An In-Depth Look:

CANINE APPENDICULAR OSTEOSARCOMA

Canine Appendicular Osteosarcoma: Curative-Intent Treatment*

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ABSTRACT:

Dogs with appendicular osteosarcoma, the most common canine primary bone tumor, can be managed with either palliative or curative-intent therapy. Curative-intent techniques must address both the local bone tumor and the potential for development of metastatic disease. Limb amputation is the most common procedure for managing the local tumor. Limb-sparing techniques, both surgical and nonsurgical, provide an alternative to amputation. Postoperative chemotherapy is essential for minimizing the risk of developing metastatic disease and for prolonging a good quality of life.

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This article describes options available for curative-intent management of dogs with appendicular osteosarcoma (OSA). It should be emphasized that because OSA is a malignant tumor with a high metastatic potential, more than 80% of dogs with appendicular OSA die despite the intent to cure.[1] Curative-intent treatment has two distinct aims: control of local disease and prevention of metastatic disease. Limb amputation or limb-salvage techniques can be used to manage the primary bone tumor. Chemotherapy is required to minimize the risk of developing metastatic disease and to prolong a good quality of life.

LIMB AMPUTATION

Limb amputation is the gold standard for local management of primary bone tumors.[1–3] Osteoarthritis, neurologic disease, obesity, and large breed have been cited as

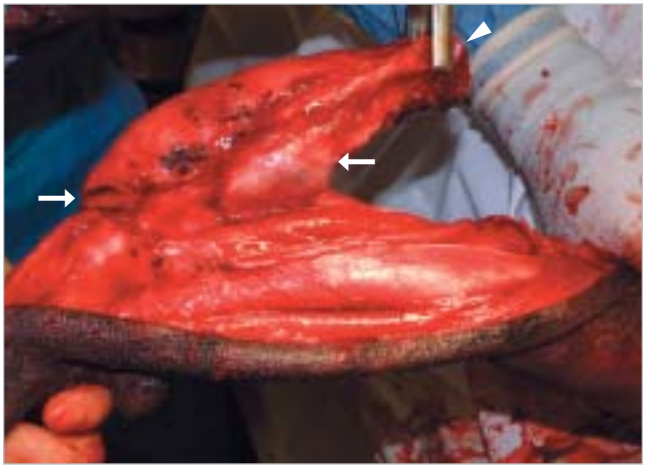


Figure 1. Intraoperative view of the marginal resection of a distal radial OSA (proximal and distal extents indicated by *arrows*). Osteotomy of the proximal diaphyseal margin *(arrowhead)* was guided by radiography, nuclear scintigraphy, and intraoperative examination.

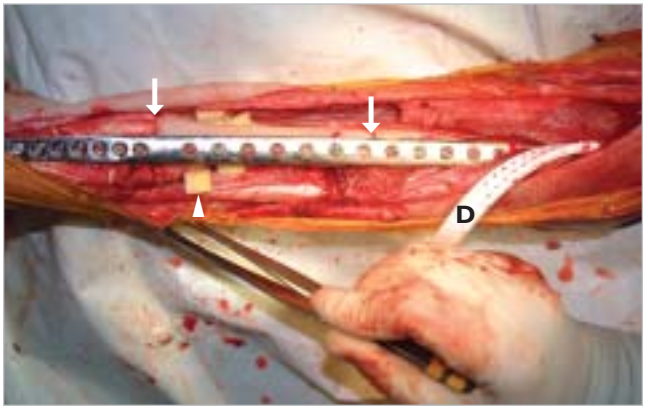


Figure 2. Intraoperative view of a limb-sparing surgical procedure with allograft and bone plate reconstruction. The proximal and distal host–allograft interfaces are indicated with *arrows*. Local biodegradable cisplatin-impregnated implants *(arrowhead)* were placed adjacent to the resection site to reduce the risk of local tumor recurrence, and an active suction drain *(D)* was placed to minimize postoperative swelling.

relative contraindications for amputation.[1–4] However, osteoarthritis, weight, and size are rarely problematic because OSA often occurs in large-breed dogs of middle to older age with preexisting osteoarthritis, and most animals have minimal difficulties after amputation.[3] Dogs with neurologic disease or severe clinical osteoarthritis are exceptions, and palliative management or limb-sparing techniques should be considered in these cases. Thoracic limb amputation should include the scapula, for both tumor control and cosmetic reasons, particularly for dogs with proximal humeral OSA.[1] In the pelvic limb, coxofemoral disarticulation should be performed for dogs with OSA distal to the proximal femur, whereas dogs with proximal femoral OSA should be treated with either en-bloc acetabulectomy or subtotal hemipelvectomy to achieve adequate tumor control and minimize the risk of local recurrence.[1] The surgical techniques for thoracic and pelvic limb amputation are described in detail elsewhere.[4]

Perioperative analgesia is important for improving postoperative recovery and minimizing hospitalization time. Analgesic techniques include acepromazine and opioid premedication, preservative-free morphine epidural, intraoperative and postoperative continuous rate infusions of an opioid (fentanyl, morphine, or hydromorphone) and ketamine, and intraoperative bupivacaine–lidocaine nerve blocks.[5,6] Bupivacaine should not be used with morphine in the epidural injection because this adversely affects motor function.[6]

Postoperatively, most dogs can ambulate unassisted within 12 to 24 hours. Dogs should be encouraged to ambulate after discharge to improve the rapidity of recovery. The median time for maximal adaptation to amputation is 4 weeks, although preexisting lameness and an owner's positive attitude improve the speed and time to adaptation.[3] Body weight and thoracic versus pelvic limb amputation do not have a significant impact on this time; however, in the early postoperative period, dogs with thoracic limb amputation have greater difficulty balancing.[3] Behavioral abnormalities, such as increased anxiety and loss of dominance, have also been reported.[3]

Complications associated with limb amputation are rare. Intraoperative complications include hemorrhage, air embolism, and inadvertent thoracotomy. Infection and recurrence of disease in the stump are possible postoperative complications.

LIMB-SPARING SURGERY

Despite the success of limb amputation in dogs with appendicular OSA, limb-sparing techniques are becoming more common for reasons related to both individual dogs and owner preference.[1,2,7–18] Dogs with severe osteoarthritis or neurologic disease and some obese dogs are poor candidates for amputation and should be considered for limb-sparing surgery.[1,2] However, reluctance of owners to proceed with amputation is the most common reason for performing limb-sparing procedures.[1,2]

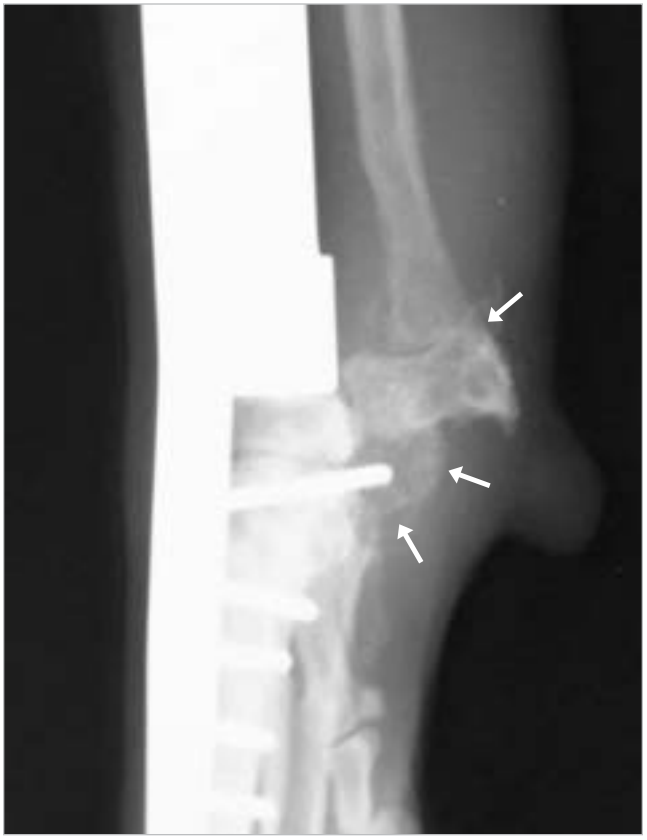


Figure 3. Lateral radiograph after limb-sparing surgery in which an endoprosthesis was used. Local tumor recurrence is seen adjacent and distal to the ulnar carpal bone *(arrows)*.

Indications

Limb-sparing surgery is indicated in dogs with primary bone tumors of the distal radius and ulna.[1,2,7–9] Such surgery in other locations is often associated with a high complication rate and poor postoperative limb function.[1,10,11] Good surgical candidates are dogs with OSA confined to the bone, with minimal extension into adjacent soft tissue and involving less than 50% of the bone length.[1,2] The extent of bone involvement is most accurately determined by using computed tomography.[19] Bone involvement is overestimated by radiography, nuclear scintigraphy, and magnetic resonance imaging.[19–21] Nevertheless, the use of imaging techniques that overestimate the degree of bone involvement may be preferable as adequate surgical margins and complete resection of the tumor are more likely.[20] Pathologic fracture is a relative contraindication for limb-sparing because of tumor seeding into adjacent soft tissue, although the risk of local tumor recurrence can be reduced by use of preoperative chemotherapy or radiation therapy.[2]

Techniques

A number of surgical techniques have been reported to preserve limb function and are described in detail elsewhere.[1,2,7–18] Marginal resection of the soft tissue component of the bone tumor is common to all techniques (Figure 1). After resection, the osseous defect is filled with a massive cortical allograft that is fixed in position with a bone plate and screws[1,2,7,8] (Figure 2). The resected bone can be pasteurized, autoclaved, or irradiated as an alternative to the use of cortical allografts.[9,22] Arthrodesis of the adjacent joint is often required because of the metaphyseal and periarticular location of appendicular OSA.[1,2] Pancarpal arthrodesis is well tolerated, but arthrodesis of the shoulder, stifle, and tarsal joints results in poor orthopedic function.[23] In dogs with ulnar OSA, segmental ulnectomy, including the styloid process, is possible without the need for either osseous reconstruction or arthrodesis.[1,2] Rarely, joint and limb preservation in dogs with nonulnar diaphyseal OSA is possible by using intercalary grafts.[24] As in the case of amputation, perioperative analgesia improves recovery and function after limb-sparing surgery. The limb is lightly bandaged, and bandages are changed every 3 days for 2 to 3 weeks.[1,2]

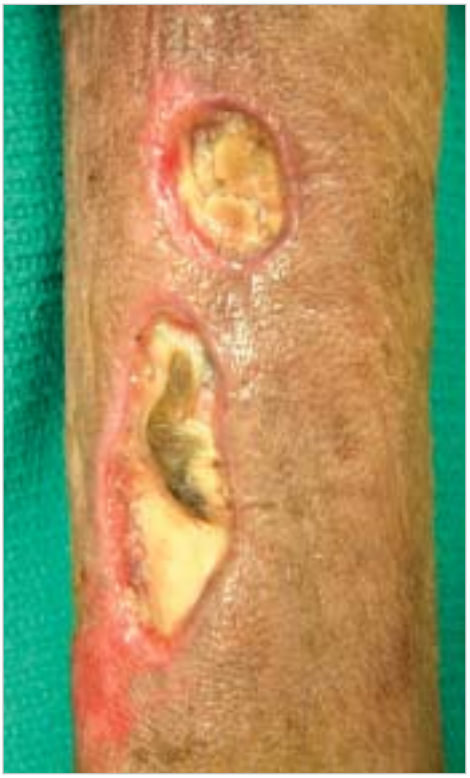
Exercise should start immediately postoperatively but should be restricted to leashed walks for the first 4 weeks.[1,2] Exercise is important for preventing flexure contracture of the digits and minimizing swelling of the foot and digits, both of which can occur as a result of resection of the digital extensor muscles and tendons and vascular structures during surgery. Good to excellent limb use can be achieved in more than 80% of dogs.[1,2,7,8]

Complications

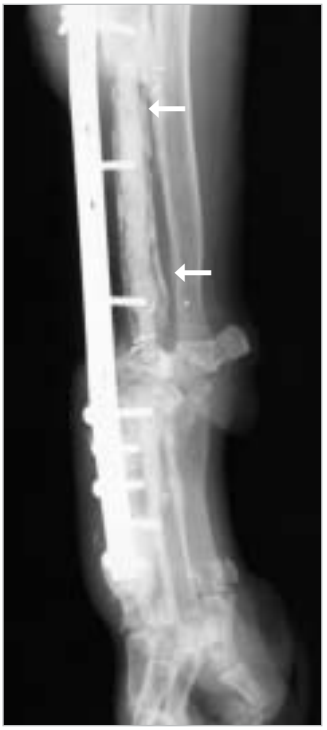
Implant Failure

The use of allografts for limb-sparing surgery is associated with a number of problems. Aseptic harvesting, preparation, and storage of cortical bone are time-consuming and expensive. Cortical allografts are available from commercial bone banks, but limited availability and range in dimensions can make it difficult to match the size and diameter of the allograft with the host bone. The complication rate for limb-sparing surgery with cortical allografts often exceeds 50%.[1,2,7,8,12–14] The most common complications are implant failure (in approximately 10% of cases), local tumor recurrence,

Figure 4. Infection after limb-sparing surgery.



Patients with infection after limb-sparing surgery can present with draining sinuses, skin loss, and exposure of the allograft and orthopedic implants.



As this lateral radiograph shows, the cortical allograft has been absorbed and only the methylmethacrylate column is visible *(arrows)*. Despite infection, limb function remained good.

and infection.[1,2,7,8,12–14] Injection of methylmethacrylate into the medullary canal of the allograft increases screw pullout strength and reduces the incidence of screw loosening, implant failure, and allograft fracture.[12]

Local Tumor Recurrence

Local tumor recurrence is caused by incomplete resection or, more often, residual neoplastic cells in the soft tissue adjacent to the tumor capsule after marginal resection of the primary tumor[1,2,18] (Figure 3). The rate of local recurrence has been reported to be as high as 28%,[8] but this rate has been reduced to less than 10% with the use of locally released chemotherapeutic agents (such as cisplatin, from open-cell polylactic acid biodegradable implants) and appropriate case selection.[1,2,13] Local recurrence may have either no effect[2] or a negative impact[10,25] on survival time. Local recurrence can be managed with a second limb-sparing surgical procedure, amputation, or palliative radiation therapy.[2]

Infection

Infection is the most significant complication encountered with limb-sparing surgery.[1,2,7,8,12,14] Although the cause of infection is unknown, hypotheses

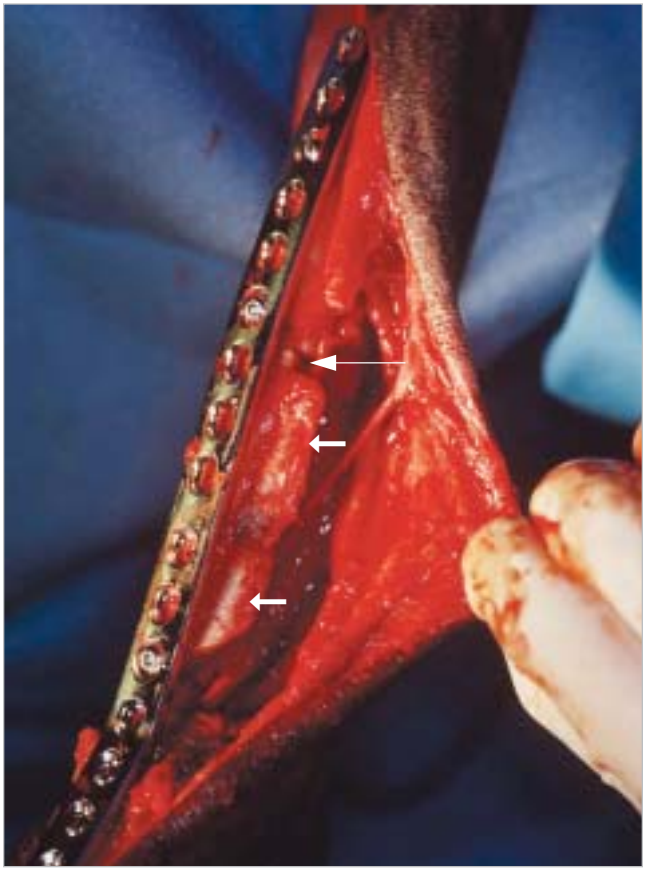


Figure 5. Intraoperative view of a limb-sparing procedure performed with microvascular implantation of the ulna, based on the common interosseous artery and vein. The proximal graft–bone interface is indicated by a *long arrow*, and the vascularized muscular cuff is indicated by *short arrows*.

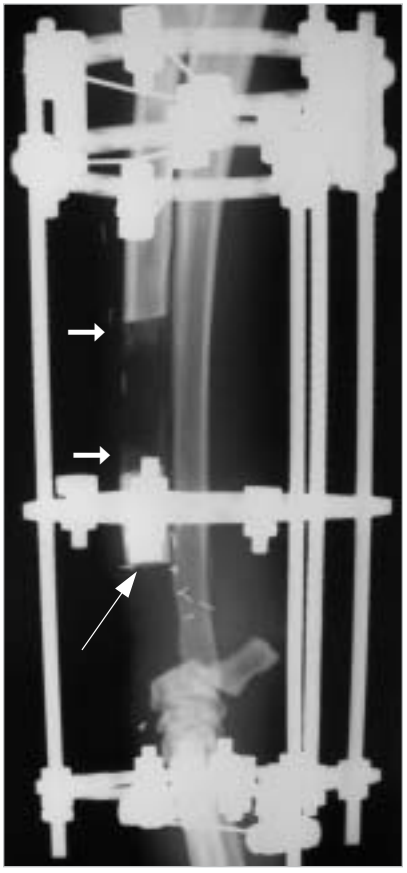


Figure 6. Lateral radiograph 5 weeks after limb-sparing surgery of the distal radius performed by distraction osteogenesis with a circular fixator. Regenerate bone and normal host bone *(short arrows)* trail the intercalary bone segment *(long arrow)*, which was transported distally 1 mm/day by means of turning bolts on the circular fixator frame. This process was completed within 16 weeks, and the circular fixator was removed after 36 weeks, when the regenerate bone had remodeled and could support full weight.

include extensive soft tissue resection with vascular compromise to a poorly perfused site, poor soft tissue coverage, implantation of orthopedic implants and nonvascularized and possibly immunogenic cortical bone, and administration of local and systemic chemotherapeutic agents.[2] Infection occurs in more than 40% of cases, and approximately two-thirds of infections are diagnosed 6 months or more after surgery[7,8,12,14] (Figure 4). A number of different bacterial organisms have been cultured, with about 50% of cases being monomicrobial infections and 50% being polymicrobial.[14] Infections are first treated with appropriate antibiotics, isotonic saline lavages, and wet-to-dry bandages.[1,14] If the infection is unresponsive to treatment or recurs, antibiotic-impregnated methylmethacrylate beads can be surgically implanted adjacent to the infection site.[14] Limb amputation is a salvage procedure and is used in 1% to 2% of dogs with uncontrollable infection.[1,12,14]

Alternative Limb-Sparing Techniques

The problems associated with bone banking and surgery-related infection have prompted investigation into alternative techniques of limb-sparing surgery. Autogenous bone is preferable to allogeneic bone and prosthetic material to minimize the risk of infection.[26] Sterilization of host bone with pasteurization, autoclaving, or radiation renders it nonviable. However, three limb-sparing techniques using viable autogenous tissue are available. An ulnar rollover technique was recently reported with good results in three dogs, despite limb shortening of up to 24%.[15] The distal ulna is osteotomized, rolled into the radial defect, and secured with a bone plate and screws. Preservation of the caudal interosseous artery and vein and a cuff of the deep digital flexor, abductor pollicis longus, and pronator quadratus muscles are important for maintaining viability of the transplanted ulna.[15] Microvascular transfer of the more substantial middiaphysis of the ulna, based on the common interosseous

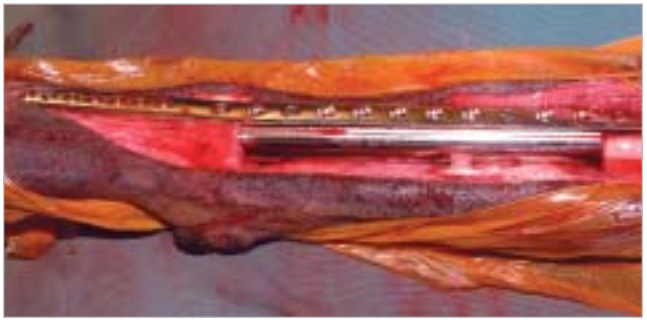


Figure 7. Intraoperative view of a limb-sparing surgical procedure in which an endoprosthesis was used as a spacer between the radial carpal bone and radial diaphysis. The endoprosthesis was stabilized with a 2.7/3.5-mm hybrid bone plate.

artery and vein, was investigated in dogs with distal radial OSA, with good results in five dogs[16] (Figure 5).

Circular fixators have been used to transport an intercalary segment of normal bone from the proximal radius to the radial carpal bone in a process called *distraction osteogenesis*, which results in the production of vascularized and viable regenerate bone[17] (Figure 6). The results following the procedure have been very encouraging, with good orthopedic function and no reported infections.[17] Problems with this technique include owner compliance in distracting the apparatus two to four times per day, implant complications such as pin-tract drainage and loosening, difficulty in docking the intercalary bone onto the radial carpal bone, maintenance of an external frame for over 70 days (depending on the size of the radial defect), and local tumor recurrence.[17]

Expandable endoprostheses are commonly used for limb-sparing surgery in children with appendicular OSA because the implant length can be increased to correspond with growth rate.[18] In dogs, cortical allografts rarely become fully incorporated and thus act as spacers.[1,7,12,26] This situation has stimulated interest in the use of a commercial, first-generation endoprosthesis as a metal spacer (Figure 7). We are conducting a prospective clinical trial comparing short-term complications of cortical allografts and endoprostheses. Preliminary results are encouraging: Endoprostheses are associated with a lower infection rate and more superfi-

Table 1. Chemotherapy Protocols Used in Managing Dogs with Appendicular Osteosarcoma[1,31–41]

Agent	Dose	Interval (wk)	Number of doses	Comments/Side Effects
Cisplatin	70 mg/m^2	3	5	Vomiting during administration, nephrotoxicity, gastrointestinal toxicity, mild myelosuppression; nadir at 10 days
Carboplatin	300 mg/m^2	3	4	Myelosuppression, gastrointestinal toxicity; nadir at 11–14 days
Doxorubicin	30 mg/m^2; 1 mg/kg (<10 kg)	2–3	5	Anaphylaxis during administration, extravasation, gastrointestinal toxicity, myocardial toxicity, myelosuppression; nadir at 10 days
Cisplatin Doxorubicin	50 mg/m^2 15 mg/m^2	3	4	Cisplatin administered on day 1, and doxorubicin on day 2
Carboplatin Doxorubicin	300 mg/m^2 30 mg/m^2	3	6	Carboplatin and doxorubicin administered alternately every 3 wk for three doses each, for a total of six doses

Table 2. Saline Diuresis Protocols Used to Minimize Cisplatin-Associated Nephrotoxicity[1]

Protocol	Phase I	Phase II	Phase III
6 hr	Saline at 18.3 ml/kg/hr for 4 hr	Cisplatin for 20 min	Saline at 18.3 ml/kg/hr for 2 hr
24 hr	Saline at 3.75 ml/kg/hr for 4 hr	Cisplatin for 16 hr	Saline at 3.75 ml/kg/hr for 4 hr

cial and curable infections, and there is no difference in the occurrences of implant failure. However, these results are preliminary, and data are still being accrued.

RADIATION THERAPY

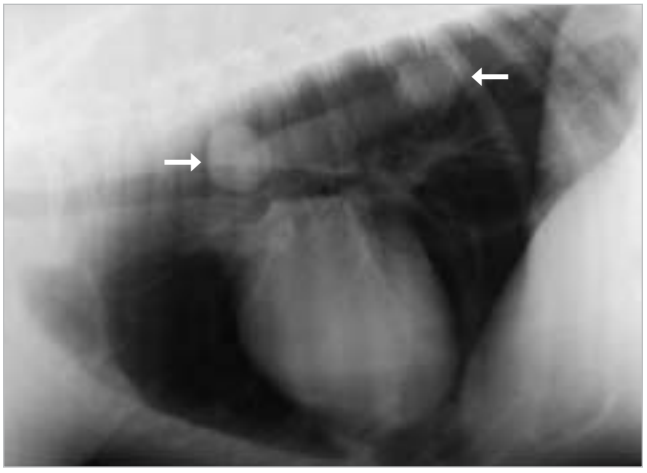
Radiation therapy is most often used for palliation but can be used for control of the primary bone tumor when surgical options are either refused or not indicated.[27,28] Full-course external beam radiation therapy was investigated as a nonsurgical limb-sparing technique in 26 dogs with OSA in appendicular and vertebral sites.[27,28] The fractionation and radiosensitization protocols varied, with total doses between 24 and 54 Gy.[27,28] Complications included moist desquamation, alopecia, depigmentation, bone marrow suppression, and pathologic fracture.[27,28] The median survival time (MST) for dogs treated with curative-intent radiation therapy and adjuvant chemotherapy has been 7 months.[27,28] Intraoperative irradiation of appendicular OSA has been used for 13 dogs at Colorado State University. The complication rate was high, but local tumor control was good and the procedure provides a novel alternative for limb salvage in nonradial sites, particularly in bone with good soft tissue coverage.[29,30]

CHEMOTHERAPY

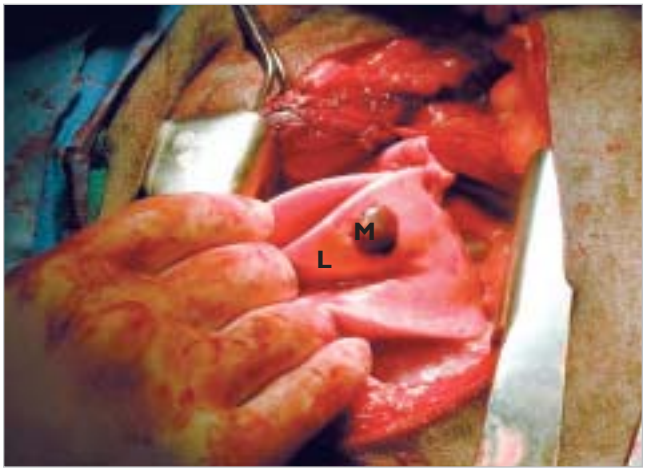
There is a minimal difference in survival times for dogs with appendicular OSA managed with analgesics, palliative radiation therapy, and surgery alone, unless surgery is combined with chemotherapy.[1,31–41] Conversely, chemotherapy without surgery does not provide a survival benefit over other palliative techniques.[42] In humans, the postoperative chemotherapy protocol is often determined by the response to preoperative chemotherapy, which is indicated by the percentage of necrosis in the primary bone tumor.[18] The preoperative chemotherapy protocol is continued when the percentage of necrosis is high, whereas the chemotherapy protocol is changed and the prognosis poor when the percentage of necrosis is low.[18] In dogs, however, no difference in survival times was seen when chemotherapy was started preoperatively, intraoperatively, or up to 3 weeks postoperatively.[38,39] Chemotherapy is usually started at the time of suture removal to minimize the risk of complications associated with perioperative administration and to permit assessment of postoperative recovery and progress.

Chemotherapy protocols include cisplatin, carboplatin, and doxorubicin, either as single agents or in combination[1,31–41] (Table 1). There are no apparent differences in survival times among the different protocols, and protocol selection usually depends on drug cost, adverse effects, and intensity of treatment. Aggressive saline diuresis is necessary to minimize the risk of nephrotoxicity associated with cisplatin administration[1] (Table 2). Nephrotoxicity can also be reduced by using carboplatin instead of cisplatin or by concurrently administering amifostine, which is used to prevent cisplatin-induced nephrotoxicity in humans.[1,35,40] Doxorubicin can be associated with myocardial toxicity, especially with cumulative doses greater than 180 mg/m^2; therefore, an echocardiogram is recommended before starting this drug, particularly in high-risk breeds.[1] After administration of chemotherapy, especially after the first dose, dogs should be discharged with antibiotics and antiemetics for palliation of gastrointestinal disease and nausea. Hematologic studies should be con-

Figure 8. Metastatic OSA.



Lateral thoracic radiograph of a rottweiler with metastatic OSA. Two pulmonary lesions are evident in the middle and caudal dorsal lung fields *(arrows)*.



Intraoperative view of lung metastasis (*L* = lung lobe; *M* = metastastic lesion). Partial lung lobectomy was performed with a surgical stapling device. The dog died 294 days after metastasectomy from causes unrelated to the tumor or metastasis.

ducted immediately before subsequent doses to assess the presence and degree of myelosuppression. Administration of chemotherapeutics should be delayed, or the dose decreased, when the neutrophil count is less than 2,000/µl or the platelet count is less than 100,000/µl.[1]

The MST for dogs treated with surgery and chemotherapy is 235 to 366 days, with a 33% to 65% 12-month survival rate and a 16% to 28% 24-month survival rate.[31–41] In some studies, dogs treated with chemotherapy and either limb amputation or limb-sparing surgery are considered a uniform population.[37,38] However, these two groups should be evaluated separately because dogs with infection after limb-sparing surgery have a significantly greater survival time than dogs with limb amputation or limb-sparing surgery without infection.[40]

METASTASIS

Metastatic disease is the most common cause of death or euthanasia in dogs with appendicular OSA after curative-intent treatment.[1] Pulmonary and skeletal sites are most frequently involved[1] (Figure 8). In dogs with skeletal metastases, management options include pain control with analgesics, bisphosphonates, palliative radiation therapy, and metronomic chemotherapy. Bisphosphonates are antiosteoclastic drugs that minimize the risk of pathologic fracture and reduce pain associated with primary and metastatic bone tumors. They may also have some antitumor effect.[43] Limb-sparing surgery and curative-intent radiation therapy have been used to treat metastatic skeletal lesions in selected cases but are not routinely recommended.

Conventional chemotherapy is not effective in prolonging the survival time of dogs with measurable pulmonary metastases.[44] In certain cases, surgical resection of pulmonary metastatic lesions by either subpleural resection or partial lung lobectomy can significantly improve survival time[45] (Figure 8). Indications for pulmonary metastasectomy include development of pulmonary metastasis more than 300 days after initial diagnosis of appendicular OSA, fewer than three radiographically evident metastatic lesions, and no doubling in size of these lesions or development of new lesions in a 4-week period.[45] Pulmonary metastasectomy can also be performed for palliative relief in dogs with hypertrophic osteopathy. The MST for dogs with appendicular OSA metastatic to the lungs is 61 days when treated with chemotherapy and 176 days when managed with metastasectomy.[44,45]

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ARTICLE #2 CE TEST

This article qualifies for 1.5 contact hours of continuing education credit from the Auburn University College of Veterinary Medicine. Subscribers who wish to apply this credit to fulfill state relicensure requirements should consult their respective state authorities regarding the applicability of this program. To participate, fill out the test form inserted at the end of this issue.

1. What are the aims of curative-intent treatment?

a. control of local tumor
b. prevention of metastatic disease
c. control of local tumor and prevention of metastatic disease
d. palliative relief of local tumor

2. Absolute contraindications for limb amputation in dogs with appendicular OSA include

a. osteoarthritis.
b. neurologic disease.
c. obesity.
d. large breed.

3. What are the indications for limb-sparing surgery?

a. tumor confined to bone, minimal soft tissue involvement, and less than 50% bone involvement
b. tumor confined to bone, minimal soft tissue involvement, and pathologic fracture
c. tumor confined to bone, minimal soft tissue involvement, and more than 50% bone involvement
d. skeletal metastasis

4. What appendicular site is most amenable to limb-sparing surgery?

a. distal radius
b. proximal humerus
c. distal tibia
d. distal femur

5. What are the most common complications associated with limb-sparing surgery with cortical allografts?

a. infection, fracture, and implant failure
b. infection, local tumor recurrence, and implant failure
c. infection, local tumor recurrence, and fracture
d. local tumor recurrence, fracture, and implant failure

6. What are the possible treatments of limb-sparing–related infection in dogs?

a. oral antibiotics
b. antibiotic-impregnated methylmethacrylate beads
c. limb amputation
d. all of the above

7. What chemotherapeutic drugs are recommended, either alone or in combination, for postoperative treatment of dogs with appendicular OSA?

a. cisplatin, carboplatin, and doxorubicin
b. cisplatin, doxorubicin, and mitoxantrone
c. carboplatin, ifosfamide, and doxorubicin
d. cisplatin, carboplatin, and vincristine

8. What hematologic changes are important when determining whether chemotherapy should be delayed or the dose decreased?

a. neutrophil count less than 5,000/µl and platelet count less than 200,000/µl
b. packed cell volume less than 40% and total serum protein value less than 50 g/dl
c. neutrophil count less than 2,000/µl and platelet count less than 100,000/µl
d. packed cell volume less than 30% and total serum protein value less than 40 g/dl

9. What are the indications for metastasectomy in dogs with pulmonary metastasis?

a. disease-free interval of more than 300 days, fewer than three metastatic lesions, and tumor doubling time of less than 40 days
b. disease-free interval of more than 300 days, fewer than three metastatic lesions, and tumor doubling time of more than 40 days
c. disease-free interval of less than 300 days, fewer than three metastatic lesions, and tumor doubling time of more than 40 days
d. disease-free interval of more than 300 days, more than three metastatic lesions, and tumor doubling time of more than 40 days

10. Which therapy does not provide effective palliative relief in dogs with metastatic disease?

a. bisphosphonates
b. radiation therapy
c. analgesics
d. chemotherapeutic agents

DECEMBER 2003 — QUIZ ANSWERS

ARTICLE #1
Bordetella Infections in Dogs and Cats: Pathogenesis, Clinical Signs, and Diagnosis—*C. Datz*

1. d	2. c	3. a	4. d	5. b
6. c	7. d	8. a	9. a	10. c

ARTICLE #2
Bordetella Infections in Dogs and Cats: Treatment and Prevention—*C. Datz*

1. d	2. c	3. c	4. b	5. b
6. d	7. a	8. c	9. b	10. a

ARTICLE #3
Local Anesthetics: Pharmacology and Novel Applications in Small Animal Practice—*T. M. Wolfe, W. Muir*

1. a	2. e	3. e	4. b	5. a
6. c	7. d	8. a	9. d	10. e

ARTICLE #4
Use of Cystostomy Tubes in Small Animals—*K. Hayashi, R. J. Hardie*

1. b	2. a	3. d	4. c	5. a
6. d	7. c	8. b	9. c	10. d

ARTICLE #5
Diagnosing Guttural Pouch Disorders and Managing Guttural Pouch Empyema in Adult Horses—*G. A. Perkins, A. Pease, E. Crotty, S. L. Fubini*

1. e	2. c	3. b	4. a	5. d
6. b	7. a	8. c	9. b	10. b

ARTICLE #6
Equine Grain-Associated Disorders—*D. S. Kronfeld, P. A. Harris*

1. d	2. d	3. c	4. b	5. e
6. b	7. c	8. b	9. a	10. a