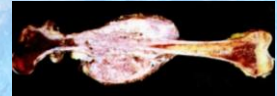


Osteosarcoma

Rebecca Newman, DVM MS DACVIM
(oncology)
Nov 2009 → Feb 11th, 2010 → March
11th 2010

Canine OSA: General Overview

- Incidence
 - Most common primary bone tumor
 - 85% of malignancies arising in from the bone
 - >8000 cases in US per year (underestimate)
 - Middle age to older dogs (median 7yr)
 - Bimodal age distribution (small peak 18-24 mo)
 - Rib OSA – younger adults – 4.5 -5.4 yr



Breeds



- Large breed dogs
 - >40kg – 29% of all cases and only 5% in axial skeleton
 - Only 5% in dogs less than 15kg – but 59% of their tumors in the axial skeleton
 - Increase wt and more specifically height
 - St Bernard, Great Dane, Irish Setter, Doberman, Rottweiler, GSD, Golden, Greyhounds
 - Size important in the breed



Etiology - ??



- Physical factors
 - Occurrence in major wt bearing bones adjacent to late closing physes
 - Repetitive microfractures/trauma → induction of mitogenic signals → increase probability of mutation
 - Metallic implants fracture repair, chronic osteomyelitis, fractures, bone allograft site
 - Ionizing radiation (plutonium exposure in people and experimentally in dogs – different distribution)
 - Radiation therapy – late side effect – 1.7-5 yrs post RT
 - speculation high dose/fx may predispose
 - Sites of bone infarct – causal relationship?

Risk Factors



- Males may be slightly more frequent than females
 - Not supported by all studies
- Intact males and females increased risk
 - Colley, Cancer Epidemiol Biomarkers Prev 2002
- In Rottweilers – male and female neutered/spayed prior to 1 yr - 1:4 life time risk to develop bone sarcoma vs intact
 - Inverse dose response relationship btw hormone exposure and incidence rate of tumor – independent of height or wt
 - Colley, Cancer Epidemiol Biomarkers Prev 2002

Molecular Biology and Genetics



- Loss of tumor suppressor genes
 - Loss of Rb
 - Loss of p53
 - Overexpression/mutation of p53 in canine appendicular OSA more than in flat bone sites – increased aggressive biologic behavior
- Increased GH, IGF-1/IGF-1R, HGF/c-met, sis (PDGF), erbB-2 (HER-2) in cell lines and tumor tissues
- PTEN, MMPs, Ezrin, Cox-2, VEGF, angiostatin, telomerase
- COX-2 upregulation prognostic in 1 study but not in another
 - Mullins, JVIM 2004; Mohammed Prostaglandins Leukot Essent Fatty Acids 2004
- Angiogenesis – increased microvascular density in primary OSA presenting with mets than not



Pediatric Osteosarcoma

- Peak incidence during the adolescent growth spurt
 - role for rapid bone growth in the pathogenesis of osteosarcoma?
- 70% of patients with localized disease at diagnosis can be cured with multidisciplinary treatment - surgical resection and intensive chemotherapy.

Pediatric OSA

- 30% of patients with localized disease and 80% of patients with metastatic disease at diagnosis will relapse. (20% present with metastatic disease)
 - Survival for these patients has remained unchanged over the past 20 years.
- Prior to the use of systemic chemo the long-term survival for patients with OSA <20%.



Pediatric OSA

- Location:
 - Metaphyseal region of long bones
 - 50% of cases occurring in either the distal femur or proximal tibia
- Few clinically useful prognostic indicators
 - Percentage of tumor necrosis at the time of surgical resection after up-front chemotherapy prognostic for DFS
 - > 90% tumor necrosis have a DFS of up to 80%, while those with 90% necrosis or less have a DFS of 40-50%.



Pediatric Osteosarcoma cont..

- Denver protocol – 92% survival
- 95% of kids get limb spare
- 50-70% allograft complications – now cemented with antibx allografts decr complications to 30%
- Single most important factor for survival is necrosis at time of sx
 - Intra-arterial cisplat
 - 48-72 hour adria 90mg/m2
 - Next day cis 120mg/m2 in 6 hour or 160mg/m2 in 24 hour
 - Cycled q3wk

Pediatric OSA continued...

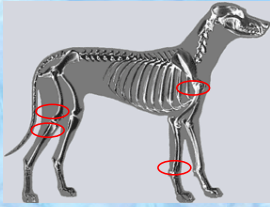
- Non-responders –
 - Tx for 12 months with ifosp, carbo and etoposide
 - Overall survival 80% (usually 40%)
- Prosthesis that grow - Rephysis



Canine Appendicular OSA: Natural Behavior

- Aggressive
- Local destruction/lysis, production, soft tissue swelling
- Pathologic fx
- Rare to cross joint – collagenase inhibitors in synovium
- Less than 15% mets at dx
- 90% die of met
- Mets – lungs, bones, soft tissues
- Increase in bone mets following chemotherapy

Sites



away from the elbow
towards the knee

- 75% appendicular
 - Front > rear limbs
 - Metaphyseal region of long bones
 - Distal radius and prox humerus
 - Distal femur, distal tibia and proximal tibia – less common prox femur
- Axial
- Extraskeletal

Clinical signs/history



- Lameness, swelling
- Often misdiagnosed initially as a orthopedic/soft tissue injury
- Pain from microfx or disruption of periosteum
- Pathologic fx



Clinical Signs

- Axial skeleton – site depend signs - swelling, pain, exophthalmus/facial deformity, hyperesthesia
- Mets – initially asymptomatic – decreased appetite, malaise, HO



FIG. 124 Photograph of a 4-year-old German Shepherd with exophthalmos secondary to the soft tissue metastasis of the bone.



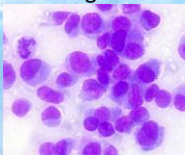
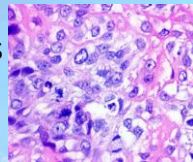
Diagnostic tests: Radiographs

- Sun burst
- Codman's triangle – not pathognomonic
- Do not cross joint, but extend into soft tissues and adjacent bone
- Similar appearance to fungal and osteomyelitis



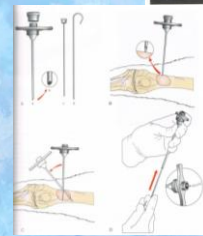
Diagnostics

- Cytology – ALP staining
- Gold standard tissue biopsy
- If planning on limb spare – need to be careful about bx – plan that skin incision and bx tract to be completely removed – ie avoiding transverse or large incisions



Bx Techniques

- Open/ incisional
 - Pro: lg tissue sample,
 - Con: hematoma, wound breakdown, infection, local seeding, pathologic fx
- Closed
 - Michell Trepine
 - Jamshidi



Diagnosis

- Malignant mesenchymal tumor of primitive bone cells
 - Produce osteoid
 - Main way of dx on histo
 - Need lg bx pieces/whole tumor
 - Subclassifications
 - Osteoblastic, chondroblastic, fibroblastic, poorly differentiated, telangiectatic
 - Subtype not prognostic but grade maybe

Case 1 – Samantha, 11yr FS Golden Retriever



http://www.michvet.com/library/oncology_bone_tumors.asp

Source: biopsy sample, only one small piece of mineralized material submitted

Mini-histopathology requested
DIAGNOSIS: reactive bone, unknown etiology

COMMENTS: the production of reactive bone can be triggered by multiple processes, including trauma, healing fracture, infection, neoplasia. The sample provided was very small and a particular etiology was not obvious.

Really???

Case 1 – Samantha, 11yr FS Golden Retriever

- small biopsy samples can lead to misdiagnoses
- collect the sample from the center of the lesion
- submit the entire lesion when removed



Case 2 – Austin, 13yr MN Labrador



Case 2 – Austin, 13yr MN Labrador



Source: the entire left rear leg was submitted

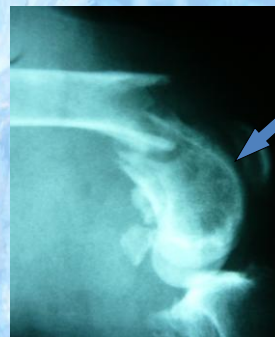
Mini-histopathology requested

MICROSCOPIC FINDINGS: femoral fracture with marked proliferative bony callus with overlying soft tissue, granulation tissue formation and hemorrhage.

COMMENTS: I see no evidence of neoplasia. This is a reparative, prominent callus within the medullary cavity, and extending through the cortical fracture. It appears to be a traumatic induced fracture. No infectious agents are seen

Case 2 – Austin, 13yr MN Labrador

Really???



Request
 ❖ second opinion

❖ additional cuts

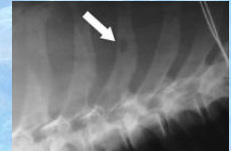
Case 2 – Austin, 13yr MN Labrador

ADDENDUM COMMENTS (**full histopathology report requested**)
I have evaluated additional sampling taken from an area distal to the previous examined tissues.

Microscopically, these sections show a **definite intramedullary neoplasm**. It is composed of fairly densely arranged fibroblasts cells, and very disorganized bundles and fascicles readily infiltrating marrow fat, and producing abundant extracellular osteoid, immature and more mature bone. The neoplastic cells have ill-defined margins and moderate amounts of fibrillar eosinophilic cytoplasm. The nuclei are round to ovoid to moderately irregular in shape. They are **markedly pleomorphic and hyperchromatic**. **Mitoses average 12 to 13/hpf. Tumor emboli** are visible in some of the blood vessels. This population represents a very highly productive **intramedullary fibroblastic osteosarcoma**, and I would classify it as a **high grade malignancy**.

Differential diagnosis

- Bacterial osteomyelitis
- Fungal osteomyelitis
- Other primary bone tumors
- Metastatic lesions
- MM/LSA – typically only lytic lesions



Staging



- LN
- CXR – mets typically soft tissue density
- Survey bone XR
- Bone scan
 - 171 dogs – 11 vs 7 dogs found lesions (6.4vs 4%) (survey and cxr vs bone and cxr)
 - 14/25 – Straw, JAVMA 1989 (7 bx confirmed OSA)
 - 1/70 – Berg, JAVMA 1990
 - 4/23 – Parchman, Vet Surg 1989
 - 7.8% of 399 – Jankowski, Vet Comp Onc 2003

Staging continued...

- Surgical staging
 - Histologic grade (G), anatomic site of primary (T), regional/distant mets (M)
 - Stage 1 – low grade (G1) w/o mets
 - Stage 2 – high grade (G2) w/o mets
 - Stage 3 – mets regardless of grade
 - Substage a – intracompartmental (T1) vs b exxtracompartmental (T2)
 - Most dogs stage 2b
- Metachronous – multicentric less than 10% at presentation

Medullary or Central Primary Bone Tumors

- 80+ % are OSA
- Distant 2nd - Medullary chondrosarcomas
- 3rd - Medullary FSA and HSA
- 4th - Medullary giant cell tumors
- 5th - Medullary hemato/lymphoid tumors including plasma cell myeloma
- 6th - Medullary liposarcoma

Prognostic Factors

- Age
 - Dogs younger than 5yr tx with sx and chemo - shorter survival than older dogs
- Tumor size
- (-) Humerus location
- (+) small dog – flat bone and complete sx
- (-) tumor grade
- Stage – 3 MST 59d vs 319 (w/o nodal mets)

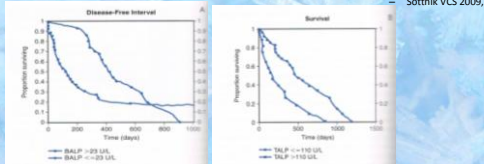
Bergman, JVIM 1996

Kirpensteijn, Vet Path 2002

Hillers, JAVMA 2005

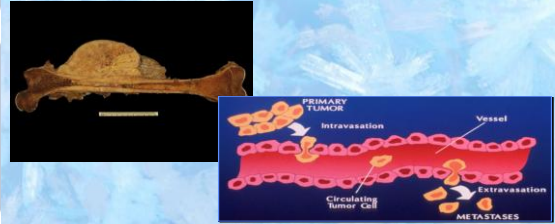
Prognostic Factor continued...

- ALP >110u/L or bALP >23u/l shorter DFI
 - Is post op ALP prognostic???
- Molecular – Cox2?, Ezrin, MIB-1, MDR, p53
- Monocyte levels at time of diagnosis



Definitive therapy

- Treatment aimed at the primary tumor
- Treatment aimed at micrometastasis



Tx for Primary Tumor

- Amputation
 - Standard tx
 - Palliative
 - Amputation alone – MST 103-175d (3-5.8mo)
- Limb spare sx



Limb Spare Sx

- 50% of bone
- Absence of path fx
- Less than 360 involvement of soft tissues
- Firm/definable soft tissue mass vs edematous lesion
- Distal radius/ulna

Surgical Limb Spare Techniques

- Allograft (remove 3-5 cm proximal to proximal radiographic margin of bone and soft tissue 2-3 cm)
 - Frozen cortical allograft – medullary cavity filled with polymethyl methacrylate bone cement
 - Advantages – absence of ex-fix
 - Disadvantages – high infection rate (40-50%) – controlled but rarely resolved



Surgical Limb Spare Techniques cont...



- Metal endoprosthesis
 - Advantages – do not need graft, possible use for other sites
- Pasteurized tumor autograft
 - Remove effected bone and pasteurizing (65 C for 40min) – 15% local recurrence, 31% infection, 23% implant failure rate
 - Advantages – no need for allograft and excellent anatomic apposition

Surgical Limb Spare Techniques cont...

- Longitudinal bone transport osteogenesis (BTO)
 - Ilizarov (circular) fixators
 - Distraction osteogenesis in the trailing distraction pathway
 - Advantage – autologous vascularized nature of replacement bone – low risk of infection
 - Disadvantages – extensive client involvement and long term fixator



Surgical Limb Spare Techniques cont...

- Ulna transposition
 - Pro - preservation of vasculature – decreased infection, autologous
 - Con- prone to biomechanical complications , need for permanent internal hardware
 - N = 26: 2 ultimately amputated, 2 euth due to surgical complications
 - 33% infection, 7% local recurrence, 22% radius fx – Sequin VCS 2008
- Intraoperative extracorporeal RT – flip and nuke! (single dose of 70gy RT)
 - Advantages – good spare of immediate jt function – good function post op
 - Disadvantages – infection, high percentage of surgical revisions – (including amputation)

Surgical Limb Spare Techniques cont...

- No significant difference in survival rates for dogs tx with amputation and cisplatin vs limb spare and cisplatin
 - With the exception of infection increasing ST
 - Infection survival 611d, non-infected 273d
- 25% catastrophic failure leading to amputation
- OPLA-Pt – decreased local relapse from 50% to 15% with marginal resection

Radiation



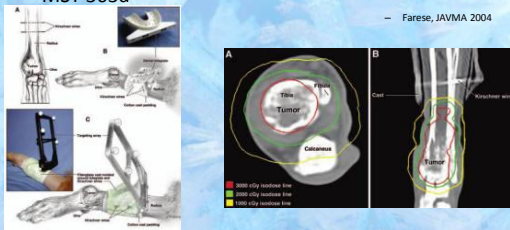
- Primary tx vs palliation
- MST 209 d – n=14 fractionated high dose (median dose of 57gy) + chemo



Walter, Vet Comp Oncol 2005

Stereotactic Radiosx – Intensity Modulated Radiation Therapy (IMRT)

- UF - Gama knife (single fx 30- 40gy)
 - N= 11, - 4 developed path fx (3-9 post post SRS)
 - MST 363d



– Farese, JAVMA 2004

Stereotactic Radiosx – Intensity Modulated Radiation Therapy (IMRT)

- CSU - 3fx of 11-14gy (32-42gy) w/ 24-72hr btw doses
 - N= 25
 - 9 fx (2 prior or during RT),
 - 5 early - median 51d
 - 2 late - median 325d
 - 1 out of field local recurrence

– Ryan, VCS 2009

Radioisotopes

- ¹⁵³ Samarium EDTMP (ethylenediamine-tetramethylene phosphonate)
 - Tx typically pain relief, delays tumor growth – not curative
 - Bone marrow suppression – about 4 wk
- T_{1/2} = 46.3hr, 50% excreted by kidneys in 8 hours
- Flare response
- Have seen some response for pulm mets

Radioisotopes continued...

- Intralesional Brachytherapy
 - Holmium (¹⁶⁶Ho and ¹⁵³Sm) (3 dogs) \$\$\$\$
 - 1.8 MeV β / 0.7 MeVβ & 103 KeVγ
 - t_{1/2} (Ho)n 26.8hr/(Sm) 46.3hr
 - Yttrium (⁹⁰Y) – (8 days) \$
 - 2.2 MeV β - t_{1/2} 64hr
 - Percutaneous or surgical approach (ports placed in a grid)
 - Most dogs improved, but 5 ultimately had amputation, no path fx

– Selting, VCS 2009

Systemic Adjuvant Tx

- Death due to metastatic dz
- Chemotherapy
 - Cisplatin/carboplatin
 - Doxorubicin
- No diff in MST if pre op, same time as sx, or post op



Chemotherapy

Chemotherapy	N=	DFI	ST
Cisplatin (40-70mg/m ²) x2-9 doses	N 11 - 26	165-226d (5.5mo-7.5mo)	262-413d; at 1yr 30%-62%, 2yr 16%-20.9%
Carboplatin	N = 28 - 155	256-257d (8.5mo)	307-321d (10.7mo); at 1 yr -35.4%
Doxorubicin x5 q14d	N = 35		366d (12.2mo); 1yr - 50.5%, 2yr - 9.7%
Alternating Dox/Cis	N = 19	210d (7 mo)	300d; 1 yr - 37%
Dox/Cis concurrent	N = 14 - 102	470d (15.7mo – smaller study)	345-540d; 1 yr – 48%, 2 yr 28% (for larger study)
Alternating Dox/Carbo x3 cycles	N = 32	227 d (7.6mo)	320d; 1yr -48%, 2 yr – 18 %
Dox/carbo concurrent	N = 24	195d (6.5mo)	235d (7.8mo)
Carbo/Gem	N=51	229d (7.6mo)	307d (10.2mo)

Investigational Systemic Adjuvant

- OPLA-pt sponges – MST 240d 1yr 41.2% - similar to 2 doses of cisplatin (not commercially available)
- Immunotherapy
 - L-MTP-PE (Liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine)
 - MST 222d (with amputation), w/ amputation and L-MTP-PE followed by cisplatin x4 MST 432d (14.5mo) vs 291d (9.7mo – empty liposomes)
 - If given together lose advantage

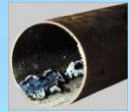
Tx of Gross Metastatic Dz

- Sx
 - MST 487d/post op 176d
 - Primary tumor CR (preferably long term >300d)
 - Few nodules, with long doubling time >30d and no new lesions during this time
- Chemotherapy
- Aerosol
 - Gemcitabine, IL2 (or liposomal DNA encoding IL2), taxol, doxorubicin

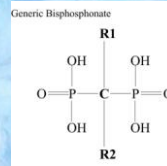
Palliative Tx For Bone Pain

- Oral pain medications, NSAIDs, opioids
 - Tx with just pain meds alone – MST 1-3mo
- Radiation
 - 2-4 fx of 8 gy – 74-92% response for 2-4 months
 - Or 3x 10gy
 - Chemo sensitization (improvement when add in cis)
- Radiopharmaceuticals (153Sm-EDTMP)
- Bisphosphonates

Bisphosphonates



- 1800s – water softener for irrigation systems
- 1900s – use in disorders of bone metabolism
 - prevent ossification of soft tissues
- high affinity for bone – bind hydroxyapatite



C – enhances chemical stability
 R1 – enhances binding to hydroxyapatite
 R2 – determines anti-resorptive potency

Bisphosphonates

Agent	R ₁ side chain	R ₂ side chain
Etidronate	-OH	-CH ₃
Clodronate	-Cl	-Cl
Tiludronate	-H	-S-
Pamidronate	-OH	-CH ₂ -CH ₂ -NH ₂
Neridronate	-OH	-(CH ₂) ₅ -NH ₂
Olpadronate	-OH	-(CH ₂) ₅ -N(CH ₃) ₂
Alendronate	-OH	-(CH ₂) ₃ -NH ₂
Ibandronate	-OH	-CH ₂ -CH ₂ -N(CH ₃) ₂
Risedronate	-OH	
Zoledronate	-OH	

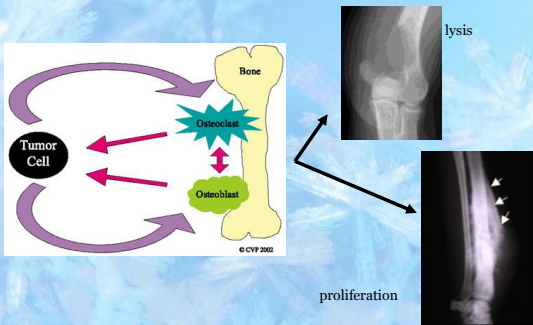
10,000x

Bisphosphonates

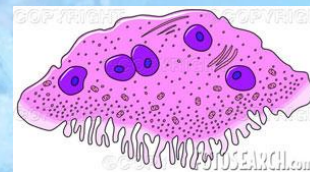
BONIVA



Bisphosphonates

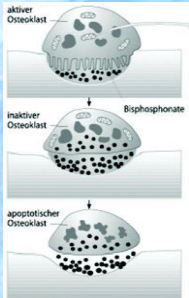


Bisphosphonates



BPP mainly act on osteoclasts

Bisphosphonates

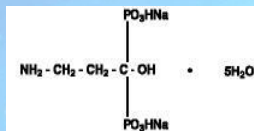


- BPP accumulate in bone
 - esp. sites of increased bone formation or resorption
 - bound to hydroxyapatite
- released during bone resorption only
- taken up by osteoclasts
- osteoclast inactivation and apoptosis

Bisphosphonates

- Clinical improvement in 50% of human patients
- Sustained palliation of bone pain over 2 years in humans
 - bone mets from prostate cancer
 - breast cancer with bone mets
- Overall significant improvement in pain symptoms and quality of life in terminally ill human patients

Bisphosphonates



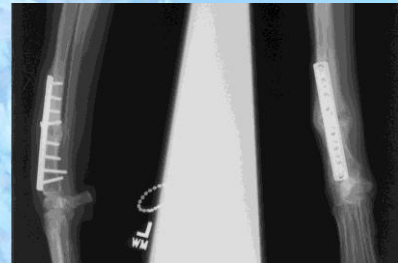
Pamidronate (Aredia)

- (1-2mg/kg) 1.4mg/kg IV over 2 hours
- every 3-4 weeks
- renal elimination
- pain palliation in 40% of dogs
- decreased risk of fracture
- most side effects described in people are not seen in dogs



Pathologic Fracture and Poor Candidate For Amputation – Fishmobile

Initial fx – 1/30/04. These rads taken 4/12/04



Pathologic Fracture and Poor Candidate For Amputation – Fishmobile

Initial fx – 1/30/04. These rads taken 7/27/04



Pathologic Fracture and Poor Candidate For Amputation – Fishmobile

Initial fx – 1/30/04. These rads taken 3/01/05



Pathologic Fracture and Poor Candidate For Amputation – Fishmobile



Outcome:

- fracture repaired
- multiple treatments of pamidronate
- 8 treatments of chemo
- screw failure at 6 months
- ambulatory 14 months
- developed multiple bone mets
- euthanasia

Pathologic Fracture Repair

While such a procedure works sometimes...

- Most of the times they are disasters!
- Very challenging even for experienced surgeons
- Poor density of the bone
- Frequent screw and plate failure
- Patients may remain painful
- Often fail - traumatic event for the patient and client
- Ethical considerations

Must think twice... and even more before recommending it....and even more before attempting it...

Possible Future tx

- Tyrosine Kinase Inhibitors
 - Sorafenib decreases cell number and induces apoptosis in a D17 K9 OSA cell line
- HSP90 inhibitors (STA1474)
- Photodynamic tx
- Bone seeking nanoparticles

Axial Skeleton OSA

- Mandible (27%)
- Maxilla (22%)
- Spine (15%)
- Cranium (14%)
- Ribs (10%)
- Nasal/sinuses (9%)
- Pelvis (6%)
- Rare reports in os penis, patella



Axial Skeleton

- Prognostic factors
 - SITE!!!
 - Non-appendicular sites are similarly aggressive with possibly exception of mandible and calvarium

Head OSA

- Mandible –
 - Sx alone 1yr survival rate 71%
 - N = 45, 58% developed mets (lung>LN>bone)
- Maxillary OSA
 - MST 5 mo post op

	Sx alone	Sx and Chemo
1yr	60%	54%
2yr	20%	54%
3 yr	5%	36%
DFI	413d	935d
MST	627d	1023d

Dickerson, JVIM 2001

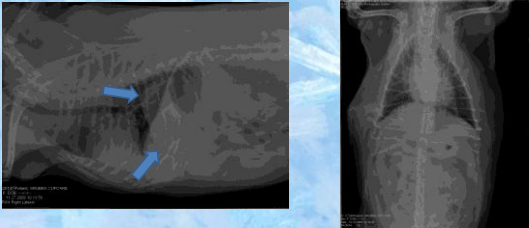
Garrett, VCS 2007

Wallace, Vet Surg 1992; Schwarz, JAAHA 1991; Hardy, J Am Vet Radiol 1967

Rib

- Sx alone 3mo
- Sx and chemo 8 mo

Matthiesen, Vet Surg 1992; VCOG, JAAHA 1993, Pirkey-Ehrhart, JAAHA 1995; Baines, Vet Rec 2002



Other OSA Locations

- Scapula – poor
- Antebrachioacarpal/tarsocrural joints – MST 466d – still high rate of mets
- Vertebral - n=15 sx, RT, chemo, MST – 4mo

– Trout JAVMA 1995, Hammer JAVMA 1995

– Gamblin JAVMA 1995

– Derneli JAAHA 2000

Extraskelletal OSA

- Rare
- Mammary gland, SQ, spleen, vagina, eye, gastric ligament, synovium, meninges and adrenal
- Tx
 - sx MST 1 mo
 - sx and chemo 5 mo
- Larger study
 - nonmammary OSA – sx alone 1 mo
 - mammary OSA sx alone 3 mo

Knutz, JAAHA 1998

Langenbach, JAAHA 1998

Tumors arising on the surface of the bone

- Periosteal osteosarcoma
 - About 0.01% of bone tumors mostly in dogs
 - All produced metastatic lung disease following amputation (n=5).
- High-grade surface osteosarcoma
 - Aggressive lesions with histologic features of medullary osteosarcomas
 - Typically invading cortex by time of bx – question if eccentric medullary osteosarcomas or of "true" periosteal origin

Tumors arising on the surface of the bone

- Low-grade osteosarcoma
 - Rare tumor - arise beneath the fibrous periosteum that remains partially intact beneath parts of this slowly expanding tumor.
 - Histologically, resembles a disorderly arranged external callus
 - Mitotic figures are very uncommon
- Periosteal chondrosarcoma
 - Most common tumors that arise on the surface a bone
 - Most common sites -dorsal rim and spine of the scapula, pelvic bones, and tibia. (possibly more common in cats than dogs).

Parosteal tumors

- Parosteal osteosarcoma (juxtacortical osteosarcoma):
 - Initially indolent bone surface-related tumor that only after several months undergo malignant progression and deeper bone involvement.
- Parosteal osteosarcomas early in their stage of development could be removed en bloc and the limb saved
- Rare

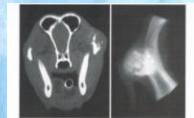


Figure 21-12
A parosteal osteosarcoma of the ilium and a parosteal osteosarcoma of the tibia. The parosteal osteosarcoma of the ilium is a large, lobulated soft tissue mass on the surface of the bone. The parosteal osteosarcoma of the tibia is a large, lobulated soft tissue mass on the surface of the bone.

Parosteal tumors

- Typically centered on the surfaces of epiphyses and apophyses, e.g. olecranon, tibial crest and several on epicondyles of the distal ulna.
- Human – long standing tumors will undergo malignant progression to osteosarcoma and have produced metastatic disease in people.
- Two dogs - both tumors produced metastatic disease but only after having been present for several months, e.g. 10 or 14 months

Questions?



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