Osteosarcoma[a]

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- diagnosis
- amputation
- limb-sparing surgery
- prognosis

Osteosarcoma (OSA) is by far the most common primary bone tumor in dogs. It accounts for 3% to 4% of all canine cancers and afflicts up to 10,000 dogs per year in North America. It bears striking similarity to the same disease in humans and serves as an excellent model for comparative investigations to the benefit of both species.[1,2]

The etiology of OSA is largely unknown but on rare occasions can be linked to prior local radiation treatment, preexisting bone infarcts, and prior fractures (often with metal implants). Familial and heritable etiologies have been suggested but not proven. Genetic alterations undoubtedly exist in dogs with OSA and are the subject of current investigations.

Management of dogs with OSA has changed from "test and slaughter" (or often don't test and euthanize) to a more proactive attack on both the primary site and metastases. Although cures remain elusive, they do occur, and moderate to marked improvements in survival over amputation alone can be expected with aggressive treatment. Limb-sparing surgery remains investigational but is an acceptable alternative to amputation in selected patients.[3,4] This article concentrates on the more common appendicular OSA locations, but the principles of management apply to all anatomic sites.

DIAGNOSIS

The diagnosis of OSA has been exhaustively covered elsewhere and will only be summarized below.

Differential Diagnoses

Differential diagnoses for OSA include:

- Bacterial osteomyelitis—Usually associated with a history of a penetrating injury or previous local surgery and a draining tract.
- Mycotic osteomyelitis—Usually associated with a travel history to an endemic area (maybe years previously) and blastic radiographic pattern ± pulmonary changes.
- Metastasis from another primary cancer—Usually secondary to a current or past known primary malignancy and often multiple and randomly distributed in skeleton.
- Other primary bone cancer—Less commonly diagnosed primary bone cancer may include lymphoma, myeloma, fibrosarcoma, and hemangiosarcoma. These lesions are predominantly lytic on radiographs and require large biopsies to rule out the more common OSA. Primary chondrosarcoma of bone accounts for less than 5% of all primary cancers and requires large biopsies to differentiate it from the more common chondroblastic osteosarcoma.

Signalment

OSA generally affects large-breed dogs of middle to

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older age. Ninety percent of cases occur in dogs heavier than 15 kg, and there is a slight predilection for male dogs over female dogs.

Site

Seventy-five percent of OSAs occur in the appendicular skeleton and 25% in the axial skeleton. Less than 1% of OSAs occur in soft tissue only, principally in mammary tissue.

History

Most patients present with a several weeks to months history of progressive lameness and local swelling. Acute pathologic fractures may occur with no antecedent signs.

Physical Examination

A physical examination usually reveals a firm, swollen, variably painful mass that is often initially misdiagnosed as a sprain or strain.

Blood Tests

Routine complete blood count (CBC) and biochemical profiles are generally noncontributory. We have recently evaluated a bone isoenzyme of alkaline phosphatase that may be prognostic when elevated at diagnosis (may be associated with large tumor volumes?) and whose elevation after primary tumor treatment may precede clinical or radiographic evidence of metastasis. Routine use of this possible serum marker is under investigation.

Radiographs

Leg

Experienced radiologists or clinicians can accurately predict an OSA in over 90% of cases. Supportive signalment and historical data are helpful. Most osteosarcomas are endosteal in origin (no pain fibers), and the animal is presented only when cortical destruction and associated extension to periosteum or soft tissues cause pain. The "classic" picture is that of a permeative (lytic) and productive (blastic) bone lesion with cortical destruction and extension into soft tissues. Purely lytic or purely blastic lesions, especially if the signalment, history, and site are not pathognomonic for OSA, require biopsy for confirmation.

Lung

Thoracic radiographs reveal metastasis in 5% to 10% of dogs at presentation.

Bone Surveys

One-view radiographs of all the bones in the body detect another 5% to 10% of dogs with occult bony metastasis.

Nuclear Scan

Technetium 99m (Tc 99m) is a bone-seeking isotope that is given intravenously. It is very sensitive for bone activity (arthritis, infection, tumor, etc.) but is not specific. Veterinary studies of nuclear bone scans on dogs with OSA at the time of presentation vary from a yield of zero to a yield of over 20% in detecting occult metastasis.

Other Imaging

Both computed tomography (CT) and magnetic resonance imaging (MRI) can be utilized to evaluate extent of disease in the lung or leg. They are especially valuable for axial skeleton disease in assessing resectability. CT is generally more sensitive for bone invasion and MRI for soft tissue disease, but both are complementary. Neither technique is in routine clinical use for dogs with OSA.

At the time of diagnosis, depending on the aggressiveness and detail of the preoperative metastasis search, between 10% to 20% of dogs can be proven to have synchronous or multicentric disease. This is an important subgroup to identify because aggressive treatment will generally not be effective and bias of case entry into various studies may be altered by unequal stage of disease.

Biopsy

The details and accuracy of bone biopsy have been covered in numerous publications.[5] The method of biopsy is not as critical when an amputation is projected for local disease control but is crucial if one is contemplating limb-sparing surgery. We generally prefer to use a Jamshidi® needle core biopsy instrument. When two samples are taken (one central and one in the transition zone), the accuracy of diagnosing a known OSA by an *experienced pathologist* is 90%. A pathology report of reactive bone is *not* a diagnosis, and further confirmatory studies are needed. Performing a biopsy does not increase the metastatic rate but may compromise local disease control if not properly positioned.

TREATMENT

In spite of all the staging tests performed, no more than 10% to 20% of dogs with OSA will be *confirmed* to have demonstrable metastasis at presentation. The other 80% to 90%, despite negative staging, almost always have occult metastatic disease. Treatment must deal with both *leg* and *survival* issues.

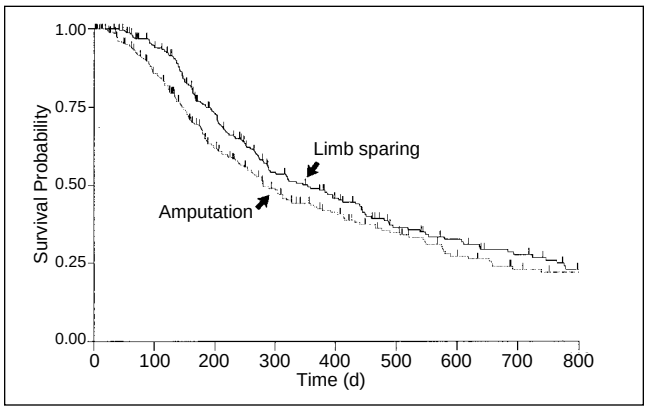

Figure 1. Kaplan-Meier survival curve for dogs treated for malignant bone tumors. The top line represents the survival curve for 220 dogs treated with limb-sparing surgery and the bottom line represents the survival curve for 272 dogs treated with amputation. There is no significant difference between the two curves. (From Straw RC, Withrow SJ: Limb-sparing surgery versus amputation for dogs with bone tumors. *Vet Clin North Am Small Anim Pract* 26:135–143, 1996. Used with permission.)

Leg: Small Band-Aids to Big Band-Aids and the Real Thing

Small Band-Aids

Most OSAs are accompanied by some degree of inflammation. The most effective antiinflammatory drug appears to be piroxicam. Dogs may experience 1, 2, or, rarely, 3 months of pain relief unless they present with a severe lameness or pathologic fracture.

Big Band-Aids

Palliative radiation (8 Gy × three fractions, M-W-F) to the local site(s) can relieve pain and extend life even though it does not generally address metastatic disease. Side effects and cost are low, and pain relief is varied; 1 to 6 months of significant local pain relief is not uncommon. Dogs with good function and small tumor volume generally do the best. This treatment is more commonly used for palliation of metastasis than as primary treatment.

The Real Thing: Amputation or Limb-Sparing Surgery

To be effective, local disease needs to be eliminated before adjuvant chemotherapy can work. Chemotherapy for measurable OSA is generally doomed to failure.[6] Permanent local disease control can only be achieved by amputation or limb-sparing surgery. Survivals are equal for amputation or limb sparing in dogs given "equivalent" adjuvant chemotherapy (Figure 1).[7]

Amputation

Complete leg amputation is well tolerated in virtually all dogs regardless of radiographic evidence of degenerative joint disease. Relative contraindications include *severe* neurologic or orthopedic conditions precluding ambulation on three legs. Well over 90% of dogs presented to Colorado State University could have undergone amputation as definitive local disease control had the owner chosen that route of treatment. Amputation is "simple," cost effective, and almost complication free compared to limb-sparing surgery. Other local disease ablative procedures akin to limb amputation include mandibulectomy, maxillectomy, hemipelvectomy, orbitectomy, rib resection, and scapulectomy.

Limb-Sparing Surgery

We have now performed over 300 limb-sparing surgeries for osteosarcoma in dogs. Case selection has been refined, and complications have been reduced but not eliminated. The "best" case selections are tumors of the distal radius or ulna with mild to moderate soft tissue extension and no pathologic fracture. Other locations including the proximal humerus or any diaphyseal site are occasionally suitable. Osteoarticular allografts, in *very* select patients, have sometimes been successful.

Ideally, limb-sparing surgery is preceded by downstaging with preoperative cisplatin and moderate dose radiation (30 Gy × 10 fractions). This results in significant local cell kill (percent necrosis), facilitates resection by defining margins, and reduces local relapse.[4,8] A slow-release form of locally implanted cisplatin polymer[9] has also reduced local recurrence, and the combination of preoperative downstaging *and* local drug delivery with limb-sparing surgery is under investigation.

A recent report showed a 75% limb "survival" rate for 220 dogs undergoing limb salvage.[7] This includes the "learning curve," and more recent data for radius or ulna indicate a limb survival rate of 90%. Limb-sparing surgery requires more technical skill and resources than amputation and should not be undertaken casually. A bad limb spare is far worse than a good amputation! Management of complications associated with limb-sparing surgery is dealt with elsewhere.[7]

Survival

Once the local disease has been eliminated, the issue becomes survival. Table 1 and Figure 1 summarize the survival of dogs receiving adjuvant chemotherapy after amputation or limb-sparing surgery. The three most active drugs are cisplatin, carboplatin, and doxorubicin.[10–13] The biologic response modifier muramyl tripeptide-phosphatidylethanolamine (MTP-PE) has shown promise in dog trials in conjunction with amputation and cisplatin.[14] Most other drugs are largely untested and/or investigational.

Table 1
OSA Chemotherapy and Survival

Protocol	*Median*	*1 year*	*2 years*
Amputation alone	3 months	10%	0%
Cisplatin (2 to 4 doses)	12 months	50%	30%
Carboplatin (4 doses)	11 months	45%	30%
Doxorubicin (5 doses)	9 months	50%	10%
Cisplatin × 4 and MTP-PE[a]	14 months	64%	40%

[a]Cases not included unless animals were metastasis free 16 weeks after amputation.

The biodegradable cisplatin polymer used in the limb-sparing procedures has been shown to be equal to two doses of intravenous cisplatin in improving disease-free interval and survival.[15] This is presumably due to its low-level but long-time serum platinum exposure (area under the curve). Further refinement of this drug delivery system is underway.

In the hands of an experienced oncologist and in a dog in good general health, the risks of serious chemotherapy-induced side effects are less than 5% to 10%. Costs of drugs vary from country to country, and one should check on the availability of generic drugs (e.g., doxorubicin in the United States and cisplatin in Canada).

The ideal adjuvant chemotherapy program with optimal efficacy, low cost, and minimal toxicity awaits further evaluation. In our opinion, some combination of a platinum compound (cisplatin or carboplatin) and doxorubicin would conceptually appear to be a good idea considering somewhat different mechanisms of action and toxicity.

PROGNOSIS (Table 1; Figure 2)

Few variables appear to influence the predilection of a dog to do well or poorly after aggressive local treatment and adjuvant chemotherapy. High-grade endosteal origin OSA is a reliably locally aggressive and metastatic disease. Known and speculated variables to predict outcome are summarized in the box at right.

SALVAGE THERAPY

Detection of metastatic disease after "adequate" initial therapy is not hopeless, although it usually is a harbinger of multicentric disease. When and where metastasis develops determines the likelihood of treatment doing any good. Chemotherapy rarely, if ever, is effective for measurable OSA either at presentation or at the time of metastasis.[6]

Lung Metastasis

The most common site of metastasis is lung tissue. If a dog has permanent control of its primary tumor, has received "adequate" adjuvant chemotherapy, has had metastasis detected at a late date (more than 300 days from initial treatment), has no other metastasis, has one or two visible lung lesions, and has a metastasis diameter doubling time of greater than 30 days based on thoracic radiographs, it may be a candidate for pulmonary metastasectomy.[16] Twenty to thirty percent of these patients may have long-term benefit from surgical resection of lung metastasis.

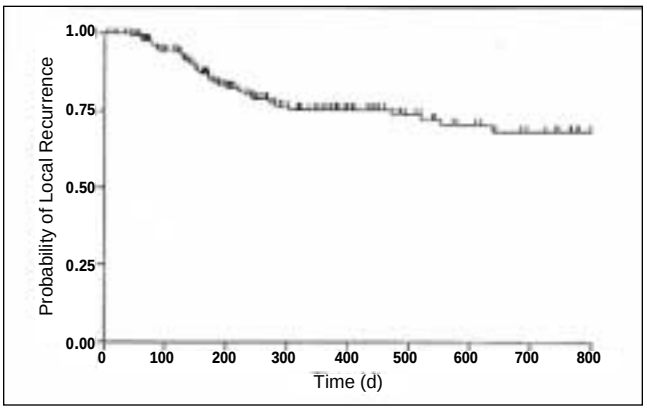

Figure 2. Kaplan-Meier curve for local disease control for 220 dogs with malignant bone tumors treated with limb-sparing surgery. These dogs also received either preoperative radiation therapy, preoperative intraarterial or intravenous cisplatin, intraoperative open-cell polylactic acid containing cisplatin (OPLA-Pt), postoperative intravenous cisplatin, postoperative carboplatin, or a combination of these treatments. (From Straw RC, Withrow SJ: Limb-sparing surgery versus amputation for dogs with bone tumors. *Vet Clin North Am Small Anim Pract* 26:135–143, 1996. Used with permission.)

KNOWN AND SPECULATED VARIABLES TO PREDICT PROGNOSIS FOR ANIMALS WITH HIGH-GRADE ENDOSTEAL ORIGIN OSA

Indifferent
Amputation vs. limb-sparing surgery
Sex
Breed
Histologic variant
Site (except mandible)

Good
Mandible site
Surface tumors (juxtacortical)
Low grade histology (rare)

Bad
Young age
Metastasis at presentation
Large volume
High serum bone alkaline phosphatase?

Bone Metastasis

Patients with suspected bone metastasis after definitive local therapy and adequate adjuvant chemotherapy are considered for salvage, much like those with primary tumor. A nuclear bone scan should be performed to help rule out multicentric bone disease. Treatment is generally with piroxicam, palliative radiation, and, rarely, a resection.

CONCLUSION

Canine osteosarcoma is an excellent model to study both local disease and metastasis. Proper case management requires close interaction of surgeons, medical oncologists, radiation oncologists, and especially nursing staff. Osteosarcoma is one of the only solid tumor types in veterinary medicine where adjuvant therapy is *consistently* and *reproducibly* effective. Cures remain elusive, however, and treatment regimens need to be further defined for both local and systemic disease.

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