# Standards of Care (How I Treat)
# CANINE OSTEOSARCOMA

*Gregory K. Ogilvie, DVM, Diplomate ACVIM*

(Specialties of Internal Medicine, Oncology)
Director, CVS Angel Care Cancer Center (www.CVSAngelCare.com)
President, Special Care Foundation for Companion Animals (www.SpecialCareFoundation.org)
100 North Rancho Santa Fe Rd #100
San Marcos CA 92024 USA
Gogilvie@aol.com

## 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.[1,2] 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.[3] A larger study of 162 dogs treated with amputation corroborated these data.[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.[4,5] 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.[6] Good functional results have been reported for partial or complete scapulectomy in dogs with osteosarcoma.[7]

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.[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%).[5] 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.[7,8] 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.[8]

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. .

Before limb salvage is performed, intra-arterial cisplatin, with or without radiation therapy, often increases tumor necrosis and reduces the risk of local recurrence.[10] In addition, a locally implanted polymer impregnated with cisplatin (open polylactic 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.

## Chemotherapy

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%.[11-16] 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.[16] In another study, OPLA-Pt was related to nonunion of limb salvage grafts.17 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.[18] Intramedullary cisplatin administration led to resolution of osteosarcoma in one dog with apparent survival benefit but was not so successful in three other dogs.[19] Cisplatin is best given intravenously with saline diuresis.

Early reports of doxorubicin failed to show efficacy.[20] 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.21 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/m$^2$ IV) was given adjunctively after surgery to 48 dogs.[22] 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.

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

A protocol alternating cisplatin (60 mg/m$^2$) with doxorubicin (30 mg/m$^2$) 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.[23]

Another study delivered doxorubicin (15–25 mg/m$^2$) 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.24 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/m$^2$ dose of doxorubicin was well tolerated in these dogs.[25] A small pilot study of 19 dogs that used lower doses of doxorubicin and cisplatin (15 mg/m$^2$ and 50 mg/m$^2$, respectively; dose intensity: 1.04) showed a greater median survival, but as more dogs were added to the study, the median survival decreased, illustrating the need for larger numbers to adequately assess efficacy.

Carboplatin (300 mg/m$^2$) and doxorubicin (30 mg/m$^2$) 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.[26] 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.

### 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[27-29] 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.[28,29]

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.[30]

### 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.

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.

References: Available Upon Request