The Pet Oncologist

I think the dog has bone cancer. What next?

Dr. Catherine Chan BVSc (Hons I) FANZCVS (Veterinary Oncology)
The Pet Oncologist
1A Norman Street, Fig Tree Pocket, Brisbane, QLD 4069

Introduction

A dog presents to you limping. You take an x-ray and discover an aggressive bone lesion. You suspect a primary bone tumour. What are the differential diagnoses? What next?

As a vet, you will encounter a dog with an aggressive appendicular bone lesion on x-rays. Most dogs will have osteosarcoma, but other types of cancers, benign lesions and infection are possible.

This presentation will go through how to diagnose and stage a dog with an aggressive appendicular bone lesion on x-rays. It will provide an overview of canine osteosarcoma with an emphasis on biologic behaviour, signalment, risk factors, cause, and clinical presentation. The main focus is on identifying and understanding the prognostic factors and treatment options available for both nonmetastatic and metastatic appendicular osteosarcoma in dogs. A few clinical examples and questions will be provided throughout. By the end of the presentation, veterinarians know more about how to approach a dog with an aggressive bone lesion on x-rays, and how to manage dogs with appendicular osteosarcoma.

Differential diagnoses

Osteosarcoma is the most common primary bone cancer (85%), followed by chondrosarcoma (<10%). Other malignant primary bone tumours (such as fibrosarcoma, haemangiosarcoma and histiocytic sarcoma are rare (<5%). In Australia, less than 1% of primary bone lesions will be benign or infection (such as fungal [*Aspergillus fumigatus*] or bacterial osteomyelitis [*Staphylococcus intermedius*]). A metastasis should also be on the list of differential diagnoses, particularly if the bone lesion is present in a non-metaphyseal location, such as the mid diaphysis.

Diagnosis

A diagnosis can be obtained via cytology or histopathology. Cytology is usually performed to rule in or out cancer. It does not usually lead to a definitive diagnosis. Cytology has a 69-83% accuracy for specific tumour subtype (e.g. sarcoma, carcinoma). A bone biopsy (e.g. Jamshidi needle bone biopsy) or amputation to obtain histopathology is required to obtain a definitive diagnosis. The accuracy for detecting cancer vs. no cancer is 92%. The accuracy for detecting specific tumour type is 82%. Bone lesions are painful. If the owners are willing to treat aggressively and understand there is a <1% possibility of a diagnosis that is not cancer, amputation followed by histopathology is a reasonable option. However, it is important to thorough stage the dog to ensure there is no evidence of metastasis present elsewhere.

Staging
An updated haematology, serum biochemistry and urinalysis are recommended in all dogs. It is important to check the general health of the dog and determine if any comorbidities may affect management. Pre-treatment elevations in serum alkaline phosphatase, and monocyte and lymphocyte counts in dogs with osteosarcoma, are associated with an unfavourable prognosis. See further below.

Three-view thoracic radiographs are recommended to check for evidence of pulmonary metastasis. Pulmonary metastasis is present in about 10% of dogs with osteosarcoma at the time of presentation. Thoracic CT has increased sensitivity for detection of pulmonary metastasis. However, most of the outcomes published for osteosarcoma are based on thoracic radiographs. Therefore, thoracic radiographs are still considered the standard of care. The incidence of bone metastasis at the time of diagnosis of osteosarcoma is between 2 and 10%. Careful orthopaedic and spinal examination is required. If there is any lameness or pain, further imaging is recommended. This can consist of playing bone survey radiographs (i.e. lateral radiographs of all bones and a ventrodorsal projection of the pelvis). Bone scintigraphy is the best imaging modality for detection of bone metastasis. MRI and PET/CT are also useful. Whole-body CT has a low sensitivity and detection of bone metastasis, and thus, not recommended. However, CT is useful as an adjunct imaging modality to confirm that the lytic bone lesion is present before making definitive treatment recommendations.

Abdominal ultrasonogram is recommended, but not a requirement. The chance of finding abdominal metastasis for dogs with osteosarcoma is low (2.5%). Moreover, approximately 5% of osteosarcoma is that have an abdominal ultrasonogram, will have the presence of another primary cancer. Abdominal ultrasonogram is a low yield diagnostic test. However, it is warranted in patients with palpable abdominal abnormalities or before pursuing expensive treatment.

Cytology should be performed and all palpably enlarged local regional lymph nodes. If the cytology results and non-diagnostic or equivocal, lymph node extirpation is recommended. When performing an amputation, the regional lymph nodes should be submitted for histopathology. Although the chance of finding nodal metastasis at the time of presentation is low (5%), the presence of nodal metastasis for dogs with osteosarcoma is associated with a worse prognosis.

Osteosarcoma
Osteosarcoma is the most common primary bone cancer in dogs, accounting for up to 85% of malignancies originating in the skeleton. Approximately 75% of osteosarcomas occur in the appendicular skeleton (e.g. leg), with the remainder occurring in the axial skeleton (e.g. ribs or flat bones of the skull). The metaphyseal region of long bones is the most common primary site, with thoracic limbs (e.g. distal radius and proximal humerus) affected twice as often as pelvic limbs.

Osteosarcoma primarily affects large dog and giant breed dogs and tends to occur in middle-aged to older dogs — median (average) age of 7 years. However, dogs as young as 6-months of age can be affected.

Increasing weight and, more specifically, height appears to be the most predictive factor for developing osteosarcoma in dogs. Dogs weighing more than 40 kg accounted for approximately 30% of all cases, and 95% of their tumours occurred in the appendicular skeleton. Only 5% of osteosarcoma occurred in dogs weighing <15 kg, and about 60% of their tumours originated in the axial skeleton.

The breeds most at risk for osteosarcoma are Rottweiler, Saint Bernard, Great Dane, German Shepherd, Golden Retriever, Irish Setter, and Doberman Pinscher. However, large size appears to be a more critical predisposing factor than breed. Males are slightly more frequently affected than females (1.1-1.5:1 male to female ratio). Intact males and females have increased risk for osteosarcoma.

The cause of osteosarcoma is generally unknown. However, evidence in dogs supports breed-associated inheritance of osteosarcoma, especially in Greyhound, Great Dane, Saint Bernard, Rottweiler, Scottish Deerhound, and Irish Wolfhound. Mutations in p53, RB and PTEN genes are speculated in the genetic pathogenesis of canine osteosarcoma. Other molecular factors, such as mutations in MET, Her2-neu, mTOR and Hedgehog cell signalling pathways, are thought to contribute to osteosarcoma pathogenesis. Osteosarcoma has developed after metallic implants used for fracture repair, chronic osteomyelitis, and fractures where no internal repair was used. Exposure to radiation therapy can induce osteosarcoma, with an incidence of <5%.

Osteosarcoma is a malignant mesenchymal cancer of primitive bone cells, that produces osteoid, an extracellular bone matrix. There are many histologic subclassifications of osteosarcoma (such as osteoblastic, chondroblastic, fibroblastic, poorly differentiated, and telangiectatic), and osteosarcoma can be classified into high or low grade. However, it has not been well established if different histologic subclassifications or histologic grades are predictive of biologic behaviour. See further below under ‘Prognosis’.

Osteosarcoma has very aggressive local effects and causes lysis and/or bone production. Most dogs present with lameness and swelling at the primary site. It is often a painful condition suspected to be mediated by loss of mechanical bone strength resulting in microfractures, infiltration or compression of nerves, and the chemotaxis of immune cells with subsequent secretion of cytokines and proteases resulting in inflammatory pain. Occasionally a pathologic fracture may result; however, does not carry a worse prognosis than patients without fracture at presentation. Dogs presenting with pathologic fractures are poor candidates for treatment with stereotactic radiation therapy and surgical stabilisation. Metastasis is common and usually arises early in the course of the disease, although usually subclinically. Although <15% of dogs have radiographically detectable pulmonary or bone metastasis at presentation, about 90% will die within one year with metastatic disease (usually to the lungs) when amputation is the only treatment. See further below under ‘Treatment’ options.

Metastasis usually occurs via the haematogenous route, predominately to the lungs. There is a lower frequency of spread to distant bones, regional lymph nodes other soft tissues.

Prognosis
Left untreated, the prognosis for canine appendicular osteosarcoma is poor. Despite the use of many different forms of pain relief medications, most dogs will become refractory to pain relief medications within a few months.

Prognostic factors
The prognosis for canine appendicular osteosarcoma is highly variable and depends on several factors, including:

1. Age.
- Increasing age appears to be associated with a worse prognosis for canine osteosarcoma.
- One large multi-institutional study found that dogs younger than five years of age had shorter survival time than older dogs. However, a recent meta-analysis suggested that age may be confounded by other factors and was not prognostic for overall survival.

2. Breed.
- One study suggested that small breed dogs with appendicular osteosarcoma may have improved survival times compared with large breed dogs after the institution of curative-intent therapies.

3. Weight.
- In one study, dogs with lower body weights (<40 kg) had longer disease-free intervals and survival times than larger dogs.

4. Serum and bone alkaline phosphatase.
- Many studies firmly support elevated alkaline phosphatase (ALP) strong association with a poorer prognosis for dogs with appendicular osteosarcoma.
- A pre-operative elevation of either serum or bone ALP is associated with a shorter disease-free interval and survival time.
- Dogs with elevated serum ALP overall had a median survival time of approximately 5.5 months, compared with dogs with serum ALP within the reference range.
- This unfavourable clinical prognosis may be due to increased turnover associated with bone destruction, larger initial tumour burden and advanced clinical stage of disease.

5. Location.
- Numerous studies support proximal humerus location having shorter disease-free intervals and survival times that dogs with osteosarcoma in other locations. Dogs with proximal humerus osteosarcoma had a median survival time of approximately 4.5 months shorter and a median disease-free interval of approximately 3.5 months shorter, compared with other locations.
- In one study, dogs with proximal humeral osteosarcoma had a higher incidence of pathologic fracture, increased tumour volume, and unusual pathologic subtype; which may contribute to the shorter disease-free interval and survival reported for dogs with proximal humeral osteosarcoma than dogs with osteosarcoma in other locations.

- Dogs with ulna osteosarcoma may have a better prognosis than dogs with osteosarcoma involving other appendicular sites. Median disease-free interval and survival time were approximately 1.2 years and 1.3 years in a study of 30 dogs with ulna osteosarcoma.
- Dogs with radius osteosarcoma have been cited in several canine studies as the location with the best prognosis for survival time and disease-free interval.

6. Tumour burden.
- The percentage of bone length affected, and larger tumour size is associated with a worse prognosis.

7. Metastases.
- Dogs presenting with stage III disease (measurable metastasis) have a guarded prognosis. However, improved survivals may be achieved with an appropriate selection of cases for pulmonary metastasectomy.
- Dogs presenting with bone metastasis have a longer median survival time of approximately four months, compared to metastasis in other locations.
- Dogs presenting with pulmonary metastasis have a median survival time of approximately two months.
- Dogs that present with lymph node metastasis have a median survival time of approximately two months.
- Dogs presenting with other soft tissue metastases have a median survival time of approximately three weeks.

8. Histologic grade.
- Higher histologic grade and mitotic index may be predictive for poorer prognosis. However, the prognostic value of histologic grade for predicting biologic behaviour remains controversial. Therefore, at this stage, low vs. high-grade osteosarcoma treatment recommendations are the same.
-

9. Histologic subclassification or subtype.
- In one study of 30 dogs with ulna osteosarcoma, dogs with telangiectatic subtype had a median survival time of approximately seven months and were about seven times more likely to die of osteosarcoma.
- Fibrosarcoma subtype may be associated with a favourable outcome.

10. Monocyte and lymphocyte count.
- In one study, higher numbers of circulating monocytes ($\geq 0.4 \times 10^3$ cells / μL) and lymphocytes ($\geq 1.0 \times 10^3$ cells / μL) before treatment were found to be associated with shorter disease-free intervals in dogs with osteosarcoma.

11. Infection.
- Several studies suggest the development of a surgical site infection in dogs with osteosarcoma undergoing limb-sparing surgery, had longer survival times, compared with dogs that did not develop infections. Infection may increase interactions between

the canine immune system against osteosarcoma cancer cells. However, more recent studies did not show an extended survival associated with surgical site infection. Therefore, the role of surgery site infection in prognosis needs further investigation.

Treatment

Amputation of the affected limb is the standard local treatment for canine appendicular osteosarcoma. Amputation is performed primarily to alleviate the pain produced by cancer, and also to prevent a pathologic fracture. Although most owners initially do not like the idea of amputation, dogs (even large and giant breed dogs) will usually function well after limb amputation. 88% of dogs have the same or near same quality of life after amputation, and 73% of dogs return to their pre-amputation activity levels after surgery. Most dogs readily compensate, although osteoarthritis may progress more rapidly in three-legged dogs, rarely does this result in a clinical problem. The median survival time following amputation is about 4 to 5 months after surgery, and approximately 10% of dogs live over one year. Amputation is the best method of relieving pain.

Amputation followed by chemotherapy is the gold standard treatment of choice. Three chemotherapeutic drugs, doxorubicin, cisplatin and carboplatin, are effective in treating dogs with osteosarcoma. When either of these drugs is used alone or in combination, the reported median survival times are approximately 10 to 12 months, with approximately 20% of dogs alive two years later. For dogs that are otherwise healthy carboplatin is the chemotherapy of choice, because carboplatin is associated with less adverse effects, treatment delays, dose reduction, and hospitalisation.

Limb-sparing surgery can be considered in suitable candidates when amputation has been declined. For example, severe pre-existing orthopaedic or neurologic disease. Limb-sparing surgery is a complicated surgery that should be performed with a specialist surgeon experienced in this procedure. Several methods of limb-sparing surgery have been described, each with unique advantages and limitations. The choice of limb-sparing surgery method depends on several factors and should be discussed with the specialist surgeon who is performing the surgery. Although limb function has been fair to good in approximately 80% of dogs, owners will require commitment because complications (including infection, local recurrence, and implant complications) can arise in any phase of treatment. Moreover, most dogs will require frequent revisits and physical therapy. Occasionally, complications may result in amputation of the affected limb. The survival outcomes for limb-sparing surgery (with or without chemotherapy) is similar to amputation (with or without chemotherapy).

Stereotactic radiation therapy (SRT) allows precision delivery of high doses of radiation to the defined tumour target and relative sparing of surrounding normal tissues. Treatment typically involves 10 or 12 Gray daily fraction treatments over three consecutive days. Adjuvant carboplatin chemotherapy is recommended to delay the onset of metastatic disease. In three studies, the median survival times reported when dogs were treated with a combination of stereotactic radiation therapy and chemotherapy were 9.6 months, 12 months, and 1.1 years respectively. The main advantages include good to excellent limb function, limb preservation for dogs that are not suitable candidates for limb-sparing surgery, and in comparison to conventional radiation therapy, normal tissues can often be spared. The primary limitations

include the high cost of treatment, a high risk of pathologic fracture (approximately 30-60% of cases, the median time of six months to 1.7 years after radiation therapy) and limited availability of stereotactic radiation therapy in Australia.

Palliative conventional radiation therapy is a less effective alternative than previous options. It is a localised form of treatment that is usually administered in 8 to 10 Gray fractions, either weekly for four weeks or over two consecutive days, to try to improve limb function and alleviate pain. More than 75% of dogs will have improved limb function and pain relief for approximately 2 to 3 months when treated with palliative conventional radiation therapy alone. However, when combined with chemotherapy, the median survival time is five months. Radiation therapy will not prevent the growth of metastasis nor the possibility of a pathologic fracture.

Samarium 153 lexidronam (^{153}Sm-EDTMP) is an intravenously administered radioactive isotope conjugated to a bisphosphonate, that concentrates in areas of high bone turnover (i.e. bone cancer). ^{153}Sm-EDTMP is used in people for the palliative treatment of multifocal skeletal metastases. It may help alleviate pain, and improvements are usually seen within two weeks. The response rates and durations are similar to radiation therapy, approximately 60-80% will demonstrate palliation of pain relief, with a median survival time of approximately three months. Treatment is generally well tolerated. Transient drops in white blood cells and thrombocytopenia are observed in some dogs, and typically resolves within 3-4 weeks. Dogs will require isolation for 3-5 days after treatment. This may not be suitable for old arthritic dogs or dogs that have other medical problems requiring regular monitoring or medications.

Bisphosphonates are medications that can be given orally at home (alendronate), or intravenously as an infusion a short infusion in hospital (zoledronate or pamidronate). Bisphosphonates bind to bone to inhibit bone breakdown. Thus, it may help alleviate bone pain and reduce the risk of bone fractures in dogs with osteosarcoma. However, the response is slow, and pain relief may not be seen for a couple of weeks. Zoledronate has been shown to alleviate pain in 50% in ten dogs with appendicular osteosarcoma for more than four months. In people, bisphosphonates are recommended for the treatment of osteoporosis and malignant skeletal osteolytic conditions, including paraneoplastic hypercalcaemia, multiple myeloma and metastatic bone cancer.

Pain relief medications (including non-steroidal anti-inflammatories, gabapentin, fentanyl patches, and codeine) may be administered alone. Despite the use of many different forms of pain relief medications, most dogs will become refractory to pain relief medications within a few months.

For dogs with evidence of pulmonary metastasis, the median survival time without further treatment is two months. Toceranib phosphate (Palladia®) is the treatment of choice. I do not recommend conventional chemotherapy (such as carboplatin) because mitoxantrone, doxorubicin and cisplatin injectable chemotherapy agents have been tried with a very low response rate of about 2.2%. Palladia® has some clinical benefit in dogs with metastatic pulmonary osteosarcoma. One study showed around 50% of dogs with metastatic pulmonary osteosarcoma had stable disease or partial remission for a median duration of approximately

six months. However, two recent reports suggest that only 10-15% clinically benefit from Palladia®. Anecdotally, I think it is hit and miss. However, I had one dog that lived for five years on Palladia® after being diagnosed with pulmonary metastasis from osteosarcoma; after amputation. In humans, aggressive treatment of metastatic osteosarcoma involves surgery to remove all metastatic lesions (i.e. pulmonary metastasectomy) followed by chemotherapy. In appropriately selected dogs, pulmonary metastasectomy may improve survival.

For dogs with evidence of bone metastasis, palliative radiation therapy and chemotherapy is recommended. The median survival time is about four months. Palladia® could be trialled with unknown survival benefits and low expectations.

References

Provided upon request.