Update on Canine Osteosarcoma: The CSU Experience

Douglas H. Thamm, VMD, DACVIM (Oncology)
Colorado State University
Fort Collins, CO

Osteosarcoma (OSA) represents the most common bony tumor of dogs and cats. Although information regarding etiopathogenesis is lacking, OSA of the long bones (appendicular OSA) is far more common in large and giant breed dogs than in smaller dogs. Rare causes of OSA include those associated with metallic implants, those formed after radiation therapy, and some feline vaccine-associated sarcomas. OSA of the axial skeleton has a more even distribution between breeds. The most common age of incidence is between 6 and 8 years, however there is another small group of dogs that can develop OSA at 18 to 24 months. Overall, axial skeletal OSA occurs at an earlier age than appendicular OSA. OSA is a clinical problem not only due to its aggressive destruction of bone and the attendant pain and structural damage caused, but also due to its high potential for metastasis.

History – Physical examination

Most dogs with appendicular OSA will present with a history of lameness. This may be acute in onset, or may have been chronic and progressive. It is common for owners to attribute some trauma to the development of lameness, and it is common for lameness to initially respond to nonsteroidal anti-inflammatory drugs or other analgesics. Owners may notice a firm swelling of the limb as well.

Physical examination will usually reveal lameness. Careful palpation and manipulation of the affected limb should be undertaken to determine the area of interest and detect any subtle swellings or asymmetries between limbs. Although lymph node involvement is uncommon, palpation of the regional lymph node should be undertaken as well. Orthopedic and neurologic examination is reasonable if amputation is to be considered.

Diagnosis, staging, prognosis

At least two radiographic views of the affected area of the limb should be obtained. The classic radiographic appearance of OSA is a mixed lytic and proliferative lesion of the metaphysis of the long bone. OSA will typically not cross a joint space. OSA is most common in the proximal humerus and distal radius of the thoracic limb (away from the elbow), and in the proximal tibia and distal femur of the pelvic limb (toward the knee).

Important differential diagnoses for bony lysis include: (1) Other primary bone tumors (chondrosarcoma, fibrosarcoma, hemangiosarcoma, synovial cell sarcoma); (2) Bone metastasis (most commonly from carcinomas of the lung, mammary gland, or prostate); (3) Bony involvement from systemic neoplasia such as lymphoma or multiple myeloma; (4) Osteomyelitis (fungal or bacterial); (5) Other diseases, such as Legg-Calve-Perthes disease, traumatic osteonecrosis, or aneurysmal bone cyst. It is also important to obtain thoracic radiographs (3 views) at the time of limb radiographs if neoplasia is a differential. Although 90% of dogs with OSA have microscopic metastasis at the time of presentation, only approximately 7% have macroscopic evidence of metastasis at diagnosis.

Following radiographs, a biopsy of the affected area is indicated. This can be obtained by several means, including: (1) Jamshidi bone core biopsy; (2) Michele trephine; or (3) Open, surgical biopsy. Unlike with most soft-tissue tumors, biopsies of bony tumors should be obtained from the center of the radiographic lesion. Biopsies of the periphery of the lesion or the apparent tumor:normal tissue interface will often yield diagnoses of "reactive bone". A fourth method which some clinicians find effective is fine needle aspiration cytology, using either the radiographs or ultrasound as a guide. Approximately 10% of bone biopsies will be nondiagnostic, irrespective of the method used. Some clinicians are comfortable proceeding to definitive surgery without a biopsy if the presentation is "classic" (e.g. correct age, breed, location, radiographic appearance) and there is no history of travel to a fungal-endemic area.

Standard presurgical screening (complete blood count, serum chemistry profile, urinalysis) should be obtained as with any patient that may undergo general anesthesia. One important parameter to evaluate is serum alkaline phosphatase (SAP). High SAP has been shown in humans, and recently in 2 separate papers in dogs, to be a poor prognostic indicator for dogs with appendicular OSA. In the more recent study, dogs treated with amputation and chemotherapy that had normal SAP had a median survival time of 12.5 months whereas dogs with increased SAP had a median survival time of 5.5 months. A second laboratory factor recently shown to correlate with outcome is monocyte count. Dogs with monocyte counts less than 400/uL had disease-free intervals twice as long as those with monocyte counts greater than 400/uL. Dogs with overt monocytosis (>1,000/uL) had extremely poor prognoses.

At CSU, a bone scan (99M-Tc nuclear scintigraphy) is always offered as part of the staging process in dogs with OSA. This noninvasive and nontoxic screening test for bone metastasis will reveal additional sites of uptake in approximately 7% of dogs, half of which may be areas of bone metastasis from OSA.

Two recent retrospective studies from CSU determined the outcome in dogs with OSA presenting with metastasis. The first study compared dogs without metastasis to those with metastasis to the regional lymph node only. Median disease free intervals and survival times were significantly shorter in those dogs presenting with lymph node metastasis (DFI 48 vs 238 days, ST 59 vs 318 days). Thus, although the incidence of lymph node metastasis is only approximately 5%, it is recommended that the lymph nodes be removed separately and submitted for evaluation in dogs undergoing surgical management for OSA. A second study evaluated the outcomes in

dogs presenting initially with distant metastasis. The median survival time was 78 days. Dogs treated with multi-modality therapy fared better than dogs treated with only surgery, and dogs with bone metastasis fared better than dogs with soft-tissue metastasis. These results underscore the importance of complete staging prior to pursuing definitive therapy.

A small percentage of dogs with OSA will present with a pathologic fracture. In humans, it is controversial as to whether this type of presentation adversely affects outcome. A recent retrospective study using the CSU OSA population evaluated whether this presentation impacted outcome. There were no significant differences in disease-free or overall survival between dogs presenting with pathologic fracture and location- and treatment-matched control dogs presenting without fracture.

Surgical treatment

There are two separate issues that must be faced when contemplating therapy for canine OSA. One is the presence of a locally destructive, painful bone lesion, and the other is the very high potential for systemic metastasis. Local disease is best dealt with by amputation of the affected limb. Amputation is a simple surgical procedure that is extremely well tolerated in the majority of patients. However, it has been well established that amputation alone results in only short-term gains. The median survival time with amputation alone is only 4 months, with less than 10% of dogs living for 1 year. Pulmonary metastasis is the eventual cause of death in the majority of patients.

For owners unwilling to perform amputation, other options may be available. Some dogs may be candidates for a limb sparing procedure. In this type of surgery, the tumor margins are sterilized by high-dose radiation or local chemotherapy, the diseased portion of bone is resected, and an allograft from a bone bank or a metal spacer is implanted. The adjacent joint is fused, and then additional postoperative chemotherapy is employed. This procedure is most successful with tumors of the distal radius. Limb sparing surgery is performed at a limited number of institutions, is expensive, and has a high rate of complications, including local recurrence, implant failure, and infection. Despite these factors, the overall outcome in patients treated with limb sparing procedures is similar to those treated with amputation. Interestingly, dogs undergoing a limb sparing procedure and developing a postoperative infection will survive twice as long as those not developing an infection.

Medical therapy

The addition of systemic chemotherapy to amputation significantly prolongs the time from diagnosis to death. For many years, cisplatin was the closest thing to a "standard of care' for dogs with OSA. The addition of cisplatin increases the median survival time to 10-12 months, with approximately 20% of dogs living longer than 2 years. Cisplatin is nephrotoxic and strongly stimulates the emetic response. It must be administered with vigorous intravenous diuresis with sodium chloride to prevent kidney damage, and antiemetics should be administered to prevent vomiting.

Some studies have suggested that carboplatin may also be effective for treating canine OSA. Carboplatin is not nephrotoxic, and usually does not cause gastrointestinal signs. Carboplatin does not require diuresis or antiemetic administration. Both older and more recent retrospective studies suggest that carboplatin and cisplatin have equal efficacy. Carboplatin recently went off-patent and thus the cost of administering a dose of carboplatin at most practices is actually less than administering cisplatin.

Other investigators have evaluated doxorubicin for the adjuvant treatment of OSA. Although 30 mg/m2 doxorubicin given every 3 weeks resulted in poor survival times in one study, the same dose given every 2 weeks for 5 treatments resulted in survival times close to those reported for cisplatin. The largest study conducted to date (300 dogs) reported a median survival time of 8 months in dogs with OSA treated with doxorubicin.

Combinations of platinum drugs and doxorubicin have been evaluated in several studies, either administered at reduced does at the same time or sequentially. The majority of published studies have revealed no significant improvement in outcome when compared with single-agent platinum protocols.

Radiation therapy

"Palliative" radiation therapy

A reasonable palliative option available in most parts of the United States is radiation therapy (RT) to the affected bone. A relatively conservative, inexpensive, and well-tolerated form of RT involving 1 to 4 weekly treatments can provide good to excellent pain control in approximately 75% of dogs with OSA, which persists for a median of 3-4 months. It is not clear whether the addition of chemotherapy or bisphosphonates (see below) to RT improves duration of response or overall survival.

Stereotactic radiosurgery (SRS)

SRS involves the delivery of one or several large doses of RT to an affected body part, using very sophisticated treatment planning and delivery devices to insure avoidance of toxicity to surrounding normal tissues. Currently, CSU, the University of Florida, and The Animal Specialty Center in Yonkers, New York are offering SRS as a limb-sparing option for dogs with OSA. Recent preliminary data suggest that a combination of SRS and chemotherapy may result in outcomes nearly as good as traditional amputation and chemotherapy, with very good preservation of function. Pathologic fracture is a serious complication following SRS in some dogs. The risk of fracture seems to be reduced in dogs with relatively small lesions with minimal lysis.

Other palliative options

A small number of dogs have been treated with Samarium-EDTMP, with a radioactive compound that localizes to bone and can cause local destruction of OSA cells. Approximately 65% of dogs experience improvement in pain, and the median survival time is approximately 100 days.

Recently, a number of studies have evaluated the in vitro and in vivo antitumor and palliative effects of bisphosphonate drugs against canine OSA. Bisphosphonates are thought to exert their analgesic effects against lytic bony diseases through selective inhibition of osteoclast function. However, bisphosphonates are also capable of direct antitumor effects, inhibition of angiogenesis, and immunomodulation. It is not clear if bisphosphonate concentrations capable of these antitumor effects are achievable in canine patients. A recent study evaluated the effects of the bisphosphonate drug pamidronate in dogs with OSA. Approximately 30% of dogs experienced meaningful improvement in pain, which persisted for a median of 7.5 months.

Therapy for metastasis

Following the completion of post-operative chemotherapy, patients are rechecked regularly for evidence of pulmonary metastasis. Unfortunately, chemotherapy is rarely effective after pulmonary metastasis has been detected, and the average survival after the clinical detection of metastatic disease is only 2 months. However, some patients may benefit from surgical removal of the pulmonary metastasis. Certain criteria should be met in order for this type of treatment to be useful: (1) A "reasonable: amount of time from primary tumor diagnosis (>10 months?); (2) A "manageable" number of metastatic lesions (3 or less?); (3) A relatively slow rate of growth. Often, when metastasis is first detected, the patient will be sent home and rechecked 4-6 weeks later to determine how quickly the lesions are changing. If rapid progression is detected, then the utility of metastasectomy is minimal. With proper case selection, the median survival time after metastasectomy is approximately 6 months, and most owners are very satisfied with the outcome. It is unknown whether the use of additional chemotherapy after metastasectomy improves prognosis.

Traditional chemotherapy as described above is rarely efficacious for dogs with measurable pulmonary metastatic disease. A recent study described treatment of a series of dogs with metastatic OSA with the receptor tyrosine kinase inhibitor toceranib (Palladia, Pfizer). Approximately 45% of dogs treated with toceranib experienced disease stabilization, which persisted for a median of 24 weeks.

Axial skeleton osteosarcoma

Although less frequent than long-bone OSA, OSA of the axial skeleton (pelvis, spine, rib, skull) is seen occasionally. It is seen more frequently in slightly older dogs, and is seen more often in small-breed dogs than is appendicular OSA. For the most part, axial OSA has a behavior similar to appendicular OSA. One difference is the fact that it can be more difficult to achieve "complete" surgical excision, and local recurrence is more common. Statistically, more aggressive forms of local treatment (i.e. protocols that include aggressive, "definitive" RT to achieve local control) appear superior to treatment with "palliative" RT. One location that may have less aggressive metastatic behavior is OSA of the maxilla and mandible. Mandibular and maxillary OSA may have metastatic rates closer to 30-40%. Again, in these forms of tumor, the use of aggressive therapy to prevent local recurrence is important if necessitated by incomplete surgical margins.

"Extraskeletal" osteosarcoma

Osteosarcomas arising in soft tissues are seen occasionally, accounting for less than 1% of all canine OSA. These are seen most frequently in the female mammary gland, but have also been reported in subcutaneous tissues, salivary gland, spleen, perianal area, liver, skin, lung, kidney, urinary bladder, mammary gland, muscle, thyroid gland, eye, and mesentery. Median survival times are short, between 25 and 90 days depending on site and study cited. Either local recurrence or metastasis may be the cause of death, and a combination of aggressive local therapy and chemotherapy is indicated. In one study, the addition of chemotherapy significantly improved prognosis in dogs with extraskeletal OSA.

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