Care Beyond a Cure:  
Extraordinary Advances in Cancer Care 2014

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Dr. Ogilvie is director of the Angel Care Cancer Center at California Veterinary Specialists as well as Professor and Division Director of Veterinary Oncology, Department of Radiation Medicine and Applied Sciences, University of California-San Diego, Moores Cancer Center. Prior to his move to Southern California, Greg was a full tenured professor, internist, and head of medical oncology and director of the Medical Oncology Research Laboratory, Animal Cancer Center at Colorado State University from 1987 until 2003. During this 16 year period at CSU, Greg also spent one year on sabbatical teaching and developing new, innovative cancer therapies at the medical school and the Laboratoire Nutrition, Croissance et Cancer at the Université François Rabelais in Tours France. Dr. Ogilvie received his DVM from Colorado State University and was in private practice in Connecticut before completing a residency at Tufts University/Angell Memorial Animal Hospital. From there he joined the faculty as a professor at the University of Illinois before moving on to his professorship in Colorado. Dr. Ogilvie is board certified in both the specialties of both internal medicine and oncology by the American College of Veterinary Internal Medicine and in oncology and is a Diplomate of the European College of Veterinary Internal Medicine-Companion Animals, Specialty of Oncology. He is co author with Dr. Antony Moore of three books, Managing the Veterinary Cancer Patient, Feline Oncology: Compassionate Care for Cats with Cancer and the book, Managing the Canine Cancer Patient: A Practical Guide to Compassionate Care. His newest book will be published in 2013. He is author of over 200 scientific articles and chapters, as well as over 120 scientific abstracts and posters. He has been awarded two international patents, over 10 million dollars in research grants and endowments as a principal or co-investigator, and is the recipient of many research awards. Greg has also been recognized with: the American Veterinary Medical Association's "Veterinarian of the Year"; the American Animal Hospital Association's "Veterinarian of the Year"; the Colorado Veterinary Medical Association Outstanding Faculty Award; and the World Small Animal Veterinary Association Hills Award for Excellence in Veterinary Healthcare. When not caring for pets and people, Greg is a certified ski instructor and enjoys camping, SCUBA and long distance cycling. He has volunteered as a counselor at the Sky High Hope Camp for children who have cancer for 15 years. Greg’s greatest joys are his daughter, Torrie and his wife, Karla.
CARE BEYOND CURE:
TEN OF THE MOST IMPORTANT ADVANCES IN CANCER THERAPY
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Cancer Prevention
Family veterinarians throughout California are incorporating cancer prevention and screening programs. The identification and management of risk factors for preventing cancer such as breed selection and modification of environmental factors that are known to cause cancer is vital to reduce cancer in the pet population.

#1: Lifetime weight management is associated with decreased risk of developing cancer and other diseases such as diabetes mellitus and osteoarthritis (J Am Vet Med Assoc 220;1315-1320, 2002). Supplementation with eicosapentaenoic and docosahexaenoic acid may reduce the risk of cancer.

#2: It is important to eliminate exposure to environmental carcinogens such as pesticides, coal or kerosene heaters, herbicides such as 2,4-dichlorophenoxyacetic acid, passive tobacco smoke, asbestos, radiation, and strong electromagnetic field exposure. These steps may be particularly important for clients of susceptible breeds (e.g., a Scottish terrier and herbicide exposure, Environ Res 32(2):305-313, 1983).

Commandments
Perhaps the greatest barrier to enhanced cure and control of cancer is that the caregiver and the veterinary health care team often have preconceived notions about cancer and its treatment. There are three commandments of cancer care that must be dealt with for patient and client comfort. They are:

• Do not let them hurt. Providing an active, preemptive, and ongoing pain management/prevention program for the dog with cancer is absolutely imperative. This reassures the caregiver that quality of life is optimal.

• Do not let them vomit or have diarrhea. Dispensing oral medication such as metoclopramide or more recently, the novel NK-1 receptor antagonist, maropitant (Cerenia) to the caregiver each and every time a potentially nauseating drug is administered, empowers the caregiver to prevent and treat this symptom at home. Tylosin, metronidazol and imodium

can reduce the risk of small and large bowel diarrhea and often dispense these drugs to their cancer patients to prevent problems.

• **Do not let them starve.** Nursing care (e.g., warming food, providing aromatic foods and comfortable environments), medicinal appetite stimulants such as cyproheptadine megesterol acetate and mirtazapine, and, when needed, assisted feeding techniques such as esophagostomy, tube placement should be employed when needed.

  #3: *Maropitant citrate (Cerenia)* is a novel, effective NK1 receptor antagonist that is approved for the treatment of vomiting in the dog and is available as an injectable and oral product.

**Recent Advances in Cancer Care: Something New, Something Old**

California Veterinarians are entering an amazing new era of veterinary cancer care where molecular therapeutics are being approved for and released to the profession to control and cure cancer. The number of new treatments is expected to increase the ability to conquer this horrible disease while maintaining and improving quality of life. While the new molecular therapeutics are exciting, so are the new uses of old drugs to treat, control and cure cancer.

  #4: *The Merial xenogeneic DNA vaccine for the treatment of oral malignant melanoma is an effective therapy that is at the forefront of a new wave of molecular therapeutics (Clin Cancer Res 9(4):1284-1290, 2003).*

  #5: *Doxorubicin is the most effective agent for the treatment of lymphoma and it has efficacy for the treatment of hemangiosarcoma, soft tissue sarcomas and osteosarcoma.*

  #6: *CCNU is effective for the treatment of lymphoma, histiocytic sarcoma, mycosis fungoides, and mast cell tumors.*

  #7: *Piroxicam +/- Mitoxantrone (Clin Cancer Res. 2003 Feb;9(2):906-11) has been shown to be very effective for the treatment of transitional cell carcinoma and squamous cell carcinoma in the dog. Prevocox also appears to have anticancer effects against transitional cell carcinoma in dogs (VCS Proceedings, 2007).*

  #8: *Vinorelbine is a promising novel agent for the treatment of pulmonary tumors in dog and cats (J Vet Intern Med 18(4):536-9, 2004).*

  #9: *Vinblastine is a relatively safe and effective therapy for mast cell tumors in the dog.*

**Compassion Fatigue**

When we care for our patients with compassionate care, we must do so by expressing empathy. The act of extending empathy as we care for our patients and their clients can lead to compassion fatigue. When any member of the veterinary health care team finds themselves giving more without allowing themselves to be replenished emotionally, it is only a matter of time before there will be a shortage of compassion. Simply put, compassionate fatigue results when there is a depletion of emotional resources from within as we care and provide compassion for others.

  #10: Recognizing and treating compassion fatigue is essential to enhance professional, personal and financial success.

**References Available Upon Request**
CLINICAL BRIEFING:

**Anal Sac Adenocarcinoma**

**Clinical Factors**
- Tumors cause dyschezia, perianal mass, and polyuria and polydipsia due to hypercalcemia
- Older dogs
- Production of PTH-like hormone causes hypercalcemia

**Staging and Diagnosis**
- MDB and Metastasis to regional lymph nodes is common and occurs early

**Prognostic Factors**
- Dogs with tumor size >10cm² have shorter survival times
- Dogs with detectable lung metastases have shorter survival times
- Dogs with hypercalcemia have shorter survival times

**Treatment**

**Initial** Surgery usually resolves hypercalcemia.
- Consider excision of sublumbar lymph nodes in addition to local excision of tumor

**Adjunctive** Radiation therapy to regional nodes may delay metastases
- Chemotherapy with platinum derivatives, doxorubicin, mitoxantrone Palladia may be active
- Best treatment combination of surgery, radiation and chemotherapy; median survival 26 months.

**Supportive** Treatment of hypercalcemia prior to surgery.
- Pain medication after surgery, nutritional support as needed
- Stool softeners if obstructed
ADENOCARCINOMA OF THE ANAL SAC
Incidence, Signalment, and Etiology

Early studies showed that anal sac adenocarcinoma occurs most commonly in old, female dogs, either intact or neutered (1-5). Two larger studies have questioned that assumption, and a combined series of 351 dogs had no gender predilection, although neutered dogs of both sexes had a higher incidence (1,2). The age of affected dogs ranges from 5 to 17 years, with an average age of 10.5 years. In most reports, there is no obvious breed predilection and crossbred and purebred dogs are affected equally. However, one European study reported that five of eight affected dogs were long-haired or wire-haired German shorthair pointers, and a study from the United States showed that English cocker spaniels, dachshunds, and Alaskan malamutes were all more than four times as likely as the general population to develop these tumors.(2)

A characteristic feature of this tumor is production of a parathyroid hormone-related protein that causes hypercalcemia and hypophosphatemia, occurring in 25% to 30% of affected dogs.(1,2)

KEY POINT:
If hypercalcemia is detected on routine blood chemistry, palpation of the anal sacs for the presence of a tumor should be performed.

Rarely, SCC may arise from the lining of the anal sac. In a series of five dogs, these tumors infiltrated surrounding tissue but were not associated with hypercalcemia or metastasis. (10)

Clinical Presentation and History

Affected dogs are often presented because of an unrelated problem, because the owner notices a swelling in the perineum, or because of dyschezia, tenesmus, or ribbon-like stools. (1-5)
Tenesmus may be due to the primary tumor or to sublumbar lymphadenopathy, which may be palpable rectally. In one study, 30% of dogs had a history of licking or biting at the perineum. (6) Other signs were perianal bleeding (24% of dogs), polyuria and polydipsia (22%), scooting (21%), and hindlimb weakness (18%). Polydipsia and polyuria are common in hypercalcemic dogs. The identification of hypercalcemia on a biochemical profile warrants careful palpation of the anal sacs. (1) Signs may be present for up to 1 year before presentation. In 40% to 60% of dogs in a reported series, the tumor was an incidental finding on rectal examination. (5-7) or was found only after hypercalcemia had been identified. (5) This emphasizes the importance of including a rectal palpation in routine physical examinations. The tumor mass is usually between 1 and 10 cm in diameter, although smaller primary masses that are difficult to palpate may be present. (5-7) In one study, the product of tumor diameters was >10 cm² in 43% of affected dogs. (7) Because the tumor may be bilateral, it is important to palpate both anal sacs. (3-8)

Staging and Diagnosis

If anal sac adenocarcinoma is suspected in a dog, routine blood chemistries should be performed to identify hypercalcemia and any secondary renal damage. Abdominal radiography or (preferably) ultrasonography should be performed to look for metastatic disease before taking thoracic radiographs, as pulmonary metastases are uncommon.

Hypercalcemia is common in dogs with apocrine gland adenocarcinoma of the anal sacs and
may occur in males and females. In one small study, 90% of dogs with anal sac adenocarcinoma had elevated serum calcium levels (average: 16.1 mg/dL). (5) In two larger studies, serum calcium was elevated in 25% of affected dogs. (3,7) Hypophosphatemia occurred concurrently with hypercalcemia in some dogs. If hypercalcemia is prolonged, calcium nephropathy may occur, terminating in renal failure. (11) Prompt treatment of hypercalcemic dogs is important (see below).

This neoplasm is highly malignant and will infiltrate the surrounding perirectal soft tissues and even the rectal sphincter. Metastasis to the sublumbar and iliac lymph nodes occurs early in the course of the disease. Other affected regional lymph nodes are the inguinal nodes and the popliteal nodes. All external nodes should be carefully palpated and fine-needle aspiration for cytology or biopsy for histopathology performed. In two studies, 94% of dogs had metastases to regional lymph nodes. (5, 8) However, a larger study found that less than half the dogs (47%) had enlarged lymph nodes at the time of diagnosis; this may reflect earlier diagnosis. (7) Lateral abdominal radiographs are useful in identifying sublumbar lymphadenopathy, but ultrasonography is more accurate than radiographs or digital rectal palpation in disclosing the extent of lymph node involvement. (12)

Less frequent sites of metastasis are the lungs, which may show a nodular or diffuse pattern radiographically, and (rarely) the lumbar vertebrae, spleen, liver, and kidneys. (3,6,10) Metastasis may occur when the primary tumor is very small, and clinical signs relating to the primary tumor may not be obvious. (1) Definitive diagnosis is made by surgical biopsy, although a high index of suspicion for this disease should follow detection of a perianal mass in an older dog with hypercalcemia.

Prognostic Factors

A large study of 113 dogs found that dogs with tumors of area >10 cm² (product of two greatest diameters) had a shorter median survival than dogs with smaller tumors: 8 months and 19 months, respectively. This and another study (3) found that dogs with hypercalcemia had a shorter median survival than dogs with normocalcemia: 9.6 months and 19 months, respectively. In the larger study, dogs with pulmonary metastases detected at surgery predictably had shorter median survival times (7 months) than dogs without metastases (18 months). However, the finding of iliac lymphadenopathy did not affect prognosis.

Treatment

Dogs with anal sac adenocarcinomas should be treated surgically in an attempt to achieve complete excision of the primary mass. Sublumbar lymph nodes should be removed if they are enlarged. Radiation therapy to the sublumbar (iliac) lymph nodes and chemotherapy using doxorubicin and/or platinum derivatives should be used adjunctively. If hypercalcemia is detected, treatment before and during surgery is important to ensure adequate hydration and urinary output. Sodium chloride is a good fluid of choice because it causes calciuresis. Bisphosphonates such as pamidronate (1-2 mg/kg given IV over 1–4 h) can be very helpful at reducing calcium. Furosemide and glucocorticoids may also be used for the well-hydrated patient as soon as a histologic or cytologic diagnosis has been made.

In one study of 113 dogs that received multiple treatment modalities either alone or in combination, dogs that had surgery as part of their treatment (alone or in combination with radiation therapy and/or chemotherapy) lived longer than dogs treated without surgery. (7) This retrospective study was limited by some selection bias (i.e., dogs in different treatment groups
were prescribed different treatments based on their extent of disease). Dogs treated with surgery alone had 90% survival at 6 months, 65% survival at 1 year, and 29% survival at 2 years. Median survival for 81 dogs treated with surgery, either alone or in combination with any other modality, was 18 months compared with 13 months for dogs treated without surgery. Similar survival times have been reported in other, smaller studies. (3,7)

Surgical excision of the primary tumor is often difficult because of the large size of these tumors and their invasive growth characteristics. Local recurrence is seen in approximately 25% of dogs. 168, 169 However, even with incomplete surgical excision, most dogs that are hypercalcemic become normocalcemic after surgery. Hypercalcemia presumably reflects some critical tumor mass because even dogs with metastases may not show recurrence of hypercalcemia until those metastases become large. (8,13) Complications of surgery reflect the difficulties encountered in any surgical procedure involving the perineal area. Fecal incontinence can follow surgery in up to 20% of dogs and may be permanent. 168 Wound infection can occur and cause dehiscence and sepsis.

**KEY POINT:**

Even with incomplete tumor excision, most dogs that are hypercalcemic become normocalcemic.

If the sublumbar nodes are enlarged at diagnosis, it may be possible to remove them surgically; however, tumor-invaded nodes are frequently friable and invade around the vessels and nerves in this area. The nodes were well encapsulated in 80% of dogs treated surgically in one study, but they were also well vascularized; thus, the surgeon should be prepared to encounter bleeding. In this study, complications during lymph node surgery caused the death of one-third of the dogs; almost one-third of the survivors developed transient urinary incontinence, presumably as a result of neurologic trauma. Overall, six of 27 dogs died within 2 weeks after undergoing surgery for removal of either the primary tumor or its metastases. (3)

At presentation, most affected dogs have metastases only in regional lymph nodes, and further spread is rare. For this reason, radiation therapy might be expected to be palliative. In a large study, 10 dogs that received radiation alone had a median survival time of 22 months, but these dogs may have been selected based on more localized disease. (7) The median survival for 27 dogs that received radiation therapy alone or in combination with either surgery and/or chemotherapy was 26 months. Clearly, radiotherapy may be worth adding into a multimodal approach to therapy. Of 27 dogs receiving radiation therapy as part of their treatment, the only significant side effect was rectal stricture in four dogs (15%); most of these dogs received multimodal treatment. (7) In a further study, radiation therapy and mitoxantrone chemotherapy gave symptomatic relief and tumor control for nearly 10 months to dogs that had only local disease or lymph node metastases. Survival times were considerably longer. None of the dogs in this study had distant (lung) metastases, and most of the improvement in survival was probably attributable to radiation therapy. (9)

Chemotherapy might be promising as adjuvant therapy, but relatively few data have been reported. A large retrospective study found that dogs with iliac lymphadenopathy were significantly more likely to receive chemotherapy. Dogs treated with surgery plus chemotherapy (most received a platinum agent, doxorubicin, or mitoxantrone) had 86% survival at 6 months, 69% at 1 year, 36% at 2 years, and 14% at 3 years (median 18 months). This slightly longer survival in dogs with more extensive disease suggests that chemotherapy can have value as an adjunct. Dogs that received chemotherapy alone (usually because tumors were too extensive to
approach surgically) had 67% survival at 6 months, with median survival of 7 months.(7) Gastrointestinal toxicity was greatest in the group of dogs receiving surgery, radiation therapy, and chemotherapy. Another, smaller study showed that approximately one-third of dogs receiving platinum chemotherapy experienced a greater than 50% decrease in tumor size.(15) Other information is anecdotal; three dogs treated with doxorubicin and cyclophosphamide, either alone or in combination with prednisone, vincristine, and L-asparaginase (for concurrent lymphoma), had survival times of 1, 2, and 14 months.(3) Another tumor did not respond to treatment with melphalan and cyclophosphamide.(4)

Supportive and Palliative care

Often, the reason for euthanasia of a dog with anal sac carcinoma is obstruction due to lymph node metastases that can be very large. One option is palliative radiation therapy to reduce the size of lymph nodes. Late effects of fibrosis and colonic or urethral stricture are high with this form of treatment, although survival will probably be shorter than the time it would take to see such effects. Palliative omentalization of a cystic lymph node prevented signs of pelvic obstruction from recurring in a dog for 18 months.(13) Palliative treatment of hypercalcemia may control clinical signs and delay renal damage in a dog that cannot be treated surgically (such as with massive lymph node metastases). Drugs that interfere with osteoclast activity (pamidronate, etidronate [10 mg/kg PO daily]) or prednisone) may provide long-term control of serum calcium, although as the tumor enlarges and hypercalcemia becomes refractory to control, dosages should be increased.(13).

References


EXTRAORDINARY ADVANCES IN OSTEOSARCOMA THERAPY

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Osteosarcoma
Incidence, Signalment, and Etiology

Osteosarcoma of the limbs is more common in dogs than in any other species and accounts for more than 80% of malignant bone tumors in dogs. These tumors are believed to arise from the medullary cavity, usually at a metaphysis, and expand outward, destroying cortex and disrupting periosteum.

Large- to giant-breed dogs with a body weight of more than 20 kg are most often affected. Compared with dogs that weigh less than 10 kg, giant-breed dogs (>35 kg) are 60 times more likely and large-breed dogs (20 to 35 kg) are eight times more likely to develop osteosarcoma. A case control study of more than 3,000 dogs with osteosarcoma confirmed that the risk of osteosarcoma rose with increasing age, increasing weight, and increasing height. The effect of weight was greatest on increasing risk of forelimb osteosarcomas. Dogs weighing more than 45 kg had 16 and eight times the risk of developing forelimb and hindlimb tumors, respectively, than dogs weighing less than 23 kg. The effect of height was similar; dogs that were taller than 54 cm had approximately 25 times the risk of developing forelimb osteosarcoma and 9 times the risk of hindlimb osteosarcoma than dogs that were shorter than 35.5 cm.

Osteosarcoma was shown to be hereditary in a family of Saint Bernard dogs, and another study found that Irish wolfhounds, Saint Bernards, and great Danes had the highest breed risks (21, 12, and 5 times the average risk, respectively). The Scottish deerhound appears to have an autosomal recessive mode of inheritance of susceptibility to this tumor. Rapid early growth and increase in stress on weightbearing limbs has been hypothesized to lead to multiple minor trauma to the predilection sites. However, one study failed to find histologic evidence of such trauma.

Dogs with osteosarcoma have a median age of 8 years (range: 8 months–13 years), although giant-breed dogs are affected at a younger age. One study found that risk rose with age, then plateaued at the age of 10 years. There is no sex predilection; however, neutered dogs of both sexes appear to be at twice the risk of intact dogs. This association of increased risk for

neutered dogs was most noticeable in rottweilers, particularly those neutered before the age of 1 year.9

Osteosarcoma has been associated with sites of healed fractures or internal-fixation devices, implying that chronic irritation may play a role in tumor development. A specific and strong example of this association has been seen with the Jonas pin.10 A number of case reports, including some of osteosarcoma formation after total hip arthroplasty, have appeared in the veterinary literature.11-13 The association with other internal fixation devices is controversial, as one study found that there was actually a reduced risk of developing osteosarcoma after internal fracture fixation compared with external fixation.14 Most veterinarians agree that if there is a risk, it is low and is possibly outweighed by the benefit of internal fixation of a fracture. In contrast, there is no controversy over the finding that osteosarcoma may occur in sites that are irradiated for treatment of other tumors. These tumors occur in less than 5% of dogs between 1.5 and 5 years after irradiation. High single-dose radiation (i.e., coarse fractionation) in one study increased the risk of tumor formation.15

Mutations in the \( p53 \) tumor suppressor gene result in high levels of the abnormal gene product that can be detected on immunohistochemistry. Inactivation of normal function results in cellular progression to the malignant state.16 Overexpression of \( p53 \) is seen in 70% to 80% of appendicular osteosarcomas, 40% to 55% of axial osteosarcomas, and 20% of multilobular osteochondrosarcomas (MLO) of bone.17,18 This overexpression is thought by some to be a result of germline mutations and may explain the breed-related increase in incidence of osteosarcoma. Overexpression of mutated \( p53 \) is higher in high-grade tumors and may correlate with more aggressive clinical behavior.18

Clinical Presentation and History

Osteosarcoma most commonly affects the appendicular skeleton. Osteosarcomas arise in the long-bone metaphyses of limbs that receive the greatest load associated with daily activity. The most common sites are the distal radius and the proximal humerus (“away from the elbow”). Less common sites are the proximal tibia and distal femur (“toward the knee”).6,7 Lameness is often intermittent early in the course of the disease and may be exacerbated by or associated with a traumatic event. Lameness then becomes chronic, and the limb can no longer bear weight. The early fluctuating course is believed to be partly due to subperiosteal bleeding and microfractures of the weakened cortex. Initially, there may be no clinically apparent lesion on palpation, and radiographs of the limb may show only subtle radiographic changes. As the disease progresses, swelling and lameness may rapidly worsen and the lesion may become painful to the touch. If the tumor is untreated, progressive erosion of the cortex may cause pathologic fracture of the affected limb. The duration of clinical signs may be very short and often ranges from 1 to 3 months.

In small dogs (<15 kg) in one study, about 25% of bone tumors were metastases, and only 46% of tumors were osteosarcomas.19 Osteosarcomas frequently affected the axial skeleton (50%). In dogs with appendicular osteosarcomas, the femur was most commonly affected; the distal radius was affected in only 12%. Appendicular osteosarcomas in small dogs still appear to have a high metastatic rate.19

Staging and Diagnosis

Suspected primary bone tumors should be imaged on high-detail radiographs. Routine blood work, urinalysis, and thoracic radiographs should also be part of a minimum database (MDB) in
these dogs. Primary bone tumors may have a lytic, productive, or mixed appearance on high-detail radiographs. The signs most suggestive of neoplasia include cortical bone lysis in a lesion that does not cross a joint. Classically, tumor extension and mineralization form periosteal spicules in the surrounding soft tissues, imparting a “sunburst” appearance on radiographs.

Tumor margins are important if limb salvage, rather than amputation, is contemplated. Bony lysis is not radiographically apparent until more than 50% of mineral has been removed; therefore, the margins or extent of neoplastic disease in osteosarcoma may be difficult to define on radiographs. Computed tomography (CT) or magnetic resonance imaging (MRI) scans may be more accurate than radiographs, but this is controversial. Bone scintigraphy overestimates tumor margins by delineating tumor plus surrounding reactive bone and may detect other lesions in bone and soft tissue sites. In a group of 66 dogs with appendicular osteosarcoma that underwent technetium scintigraphy, none manifested other bony lesions. However, in 7.8% of 399 dogs, scintigraphy detected suspicious lesions that also appeared on radiographs. It was unclear how many of these dogs also had pulmonary metastases and whether scintigraphy improves the staging procedure. The difficulties in performing scans in private practice, combined with the relatively low yield, mean that routine use of scintigraphy is probably not warranted.

Based on studies of survival following amputation, the metastatic rate for appendicular osteosarcomas is 98%, and the most commonly detected site of metastases is the lungs. Although pulmonary metastases are rarely detectable at the time of diagnosis, thoracic radiographs still should be taken because the finding of measurable metastases profoundly negatively influences the effectiveness of adjuvant therapy and, hence, survival time. Right and left lateral views and a dorsoventral view should be obtained to improve the likelihood of detection. Dogs with clinically detectable pulmonary metastases rarely respond to treatment. Some investigators have suggested that CT scanning of the lungs might improve the detection of pulmonary metastases that are just below the detection level of radiographs. Identifying dogs that have metastatic disease with CT may result in enhanced patient comfort by directing the care towards palliative procedures such as pain control rather than using chemotherapy with curative intent. Regional lymphadenopathy from tumor metastasis is observed in less than 3% of dogs at the time of presentation, which approximates the incidence of pulmonary metastases.

Fine-needle aspiration cytology may be suggestive of an osteosarcoma, but more than 50% of dogs will have a nondiagnostic sample. Ultrasound-guided aspirates may increase the percentage of diagnostic samples; however, histopathology is still preferred for definitive diagnosis. For older animals with a large lytic metaphyseal bone lesion, osteosarcoma is the most common diagnosis. Differentials include other neoplastic conditions and fungal and bacterial infections. A preoperative biopsy is recommended with a confirmatory biopsy at the time of amputation. However, if the dog’s age, breed, and weight and the tumor’s metaphyseal location and radiographic appearance are strongly suggestive of osteosarcoma, an excisional biopsy taken at the time of amputation is not only diagnostic but also therapeutic. Unlike soft tissue tumors, diagnostic biopsy samples of bone tumors are best obtained from the center of the lesion. Multiple biopsy specimens increase the chance of diagnosis. A Jamshidi bone marrow biopsy needle is an excellent instrument for this purpose.

Osteosarcoma frequently includes areas of cartilage and fibrous tissue as well as osteoid and is often surrounded by new bone. For these reasons, a histopathologic diagnosis of chondrosarcoma, fibrosarcoma, or reactive bone should be considered suspect, and further
samples obtained at amputation or limb-sparing surgery should be submitted for histopathologic examination. Tumor histologic grade has been identified as an important prognostic factor for dogs with appendicular osteosarcoma, and the ability to assign such a grade is a benefit of preoperative biopsy. Tumors that invade vessels or lymphatics are classified as grade 3. Grade 3 tumors are also characterized by high number of mitoses, increased cellular pleomorphism, small amounts of tumor matrix, and more than 50% necrosis in the tumor biopsy. These tumors account for more than 75% of osteosarcomas in dogs and have a worse prognosis. Histologic subtypes of osteosarcomas have been described, depending on the proportion of other tissues in addition to osteoid-producing cells. For example, a chondroblastic osteosarcoma may have a high proportion of tumor cells producing cartilage matrix in addition to osteoid. Telangiectatic osteosarcomas have a high proportion of blood vessels and cavernous blood-filled spaces and may be confused with hemangiosarcoma of bone. These subtypes appear to have little clinical significance, although one study found some differences in p53 expression among them.

Prognostic Factors

Prognostic factors that do not influence survival after amputation are gender, tumor site (i.e., distal or proximal; forelimb or hindlimb), and whether a presurgical biopsy was performed. Recent studies have shown that the level of serum total alkaline phosphatase (T-ALP) is highly prognostic for dogs undergoing amputation and chemotherapy; dogs with a T-ALP greater than the upper limit of normal have a worse prognosis than dogs with a normal level, regardless of the chemotherapy used. In one study, dogs with normal T-ALP that were treated with cisplatin and doxorubicin had a median survival of 12.5 months, while dogs that had an elevated T-ALP and were treated with the same protocol had a median survival of 5.5 months. In a further study, 293 dogs treated with doxorubicin alone also lived longer if they had a normal T-ALP. Because T-ALP activity consists of isoenzymes derived from liver and steroid as well as bone, some investigators have investigated the prognostic significance of bone alkaline phosphatase (B-ALP). Measuring B-ALP may further predict dogs that are unlikely to respond to chemotherapy, allowing caregivers to choose more aggressive treatments or palliative options.

The other very important prognostic factor identified for dogs with appendicular osteosarcoma is the histologic grade. In one study, grade 3 tumors accounted for more than 75% of osteosarcomas; those with low-grade tumors had a better prognosis. Low-grade tumors may be controlled with less aggressive treatments. In another study, mitotic index alone was a predictor of survival, with increasing numbers of mitoses correlating with a poor prognosis. Early studies indicated a relatively favorable prognosis for dogs with the fibrosarcomatous variant of osteosarcoma; however, this has not been recently substantiated. In two studies, age at time of diagnosis was important for determining survival in dogs treated with amputation alone. In one study, dogs between the ages of 7 and 10 years had the longest survival times, and both old and young dogs fared less well. In the other study, survival times decreased with increasing age. Two studies that used adjuvant single-agent chemotherapy (carboplatin and doxorubicin) retrospectively showed that smaller dogs had longer survival times. This may be due to a higher dose-per-kilogram delivered to these dogs, and it argues for increasing dosages in dogs that do not have toxicity after initial doses.

In studies of adjuvant therapy for appendicular osteosarcoma, the percentage of tumor necrosis following doxorubicin chemotherapy correlated with survival. The percentage of necrosis
following preoperative cisplatin or radiation correlated with local tumor control after limb-sparing surgery but not with survival.\textsuperscript{38}

Treatment

Amputation

Surgical treatment of osteosarcoma by amputation is palliative and increases survival by pain relief, thereby delaying euthanasia. Amputation usually eliminates the primary tumor and causes little to no reduction in mobility and quality of life for the dog. Although most clients do not initially embrace the concept that their dog will have three legs, the procedure is very acceptable to caregivers after amputation. In two studies in the United States and Europe, dogs learned to walk well on three legs within a month, which exceeded most clients’ expectations.\textsuperscript{39,40} It is also our experience, after sending many hundreds of dogs to amputation, that clients are very happy with their decision; the veterinarian should be confident in offering amputation to these clients. For lesions in the forelimbs, complete forequarter amputation, including the scapula, provides cosmetically and functionally good results. For distal hindlimb tumors, amputation at the proximal third of the femur is performed. For distal femoral tumors, a hip disarticulation is performed; proximal femoral lesions are treated by hemipelvectomy.

In one study, the median survival of 65 dogs treated with amputation was 126 days; only 10.7\% of dogs were alive 1 year after surgery.\textsuperscript{41} A larger study of 162 dogs treated with amputation corroborated these data.\textsuperscript{6} Surgery of any type is only palliative, and dogs with appendicular osteosarcoma should be given chemotherapy.

Limb-sparing surgery

Limb-sparing surgery is important in human patients, for whom cosmetic appearance and function are impaired by amputation. This procedure may be appropriate for dogs that are poor candidates for amputation (e.g., very large dogs, dogs with other orthopedic or neurologic problems) or for dogs whose owners refuse amputation.\textsuperscript{42,43} Caution is advised because dogs that are not good candidates for amputation may not be good candidates for limb-sparing surgery due to the prolonged period of postoperative recovery. During limb-sparing surgery, a cortical bone graft is used to replace the widely excised tumor, and arthrodesis of the nearby joint is usually performed. The best results are obtained with distal radial lesions or lesions of the ulna. It is possible to perform limb salvage for proximal humeral or scapular lesions, but function is poor, and the rate of postoperative complications is high, including a high rate of incomplete resection.\textsuperscript{44} Good functional results have been reported for partial or complete scapulectomy in dogs with osteosarcoma.\textsuperscript{45}

Limb salvage is not an option for large lesions that involve more than 50\% of the bone, tumors that invade adjacent soft tissue, and tumors of the hindlimb. Complications of limb salvage include allograft rejection and implant failure. Complications occurred in 86 (55\%) of 145 dogs treated with limb salvage in one study.\textsuperscript{43} Implant failure was seen in 12 dogs (8\%) and infection in 71 (49\%). Infection required allograft removal or limb amputation in 16 dogs (11\%).\textsuperscript{43} Local recurrence of osteosarcoma is a frequent problem with limb salvage procedures and affects up to 40\% of dogs. Even at institutions that perform limb salvage frequently and use adjunctive chemotherapy, recurrence rates of 17\% to 27\% are seen.\textsuperscript{43,46} Local recurrence is not a significant problem when amputation is performed.

Another disadvantage of limb-sparing procedures is the need for allografts from normal donors (usually dogs euthanized for another disease). These grafts must be stored, and fitting to the
patient is always approximate. Pasteurized excised tumor has been used as an autograft for dogs with distal radial osteosarcoma. Local recurrence and infection rates were similar to those from the use of an allograft.\textsuperscript{47}

Some surgeons use surgical metallic ‘spacers’ attached to the surgical plate. These devices fill the space where the tumor is excised. Benefits include the lack of need for a bone bank and, potentially, a lower complication rate. Another technique adapted by surgeons at Colorado State University has been used on a small number of dogs with osteosarcoma that does not involve the bone or cartilage at or near a joint. In this procedure, the involved bone is stripped of attachments to soft tissues. A cut is made distal to the tumor, and the bone containing the tumor is exteriorized surgically. The tumor in the bone is given very high dosages of external beam radiation therapy and then replaced in its normal position and fixed in place with a surgical plate. Dr. Ogilvie has observed that complication rates with this technique may be higher than with more routine limb-sparing procedures.

Before limb salvage is performed, intra-arterial cisplatin, with or without radiation therapy, often increases tumor necrosis and reduces the risk of local recurrence.\textsuperscript{38,48} In addition, a locally implanted polymer impregnated with cisplatin (open polyactic acid–cisplatin or OPLA–Pt) can be used. OPLA–Pt releases cisplatin slowly into the tumor bed, and its use reduces local recurrence rates from 27% to 17%. The survival time and disease-free interval for dogs treated with OPLA–Pt are similar to those of dogs receiving systemic cisplatin, presumably because locally implanted cisplatin is dispersed systemically. Because cisplatin release is slow, systemic toxicity is reduced.

A limb-salvage technique that abrogates the need for any graft is the use of bone transport osteogenesis.\textsuperscript{49} This technique slowly transports a small portion of normal bone adjacent to the defect caused by tumor resection into the defect (0.25 mm every 6 hours) while new bone forms behind the distracted bone. The resulting bone is a well-vascularized autogenous graft. The limb is held with the ends of the defect distracted by an external fixation device. A report of this method in six dogs found that local recurrence was a problem, but some long-term survivors were seen.\textsuperscript{49} Radiation therapy may have contributed to graft failure in one dog. Chemotherapy was also used in this report and did not appear to impair new bone formation.\textsuperscript{49,50}

**Chemotherapy**

Survival of dogs with osteosarcoma can be significantly prolonged by adjuvant chemotherapy. When chemotherapy protocols for the treatment of osteosarcoma are evaluated, median survival times are often very similar, and the use of 1-, 2- and 3-year survival rates will provide more information as to the likelihood of long-term control and even cure. Dog owners often understand these figures better than median survival times.

**Single agents**

Methotrexate was given intravenously to five dogs with osteosarcoma at doses ranging from 3 to 6 g/m\textsuperscript{2}. Treatment was preceded by vincristine at 1 mg/m\textsuperscript{2}. Leucovorin rescue was used. Myelosuppression was the dose-limiting toxicity, and no clinical response was seen.\textsuperscript{51} In another study, 17 dogs with osteosarcoma were treated by local resection and implantation of acrylic cement containing methotrexate at total doses ranging from 1.6 mg/kg to 16 mg/kg.\textsuperscript{52} Gastrointestinal toxicities were seen in four dogs receiving more than 4 mg/kg of methotrexate, and one of these dogs died. Four dogs showed delayed wound healing and sepsis. At 8 months, 10 of 17 dogs were alive without metastases; however, no further follow-up examination was
reported. With the toxicity and uncertain efficacy of methotrexate and the availability of proven alternatives, we cannot recommend treatment with methotrexate at this time.

Cisplatin markedly improves survival rates to a median survival of between 6 and 13 months and 1-year survival rates to between 30% and 62%; 2-year survival rates are between 7% and 21%. Whether the drug is administered intravenously or intra-arterially does not appear to affect efficacy.

Other methods of administration have been investigated. OPLA-Pt appears to release a controlled amount of cisplatin over a prolonged period as well as provide high local concentrations in the site of limb-sparing surgery. OPLA-Pt was implanted in the surgical wound of 39 dogs that had an amputation. Median survival was 8 months, and 1-year survival rate was 41%, which was similar to that achieved with systemic chemotherapy. In another study, OPLA-Pt was related to nonunion of limb salvage grafts. OPLA-Pt is not readily obtainable, so another study evaluated the utility of subcutaneously administered cisplatin and saline for slow-release chemotherapy; renal, gastrointestinal, and bone marrow toxicities and local tissue reaction were seen in five of six dogs, and this treatment is not recommended. Intramedullary cisplatin administration led to resolution of osteosarcoma in one dog with apparent survival benefit but was not so successful in three other dogs. Cisplatin is best given intravenously with saline diuresis.

Early reports of doxorubicin failed to show efficacy. Larger studies have shown benefit for the use of doxorubicin given as five biweekly doses at a dosage of 30 mg/m². In one study, two or three doses were given before surgery; subsequent doses were given the day after surgery and 2 weeks later. Median survival was 12 months, and the efficacy approached that of cisplatin; 50% of the dogs were alive at 1 year, and 10% were alive at 2 years. Another group of more than 300 dogs received five doses of doxorubicin every 2 weeks, starting 2 weeks after amputation. Median survival was 8 months, and 1-year, 2-year, and 3-year survival rates were 35%, 17%, and 9%, respectively, which is very similar to results from cisplatin chemotherapy. Survival times were greater in younger dogs, lighter-weight dogs, and dogs with normal T-ALP and B-ALP.

Carboplatin (300 mg/m² IV) was given adjunctively after surgery to 48 dogs. Median survival was 10.5 months; 35% of the dogs were alive 1 year after surgery. In this study, smaller dogs had longer survival times. Slightly lower survival rates were seen in a smaller group of dogs, but overall results are similar to that achieved with other drugs.

Lobaplatin (35 mg/m² IV) was given adjunctively after surgery to 28 dogs. Median survival was not reported, but 32% of the dogs were alive 1 year after surgery. In this study, dogs with grade 1 tumors and with normal T-ALP had longer survival times.

Liposome encapsulation of cisplatin did not improve survival times compared with carboplatin in another randomized study.

Single-agent treatment with carboplatin or doxorubicin seems to be as effective as cisplatin in treating canine appendicular osteosarcoma, and the choice of which drug to offer may depend on other factors. For example, doxorubicin may be less expensive than either of the platinum drugs; however, doxorubicin causes a cumulative cardiotoxicity, the risk of which is higher in breeds predisposed to cardiomyopathy. Many dogs with osteosarcoma are also breeds that are at risk for cardiomyopathy (e.g., Dobermans, great Danes), so doxorubicin may not be a good choice for these dogs. Even with prescreening of prospective patients and elimination of those with early cardiac changes or significant breed risk, more than 7% of patients developed cardiomyopathy in one study of more than 300 dogs treated with five doses of doxorubicin. Similarly, the fluid
diuresis required to prevent renal toxicity of cisplatin may make it unsuitable for a dog with clinical or subclinical heart disease. Dogs that cannot be admitted as day patients for fluid diuresis and cisplatin may be better treated with carboplatin or doxorubicin because these drugs can be given on an outpatient basis.

**Combination chemotherapy**

Combinations of drugs that show activity as single agents should, in theory, be more effective than single agents alone because of their effects on dose intensity (combined mg/m² of drugs per week). A dose intensity of “1” is a drug given at the prescribed maximum dosage at the prescribed interval; in combinations, the dose intensity of each drug is proportional according to dosage and interval, and the results for each drug are added together. Thus, it is possible to have a dose intensity greater than 1 with combination chemotherapy. It is also possible to have a dose intensity less than 1 because combination requires either reductions in dosages or lengthening of the inter-treatment interval between individual drugs, particularly when both drugs cause similar toxicities. For example, doxorubicin and cisplatin each have a dose intensity of 1 when given at maximum dosage every 3 weeks. Because they have the same dose-limiting toxicity (myelosuppression), combination of these two agents requires significant dose reduction for each. When they are combined by giving each drug on its own, alternating every 3 weeks, the dose intensity of each drug is effectively halved because the drug is given every 6 weeks. Thus, the combined dose intensity would be 1. Cisplatin is limited by nephrotoxicity, but it is mildly myelosuppressive, so maintaining close to full dosages in combination therapy may be possible. Combining cisplatin and doxorubicin on the same day would require a reduction in dosage of one or both drugs, but both could be given every 3 weeks, so dose intensity may be increased. Increased dose intensity should, in theory, be associated with improved efficacy.

A protocol alternating cisplatin (60 mg/m²) with doxorubicin (30 mg/m²) every 21 days for two cycles was delivered after amputation to 19 dogs with appendicular osteosarcoma. The median survival was 10 months, with 37% of dogs alive at 1 year and 26% alive at 2 years. Despite the lower dose intensity (0.76) of the two drugs compared with single-agent protocols, survival rates were comparable to those for cisplatin chemotherapy alone.65

Another study delivered doxorubicin (15–25 mg/m²) and cisplatin (60 mg/m²) on the same day (doxorubicin in postdiuresis fluids) to 102 dogs with osteosarcoma. Median survival was 11.5 months, and 1-year, 2-year, and 3-year survival rates were 47%, 28%, and 17%, respectively.66 The dose intensity of this protocol was greater than that of either single agent (1.19–1.30). A later evaluation of toxicity showed that a 20-mg/m² dose of doxorubicin was well tolerated in these dogs.67 A small pilot study of 19 dogs that used lower doses of doxorubicin and cisplatin (15 mg/m² and 50 mg/m², respectively; dose intensity: 1.04) showed a greater median survival,68 but as more dogs were added to the study, the median survival decreased, illustrating the need for larger numbers to adequately assess efficacy.

Carboplatin (175 mg/m²) and doxorubicin (15 mg/m²) were given on the same day every 3 weeks after amputation to 24 dogs with osteosarcoma. Dose intensity was 0.91 because lower dosages of these drugs were needed to avoid myelosuppression. Median survival was 8 months; the 1-year survival rate was not reported.69

Carboplatin (300 mg/m²) and doxorubicin (30 mg/m²) were given in an alternating protocol every 3 weeks for three cycles for a dose intensity of 1.0. Median survival was 10.5 months, and 1-year and 2-year survival rates were 48% and 18%, respectively.70 The dogs that finished the protocol had a median survival of 18 months. Clients often want to know how their pet is likely
to do after completing a course of chemotherapy; this finding serves as encouraging news for dogs that have not developed metastatic disease during chemotherapy.

Carboplatin (100 mg/m$^2$) and cisplatin (60 mg/m$^2$) were combined to assess the influence of increased platinum compounds (dose intensity: 1.19) on osteosarcoma. Median survival was 9 months in this preliminary report, and the 1-year survival rate was not reported.

In conclusion, the best reported long-term survival rates have been reported for doxorubicin and cisplatin given together on the same day. Dosages of cisplatin 60 mg/m$^2$ and doxorubicin 20 mg/m$^2$ should be well tolerated by this population of mainly large dogs.

**Number of doses and timing of chemotherapy**

There are trends toward longer survival times with increasing the number of doses of cisplatin, but statistical evaluation is lacking. More than two doses of cisplatin may improve survival.

There are theoretical data to suggest that chemotherapy very soon after amputation may take advantage of a “growth spurt” that renders micrometastases more sensitive to chemotherapy. In order to test this hypothesis, one study randomized 100 dogs to receive cisplatin and doxorubicin (together on the same day) starting either 2 days or 10 days after amputation. There was no difference in survival, but dogs that were treated 2 days after surgery were more likely to show myelosuppression, presumably because the bone marrow had been stimulated by postoperative inflammation. It is recommended that because efficacy is not improved, and toxicity is increased, chemotherapy be delayed until wound healing has occurred, usually 10 to 14 days after surgery.

**Biological Response Modifiers**

In early studies, nonspecific immunostimulation appeared to improve survival. Median survival was 10 months for dogs treated with bacille Calmette-Guérin after surgery. More recent studies have been performed on small numbers of dogs, using biological response modifiers that are not commercially available. It seems, however, that immunotherapy may have a future role to play in multimodality treatment of canine osteosarcoma.

Liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE) is a nonspecific activator of monocytes and macrophages that induces tumoricidal activity in these cells. Dogs treated with L-MTP-PE showed prolonged median survival (7 months) over dogs receiving liposomes alone (2.5 months). In a further study, 11 dogs that had received four doses of cisplatin (70 mg/m$^2$ every 28 days) after amputation were treated with L-MTP-PE. These dogs had a median survival of 14.4 months, and 3 dogs did not develop metastases. Clinical data from small numbers of dogs may be misleading, and further studies to confirm these results have not been performed.

A further study of 23 dogs that were treated by surgical excision of the osteosarcoma, chemotherapy, and human cytotoxic T-cells from a cultured cell line lived a median of 11.5 months, which is not much different from survival after chemotherapy alone; however, approximately 40% of dogs were alive 2 years after surgery.

Interleukin-2 (IL-2) is a lymphocyte-derived stimulator of natural killer cells and macrophage/monocytes; hence, it is a potent immunostimulant. IL-2 was delivered in liposomes via aerosol to four dogs with pulmonary metastases from osteosarcoma. Two dogs had complete regression of metastases that was ongoing 12 and 20 months later.

Antiangiogenic therapy is a new area of interest in veterinary medicine. Angiogenesis is a complex, multifactorial process by which new blood vessels sprout from existing vessels and
then dissolve surrounding matrix to extend further into tumors. New blood vessel growth is rarely needed in existing normal tissue (except during pregnancy and wound healing), so inhibiting aspects of the angiogenic pathway should target tumors specifically. Without new blood vessels, tumors cannot expand beyond a size that allows passive diffusion of nutrients and oxygen to the tumor cells, and existing tumors may shrink. Blood vessel density has been found to be highest in osteosarcomas that metastasize early. Tumors also need to dissolve surrounding cellular matrix in order to invade blood vessels and to form metastases. Osteosarcomas have been found to contain matrix metalloproteinases that are important in the dissolution of collagen, allowing angiogenesis to occur and tumor invasion to proceed. Various drugs may target angiogenesis and matrix dissolution through various pathways. The antibiotic doxycycline has been found to inhibit collagenase (metalloproteinase) activity by canine osteosarcoma cells, although clinical activity has not been documented. Three of four dogs that had presumed spontaneous regression of osteosarcoma had been treated with the anti-inflammatory drug carprofen. It is possible that the anti-inflammatory drug played a role in tumor regression. It has been suggested that inhibitors of cyclooxygenase-2 (COX-2) may also inhibit tumor growth and angiogenesis; only 3 of 13 tumors expressed COX-2 in one preliminary study, but 79% expressed COX-2 in a larger study and expression appeared to correlate with poorer survival. Definitive treatment is still preferred, and the clinician is cautioned against relying on COX-2 inhibitors as sole treatment.

A large, multi-institutional, randomized clinical trial found that there was no survival benefit to the oral administration of an inhibitor of metalloproteinases 2 and 9 (MMP-2 and MMP-9) in conjunction with amputation and doxorubicin chemotherapy, despite the finding that serum levels of MMP-2 and MMP-9 activity influenced survival.

Metastatic Disease

Once osteosarcoma metastases are clinically or radiographically evident, good response to chemotherapy is rare. In one study, two of three dogs with metastatic osteosarcoma responded partially to cisplatin chemotherapy. In another report, 45 dogs with osteosarcoma metastases were treated with cisplatin, doxorubicin, mitoxantrone, or sequential combinations of these drugs every 3 weeks. Only one dog experienced a partial remission for 21 days with doxorubicin. Cisplatin had been given before the development of metastases in 29 of the 45 dogs.

Pulmonary metastatectomy seems to prolong survival only if the animal develops clinically evident metastases more than 10 months after the initial diagnosis and if fewer than three nodules are radiographically apparent. Median survival time after metastatectomy was 6 months in one study. Median survival of dogs with few metastases that are not treated with metastatectomy is uncertain.

In 90 dogs with metastatic osteosarcoma at the time of diagnosis (dogs euthanized at diagnosis were excluded), the median survival time was 2.5 months. Dogs that were treated with either surgery or adjuvant therapy lived longer than those treated supportively.

Palliative Radiation Therapy

If caregivers refuse definitive treatment for a pet with osteosarcoma, or if an animal is not considered eligible for amputation or limb-sparing surgery, consideration may be given to palliation of tumor pain with radiation therapy.

Radiation delivered in two to four weekly fractions of 8 to 10 Gy has been reported as a palliative treatment for 125 dogs with pain or other symptoms related to osteosarcoma. Improved
limb function was seen in approximately 75% of dogs treated with either 8 Gy on days 0, 7, 14, and 21; 10 Gy on days 0, 7, and 21; or 8 Gy on days 0 and 7. Improvement lasted for a median of 2 to 3 months regardless of the protocol, and toxicities were rare and acute.\textsuperscript{86-88} Chemotherapy appeared to improve response rate and duration. Dogs with large lesions extending to involve a greater length of limb were less likely to respond for long.\textsuperscript{87,88} Many radiation therapists agree that a reasonable clinical approach may be to deliver a single large dose to the affected site and then to repeat a single dose as necessary to maintain pain control.

Targeted stereotactic “radiosurgery” may offer some advantages in delivering a single high dose of 30 Gy to the tumor alone. Preliminary results are encouraging.\textsuperscript{89}

Samarium-153-ethylene diamine tetramethylene phosphonate (EDTMP) emits b particles and accumulates in areas of increased bony activity, thereby providing high-dose localized radiation therapy. This compound was given to 28 dogs with osteosarcoma of the appendicular (n = 20) or axial (n = 8) skeleton.\textsuperscript{90} Many dogs showed functional improvement, and the average survival for the dogs with appendicular osteosarcoma was 8 months. This treatment may palliate in a manner similar to that of external beam radiation. Another study found that with the exception of one dog that had a long-lasting complete response, pain relief was poor in a series of nine dogs with presumed osteosarcoma; survival was for a median of 4 months.\textsuperscript{91} There are anecdotal reports of long survival after surgery and samarium therapy.\textsuperscript{36,92}

\textit{Other Palliative Therapy}

Bisphosphonates are inhibitors of osteoclast activity that have been used in human patients with osteolytic disease, including metastatic neoplasia. Pamidronate is an intravenously administered drug that has anecdotally been associated with decreased pain from osteosarcoma. Unpublished observations by Dr. Moore suggest that the improvement is subjective but not associated with increased weightbearing as measured by force-plate analysis. Alendronate is an orally administered bisphosphonate that was reported to reduce pain in two dogs for 10 to 12 months, despite neither dog being treated with amputation.\textsuperscript{93} The dose used was approximately 0.25 mg/kg.

Pamidronate has also been used in combination with radiation therapy; it is difficult to decide whether the subjective improvement is due to the combination or the individual components.

\textit{Supportive Therapy}

Palliation of pain as described above should be considered supportive. Dogs with osteosarcoma have alterations in energy expenditure and are in negative nitrogen balance.\textsuperscript{94} Nutritional support with a high percentage of calories from protein may be beneficial to dogs with osteosarcoma.
CARE BEYOND A CURE:

10 BEST KEPT SECRETS FOR TREATING CATS WITH CANCER

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Feline medicine and, in particular, feline oncology is associated with a great deal of myth and mystery. Cats are unique in physiology, behavior, anatomy, social structure, and in the types of diseases they have and the pathogenesis of these diseases. Cancer is rarely discussed in great detail in textbooks and often the data that is used to reference the information is outdated or incorrect. The purpose of this document is to review some of the unique aspects associated with feline medicine and to outline the unique biological behavior of several different malignancies and the cats’ response to those malignancies. By understanding this information, a clinician can have a much higher probability for enhancing and improving quality of life.

Secret #1: Cats generally resist restraint; and therefore, the less restraint is generally the best restraint.

Secret #2: Cats are not small dogs. Despite how feline medicine is presented in most veterinary schools and conferences, the diseases are unique, as is the therapy.

Secret #3: Cats are made of steel. Indeed, unlike what many veterinarians are taught, cats generally do extraordinarily well in adversity and generally do well with cancer therapy. When comparing dogs and cats who are treated with chemotherapy and radiation therapy, cats generally do far better than dogs.

Secret #4: Evil cats live forever. This is subjectively true, as the meanest cats tend to be those that are more aggressive, and therefore more willing to fight to stay alive, regardless of the threat in front of them.

Secret #5: Clients are not truthful if they say they give all the medications. Indeed, the fewer medications the client is to give, the more likely they are to administer it. Therefore, prescribing medications with the least number of administrations per day will result in the highest compliance rate. Studies have shown that only 30% of all the medications given to cats are given as prescribed.

Secret #6: Most cats with cancer are anemic. Indeed, anemia of chronic disease is a powerful influence on the hemogram. Since cats disassociate oxygen from the hemoglobin of red blood cells far easier, and the oxygen disassociation hemoglobin curve is far different in the cat than the dog, this is not as high of an issue.

Secret #7: Cats with metastasis rarely cough until the end-stage of the disease, whereas cats with reactive airway disease frequently cough very early on in the course of the disease.

Secret #8: Size of the feline mammary tumors is prognostic.

Secret #9: A dyspneic cat is a cat with severe intrathoracic or upper airway pathology.

Secret #10: Chest radiographs are often the best tool for diagnosing respiratory abnormalities.
However, because cats present late in the course of their disease, extreme caution should be taken when taking chest radiographs in the cat. Obviously, with CT scans becoming more available in veterinary medicine, this is often used to provide greater understanding of intrathoracic disease. This is accentuated by performing bronchoscopy and bronchoalveolar lavage.

Secret #11: A cat with severe dyspnea plus normal chest radiographs almost always is associated with a functional airway disease, such as asthma, thromboemboli, etc. Feline asthma is frequently associated with radiographic “doughnuts.”

Secret #12: Collapse of the right middle lung lobe is a common sequela to chronic lung disease and often results in the inability to obtain a normal-looking chest radiograph on a VD because the heart shifts towards the side of the collapsed lung lobe.

Secret #13: As with the dog, the three commandments of cancer care are extraordinarily important. The first commandment is “Don’t let them hurt,” the second commandment is “Don’t let them vomit or have diarrhea,” and the third commandment is “Don’t let them starve.”

The first commandment, “Don’t let them hurt,” is of extreme importance; in one study, published in the Journal of the American Veterinary Medical Association in 2005, a survey of clients revealed that at least 50% of cats with cancer are in pain. So, even if we don’t think that cats are medically in pain, we should take into account the clients’ perception of what is going on. Therefore, prevention of discomfort is of extreme value; considering preemptive analgesics, non-steroidalals, opiates, tramadol, acupuncture, and local blocks can be of great value.

Secret #14: Piroxicam, Metacam, ketoprofen and, even in some countries, carprofen, have been shown to be of great value at alleviating pain and suffering. The chronic use of oral meloxicam in the United States is now no longer possible because of the black labeling by the Food and Drug Administration. This is really unfortunate because this drug is easy to administer, very tolerable, and has great efficacy. Piroxicam itself has been shown to have an anti-cancer effect in the cat, including transitional cell carcinoma, mammary carcinoma, intestinal carcinoma, and squamous cell carcinoma.

Secret #15: Tramadol is very effective for treating pain in the cat despite its bitter taste and, therefore, poor palatability. Indeed, this particular drug must be compounded and hopefully can be created by a compounding pharmacist in a palatable liquid or in a capsule to hide its bitter taste. Adverse effects are rare in the cat; however, respiratory depression has been reported.

Secret #16: Morphine and fentanyl are two of the most commonly used opiates in the cat other than buprenorphine and butorphanol. When morphine and fentanyl are compared, fentanyl has at least a theoretical benefit over morphine, because morphine is far more lipid soluble, and therefore more rapid-acting. Morphine has the advantage of being less costly.

Secret #17: Fentanyl patches are very effective at providing continuous analgesia in the cat. It has an efficacy of analgesia for three to five days. When fentanyl is administered intravenously, it is rapidly absorbed and has at least and hour and a half of analgesia.

Secret #18: Hydromorphone has an advantage over morphine in the fact that it does not cause histamine release and the hyperexcitability, gastrointestinal and respiratory problems associated with morphine administration. Other opiates that are commonly used in veterinary practice include butorphanol, which has analgesia of one half to two hours, but a sedation that lasts for four hours; morphine, which has sedation, as well as analgesia, and lasts for six hours; and buprenorphine, which has a duration of analgesia that lasts for 8 hours.

Secret #19: If a splenic mast cell tumor is identified, then the prognosis can actually be quite good. Survival times with splenectomy have been reported to exceed two years.
Secret #20: Radiation therapy with a radiation sensitizer, such as gemcitabine, has been touted as being highly effective; but ultimately, when comparing oral facial squamous cell carcinomas, bone involvement is generally a good prognosis.
Secret #21: Unlike in the dog, surgery alone is often associated with long-term control and/or cure.
Secret #22: A jaundiced cat is not necessarily a dead cat. In fact, jaundiced cats can live for a long period of time with limited impact to the quality of life.
Secret #23: Liver enzymes are not elevated in 25% of cats with significant liver disease. A liver biopsy is absolutely essential to be able to identify the liver disease.
Secret #24: Ptyalism is the most common clinical sign in cats with portosystemic shunts.
Secret #25: Clinical icterus should be present if the bilirubin value is greater than 2mg/dl. If clinical icterus is not present, then one should consider that the bilirubin elevation is likely due to a lab error, lipemia, or hemolysis.
Secret #26: Serum alkaline phosphatase in the cat has a half-life of six hours and there is no steroid isoenzyme in the cat.
Secret #27: If the serum alkaline phosphatase is much greater than the ALT, and the ALT somewhat greater than the GGT or the GGT is normal, then hepatic lipidosis is often the cause. If the ALT is substantially elevated and the serum alkaline phosphatase is greater than the GGT, then hepatitis or chronic hepatocellular disease is likely the cause.
Secret #28: The AST is not liver specific in the cat.
Secret #29: Any bilirubin in the urine is abnormal in the cat.
Secret #30: If the bilirubin is greater than 3mg/dl, 90% of the cats will have a hepatic problem. If the serum bilirubin is less than 3mg/dl, 50% of cats will have a non-hepatic problem.
Secret #31: Feline needle aspiration is often very helpful for diagnosing hepatic lipidosis.

**Conclusion:**
Feline medicine and feline oncology specifically is a unique art form that requires a revised understanding of the pathogenesis of disease and the physiology of the cat. Approaching the cat as a unique species and not as a small dog can enhance the ability to diagnose underlying disease as well as to provide a treatment plan. Cats are far more likely to recover from serious disease than the dog; however, the cats present much later in the course of the disease, making it a challenge to proceed ahead with diagnostics and therapeutics in a swift format.

**Reference Available Upon Request**
Canine lymphoma are rewarding to treat as long as a few secrets or rules are known. The following are a few important prognostic variables for canine lymphoma.

- Clinical Stage: IV + V worse than I-III; dogs with clinical signs worse than if asymptomatic.
- Hypercalcemia: worse when associated with an anterior mediastinal mass.
- Sex: female dogs better than male dogs. Body size: small dogs better than large dogs.
- Pretreatment corticosteroids: worse.
- High grade: higher response rate and longer duration of remission.

When considering treatment, one must remember that the more complex the protocol, the longer the first remission, higher the cost and toxicity. The following is a general overview of canine lymphoma.

Background

Malignant lymphoma (lymphosarcoma) is a lymphoproliferative tumor of solid lymphoid tissues with possible marrow metastasis and a leukemic phase. In dogs, it accounts for 5-7% of all tumors seen and occurs at an incidence rate of 24 cases per 100,000 dogs. It occurs most commonly between 5 and 12 years of age. Boxers, Cocker Spaniels, Fox Terriers, German Shepherds, Scottish Terriers and Golden Retrievers are at an increased risk when compared with other breeds. Etiology for the canine is unknown. In the cat, 90% of the cases are FeLV related and it occurs at an incidence rate of 41.6 cases per 100,000 cats. This accounts for one third of all feline neoplasms and is two and one-half times the rate of lymphoid neoplasia in man. There is a slight male>female predominance in cats.

Diagnosis

Once clinical findings compatible with a diagnosis of malignant lymphoma have been found, aspiration and cytology of accessible lesions should be completed. Malignant lymphoma is characterized by the replacement of normal lymph nodes by a uniform population of pleomorphic and bizarre lymphocytes. After a tentative diagnosis of malignant lymphoma has been supported through rapid cytologic methods, confirmation of the diagnosis may be conducted by biopsy. A tissue core may be obtained by Tru-Cut biopsy or, preferably, a node may be excised for final confirmation.

If a dog or cat is to undergo therapy, clinical staging is mandatory. Clinical staging determines the extent of disease in the living animal. Once a baseline of data has been obtained, the clinical oncologist will be able to know which parameters should be monitored in order to
reach complete remission. Clinical staging should include radiography of the thorax and abdomen, a complete blood count and platelet count, a bone marrow aspirate and core, an ophthalmic exam, measurement of representative enlarged lymph nodes and a biochemistry panel with special emphasis on calcium and protein levels. Abnormal findings beyond lymphadenopathy are rare, however marrow infiltrate with subsequent release of cells into the peripheral blood is occasionally seen. Hypercalcemia associated with a parathyroid-hormone-like substance is observed in some dogs with malignant lymphoma. This is most often encountered in dogs with anterior mediastinal lymphoma and bone marrow involvement.

**Prognostic Factors**

Prognostic factors are difficult to confirm due to the variation from study to study. Most treatment reports indicate that hypercalcemia and poor performance status are predictive of short remission and survival times. Animals with advanced clinical stages (World Health Organization Stage IV and V), or at least those with malignant cells in their bone marrows, are also considered to have a poorer prognosis than those animals with less advanced clinical stages (WHO Stage I-III). Some reports suggest that treatment with glucocorticoids prior to therapy with more aggressive chemotherapeutic agents cause a poorer response to therapy than seen in dogs which have not been treated with glucocorticoids, but this finding has not been consistently observed.

**Therapy**

Treatment for malignant lymphoma must be systemic in nature since it is a multi-system disease. Chemotherapy is most frequently utilized; however, some immunotherapy has been effective. Untreated, dogs affected with malignant lymphoma live an average of only six weeks once a diagnosis has been made. With chemotherapy, dogs can survive for 6-10 months with an excellent quality of life. Dosage of chemotherapeutic agents for the cat is the same as for the dog except when Adriamycin is used. While dogs may receive Adriamycin every 21 days at a dosage of 30 mg /m2, cats appear to be more sensitive to the drug and many of them can only tolerate a dosage of 20 mg/m2 given every 21 days. Anorexia and renal failure have been reported as significant side effects in cats.

Malignant lymphoma is one of the most responsive forms of cancer presented to the practitioner. With appropriate chemotherapy protocols, nearly 90% of animals placed on therapy should reach complete remission. Of those that reach remission, approximately 80-90% will maintain a reasonable (>6 mos) timeframe of excellent quality life. Cost is not inexpensive; however, it is within reasonable financial reach of many clients, thus allowing therapy to be possible.

Although marginally effective, prednisone is inexpensive and often used in combination with other drugs to treat lymphoma. With prednisone therapy, the average pet lives 2 months. One-third of the dogs and cats treated with prednisone will go into complete remission, one-third will go into partial remission, and one-third will not respond at all.

Adriamycin is one of the most effective single agent treatments for lymphoma in dogs. Of the dogs treated with adriamycin, 81% developed a complete and partial remission. The duration of remission is approximately 9 months. Dogs treated with Adriamycin and then switched to COP (cyclophosphamide, oncovin, prednisone) had a higher second remission rate compared to those started on COP and then switched to Adriamycin.

The COP protocol is effective for inducing a remission in 75% of dogs with lymphoma. A median duration of remission of 6 months is commonly seen. Approximately twenty percent of the dogs treated with the COP regimen are in remission at 1 year. In one study, 79% of cats with lymphoma treated with COP achieved a complete remission whereas only 29 percent of cats
treated for lymphoblastic leukemia achieved a complete remission. Cats with lymphoma treated with COP had a shorter remission time (64% achieved a complete remission, median remission 5 months) but proportionately more long-term, survivors than dogs. Cats with renal lymphoma tend to have recurrence of tumor in the brain, therefore cytosine arabinoside is frequently recommended as an additional therapy.

The addition of adriamycin to the COP regiment resulted in longer remission time (7 months vs 6 months). A complete remission was attained in eighty-four percent of dogs treated with COPA. An additional 7% achieved a partial remission. Twenty-two percent of dogs treated with the COPA protocol were in remission at one year.

Garrett et al (JVIM 16: 704-709, 2002) compared a maintenance-free chemotherapy protocol based on CHOP to a similar protocol with a maintenance phase for the treatment of canine lymphoma. Fifty-three dogs with multicentric lymphoma were treated with a 6-month modified version of the University of Wisconsin (UW)-Madison chemotherapy protocol. Disease-free interval (DFI) and survival were compared to a historical control group of 55 dogs treated with a similar protocol with a prolonged maintenance phase. Remission rate for the study dogs was 94.2% The remission and survival between the 2 groups did not differ significantly. Thus, we and others believe the 6-month chemotherapy protocol based on CHOP with no maintenance phase provides is equal to a similar protocol with a prolonged maintenance phase.

**WISCONSIN PROTOCOL - SHORT Lymphoma Protocol Treatment**

<table>
<thead>
<tr>
<th>Week</th>
<th>Vincristine, 0.5-0.7 mg/m² IV</th>
<th>DATE</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Asparaginase, 400 U/kg SQ</td>
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<td>Prednisone, 2 mg/kg PO s.i.d.</td>
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<tr>
<td>Week 2</td>
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<tr>
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<td>Prednisone, 1.5 mg/kg PO s.i.d.</td>
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<tr>
<td></td>
<td>Prednisone, 1.0 mg/kg PO s.i.d.</td>
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<tr>
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<tr>
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<td>Prednisone, 0.5 mg/kg PO s.i.d.</td>
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<tr>
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<tr>
<td>Week 21</td>
<td>Adriamycin, 30 mg/m² IV</td>
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</table>

another protocol involves administering adriamycin at 30 mg/m² body surface area q3 weeks for 5 treatments as long as the dog stays in remission. One day after the first adriamycin therapy, L-asparaginase is administered IM weekly for 3 treatments (10,000 Units/m²). When the patient comes out of remission, then COP therapy is started as mentioned above. The duration of remission 1 plus remission 2 is similar the the COPA protocol noted above with less toxicity and less cost to the client.

Rassnick and colleagues (J Vet Intern Med 16[5]:576-580 2002) evaluated the efficacy and toxicity of the MOPP chemotherapy protocol (mechlorethamine, vincristine, procarbazine,
and prednisone) as a rescue regimen in dogs with lymphoma. In that study, one hundred seventeen dogs that had resistance to previously administered chemotherapy were evaluated. Thirty-one percent had a complete response (CR) to MOPP for a median of 63 days. Five dogs developed septicemia, and 2 died as a result. MOPP was an effective treatment for dogs with resistant lymphoma but caution should be employed to monitor for septicemia.

One monoclonal antibody developed for the treatment of cancer in humans or animals is canine lymphoma/monoclonal antibody 231 (CL/MAb 231; Synbiotics Corporation, San Diego, California), which recognizes canine lymphoma cells.\(^{38,39}\) It mediates antibody-dependent cellular cytotoxicity against a canine lymphoma cell line and has been reported to prolong remission duration when used in combination with chemotherapy in dogs with lymphoma.\(^ {39}\) The median survival time of dogs treated with the monoclonal antibody and chemotherapy was 591 days, as compared to historical controls, which had a median survival time of 189 days. Additional studies are needed to further understand the clinical utility of this treatment modality.

Rituximab, a chimeric murine/human IgG monoclonal antibody that targets the B-cell antigen CD20 is now considered the standard of care for the management of human B-cell lymphoproliferative disorders including diffuse large B-cell lymphoma (DLBCL).\(^ {33,34}\) This aggressive form of DLBCL has many similarities to the most common form of lymphoma in dogs.\(^ {33-35}\) In both species, DLBCL generally responds well to combination chemotherapy, however the duration of remission is often limited. The addition of the species-specific antibody Rituximab in combination with chemotherapy to treat DLBCL in people is associated with little increase in toxicity, yet enhanced efficacy. The increased frequency in the use of Rituximab in the management of lymphoid malignancies has grown to the point that it presented a huge logistical challenge for the human medical system because the antibody was originally given by slow infusion, a time intensive procedure. Therefore, more cost and time effective procedures have been developed to safely and effectively infuse the antibody.\(^ {36}\) Thus, the availability of a similar antibody that targets the canine CD20 antibody combined with the lessons learned on how to safely and effectively incorporate this type of therapy could have a powerful impact for the management of DLBCL.

The discovery, development and commercial production of a Rituximab-like chimeric murine/canine monoclonal antibody that specifically and precisely targets the B-cell antigen CD20 in dogs is notable.\(^ {1}\) In fact, if this construct is confirmed to be safe and effective, then the potential to benefit dogs with a long list of benign or malignant diseases that are caused by B-cell lymphocytes that express CD20 is high. That is exactly what occurred with the development and subsequent use of Rituximab. We therefore embarked on this double blind, randomized, placebo controlled study to be the very first to test the hypothesis that the Rituximab-like chimeric murine/canine monoclonal antibody is safe and effective for the treatment of CD20 positive DLBCL in the dog. In that study, dogs were enrolled in a prospective, randomized, double blind, placebo controlled clinical trial. All dogs were treated with one 4-week cycle of an L-CHOP chemotherapy protocol followed by either the canine lymphoma antibody or a placebo. Once remission was lost, a single dosage of doxorubicin was given followed by the antibody. Assessment of antitumor efficacy was based on modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines and toxicity based on criteria delineated by Veterinary Cooperative Oncology Group’s common terminology criteria for adverse events (VCOG-CTCAE). The median proliferation free interval and overall survival time respectively of dogs with DLBCL
treated with one cycle of the L-CHOP protocol followed by the antibody or the placebo was much longer in the antibody arm compared to the placebo arm. Toxicities that were observed in this protocol were mild and restricted to the L-CHOP cycle with no significant adverse events in the antibody or placebo arms. On the contrary, there was a significant improvement in client perceived quality of life parameters in the antibody, but not the placebo treated dogs.

References Available Upon Request