Bone Cancer in Greyhounds

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Primary bone neoplasms are common in dogs. Most primary bone tumors in dogs are malignant, in that they usually cause death as a result of local infiltration (e.g., pathologic fractures or extreme pain leading to euthanasia) or metastasis (e.g., pulmonary metastases in osteosarcoma). Neoplasms that metastasize to the bone are extremely rare in dogs; some malignant tumors that occasionally metastasize to bones are transitional cell carcinoma of the urinary tract, osteosarcoma of the appendicular skeleton, hemangiosarcoma, mammary adenocarcinoma, and prostatic adenocarcinoma.

Osteosarcomas (OSAs) are the most common primary bone neoplasm in dogs and the most common tumor in Greyhounds in the United Kingdom, where it accounted for 50% of all tumors, and for 22% of the deaths in the breed ([www.gurk.demon.co.uk /ghsurvey](http://www.gurk.demon.co.uk/ghsurvey)). Cancer in general (44%), and OSA in particular (22%) were the leading cause of death in the breed. They can affect either the appendicular or axial skeletons, and occur primarily in large (and giant)–breed, middle age–to–older dogs. Preferential locations for OSA include the distal radius, proximal humerus, and distal femur, although they can occur in any bone or location.

Their biologic behavior is characterized by aggressive local infiltration of the surrounding tissues and rapid hematogenous dissemination (usually to the lungs). Although historically it was believed that OSAs of the axial skeleton had a low metastatic potential, it now appears that their metastatic rate is similar to that of the appendicular OSAs.

Clinical Features

Appendicular OSAs occur predominantly in the metaphyses of the proximal humerus, distal radius, and distal femur, ("TOWARDS THE KNEE AND AWAY FROM THE ELBOW"), although other metaphyses can also be affected. They typically affect male dogs; large and giant breed dogs are also commonly affected, and owners seek veterinary care because of lameness or swelling of the affected limb. Physical examination usually reveals a painful swelling in the affected area, with or without soft tissue involvement. The pain and swelling can be acute in onset, leading to the presumptive diagnosis of a non-neoplastic orthopedic problem, and thus considerably delaying diagnosis and definitive therapy for the neoplasm. In contrast with other breeds, where dogs with OSA typically present for bone swelling and/or lameness, in Greyhounds, they frequently present as a spontaneous pathological fracture (1 in 5 tumors present with a spontaneous fracture without prior history of lameness).

Diagnosis

Radiographically, OSAs exhibit a mixed lytic-proliferative pattern in the metaphyseal region of the affected bone. Adjacent periosteal bone formation leads to the development of the so-called Codman's triangle, which is composed of the cortex in the affected area and the periosteal proliferation. OSAs typically do not cross the articular space, but occasionally they can infiltrate adjacent bone (e.g., ulnar lysis resulting from an adjacent radial OSA). Because other primary bone neoplasms and some

osteomyelitis lesions can mimic the radiographic features of OSAs, biopsy specimens of every lytic or lytic-proliferative bone lesion should be obtained before the owners decide on a specific treatment. An exception to this rule is an owner who has already decided that amputation is the initial treatment of choice for that lesion (i.e., the limb is amputated and the lesion is submitted for histopathologic evaluation).

Once a presumptive radiographic diagnosis has been established and if the owners are contemplating treatment, thoracic and/or bone (i.e., skeletal survey) radiographs should be obtained to determine the extent of the disease. We usually obtain three radiographic views of the thorax and do not do a skeletal radiographic survey (or radionuclide bone scan). Only approximately 10% of dogs with OSA initially have radiographically detectable lung lesions; the presence of metastases is a strong negative prognostic factor.

The radiographic diagnosis can be confirmed before surgery (i.e., limb amputation or limb salvage) on the basis of the findings yielded by fine-needle aspiration (FNA) (if there is considerable cortical lysis) of the affected area; this is a simple, painless procedure that rarely requires chemical restraint (i.e.; sedation). OSA cells are usually round or oval, have distinct cytoplasmic borders, have a bright blue, granular cytoplasm, and have excentric nuclei with or without nucleoli.

A preamputation diagnosis can also be made after histopathologic evaluation of core biopsy specimens from the affected areas. To obtain a bone biopsy, a 13- or 11- gauge Jamshidi bone marrow biopsy needle (Monoject) is used under general anesthesia, and a minimum of two (and preferably three) cores of tissue are obtained from both the center of the lesion and the area in between affected and unaffected bone. The diagnostic yield of this procedure is quite high (approximately 70% to 75%). We do not recommend this approach in Greyhounds because we typically do not obtain a diagnostic sample, and because due to the small, fragile bones in the hounds we are more concerned about post-biopsy fractures.
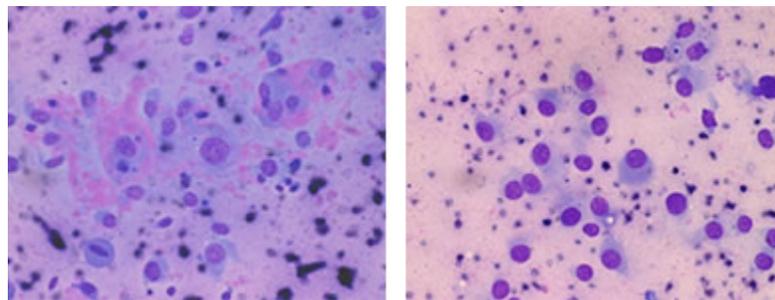
As long as the owners understand the biologic behavior of the neoplasm (i.e., the high likelihood of their dog dying of metastatic lung disease within 4-6 months of amputation if no chemotherapy is used) and as long as the clinical and radiographic features of the lesion are highly suggestive of OSA, the limb can be amputated in the absence of a cytologic or histopathologic diagnosis. However, the amputated leg (or representative samples) should always be submitted for histopathologic studies.

Treatment and Prognosis

The treatment of choice for dogs with OSA is amputation (View "Bosha's" video) with adjuvant single-agent or combination chemotherapy. The median survival time in dogs with appendicular OSA treated with

amputation alone is approximately 4 months, whereas in dogs treated with amputation and carboplatin, or amputation and doxorubicin it is approximately 1 year. As of now, survival and remission times in

Greyhounds do not appear to be any different from those in other breeds. Anesthetic protocol for amputation consist of torbugesic (0.1 mg/kg) and acepromazine (0.5 mg TOTAL) IM as premedication, induce with propofol, and maintain with isoflurane (if needed).One thing to have in mind is that propofol is handled by a liver enzyme (cytochrome P450), and Greyhounds have very little amounts of them; so, if they are on drugs that tie up the enzyme (ie; chloramphenicol) they may sleep for a couple of hours after an induction dose. Post surgery protocol consist of Cefazolin 22mg/Kg IV q8h and FLK in constant rate infusion as follow: Fentanyl 2 to 4mg/Kg/h, Lidocaine 25 to 50µg/Kg/h, Ketamine 5 to 20µg/Kg/h. Amputation in Greyhounds with OSA frequently results in severe postoperative bleeding (24-48h post-surgery) around the surgical site, leading to subcutaneous blood accumulation in the other limbs, ventral thorax, and ventral abdomen; these dogs typically have normal hemostasis profiles (APTT, OSPT), and the severity of bleeding decreases after administration of fresh frozen plasma. Aminocaproic acid (AA - Amicar®) is a commercially available inhibitor of fibrinolysis (procoagulant) commonly used in humans with postoperative bleeding that can be administered IV or by mouth. Administration of AA (500-1,000 mg PO q8h for 5 days starting the day of the surgery) prevented severe postoperative bleeding in Greyhounds undergoing surgery.

A novel surgical approach for dogs with distal radial osteosarcomas consists of sparing the affected limb. Instead of amputation, the affected bone is resected and an allograft from a cadaver is used to replace the neoplastic bone; novel biomaterials are also currently being investigated for this purpose. The dogs are also treated with intravenous carboplatin or doxorubicin and, in general, have almost normal limb function. The main complication is the development of osteomyelitis in the allograft; if that occurs, the limb frequently needs to be amputated. Survival times in dogs treated with limb-sparing procedures are comparable to those in those that undergo amputation plus chemotherapy, with the added benefit to the owners of having a four legged pet.

The dosages and the recommended ways of administering chemotherapy for dogs with OSA are given in Table 1. At our hospital, we use either of the drugs mentioned above immediately after amputation, and for a total of 4 to 5 treatments. The cost of carboplatin chemotherapy is quite high, approximately, $7.50/kg of body weight/dose and in the case of the doxorubicin reaches almost $2/kg of body weight/dose.

We are currently investigating a novel approach to modulation of chemotherapy in Greyhounds with OSA, by administering suramin, a polysulfonated naphthylurea that, at low doses, has been shown to increase sensitivity to doxorubicin in in vitro and laboratory animal models of cancer, by inhibiting binding of fibroblast growth factor (FGF) to its receptors. Preliminary results are encouraging, and the administration of suramin prior to doxorubicin does not appear to potentiate the toxicity of the chemotherapeutic agent.

Limb amputation alone results in typical survival times of 3-4 months. Postoperative adjuvant chemotherapy prolongs survival times to 12-18 months in most dogs. As of now, it appears that survival times in Greyhounds treated by amputation and conventional chemotherapy are somewhat shorter (8-12 months).

If owners are reluctant to allow the veterinarian to amputate the limb, local radiotherapy plus carboplatin may be of some benefit. However, in our limited experience, most dogs are eventually euthanized within 3 to 4 months of the initial diagnosis because of the development of pathological fractures (i.e., after

radiotherapy the tumor is not as painful; therefore the dog regains normal use of the limb and fractures the area), osteomyelitis, or metastatic lesions.

Pain control is essential in dogs where surgery is not an option; we have used either NSAIDs (carprofen, deracoxib, meloxicam) at recommended doses, or bisphosphonates such as alendronate (Fosamax®), at a dose of 10 mg/dog once a day or pamidronate (Aredia®), at a dose of 1 mg/kg, IV as a 30-minute CRI, every 3 to 6 weeks. Drugs such as tramadol (Ultram) at dosages of 1-2 mg/kg, PO, q8-12h may also be beneficial.

Chemotherapy may modify the biologic behavior of the tumor, resulting in a higher prevalence of bone metastases and a lower prevalence of pulmonary metastases. Moreover, the doubling time (i.e., growth rate) of metastatic lesions appears to be longer than that in dogs that have not received chemotherapy, and there appear to be fewer metastatic nodules in treated than in untreated dogs. Therefore, surgical removal of the metastatic nodules (i.e., metastasectomy) followed by additional carboplatin or doxorubicin therapy may be recommended for a dog that has been treated with chemotherapy after amputation of the limb and in which one to three pulmonary metastatic lesions are detected.

Chemotherapy Protocols for Dogs with Osteosarcoma

1. Cisplatin (Platinol®): 50-70 mg/m2, IV drip, q3weeks. Prior intensive diuresis is required.
2. Carboplatin (Paraplatin®): 300 mg/m2, IV, q3-4 weeks
3. Doxorubicin (Adriamycin®): 30 mg/m2, IV, every 2 weeks, for 5 doses
4. Carboplatin (Paraplatin®): 300 mg/m2, IV, on weeks 1 and 6 plus Doxorubicin (Adriamycin®): 30 mg/m2, IV, on weeks 3 and

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