CE

An In-Depth Look:

CANINE APPENDICULAR OSTEOSARCOMA

Canine Appendicular Osteosarcoma: Diagnosis and Palliative Treatment*

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ABSTRACT:

Appendicular osteosarcoma (OSA) is the most common primary bone tumor in dogs. Signalment, physical and orthopedic examinations, regional and thoracic radiography, bone biopsy, and nuclear scintigraphy can be used for diagnosing and staging of OSA in dogs. Palliative treatment options for appendicular OSA, which include analgesia, radiation therapy, limb amputation, and metronomic chemotherapy, are described.

Osteosarcoma (OSA) is the most common primary bone tumor of the appendicular skeleton in dogs.[1] Chondrosarcoma (CSA), fibrosarcoma (FSA), and hemangiosarcoma (HSA) are also considered primary bone tumors, although they are diagnosed much less frequently.[1] Other tumors with skeletal involvement, such as multiple myeloma, lymphoma, and metastatic neoplasia, particularly prostatic and urothelial carcinomas, usually occur in multiple sites and have concomitant systemic signs.[1] A review of the bone tumor database at the Animal Cancer Center at Colorado State University revealed that OSA accounted for 98% of 1,273 appendicular primary bone tumors diagnosed in dogs.

DIAGNOSIS

Signalment

Appendicular OSA is a disease of large to giant canine breeds.[1,2] A number of breeds reportedly have an increased risk of developing appendicular OSA.[1,2] However, size and especially height are considered more important risk factors than breed.[1,2] A male predisposition for the disease has been reported,[1] but neutering may be more important because neutered dogs, regardless of sex, have a twofold greater risk of developing appendicular OSA compared with sexually intact dogs.[2] The age at presentation is bimodal: Fewer dogs are diagnosed at 1 to 2 years of age, but most dogs are diagnosed at 7 to 9 years of age.[1,2]

*A companion article on curative-intent treatment appears on p. 186.

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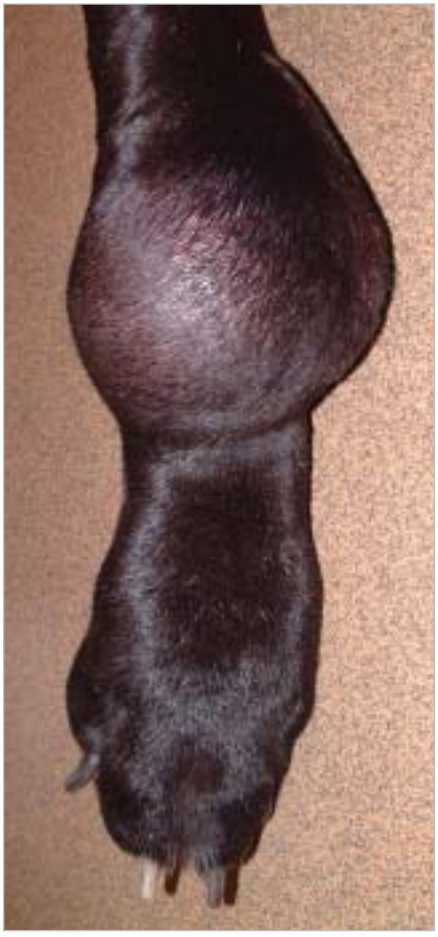


Figure 1. Marked swelling of the distal radius in a 7-year-old Great Dane caused by extension of OSA into adjacent soft tissue.

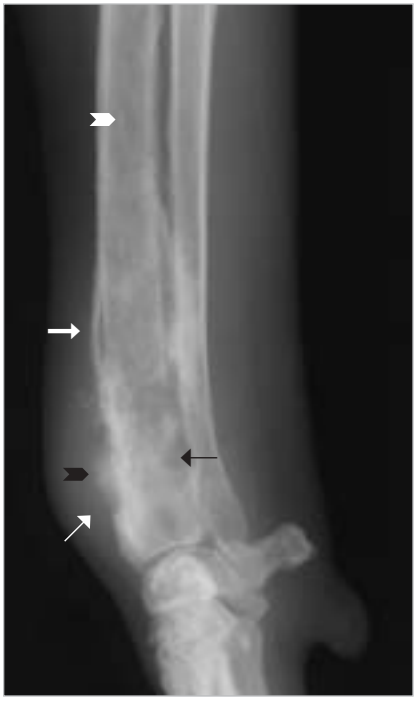


Figure 2. Lateral radiograph of the distal radius and ulna of a dog with OSA. Radiographic signs consistent with a primary bone tumor include cortical lysis *(black arrow)*, periosteal proliferation *(black arrowhead)*, lifting of the periosteum *(thick white arrow)*, endosteal lysis *(white arrowhead)*, and soft tissue swelling *(thin white arrow)*. Subsequent nuclear scintigraphy and magnetic resonance imaging of this antebrachium showed the tumor extending to just below the radial head.

Physical and Orthopedic Examinations

Lameness and localized limb swelling are the most common owner complaints.[1] Appendicular OSA occurs in the metaphyseal region of long bones, particularly the distal radius and proximal humerus.[1,3] The proximal and distal aspects of the femur and tibia are affected less frequently.[1,3] Rarely, OSA originates in diaphyseal bone or involves metaphyseal bone on both sides of a joint.[1,3] Lameness is caused by periosteal inflammation, microfractures, and occasionally pathologic fracture. Swelling usually results from extracompartmental extension of the bone tumor into adjacent soft tissue[1] (Figure 1). A thorough orthopedic examination is necessary in large-breed dogs to localize the source of lameness and to differentiate metaphyseal pain from other common orthopedic diseases such as osteoarthritis, cranial cruciate ligament rupture, and hip dysplasia. Physical examination and a minimum database, consisting of results of hematologic and serum biochemical studies and urinalysis, are important for evaluating general health status and ability to tolerate surgery and chemotherapy.

Regional Radiography

Regional radiographs of the affected area are recommended for a tentative diagnosis and differentiation from other orthopedic diseases. The three basic types of OSA are endosteal, periosteal, and parosteal.[1,4] Periosteal and parosteal OSA originate from the periosteal surface and rarely involve the endosteum and medullary canal.[1,4] However, periosteal and parosteal OSA are very rare compared with endosteal OSA.[1] The radiographic appearance of endosteal OSA can range from lytic to blastic and is usually a mixture of both patterns.[1,4,5] Other characteristic, but not necessarily pathognomonic, radiographic signs of appendicular OSA include loss of cortical bone, periosteal proliferation, palisading cortical bone (sunburst effect), periosteal lifting caused by subperiosteal hemorrhage (Codman's triangle), loss of the fine trabecular pattern in metaphyseal bone, and pathologic fracture with metaphyseal collapse[1,4,5] (Figure 2). Appendicular FSA and CSA have a similar radiographic appearance to OSA and cannot be differentiated radiographically. However, classic signalment, presentation, and radiographic findings are often sufficient for diagnosing a primary bone tumor.[1,4]

The principal diagnostic differential for appendicular OSA is fungal osteomyelitis, especially that caused by *Coccidioides immitis* and *Blastomyces dermatitidis*.[1,4,5] A thorough history is necessary to determine whether the dog lives in or has traveled through an area endemic for fungal disease. Dogs with fungal osteomyelitis often present with systemic illness and polyostotic bone involvement.[1,4,5] In contrast, dogs with appendicular OSA rarely have systemic illness, and bone involvement is usually

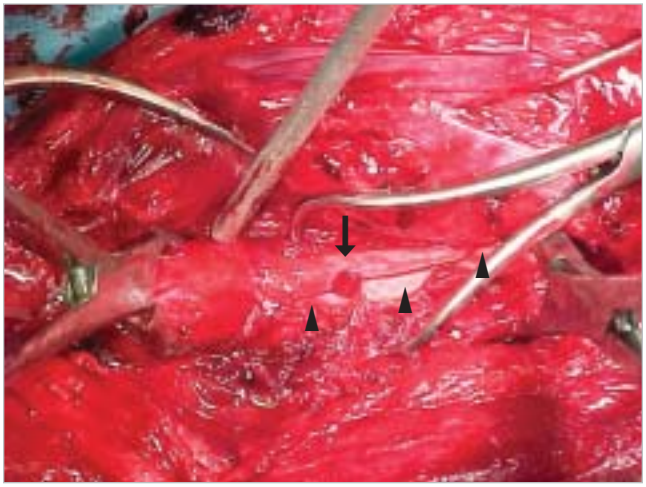


Figure 3. Intraoperative view of a pathologic fracture *(arrowheads)* through the site of a biopsy performed with a Michele trephine *(arrow)*. The lesion was a primary middiaphyseal femoral OSA in a greyhound.

confined to a single site.[1,4,5] Bacterial osteomyelitis, atypical bone cysts, and metastatic neoplasia are other potential diagnoses, although these disorders rarely occur. History, physical examination findings, and radiographic appearance are usually adequate for differentiation of these conditions from classic OSA.

Bone Biopsy

Bone biopsy can be performed via closed or open techniques to confirm the diagnosis of OSA.[1,6–10] Fine-needle aspiration, with or without ultrasound guidance, is a useful, minimally invasive technique for diagnosing sarcoma or OSA and for differentiating primary bone tumors from metastatic disease and fungal osteomyelitis.[6,7] Closed needle-core biopsy, by means of either a Jamshidi needle or a Michele trephine, is more invasive and requires general anesthesia.[1] Radiography of the bone lesion is necessary to plan the biopsy procedure.[1] Bone biopsy should be planned and performed meticulously, preferably by the primary surgeon, so that amputation or limb-sparing surgery is not compromised (such as with large or transverse incisions or hematoma formation) and the biopsy tract can be removed en bloc with the tumor during definitive surgery.[1,8]

We prefer to use a Jamshidi needle for a closed bone biopsy. Larger core samples can be obtained with a Michele trephine, with a diagnostic accuracy rate of 94%, but the larger bone defect also increases the risk of pathologic fracture[1,9] (Figure 3). Multiple, unicortical

Figure 4. Jamshidi needle with multiple core biopsy samples from a distal radial OSA. Multiple samples increase the diagnostic yield.

biopsy samples should be obtained from the center and periphery of the lesion[1] (Figure 4). A correct diagnosis is made for 82% of bone biopsy samples procured using a Jamshidi needle.[10] Multiple biopsies increase the diagnostic accuracy because small, single biopsy samples can be misdiagnosed as HSA, FSA, or CSA as a result of the heterogenous nature of OSA.[1,10] Biopsy of the central area of the bone lesion is recommended because the peripheral aspects of bone tumors often contain reactive, healing bone, which can lead to an erroneous diagnosis.[1,10] The risk of pathologic fracture is higher when the biopsy needle penetrates both near and far cortices.[1]

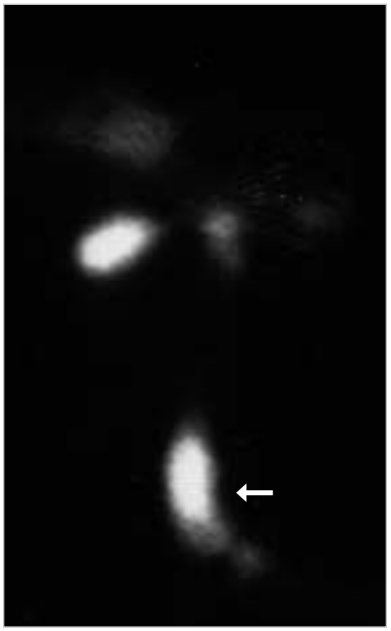
We do not routinely recommend a bone biopsy unless the presentation is atypical, such as an unusual tumor location, presence of systemic illness, or travel history to an area of endemic fungal disease, or when knowledge of the tumor type will change the owner's willingness to proceed with curative-intent treatment, such as the need for adjuvant chemotherapy in dogs with appendicular OSA but not necessarily FSA or CSA. After curative-intent surgery, the tumor should be submitted for histopathology to substantiate the biopsy diagnosis, especially if OSA was not originally diagnosed because of the possibility of a misleading diagnosis from a small biopsy sample.

Metastasis Evaluation

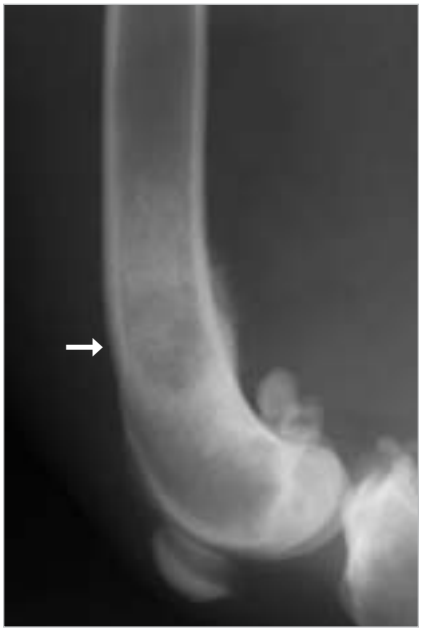
Appendicular OSA is a highly malignant tumor: More than 90% of dogs have micrometastatic disease, although less than 15% of dogs have clinically detectable metastasis at the time of initial diagnosis.[1] Metastasis occurs primarily through hematogenous routes, particularly to the lungs and other bones, although a 25% rate of metastasis to regional lymph nodes was recently reported.[1,7] Palpation of regional lymph nodes, thoracic radiography, and nuclear scintigraphy are essential tools in staging the tumor in dogs with suspected or diagnosed appendicular OSA because the presence of metastatic disease significantly impacts management options.[1,4,5,8,11–14]

Three-view thoracic radiography, including right and left lateral and ventrodorsal projections, are required for diagnosing pulmonary metastasis.[1,4] The lateral projections are important as the nondependent lung fields are better aerated and closer to the anode, resulting in better contrast and magnification, respectively, of metastatic lesions.[1,4] Lesions of 6 mm or more in diameter can be detected on good-quality radiographs.[1] Smaller lesions can be visualized with greater sensitivity by using computed tomography, but advanced imaging is expensive and associated with a high rate of false-positive diagnoses.[1,11] Whole-body bone scans, with radiolabeled technetium pertechnetate, are sensitive for detecting skeletal abnormalities, including both primary and metastatic tumors, but are not specific for OSA.[1,12,13] In one study, a second asymptomatic bone lesion consistent with metastatic disease was identified in 7.8% of 399 dogs with OSA.[13] Radiographs of suspected lesions should be obtained to confirm the presence of a bone abnormality (Figure 5). Alternatively, if nuclear scintigraphy is unavailable, survey radiography of the skeleton, consisting of lateral radiographs of long bones and ventrodorsal radiographs of the pelvis, can be used to screen for bone metastasis.[14] Identification of metastatic skeletal disease is important when limb amputation is planned, as amputation may lead to early and catastrophic failure through the metastatic lesion as a result of redistribution of weight-bearing forces.

Figure 5. Distal radial OSA in a dog.



Nuclear scintigraphy of a dog with a distal radial OSA. A secondary asymptomatic lesion is evident in the distal right femur *(arrow)*.



Lateral radiograph of the femur of the same dog. A secondary and asymptomatic lytic lesion is seen in the distal femur *(arrow)*, consistent with metastatic OSA.

Prognostic Factors

A number of clinical factors have been identified as prognostic in dogs with appendicular OSA. Factors indicating a poor prognosis include age younger than 7 years, large tumor volume, OSA in the proximal humerus, elevated total and bone-specific serum alkaline phosphatase levels, failure of this phosphatase level to normalize within 40 days of surgical treatment, high tumor grade, and presence of metastasis.[7,15–18] In humans, clinical parameters such as histologic grade and metastasis are still used for prognostication, although application of cellular, molecular, and genetic factors to determine treatment options and prognosis is becoming more common.[8]

PALLIATIVE MANAGEMENT

Management options for dogs with appendicular OSA are broadly classified as palliative or curative-intent. Palliation is indicated for dogs with metastatic OSA or when owners do not want to pursue more aggressive treatment options. Palliative management aims to control pain and lameness associated with the primary tumor but does not attempt to modify disease progression or improve survival time. Palliative options include analgesia, radiation therapy, limb amputation, and metronomic chemotherapy.

Analgesics

Analgesia is the cornerstone of palliative management of dogs with appendicular OSA[19] (Table 1). Initially, NSAIDs may be sufficient to control pain and improve quality of life. Cyclooxygenase-1–sparing NSAIDs are preferred because they have reduced adverse effects.[19] Aspirin should be avoided because of irreversible impairment of platelet function and a high likelihood of gastrointestinal ulceration.[19]

More potent analgesics and combinations of these drugs are often required for effective pain relief during the course of therapy[19] (Table 1). These drugs include codeine–acetaminophen, partial agonists or agonist–antagonists, sustained-release oral morphine, fentanyl patches, and adjunctive drugs such as *N*-methyl-D-aspartate (NMDA) antagonists and tricyclic antidepressants.[19] Codeine–acetaminophen should be used with caution because drug-related toxicities have been reported.[20] Drug combinations are often preferable, as these drugs target different aspects of the pain pathway, resulting in an additive or synergistic analgesic effect. Amantadine, an oral NMDA antagonist, may minimize dorsal-horn "wind-up" and pain sensitization and can be used in combination with NSAIDs, codeine–acetaminophen, partial agonists, and opioids. Codeine–acetaminophen has minimal antiinflammatory effects and can be administered with NSAIDs, partial agonists, opioids, and amantadine.[19] Opioids have potent analgesic properties and can be used with NSAIDs, codeine–acetaminophen, and amantadine. Furthermore, oral morphine and fentanyl patches can be used concurrently without ill effects. Opioids should not be used with partial agonists such as butorphanol because the analgesic effects are antagonized.[19] Alternative analgesics and techniques include corticosteroids, tricyclic antidepressants, anticonvulsants, epidural analgesia with opioids delivered through an epidural catheter, and acupuncture.[19,21]

The median survival time (MST) for dogs with appendicular OSA treated solely with analgesics is not known, although 1 to 3 months is a reasonable expecta-

Table 1. Analgesics Used for Palliation of Canine Appendicular Osteosarcoma

Analgesic	Dosage	Comments/Side Effects
NSAIDs		
Carprofen	2.2 mg/kg q12h PO	Idiosyncratic hepatic failure, gastric ulceration, renal failure, lethargy
Deracoxib	1–2 mg/kg/day PO	Gastric ulceration, renal failure
Etodolac	10–15 mg/kg/day PO	Gastric ulceration in dogs, renal failure in humans
Meloxicam	0.05–0.1 mg/kg/day PO	Gastric ulceration, renal failure
Ketoprofen	0.5–1.0 mg/kg/day PO	Gastric ulceration, renal failure, platelet aggregation inhibition
Piroxicam	0.3 mg/kg q48h PO	Gastric ulceration, renal failure
Partial Agonist		
Butorphanol	0.55 mg/kg q1–2h PO	Controlled substance; short duration of activity; ceiling effect of analgesia, sedation, and respiratory depression
Opioids		
Morphine	0.5–1.0 mg/kg q8–12h PO	Controlled substance; sedation, euphoria, bradycardia, vomiting, urine retention, constipation
Fentanyl patch	50 µg/hr q72h (10–20 kg) 75 µg/hr q72h (20–30 kg) 100 µg/hr q72h (>30 kg)	Controlled substance; variable serum concentration because of application site, skin blood flow and temperature, and hydration; correct disposal is required because a residual dose can be lethal to humans
Miscellaneous		
Codeine–acetaminophen	0.5–2.0 mg/kg q6–8h PO (codeine)	Controlled substance; anemia
Amantadine	3 mg/kg/day PO	NMDA antagonist
Prednisone	0.5–1.0 mg/kg q12–24h PO	Antiinflammatory; synergistic activity with opiates, contraindicated with NSAIDs
Amitriptyline	1–2 mg/kg q12–24h PO	Tricyclic antidepressant; serotonin and norepinephrine activity altered

tion. Analgesics can also be used together with radiation therapy.

Radiation Therapy

Radiation therapy can be used for palliation and curative-intent therapy in dogs with appendicular OSA. A number of different palliative radiation protocols have been described.[22–26] We currently use 8 Gy on 2 consecutive days, followed by additional doses of 8 Gy either on a monthly basis or as required. Radiation therapy reduces local inflammation, minimizes pain, slows progression of metastatic lesions, and improves quality of life in both dogs and humans with primary and metastatic lesions.[22–27] A 50% to 92% response rate has been reported, with the median onset of response 11 to 14 days after initiation of therapy and median duration of response 73 to 130 days.[22–26] The duration of response is significantly improved when less than 50% of the bone is involved and with OSA located in the proximal humerus.[25,26] Higher cumulative doses, higher intensity of treatment, and addition of chemotherapy to palliative radiation protocols improve both the response rate and the duration of response.[24–26]

Palliative radiation therapy is not associated with acute effects and thus does not reduce quality of life.[22–26]

Table 2. Radiation Protocols for Palliative Management of Dogs with Appendicular Osteosarcoma

Study	Dose (Gy)	Interval	Total Dose (Gy)	Response Rate (%)	Response Onset (days)	Response Duration (days)	Survival Time (days)
McEntee et al[22]	10	Days 0, 7, and 21	30	80	—	130	125
Thrall and LaRue[23]	8	Days 0, 7, and 21	24	50	—	—	—
McEntee[24]	10	Days 0, 7, and 21	30	70 (overall)	—	180	240 (overall[a])
	8	Days 0 and 7	16	70 (overall)	—	90	—
Ramirez et al[25]	10	Days 0, 7, and 21	30	84	11	73	122[a]
	8	Days 0 and 7	16	87[b]	—	—	—
Green et al[26]	8	Days 0, 7, 14, and 21	32	92	14	95	313[a]

[a]With chemotherapy.
[b]With repeated radiation following initial three palliative doses.

Table 3. Suggested Metronomic Chemotherapy Protocols

Drug	Dosage	Metronomic Effect
Protocol A		
Doxycycline	5 mg/kg q24h	Matrix metalloproteinases implicated in tumor metastasis; antagonist; antiangiogenic
Piroxicam	0.3 mg/kg q48h	Prostaglandins important in growth and metastasis of some tumors; antagonist; antiangiogenic
Cyclophosphamide	25 mg/m^2 q48h	Antiangiogenic and possibly cytotoxic
Protocol B		
Doxycycline	5 mg/kg q24h	—
Piroxicam	0.3 mg/kg q48h	—
Tamoxifen	40 mg/m^2 q12h for 7 days then 10 mg/m^2 q12h	Antiangiogenic; vascular endothelial growth factor–mediated activity inhibited

However, we have seen alopecia and depigmentation in dogs given more than four doses of palliative radiation. Late effects are uncommon but can occur with high doses per fraction and high total cumulative doses. Repeated palliative radiation in dogs and humans has been described as having minimal adverse effects and benefits for both pain control and survival time.[25,28] The MST for dogs treated with palliative radiation is 122 to 313 days[22–26] (Table 2). Radiopharmaceuticals such as samarium have been used for palliation of primary and metastatic bone lesions but are expensive and not readily available.[29–31]

Limb Amputation

Limb amputation is an effective means of controlling pain in dogs with appendicular OSA, particularly dogs with pathologic fracture and lameness unresponsive to analgesics and palliative radiation therapy. Kirpensteijn et al[7] reported that the survival times of dogs treated with amputation alone were significantly better than with the use of analgesics or palliative radiation therapy. The MST for dogs having limb amputation alone is 103 to 175 days, with survival rates of 47% to 52%, 11% to 21%, and 0% to 4% at 6, 12, and 24 months, respectively.[15,32–35]

Metronomic Chemotherapy

Metronomic chemotherapy is a relatively new concept in which cytotoxic drugs are delivered at low and constant doses to target tumor angiogenesis. The goals are to minimize the growth of primary and metastatic lesions and prevent new metastastatic growth. Drugs with known antiangiogenic effects include cyclophosphamide, mitoxantrone, NSAIDs, tamoxifen, doxycycline, bisphosphonates, and paclitaxel[36–41] (Table 3). The adverse effects commonly associated with these drugs are usually not encountered because of the low doses administered.[38] However, the efficacy of antiangiogenic therapy in dogs is unknown and requires further investigation.[38] As anecdotal evidence, we have used a metronomic chemotherapy protocol (protocol A in Table 3) with occasional success as palliative relief in dogs with metastatic appendicular OSA, metastatic prostatic carcinoma, and malignant histiocytosis.

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1. What are the four primary bone tumors?
a. OSA, CSA, FSA, and HSA
b. OSA, CSA, HSA, and lymphoma
c. OSA, FSA, HSA, and multiple myeloma
d. OSA, CSA, FSA, and multiple myeloma

2. What are the classic signalment and presentation in a dog with appendicular OSA?
a. small-breed dog, young age, and lameness with metaphyseal swelling
b. large-breed dog, middle to older age, and lameness with metaphyseal swelling
c. large-breed dog, young age, and lameness with diaphyseal swelling
d. small-breed dog, middle to older age, and lameness with diaphyseal swelling

3. What are the indications for performing a bone biopsy in a dog with suspected OSA?
a. single metaphyseal lesion
b. atypical history, signalment, and/or presentation
c. unwillingness of owner to treat with postoperative chemotherapy
d. b and c

4. What are the recommended diagnostic tests for clinical staging of metastatic disease?
a. thoracic radiography, bone biopsy, and whole-body nuclear scintigraphy
b. regional radiography and whole-body nuclear scintigraphy
c. thoracic radiography and whole-body nuclear scintigraphy
d. thoracic radiography and limb computed tomography

5. Which factor is not useful for determining a prognosis for dogs with appendicular OSA?
a. elevated total serum alkaline phosphatase level
b. large tumor volume
c. proximal humeral location
d. proximal femoral location

6. Which of the following should not be used for palliative relief in dogs with appendicular OSA?
a. curative-intent chemotherapy
b. analgesics
c. radiation therapy
d. limb amputation

7. Which combination of drugs should not be used for palliative relief in dogs with OSA?
a. codeine–acetaminophen and carprofen
b. amantadine and sustained-release oral morphine
c. transdermal fentanyl patch and sustained-release oral morphine
d. butorphanol and sustained-release oral morphine

8. What is the rationale for palliative radiation therapy?
a. antiinflammatory, analgesic, and antitumor effects
b. antiinflammatory and analgesic effects
c. antiinflammatory and analgesic effects, with slowing of tumor growth
d. analgesic effect

9. What is the MST for dogs with OSA treated with limb amputation alone?
a. 1 to 3 months
b. 3 to 5 months
c. 5 to 12 months
d. more than 12 months

10. What is the rationale for metronomic chemotherapy?
a. antiangiogenic
b. cytotoxic
c. antimetastatic
d. analgesic