmation of pulmonary metastasis by necropsy (no other abnormalities were noted). Time to radiographic evidence of metastasis from the time of amputation was reported in 4/7 dogs with pulmonary metastasis. For these 4 dogs, the number of days to detection of metastasis and survival time, respectively, were as follows: 191 and 252 days, 325 and 387 days (still alive at the time of this report with pulmonary hypertrophic osteopathy), 453 and 455 days, and 712 and 723 days. For the other 3 dogs, the radiographic diagnosis of pulmonary metastasis and euthanasia occurred on the same day. There was no evidence of local recurrence in any of the cases.

Histopathology slides created from the amputated specimens were available for 25 dogs: 6 (24%) were grade 1; 13 (52%) grade 2; and 6 (24%) grade 3 tumors. The rates of pulmonary metastasis were as follows: grade 1–0%, grade 2–31%, and grade 3–50%. The difference in rate of pulmonary metastasis between dogs with tumor grade 1, 2, or 3 was not statistically significant ($P = .18$). Two of the 6 grade 3 tumors died of unknown causes at 85 and 171 days. Overall MST was 979 days (2.7 years, Fig 3). From univariate analysis, age, weight, and sex were not significantly associated with survival ($P = .16$, .33, and 0.31, respectively). Survival was significantly associated with tumor grade ($P = .008$), with dogs with tumor grade of 1, 2, and 3 having MSTs of 6, 2.7, and 0.9 years, respectively (Fig 4). By multivariate analysis with survival as the dependent variable and with age, weight, sex, and tumor grade as independent variables, only tumor grade was significantly associated with survival ($P = .039$).

**DISCUSSION**

There has been great discrepancy in the published MSTs for dogs with appendicular chondrosarcoma treated by amputation. Some studies have linked the clinical outcome to that of canine appendicular osteosarcoma (OSA; Obrodovich et al. $n = 7$, MST = 163 days), whereas others have reported moderately higher (Popovitch et al. $n = 5$, MST = 540 days) or substantially higher survival times (Waltman et al. $n = 7$ mean survival time = 2618 days). We speculate that, given the higher number of cases in our study, the overall MST of 2.7 years (979 days) may better estimate the survival of dogs with ap-
appendicular chondrosarcoma treated by amputation alone. In our study, the rate of metastasis was 28% (7/25 dogs) and the lungs were the only documented anatomic site. This rate is in agreement with the 31% rate reported for long bone tumors by Waltman et al (n = 13; 10 treated and 3 untreated); however, it is substantially lower than reported rates for dogs treated by amputation by Popovitch et al (60%; n = 5) and Obradovich et al (57%; n = 7). We also speculate that our findings, and those reported by Waltman et al may better represent the rate of metastasis for appendicular chondrosarcoma given the higher number of cases in the more recent studies.

In humans, grading of chondrosarcomas is one of the most important prognostic predictors. Grade I human chondrosarcomas are not typically metastatic, whereas 10–33% of grade II and ~70% of grade III chondrosarcomas metastasize. Six of the dogs in our study were diagnosed as grade 1, 13 as grade 2, and 6 as grade 3. The association between grade and metastasis in our dogs (grade 1–0%, grade 2–31%, and grade 3–50%) is similar to the association reported for human chondrosarcoma.

Two tumors in this study had been provisionally diagnosed as chondrosarcoma, but were re-classified as chondroblastic osteosarcoma by our pathologist and therefore excluded. Such disagreement, between histopathologic diagnosis obtained preoperatively by needle core biopsies and the postoperative diagnosis based on the larger tissue specimen submitted after amputation, is common in the clinical setting. Given the apparent difference in MST between appendicular chondrosarcoma and appendicular osteosarcoma treated by amputation alone (2.7 years and 18–19 weeks, respectively), it is important for clinicians to be aware of this possibility and to educate clients accordingly. It is also possible that previous studies could have mistaken some chondroblastic osteosarcomas for chondrosarcomas and this may in part have accounted for the some of the shorter survival times.

A preoperative biopsy was performed in 12 of the 25 dogs; however, none of these slides were made available to our pathologist. In 8 of these cases, a diagnosis of chondrosarcoma was made. Thus, ~66% of the preoperative diagnoses agreed with the postoperative diagnosis. Preoperative diagnoses that did not agree with the postoperative diagnosis tended benign in nature (e.g., chondroma). Although it cannot be determined from our retrospective study, we speculate that the discrepancy may be attributed to the small size of most preoperative biopsies. We found that the tibia was the most commonly affected bone (10/25 [40%] dogs; 6 proximal, 4 distal), followed by the femur (5/25 [20%]) and humerus (4/25 [16%]). Unlike osteosarcoma, the radius was infrequently affected and the 1 documented case in our series was in the proximal aspect. Popovitch et al. found the femur most commonly affected, equally distributed between the proximal and distal metaphyses. In the reports by Sylvestre et al and Waltman et al the tibia and humerus were the most commonly affected bones. Collectively, these studies and our study indicate that the proximal tibia is the most commonly affected bone, specifically the proximal aspect. Thus, it appears that the skeletal distribution differs from that of appendicular osteosarcoma, where the distal radius is the most common site.

In our study, radiographic changes were observed osteolytic (7 dogs), osteoproliferative (2 dogs), or a mixed process (6 dogs; Fig 1). These observations are consistent with those reported where chondrosarcoma has been described to produce predominantly osteolytic changes or a mixed process. In 1 dog (Fig 2), the tumor caused osteolysis that extended across a joint, affecting the distal humerus and olecranon. Sylvestre et al also reported an appendicular chondrosarcoma that crossed a joint. In that dog the tumor was located primarily in the proximal humerus and extended along the shoulder joint capsule into the distal scapula.

Our study has several limitations because of its retrospective nature. First, inconsistent follow-up information and postoperative radiographic evaluation of the lungs do not allow consistent and complete assessment of time to metastasis and disease progression. Secondly, necropsies were not performed in all dogs. This may have resulted in an underestimation of the frequency and location of metastatic disease. Other reported sites of metastasis include pleura, mediastinum, pericardium, lymph nodes, bone, eyes, kidneys, liver, and the adrenal gland. Also, there were a number of dogs for which preoperative radiographs and serum alkaline phosphatase concentrations, and preoperative biopsy samples were either not performed or not available.

We conclude that for dogs with canine appendicular chondrosarcoma, extended survival times are possible with amputation alone. Our data suggest that low to intermediate grade chondrosarcoma carries a good prognosis, whereas high-grade tumors appear to behave aggressively. Future studies should evaluate whether postoperative chemotherapy provides a survival advantage over amputation alone, particularly with high-grade tumors. Clearly, the overall prognosis for appendicular chondrosarcoma is better than that of appendicular osteosarcoma treated by amputation alone or in combination with chemotherapy.

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