Appendix B: Canine Osteosarcoma

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INTRODUCTION AND USE OF CANINE OSTEOSARCOMA AS A MODEL FOR HUMAN OSTEOSARCOMA (Figure B1A)

Osteosarcoma occurs commonly in the dog. It has been estimated that there are 8000 new cases per year in the United States alone. This high frequency makes it an excellent model for human osteosarcoma and it has frequently been used for this purpose.[1,2] Similarities between canine and human osteosarcoma include metaphyseal occurrence, typical metastasis to lungs and other bones, and response to doxorubicin and platinum-based protocols. Canine osteosarcoma appears to be more malignant than human osteosarcoma in that, without treatment, death usually occurs within 4–5 months. This offers another advantage when considering it as a model for the human disease. Research protocols very rapidly demonstrate effectiveness of therapeutic attempts. Researchers can frequently demonstrate effectiveness within 2 years of beginning a therapeutic trial. Because financial incentives can be offered clients, identifying candidates has not been a problem. Necropsy compliance is usually very high. Alternatives for treatment can be attempted relatively easily if a therapeutic protocol can be logically justified based on experimental data in other species.

DEMOGRAPHICS AND PRESENTING CLINICAL SIGNS

Osteosarcoma is the most common malignant bone tumor in dogs. There is a biphasic prevalence age distribution curve for canine osteosarcoma, with peaks at 2 and 7 years. A male predominance has been shown in some studies, whereas others have shown no sex predilection. It most commonly occurs in metaphyseal bone. Commonly affected sites, in order of frequency, include the distal radius, proximal humerus, distal ulna, distal femur, proximal tibia, distal tibia, and diaphyseal ulna. Other affected sites include ribs, skull, vertebral bodies, scapula, metatarsal and metacarpal bones, lung, spleen, and mammary tissue. Primary soft tissue occurrences are rare.[3,4]

Most affected dogs present with lameness resulting from appendicular osteosarcoma. Usually, a painful swelling is identified over the affected region. Dogs with mandibular and orbital sites may present with dysphagia. Dogs with cranial or vertebral tumors will present with neurologic deficits. Dogs with pelvic masses may present with dyschezia. Some dogs will present with a history of acute exacerbation of clinical signs following trauma. This may mislead the clinician into suspecting a fracture or anterior cruciate ligament rupture. Radiographs of the affected region will usually confirm the diagnosis.

DIAGNOSTIC WORKUP (REGIONAL DISEASE)

Regional radiographs, in addition to predisposing factors such as large breed and advanced age, usually confirm the diagnosis of osteosarcoma and show the tumor's extent in commonly affected anatomic sites. Typical lesions are a mixed pattern of cortical lysis and periosteal proliferation. Although a previous study suggested that radiographs underestimate the local extent of the tumor,[5] a recent study showed that high-detail radiographs overestimate the local extent of extent of the tumor. Nuclear scintigraphy also overestimates the local extent of the tumor, and to a greater degree than radiographs. Computed tomography is helpful in delineating skull[6] and thoracic wall tumors.[7] It can also be used for appendicular tumors to determine the extent of resection required to attain complete surgical margins. Determination of tumor volume and tumor length is of prognostic value in dogs with osteosarcoma in that large tumor size is associated with a poorer prognosis.

Biopsy may be performed, although it is usually not necessary to confirm the diagnosis. If performed, a Jamshidi biopsy needle should be used, and two samples taken, including the center and the periphery of the lesion. If this protocol is followed, a diagnostic accuracy of 90% can be achieved.[8] Reactive bone may be identified, and this suggests that more aggressive biopsies are indicated.

DIAGNOSTIC WORKUP (METASTATIC DISEASE)

Approximately 10% of dogs will show gross evidence of distant metastasis at the time of diagnosis. Sixty percent will metastasize to lung and 40% will metastasize to other musculoskeletal sites. Thoracic radiographs, including right and left lateral and anterior/posterior, views are performed. Thoracic radiographs are limited in that they delineate only lesions which are greater than 6 mm in diameter. Computed tomography can also be used to screen for thoracic metastasis, but is not widely used. When available, nuclear scintigraphy is also performed, and will show occult bony metastasis in 10% of cases.

TREATMENT OPTIONS

Cure is achieved in less than 15% of dogs diagnosed with osteosarcoma. Treatment is directed at palliating or eliminating locoregional disease and preventing distant metastasis. Preventing of distant metastasis without eliminating the primary tumor offers no survival advantage. Analgesic therapy alone, using aspirin or piroxicam, has a median survival time of 90 days. It is most effective in dogs with relatively small tumors, in

the absence of pathologic fractures. Most of these dogs are euthanized because of pain and/or pathologic fracture of the affected bone. Palliative radiation therapy has also been attempted with coarsely fractionated radiation therapy (24–28 Gy in three or four dose increments). This does appear to reduce bone pain, but does not significantly improve survival. Patients with small tumors in the absence of pathologic fractures appear to have the best survival. The median survival time is 120 days. Most dogs are euthanized because of intractable pain and/or pathologic fracture.

Amputation offers significant improvement in survival over medical management in dogs with appendicular osteosarcoma.[9] Amputation is well tolerated in almost dogs in which it is performed, including those who are obese and those with neurological deficits. The author has performed approximately 300 amputations in dogs and has had only one, who had degenerative myelopathy, who had difficulty walking after surgery. This dog eventually was fully ambulatory 40 days after surgery. Most other dogs are fully ambulatory within 3 postoperative days. Regardless of the location of appendicular tumor, all amputations are performed using scapulectomy or coxofemoral disarticulation for forelimb and hindlimb lesions, respectively. Amputation by scapulectomy is associated with better function and cosmesis than amputation by scapulohumeral disarticulation or humeral–antebrachial disarticulation, and is technically less challenging. Coxofemoral disarticlation is also associated with better cosmesis and is also technically less challenging than amputation by midfemoral osteotomy or femorotibial disarticulation. Preservation of the extremity in dogs is not beneficial because they do not tolerate prostheses, and they function well without them. In two surveys, function and client satisfaction were very good to excellent in 98% of pets.[10] Dogs having amputation alone for the treatment of appendicular osteosarcoma have a median survival time of 5 months. These dogs usually die of metastasis.

Rib tumors are treated with thoracic wall resection and, when treated with adjuvant chemotherapy, patients have a median survival time of 1 year. Mandibular tumors are treated with hemimandibulectomy; maxillary tumors are treated with partial maxillectomy and/or orbitectomy. Spinal tumors are treated with decompression and rarely have long-term survival. Pelvic tumors are usually treated with amputation and hemipelvectomy, and these patients usually have excellent function.

Limb salvage surgery can be performed in some dogs with appendicular osteosarcoma (Figures B1A,B and B2A,B).[11] Dogs with tumors of the scapula, diaphyseal and distal radius and ulna, metacarpus, metatarsus, diaphyseal humerus, femur and tibia and distal tibia treated with limb salvage surgery are associated with good to excellent function. Allograft implantation is not required for tumors of the scapula, metatarsus, metacarpus or ulna (distal or diaphyseal). Most other diaphyseal tumors and tumors of the distal radius treated with limb-salvage surgery require allograft implantation and are associated with good function. Dogs tolerate removal of up to 90% of the scapula with good function. Dogs with tumors of the proximal humerus treated by scapulohumeral arthrodesis following allograft implantation have poor functional outcome.[12] The median survival time in dogs treated with limb-salvage surgery for appendicular osteosarcoma and chemotherapy is equivalent to those treated with amputation and chemotherapy, and is approximately 1 year. There is a 25% local recurrence rate following limb-salvage surgery, and local recurrence does not appear to negatively affect survival. If local recurrence occurs, a second limb-salvage surgery can be attempted, or amputation can be performed.

Allograft implantation usually requires maintenance of a bone bank. Bones can either be harvested sterily and directly implanted, or harvested cleanly and secondarily sterilized prior to implantation. Transmission of infectious agents from the donor to the recipient has not been a significant problem. Infectious agents are usually introduced during the preparation of the graft, resulting in local infection. Methods for sterilization include steam sterilization, ethylene oxide sterilization and, more recently, low-temperature hydrogen peroxide plasma gas sterilization. Low-temperature hydrogen peroxide plasma gas sterilization does not cause deterioration of biomechanical properties of allograft bone.[13] The author has performed limb-salvage surgery in two dogs using autograft bone which was autoclaved during the surgical procedure, and reimplanted in the tumor bed, with good results. This offers the advantage of no requirement for a bone bank. The allograft is filled with sterile methylmethacrylate prior to implantation. This has been shown to improve the biomechanical properties of the implant without negatively affecting bone incorporation. Limb-salvage surgery, where an allograft is implanted, is associated with a 50% infection rate. Interestingly, dogs who have a culture-positive infection are associated with a significant improvement in survival (median survival time of 600 days, compared with 290 days in dogs not having postoperative infection).

ADJUVANT CHEMOTHERAPY

Chemotherapy significantly improves survival in dogs with appendicular osteosarcoma when locoregional disease is eliminated using surgery. Protocols which have shown significant improvement in survival

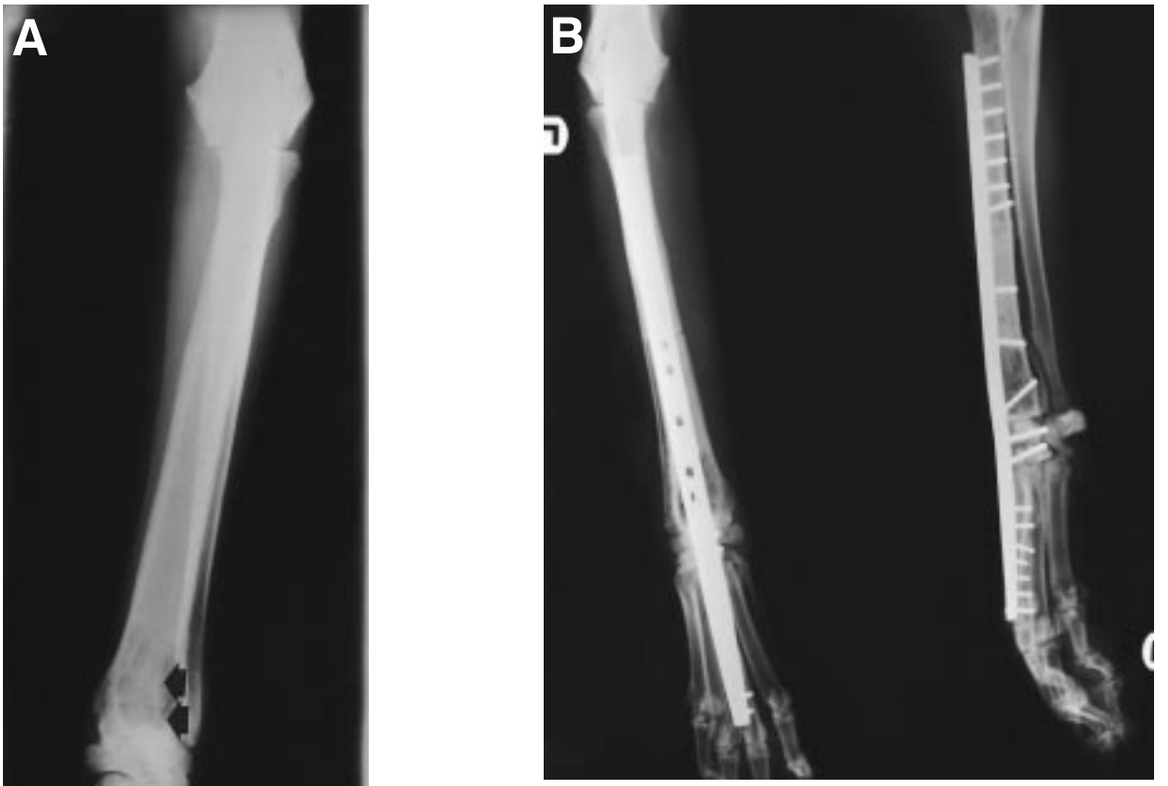

Figure B1 (**A**) Preoperative view of canine osteosarcoma (arrow indicates tumor). (**B**) Postoperative view following limb-sparing surgery.

include doxorubicin,[14] cisplatin,[15,16] carboplatin,[17] and to a lesser extent, loboplatin.[18] The median survival times for the former three is approximately 1 year, and for the latter, 7 months. There has been no advantage to combination chemotherapy demonstrated. Dogs usually are euthanized because of the development of distant metastasis. Chemotherapy is well tolerated in most dogs. Eighty percent of dogs complete the course of chemotherapy without any significant side-effects. Eighteen percent have mild side-effects including bone marrow suppression, and gastrointestinal complications. Two percent have side-effects significant enough to require hospitalization.

Implantable cisplatin chemotherapy has been used to treat dogs with osteosarcoma,[19] with encouraging results. Cisplatin is invested in a polylactic acid polymer which allows gradual release of the cisplatin over approximately 3 weeks. Peak levels, commonly associated with side-effects, are 10–30% of those attained with equivalent intravenous doses, but the area under the serum concentration curve (AUC) is seven to 22 times that attained with intravenous doses. Side-effects are rare but include nephrotoxicity (rare) and infection (common). Infection of the chemotherapy site appears to offer protection against metastasis, similar to that seen with infected limb-salvage allografts. The chemotherapy takes the form of a sponge which is implanted in the amputation stump or limb-salvage tumor bed, or of a gel which is a liquid at room temperature and becomes a solid at body temperature. Implantation of sponges in the limb-salvage tumor bed also reduces the incidence of local recurrence.

PROGNOSIS

Tumor size, calculated as the percentage of bone length affected by tumor, or as an actual tumor volume, has been found to be prognostic in dogs with osteosarcoma. Larger tumors have been found to have a poorer prognosis. Anatomic site is also prognostic in that appendicular osteosarcoma (radius, ulna, humerus,

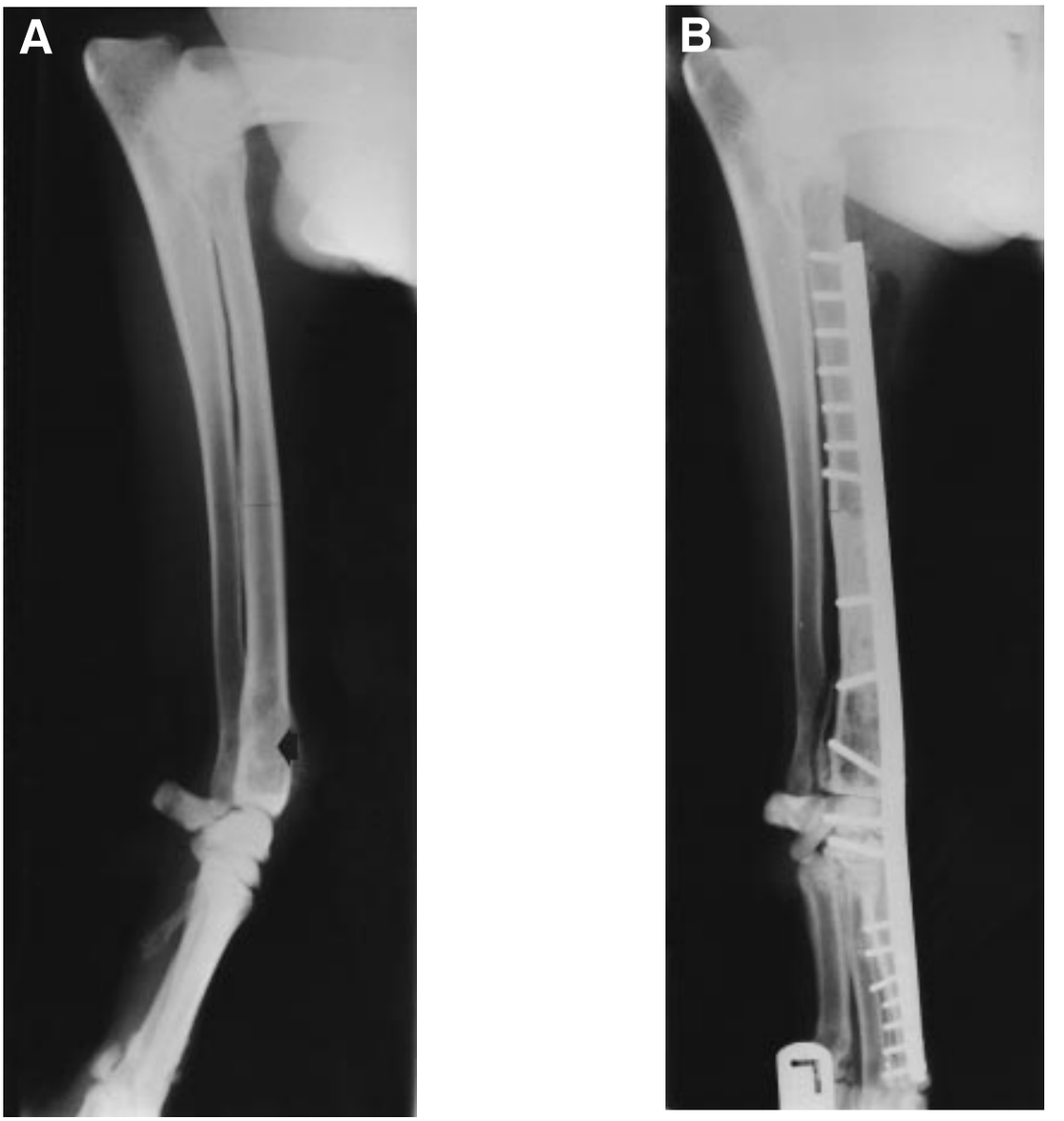

Figure B2 (**A**) Preoperative view showing an osteosarcoma (arrow) of the distal humerus. (**B**) Postoperative view of the same patient.

femur and tibia) is associated with a median survival time of 1 year when treated with aggressive surgery and chemotherapy. Tumors of the mandible and scapula have a slightly better prognosis with a median survival time of about 15–18 months. Tumors of spine and skull have a poorer prognosis because of anatomic limitations on aggressive surgical resection. Extraskeletal osteosarcoma has a dismal prognosis with a median survival time of 73 days.[3,20–25] The bone isoenzyme of alkaline phosphatase has been shown to be prognostic in that high levels before surgery are associated with a poorer prognosis. After the initial decrease following surgery, an increase helps predict impending gross metastasis. Quantification of metalloproteinases two and nine have shown some predictive value, and further studies are under way. Recent studies have suggested that tumor grade, characterized by degree of necrosis, mitotic rate and cell differentiation, is highly prognostic; further study is necessary.[18]

CONCLUSION

Osteosarcoma is a common tumor in the dog. It serves as an excellent model for human osteosarcoma studies. It is malignant, and affected patients usually die of their tumors. Aggressive surgery and chemotherapy have been shown to significantly improve survival.

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