Tumors of the skeleton require a multimodality approach to therapy. The treatment modalities are surgery, radiation, chemotherapy, and immunotherapy. The application of these forms of therapy depends upon the histologic type of the tumor, as well as its stage of disease and biological behavior. Surgery and radiation therapy are used to control local and regional diseases. Surgical excision of osteosarcoma in humans is unsuccessful in 90% of patients if the necessary precautions are taken in selecting the level to amputate. Standard radiographs and bone scans provide good approximations as to the proximal spread of the lesion and possible "skip" metastases. Limb salvage procedures are performed only in select patients. Helfand and co-workers attempted limb salvage in canine osteosarcoma. (16) The treatment included radiation to the involved limb and intra-arterial chemotherapy prior to en bloc tumor resection. Massive tumor necrosis was present in the surgically resected limb. However, the treatment did not affect overall survival and death by metastasis.

In humans, the primary indications for definitive radiation therapy of bone tumors are limited almost exclusively to Ewing's sarcoma, primary lymphoma of bone, and solitary myeloma. Ewing's sarcoma does not occur in domestic animals, and the other two diseases are relatively rare. Radiation can be used in tumors that are not surgically excisable for technical or medical reasons. Bone tumors of the mandible or maxilla are often irradiated, and results are mixed depending on tumor type. Radiation may be a palliative procedure for primary and metastatic tumors of bone.

Chemotherapy uses anticancer or cytotoxic drugs to treat unresectable primary tumors, microscopic disease, and metastatic diseases. Most bone tumors are reasonably resistant to chemotherapeutic agents. Many of the breakthroughs with chemotherapy in humans are not applicable to veterinary oncology because of the high dosages of drugs required and their side-effects.

Immunotherapy of cancer is aimed at stimulating the patient's immune system to recognize and destroy small numbers of residual tumor cells. The major limitation of immune modulation is the ineffectiveness of treatment in patients with a large tumor volume. Its potential efficacy is in patients with minimal or microscopic residual tumors. Dogs with long-bone osteosarcoma should not be treated with immunotherapy alone. The accepted sequence of treatment would be amputation and adjuvant chemotherapy followed by immunotherapy. (12)

The medical management of tumors in veterinary medicine is new and progressing rapidly. Since the majority of bone tumors in the dog are malignant, they represent a challenge to the veterinary oncologist. Chemotherapy of primary bone tumors, soft tissue tumors invading bone, and metastatic bone tumors is still relatively unsuccessful compared with chemotherapy of lymphomas and soft tissue tumors. Osteosarcoma is the most common bone tumor in humans and animals. Canine osteosarcoma is an excellent animal model for the disease in humans. (2) However, the tumor is generally detected in a later stage in the dog. Review of the literature reveals that osteosarcoma is the only bone tumor that has been treated by modalities other than surgery in significant numbers.
Osteosarcoma

Classically osteogenic sarcoma has been considered to be one of the cancers most resistant to chemotherapy. Historically in humans, there was a 5-year survival rate of only 20%. In the 1970s a major breakthrough occurred. Metastatic osteosarcoma responded to various single cytotoxic agents. Doxorubicin hydrochloride (Adriamycin) was first shown to be effective inevaluating osteosarcoma by Cortes and co-workers in the early 1970s. Response rates were as high as 50% in metastatic disease with a dosage of 90 mg/m2. Further studies using more tolerable drug dosages lowered response rates to approximately 20%. By combining doxorubicin with alkylating agents, cyclophosphamide and phenylalanine mustard, Sutow pioneered the adjuvant treatment of osteosarcoma. He demonstrated an increase in disease-free survival at M.D. Anderson Hospital from roughly 15% with surgery alone to 55% following adjuvant chemotherapy.

The most exciting and controversial advance in single-drug treatment of osteosarcoma was the use of high-dose methotrexate with citrovorum rescue by Jaffe and Djerassi in 1972. They demonstrated a response rate of 42% in metastatic disease. High-dose methotrexate was then used prior to en bloc resection in previously untreated patients. Rosen observed a 68% response rate in a group of patients treated in this manner. The next major drug to be used inevaluable osteosarcoma patients was cisplatin at a dosage of 90 mg to 120 mg/m2. The overall response rate was 20% to 25%. I have given cisplatin to dogs with metastatic osteosarcoma. No objective response was seen at the dosage of 50 mg/m2. Higher doses are intolerable in dogs because of bone marrow suppression.

Combinations of drugs known to be effective as single agents in evaluable tumors have yielded more consistent and higher response rates than single drugs. Combinations of drugs include high-dose methotrexate and doxorubicin or cyclophosphamide, and dacarbazine (DTIC-Dome) plus vincristine and doxorubicin. Aggressive adjuvant chemotherapy following surgery, with or without radiation therapy, has improved the disease-free interval in humans with osteosarcoma. Human limb salvage has also become a reality owing to the effectiveness ofanticancer drugs and the techniques of regional intra-arterial administration.

A review of the literature fails to show that advances in the treatment of osteosarcoma in humans apply to the dog. Osteosarcoma remains a fatal disease in the majority of afflicted dogs. Historically, amputation has been the sole treatment; the dogs die of metastatic disease at a median of 18 weeks following surgery. Owen and co-workers attempted lung irradiation with a dose of 600 rads for two treatments at a one week interval following amputation. There was no benefit with this treatment. In 1974, Owen and Bobstock administered intravenous Bacille Calmette-Guerin (BCG) or BCG and x-irradiated autologous tumor cell following amputation or irradiation of the involved bone. Four of the six dogs treated with amputation and BCG or BCG and x-irradiated autologous tumor cells lived one year after amputation. Most dogs that had received the primary irradiation were killed because of pain caused by recurrence. In a subsequent study, 20 dogs were treated with amputation and intravenous BCG. Four of these dogs also received autologous x-irradiated tumor cells mixed with BCG on the first treatment. Eleven of the twenty dogs lived 6 months or more and seven of these lived over a year. The site's radiographic appearance of the lesion did not affect the results. Although there appeared to be a delay in development of metastasis and prolongation in survival, these studies were not randomized prospective clinical trials. Historical controls were inadequate to evaluate such a study.

In 1977 Bech-Nielsen conducted another study using BCG as immunotherapy following amputation of the involved limb. The first six dogs were treated with intradermal BCG following surgery and the next five dogs served as controls. This was not a randomized prospective study. The median survival time of the BCG-treated dogs was 40 weeks compared with a 13-week median survival time in the control group. A cumulative life table method for estimating survival rate showed no effect of BCG on survival. In vitro immune parameters were conducted on these dogs. Serum-blocking activity appeared slightly higher in the control dogs after surgery. However, in vitro immune evaluation has changed significantly since this study. With the many new concepts that have evolved around the clinical application of immunotherapy in cancer patients, these studies are very difficult to interpret. The tumor burden due to microscopic metastasis is probably too high for immunotherapy to affect. Therefore, reduction of the tumor burden with cytotoxic drugs is important. Weiden and co-workers conducted a study of amputation with and without adjuvant immunotherapy. Thirty-one dogs were treated by amputation alone, and seventeen dogs were treated postsurgically with intradermal BCG and autologous tumor homogenate. Twelve of these dogs were prospectively randomized clinical trial with 11 control dogs treated by amputation alone. Disease-free interval and survival were not prolonged by immunotherapy.

The major advances in the treatment of osteosarcoma in humans have revolved around the advent of new chemotherapeutic drugs. These advances have not been effectively extrapolated to the treatment of dogs. Hennessand co-workers treated 11 dogs with chemotherapy following limb amputation (10 dogs) or subtotal resection of the primary lesion (1 dog). Two of
these dogs received irradiation prior to amputation and two received immunotherapy with chemotherapy. Thus, many different protocols were used in these 11 dogs. The drugs used included cyclophosphamide, methotrexate-leucovorin rescue, vincristine, and doxorubicin. Since this was the first report of chemotherapy in canine osteosarcoma, it was important that the drugs be generally well tolerated. The median survival of ten dogs was 6 months, with a median time to metastasis of 3 months. One dog with early-staged disease was still alive at 45 months without evidence of metastasis.

One of the most important factors in treating canine osteosarcoma is the advanced stage of disease at the time of diagnosis. The World Health Organization and Veterinary Cancer Society have established a clinical staging system for tumors, including osteosarcoma, in domestic animals (Fig. 79-1). Most dogs at the time of diagnosis of osteosarcoma have advanced local disease (stage III) with or without associated clinical symptoms. Misdorp and co-workers have found that the size of the tumor at diagnosis is a significant prognostic factor, especially as it relates to the presence of metastasis. Thus, canine osteosarcoma is a more advanced disease and a more difficult disease to treat compared with that in humans.

![FIG. 79-1 Clinical staging system for tumors of the bone.](image)

Cotter and Parker treated five dogs with osteosarcoma with amputation followed by high-dose methotrexate and leucovorin rescue. The dosages were a modification of those used successfully in humans. Although the dogs tolerated the large doses of methotrexate when accompanied by leucovorin rescue, the disease-free interval and time to metastasis were not altered. The median time to relapse was 4 months. The pattern of metastasis may have been changed by the chemotherapy. Bone metastasis of osteosarcoma following amputation has been reported in only 5% of cases. In this report two of three dogs given methotrexate for more than 4 months developed bone metastasis. Early metastasis, after two drug cycles, occurred in two dogs. Drug metabolism did not explain the failure of this treatment in dogs. This study has been the most aggressive chemotherapy protocol in canine osteosarcoma to date. It is interesting to note the lack of success with the treatment.

Doxorubicin has been shown effective as a single agent in treating disseminated metastatic advanced osteosarcoma in humans. Madewell and co-workers treated 14 dogs and 3 cats with doxorubicin alone following amputation. The dosage was 30 mg/m² every 3 weeks for 6 months or until radiographic evidence of metastasis. Again there was no significant prolongation of median survival. The disease-free interval was not measured in all of the animals.

Researchers at the University of Pennsylvania have concluded a study comparing doxorubicin alone with doxorubicin plus intralymphatic BCG. All dogs were given doxorubicin at 30 mg/m² every 3 weeks. The dogs in the chemotherapy group received Chicago-Tice BCG intralymphatically 2 weeks after the first drug treatment. All dogs were examined every 3 weeks and chest radiographs were taken at that time. Dogs were treated sequentially according to the time of presentation. The first 12 dogs were treated with doxorubicin alone. Median survival or those dogs was 5.5 months. The results of Madewell and co-workers, as well as those in our 12 dogs at the University of Pennsylvania, curtailed further entry of dogs into the chemotherapy group.

The next 21 dogs were treated with chemotherapy-immunotherapy. The median survival of this group was 7 months. Although statistical analysis is not available at the time of writing, there appears to be no significant difference.

However, examination of the median time to metastasis for both groups suggests that those dogs receiving doxorubicin plus intralymphatic BCG had a longer median disease-free interval than those animals treated with chemotherapy alone. The disease- or metastasis-free interval is calculated in weeks and starts from the date of amputation to the date of clinical or radiographic evidence of metastasis. In the group of 12 dogs treated with doxorubicin alone, 9 dogs developed metastasis. The median disease-free interval was 13.5 weeks. The other three dogs in that group died suddenly of unknown causes with no radiographic evidence of chest metastasis and no clinical abnormalities. The median survival of those three dogs was 7 months.

In the group of 21 dogs treated with doxorubicin and intralymphatic BCG, 18 died of metastasis. The median disease-free interval was 22 weeks. The other three dogs died suddenly. One dog died of gastric and splenic torsion, and the autopsy showed no metastasis. One other dog died of doxorubicin-induced cardiomyopathy. The third dog died of unknown causes. None of the three dogs had evidence of metastasis. The median survival of those three dogs was 8.5 months. There is a suggestion in both treatment groups of prolonged survival in the six dogs that died suddenly with no evidence of metastasis. Further analysis of the data with regard to clinical staging, including size of the primary osteosarcoma, is necessary before drawing any conclusions about the possible effects of adjuvant immunotherapy.

In 1978, Hoover and co-workers reported a prolonged survival and disease-free interval in humans with osteosarcoma who were being treated with anticoagulation therapy at the time of surgery. Patients were treated with warfarin sodium prior to surgery, during surgery, and after surgery. The theoretical basis for this treatment is that tumor cells require a “stickiness” in
order to adhere to tissue atmetastatic sites. This factor is supplied by the patient's owncoagulation abilities. This theory also suggests that metastasisoccurs around the time of surgery and is not necessarily presentat time of diagnosis. Barton has attempted similaranticoagulation treatment during amputation ofosteoarcoma-involved limbs in the dog.*

In 1982, Meyer anda group of veterinarians in various institutions conducted astudy using an innovative treatment in canine osteosarcoma.(23) The study was based on two premises. First,there had been the implication in previously mentioned studiesof a benefit of immunotherapy, namely, BCG, in the dog.Secondly, in mice with induced fibrosarcomas, there wasasuggestion of amelioration of immune defect by splenectomy. Therefore, a prospective randomized clinical trial was conductedcomparing amputation followed by treatment withmethanol-extracted residue BCG (MER) with amputation andsplenectomy plus MER. However, the group undergoing splenectomyshowed a higher mortality, and the randomization wasdiscontinued. The five dogs treated with amputation and MERshowed no differences in survival and disease-free intervalcompared with historical controls.

* Barton C: Personalcommunication, 1980.

---

**Feline BoneTumors**

The treatment of bone tumors in cats has been primarilysurgical. The clinical course or biologic behavior ofosteoarcoma in cats is slower. Amputation of the involved limb or excision of the involved bone prolongs survival moreeffectively than in the dog. However, there are few reports ofosteoarcoma or other primary or secondary bone tumors in cats treated with surgery or medical treatment. Brown and co-workersreported treatment of 13 cats with solid tumors.(4 ) All cats were treated with surgery first to reduce tumor burden or to biopsy for diagnosis. Immunotherapyand combination chemotherapy were administered postsurgically.Eight cats (61%) had a partial remission, which was defined as areduction in tumor volume. Surgical times varied according totumor type. The data is difficult to interpret as far asbenefits of the chemotherapy and immunotherapy are concerned.

---

**Other Bone Tumors, Primary andSecondary**

In general, nonsurgical treatment of primary bone tumors other than osteosarcoma is not documented in veterinarymedicine. The other primary bone tumors include chondrosarcoma,fibrosarcoma, hemangiosarcoma, and liposarcoma. The number ofcases seen are not sufficient to perform prospective randomizedclinical trials. Stage of disease in these isolated cases ofbone tumor is extremely variable and is critical to potentialtreatment response or failure.

---

**Multiple Myeloma**

One group of primary bone tumors is of significance inregard to treatment success. Those tumors are plasma cellmyeloma and lymphosarcoma involving bone. Multiple myeloma inthe dog and cat can be treated successfully with chemotherapy.Solitary plasma cell tumors are rare in humans and animals.Those potential patients are treated with surgery with or without radiation therapy. Radiation can also be used forpalliation of bone pain. Since most patients have disseminateddisease, chemotherapy is the most common treatment. For the past20 years, melphalan (Alkeran) has been the drug of choice.Cyclophosphamide (Cytoxan), another alkylating agent, is thenext most commonly used. The addition of prednisone hasincreased response rate and survival. In humans there has beencontroversy over the best drug schedules, use of otherchemotherapeutic agents, and the value of maintenance treatmentafter patients are in remission.(5) There is also
difficulty in establishing criteria for the diagnosis ofmultiple myeloma, which leads to variability in interpreting theoptimal treatment protocols. These same problems exist in veterinary medicine.

Most recent studies in humans suggest that the preferred drug protocol depends on stage of disease, that is, tumor load.(21) The amount ofimmunoglobulin produced by the myeloma cells can be used toestimate total body tumor mass. The total myeloma cell mass canbe used to assess response to treatment. In humans, most currenttreatment studies report a median survival of approximately 2years. Animals with high tumor loads should receive a drugcombination or more intensive chemotherapy regime. Other drugsused in such protocols include the nitrosources (carmustine[BCNU]), vincristine, and
doxorubicin. However, the use of intensified chemotherapy in patients with low tumor mass may shorten survival. New chemotherapeutic drugs are needed for the poorer prognostic group. Other factors indicative of poor prognosis include anemia, hypercalcemia, and azotemia.

The management of multiple myeloma in the dog and cat has been a direct extrapolation of chemotherapeutic trials in humans. MacEwen and Hurvitz reported a protocol consisting of melphalan at a dosage of 0.1 mg/kg once daily for 10 days then maintenance dose of 0.05 mg/kg once daily. Prednisolone is also given in conjunction with the alkylating agent at a dose of 0.5 mg/kg once daily. They reported results in 11 dogs with a median survival of 12 months, and 3 dogs were still alive. A decrease in serum globulin of 50% or more was considered a good response. My current treatment regimen is as follows:

- Melphalan 7 mg/m² once daily orally x 5 days
- Vincristine 0.03 mg/m² IV on day 1 of treatment
- Prednisolone 0.5 mg/kg once daily continuously
- Melphalan and vincristine may be repeated every 3 weeks

Various criteria are used to evaluate response to treatment. Remission or response is measured individually in each animal depending on type of involvement at the time of diagnosis. The Mpeak, or monoclonal gammopathy, should be reduced by the least 50%. Bone marrow involvement and hematologic abnormalities should improve.

New approaches to treatment of multiple myeloma are sorely needed. Interferon is being used in human clinical trials. Antitumor effects measured at a decrease of at least 50% in serum myeloma protein levels or Bence Jones protein excretion are demonstrable in over 50% of patients. Myeloma in the dog may offer a model to study new chemotherapeutic agents and innovative methods of management.

**Lymphoma in Bone**

Lymphoma in the bone, formerly referred to as reticulum cellsarcoma, initially was considered a solitary, extranodallymphoma that could be treated successfully with amputation or local radiation therapy. However, in humans a retrospective analysis showed that staging procedures including lymphangiogram, bilateral bone marrow evaluation, and liver biopsy were not performed. Also, patients who developed disseminated disease within 6 months of presentation were eliminated from the reports of results of localized treatment. In reality, most cases of bone lymphoma are not solitary and are just another site of involvement of disseminated lymphoma. In one report in humans, 12 of 14 patients undergoing extensive workup had stage IV, or advanced, disease.

In the dog and cat bone involvement is most likely associated with multicentric lymphoma. Treatment includes systemic chemotherapy using one of several drug protocols reported in the literature. Localized radiation in conjunction with chemotherapy, may be needed to control local bone involvement. Prognosis is based on the stage of disease, especially the tumor of bones involved. One animal that I treated was a 10 month-old Afghan that showed lytic lesions on every bone, appendicular and axial, on bone survey. The decision was made to kill the dog because of central nervous system involvement.

**Metastatic Bone Tumors**

There are no reports of medical treatment of metastatic bonetumors in the dog or cat. The two options available for treatment of these lesions are radiation therapy and chemotherapy. Although cure is unlikely, owing probable organ involvement, these two treatment modalities may offer palliation for the animal. I have been treating metastatic organ and bone disease with a combination of doxorubicin and cyclophosphamide. One cat with mammary adenocarcinoma developed metastatic disease in the lungs and lysis of the entire right scapula. The cat was not bearing weight on the limb. Within 24 hours of chemotherapy, the cat was walking normally on the limb. There was also regression of pulmonary metastasis. The decision was made to kill the cat 1 year after it developed pulmonary involvement and 2 months after the scapular metastasis.
References


All rights reserved. This document is available on-line at www.ivis.org. Document No. B0080.0685.