

Bone Cancer in Dogs – What is the State of Practice and New Research?

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In this article, I will briefly review what is bone cancer, how it is diagnosed, options for treatment, expected outcomes, and new information that will help us improve strategies for prevention, control, and treatment of primary osteosarcoma in dogs and children alike.

Introduction

Bone cancer can occur as a primary disease (originates from cells that normally reside in the bone space) or as a metastatic disease (spreads from cancers that arise elsewhere). In humans, most bone malignancies are metastases that arise from tumors outside the bone (breast, prostate). Primary bone tumors are less common, and osteosarcoma (primary bone cancer arising from bone-forming cells) is an orphan disease, meaning that these diseases have such a low prevalence that a general practice physician would not be expected to see more than one case in a year. In dogs, bone cancer also can occur as a primary or metastatic disease, but in contrast to humans, the most common form of bone cancer seen in dogs in the U.S. is osteosarcoma. This is probably due to various factors, including a higher relative risk in large and giant breed dogs to develop the disease over their lifetime (as compared to other dogs, and also to humans), as well as to the low incidence of mammary cancer in female dogs in the U.S. due to the practice of spaying and the relatively low incidence of other carcinomas in dogs that spread to bone in general, such as prostate, lung, colon, and renal cancer as well as of other common cancers of bone such as multiple myeloma. The remainder of this review will focus on the biology and treatment of osteosarcoma.

Osteosarcoma occurs in humans, dogs, and cats. In people, it is predominantly a pediatric disease with peak onset by ~15 years of age. It is infrequent in adults, and incidence increases somewhat with age, with a second smaller peak after age 60. Primary osteosarcoma is a rare tumor, with fewer than 1,000 diagnoses per year. However, because of the demographics of the disease (*i.e.*, the adolescent peak), it is considered an oncologic priority. Osteosarcoma is much more common in dogs than in people (~15 times). An estimated ~10,000 new diagnoses are made yearly, mostly in large and giant breed dogs, and it is seen only rarely in cats.

Osteosarcoma accounts for approximately 85% of bone tumors in dogs. The median age at diagnosis is ~8 years, with a small peak of incidence in young animals (younger than 3 years). Still when the effect of body mass is taken into account, the overall risk for any dog to develop primary osteosarcoma is not magnified with increasing age. Dogs heavier than 90-lb account for almost 1/3 of cases, and most tumors in this group occur in the appendicular skeleton (limbs). Dogs under 30-lb account for less than 5% of cases, and in this group, most osteosarcoma occurs in the axial skeleton. In cats, there is no association with size or breed and the frequency of axial tumors is about the same as skeletal tumors.

In dogs, appendicular osteosarcoma occurs in the metaphysis (at the site of the growth plates), “near the knee and away from the elbow.” Occasionally, osteosarcoma will occur in the digits. Axial osteosarcoma can occur in any bone outside the limbs (skull, ribs, spine). Extraskelatal

tumors are rare; in humans they occur almost exclusively in adults and most often in the skin. In dogs they can arise anywhere, including visceral organs (liver, spleen, heart), eyes, etc.

Etiology and Risk Factors of Osteosarcoma

A major component of this disease in dogs, and possibly in people, appears to be genetic (*i.e.*, heritable). Risk is most accurately defined by body mass, although there is a direct correlation with size as well. In children, osteosarcoma is frequently seen in kindreds with mutations of the retinoblastoma susceptibility gene (RB-1), and this risk is paternally imprinted. In dogs, there are clear breed predispositions. A recent study by Phillips and colleagues published in *Genomics* (Phillips et al., 2007) showed that the narrow heritability in Scottish Deerhounds was 0.69; in other words, almost 70% of the cause is due to heritable traits. Narrow heritability (h^2) is the proportion of the total variability due to genetic factors. It is not surprising heritable factors account for a significant component of risk in Scottish Deerhounds; more than 15% of dogs from this breed die from osteosarcoma. The best-fit model for inheritance of the risk traits in Scottish Deerhounds was a Mendelian major gene with dominant expression. Furthermore, Comstock and colleagues (Comstock et al., 2006) reported at the 2006 Genes Dogs and Cancer meeting (Chicago, IL) there are 4 regions of the genome that appear to be associated with an increased risk of osteosarcoma in Rottweilers, another breed where risk appears greater than what would be attributable to size alone (incidence estimated at more than 12%).

Environmental factors that increase risk for osteosarcoma include rapid growth (therefore “large breed” puppy food has reduced levels of available energy to increase the time needed for these dogs to achieve their full size and mass potential), gender (the risk for males is 20 - 50% greater), and metallic implants to fix fractures. Chronic trauma and microscopic fractures have been proposed as risk factors, but this is difficult to prove conclusively. There was a study from David Waters group (Cooley et al., 2002), where survey data provided by owners showed an increase in risk to develop osteosarcoma in dogs that were spayed or castrated at an early age. The relative risk estimated from this study was as high as 4-fold higher for dogs neutered before one year of age than for intact dogs. Glickman’s group published similar data in 1998 based on analysis of cases in the Veterinary Medical Database (Ru et al., 1998). These studies generated significant debate and concern among veterinarians and owners. Nevertheless, the results have not been reproduced consistently in other large population studies (for example, Phillips et al and Scottish Deerhounds). While these results may have increased some owners’ reluctance to neuter or spay dogs, the *possible* 3-fold increase in risk of osteosarcoma in females should be placed in context of the 80 – 260-fold reduced risk of mammary cancer by early spaying, and the *possible* 4-fold increase in risk in males should be placed in context of behavioral problems, such as territorial aggression, roaming, marking behavior, and physiological problems such as prostatic hyperplasia and testicular cancers that appear more commonly (or exclusively) in intact male dogs.

Natural History of Canine Osteosarcoma

There are three common histologic types of osteosarcoma: *osteoblastic*, where tumor cells produce large amounts of tumor osteoid; *chondroblastic*, where tumor cells produce cartilage (chondroid) in addition to some amount of tumor osteoid (without osteoid the diagnosis is chondrosarcoma); and *fibroblastic*, where tumor cells are predominantly fibroblasts and can produce both collagen and tumor osteoid. The disease is highly metastatic, with distant spread

mostly to lungs and other sites in bone. Osteosarcoma can also metastasize to lymph nodes and intra-abdominal organs. The metastatic pattern is similar for dogs and humans.

Diagnosis of Canine Osteosarcoma

Diagnosis is based on clinical signs, imaging, and biopsy. The clinical signs for appendicular osteosarcoma range from mild lameness with some evidence of pain to pathological fractures. The signs for axial and extraskeletal osteosarcoma are site-dependent. Imaging includes survey radiographs, and may be supplemented by magnetic resonance imaging (MRI) and/or computed tomography (CT) and nuclear scintigraphy. Imaging studies should include the primary tumor site and common sites of metastasis. Radiographic signs of osteosarcoma can range from severe lysis to severely sclerotic (increased density or hardening) lesions with new bone formation. There is usually loss of trabecular (internal) detail and indistinct demarcation of the tumor, associated soft tissue swelling, lysis of the outer boundary (cortex), and exuberant periosteal reactions that form the so-called “Codman’s triangle.” Although this is seen commonly, it is not always present and should not be considered the major determinant to make or rule out a diagnosis. Osteosarcoma rarely crosses joint space, except for an unusual type of necrotizing osteosarcoma of the tibia that is seen in Scottish Terriers and other smaller dogs.

Nuclear scintigraphy is very sensitive, but not specific to identify lesions associated with osteosarcoma, as any region of osteoblastic (bone growth or remodeling) activity will be identified (*i.e.*, arthritis). Nuclear scintigraphy is useful to determine the extent of primary tumor involvement. Fine needle aspiration cytology is commonly used as an adjunct to confirm a radiographic diagnosis. Cytology alone is generally not sufficient to make a definitive diagnosis, but the presence of “flag cells” with eosinophilic material, granular cells, and variable cell size and shape can support the diagnosis. Definitive diagnosis requires a biopsy, which can be obtained through an open incisional biopsy, a trephine biopsy, or a Jamshidi bone marrow biopsy needle. The diagnostic accuracy is almost 100% for open biopsies, ~95% for trephines, and >90% for Jamshidi needle biopsies. Biopsies should be obtained from center of lesion, and if a limb-sparing procedure is elected, the surgeon performing the surgery should perform the biopsy whenever possible.

The pathologist will define the cell type (osteoblastic, chondroblastic, fibroblastic, mixed), grade (pleomorphism, proliferative fraction, etc.), and verify the presence of tumor osteoid, which is diagnostic. Other confirmatory tests can include immunohistochemistry, staining for osteocalcin, osteonectin, and alkaline phosphatase (ALP).

Staging and Prognosis for Canine Osteosarcoma

Staging uses the “TNMG” (tumor, node, metastasis, grade) system. Stage I includes low-grade tumors (G1) without evidence of metastasis; stage II includes high-grade tumors (G2) without metastasis; and stage III includes dogs with metastatic disease. Substages “a” and “b” reflect intramedullary lesions (T1) and local extramedullary spread (T2), respectively. Most dogs with osteosarcoma are diagnosed in Stage IIb.

In children, the site of primary disease is prognostic with tumors in the distal extremity carrying the best prognosis, tumors in the distal femur carrying intermediate prognosis, and tumors in the axial skeleton carrying the worst prognosis. In dogs, tumors of the mandible and scapula carry

the best prognosis with a median survival of ~18 months, appendicular tumors have intermediate prognosis with a median survival of ~11 months, tumors of the spine and skull carry a worse prognosis with a median survival of ~6 months, and extraskkeletal tumors carry the worst prognosis with a median survival of ~2 months.

Tumor size is prognostic (the larger the tumor, the worse the prognosis), as is age (younger dogs do worse). Serum ALP levels also are predictive. Dogs with pre-operative levels of ALP > 110 U/L carry a worse prognosis than dogs with ALP < 110 U/L (levels may be variable depending on lab), and dogs that have elevated serum ALP 40 days after amputation are likely have the worst outcome among all groups of treated dogs.

Treatment of Canine Osteosarcoma

Osteosarcoma in dogs is a treatable, but generally not curable disease. Even now, the decision usually boils down to “leg or life”. Survival times of approximately 1 year (or about 10% of a lifetime) are achievable for 50% of dogs with osteosarcoma treated using the current standard of care (~50% of cases), and some dogs can survive 5 - 6 years after diagnosis. The standard of care is surgery (amputation of limb sparing surgery) with adjuvant chemotherapy. The choice of chemotherapy drugs does not seem to have a great impact on survival, so anticipated toxicity, quality of life, and cost tend to be driving factors. At present, the drug of choice for most cases is carboplatin. Chemotherapy is only recommended when the primary tumor is removed. It is ineffective in cases that are not surgical candidates. It is important to note that this tumor does not respond well to other treatments, and anything other than standard of care should be considered palliative. No herbal or “alternative” treatments, including Artemisin, have shown efficacy in controlled clinical trials.

Surgery is the mainstay for local control. In most cases, it provides immediate pain relief with high level of function. The only contraindication is poor structural soundness (not size). Case selection and an experienced surgeon (and recovery team) are important. Physical therapy and rehabilitation appear to improve quality of life and both patient and owner satisfaction. Complementary therapies like massage also may be beneficial. Complications are more frequent with limb sparing surgeries, where infection is the most common adverse event. Curiously, dogs that get infections at the surgical site and that respond well to antimicrobial therapy have better outcomes than dogs that do not get infections. This has been postulated to be secondary to activation of antitumor immune responses as a bystander effect of the response to the infection.

Radiation therapy provides local control and is palliative. The use of radiation therapy offers no added benefit to overall survival. Generally, there are no side effects and more than 70% of treated dogs show improvement, especially regarding pain. However, dogs that are not treated surgically remain at very high risk to develop pathologic fractures. An approach using Stereotactic RadioSurgery (STS) was recently adapted for use in dogs and is available at various institutions in the U.S. (e.g., University of Florida, Colorado State University, and others). It is too early to determine how this approach will compare to conventional surgery or limb-sparing surgery.

Metastasis is common, and almost inevitable. Treatment can include pulmonary metastasectomy. Metastasis treatment is only recommended if the primary tumor remains in complete remission

and if there are only 1 or 2 nodules detectable in the lungs on three thoracic views. Results from bone scans should be negative. The median survival after pulmonary metastasectomy can be up to 6 months, but without procedure, survival is usually less than 2 months.

Other adjuvant therapies have been tested. Non-specific immunotherapy using an agent called L-muramyl-tripeptide-phosphatidylethanolamine (L-MTP-PE or 3-mifamurtide) as an add-on to amputation + cisplatin showed a median survival of 14 months with 40% of dogs surviving 2 years (Kurzman et al., 1995). This compound is being tested again as a possible addition to the current standard of care, and it recently was shown to improve survival for children with osteosarcoma when combined with standard of care therapy. No other therapies have shown any promise so far, although there are numerous ongoing clinical trials using compounds that activate the immune system (TNF, FasL) or targeted drugs (Rapamycin). An example of one such trial was recently published (Paoloni et al., 2009), and although improvement over the standard of care was marginal, it documents the infrastructure available to investigate new approaches for this disease.

The Future of Prevention, Diagnosis and Therapy

Ongoing work supported by the AKC Canine Health Foundation, the National Institutes of Health, and other agencies is rapidly unraveling risk factors, causality, and potential new targets for therapy of bone cancer. Reports from two groups (Gavin et al from Minnesota (Gavin et al., 2009) and Duval et al from Colorado (Duval et al., 2009)) at the 5th Genes Dogs and Cancer Meeting in 2009 (Orlando, FL) showed gene-based signatures that could distinguish dogs based on response to therapy or overall survival outcomes. Further refinement of this work could lead to predictive tests that would allow owners to make educated decisions regarding treatment, based on the probability that their dog had a tumor that was likely to respond (or not) to conventional surgery plus adjuvant chemotherapy. The data from Gavin are complementary to published results by Thomas et al (Thomas et al., 2009) showing that a dog's genetic background (breed) influences not only risk of developing a tumor, but also tumor behavior. Innovative approaches using gene-based immunotherapy and targeted therapies also show promise to improve outcome for this disease. And finally, recently published as well as soon-to-be-published work from a long-term collaboration between our group and the Breen group, as well as others (Selvarajah et al., 2009) show remarkable similarity in canine and human osteosarcomas at the molecular level. These data will further validate the opportunities to develop new treatments that will simultaneously improve the health and wellbeing of our dogs and our kids.

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