Diagnosis and Treatment of Canine Osteosarcoma

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Disclosures

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Canine Osteosarcoma

- **Osteosarcoma (OSA):**
  - Most common primary bone tumor
  - Accounts for approximately 85-90%
  - ~8,000 cases/year in US

- **Other primary sarcomas:**
  - CSA, MLO, FSA, HSA

- **Other OSA variants**
  - OSA of soft tissues-kidney, liver
  - Mammary gland OSA
  - Periosteal OSA
  - Parosteal OSA
Canine Osteosarcoma

• Dog = species with highest incidence
  • Model for OSA in humans
    • Breed: Large or giant
  • Greyhound 6.2%, Rottweiler 5.3%, Great Dane 4.4% (Rosenberger et al, JAVMA 2007)
  • Other: Irish Setter, St Bernard, Irish Wolfhound
    • Median age = 8 years
Canine Osteosarcoma

Risk factors?

• Radiation Therapy
• Bone infarcts (small dogs)
• Fatigue microdamage, inflammation
• Fracture/implant
• ‘Gonadal exposure’
  • Early spay/neuter?
Canine Osteosarcoma

Risk factors?

• People vs. dogs
  – Tumor suppressor genes:
    • *P53* (38-50% are abnormal)
    • *pRb*
    • *PTEN*
  – Oncogenes:
    • *sis, myc, MET*
  – Growth factors:
    • *PDGF, IGF, VEGF*

Canine Osteosarcoma

Common sites for OSA

- Approximately 75% appendicular
- Metaphysis
- “Away from elbow, towards the knee”
- 25% axial skeleton
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History and clinical signs

- Typical = lameness +/- acute
- Microfx and periosteal new bone
- Palpable or visible mass
- Soft tissue inflammation
- History of ‘trauma’
- Pathologic fx (3-4%)
  - Boulay et al, JAAHA 1987
- Partial response to NSAIDs
- Signalment: Age, breed, right site
Canine Osteosarcoma

History and clinical signs

• Axial skeleton:
  – “neuro signs” due to spinal cord compression
  – Dyspnea due to intrathoracic mass (rib)
  – Facial or skull deformation
    • Secondary to local bone invasion and destruction
      – Exophthalmia
      – Dysphagia
      – Pain opening mouth

• Rare: initial presentation of dyspnea secondary to pulmonary metastasis
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Diagnosis and staging

• Thorough physical exam
• Radiographs of affected site
  • Cortical Lysis (osteolytic)
  • Trabecular lysis (loss of trabecular pattern)
  • Bone production (osteoblastic)
  • Codman’s Triangle (not pathognomonic)
  • Sunburst pattern into local soft tissues
  • Generally metaphyseal & does not cross joint
Canine Osteosarcoma

1. Cortical Lysis
2. Trabecular Lysis
3. Codman’s Triangle
   (periosteal new bone)
Canine Osteosarcoma

4. Sunburst appearance

What causes this??
Canine Osteosarcoma
Canine Osteosarcoma

Definitive Diagnosis

• Confirm with excisional biopsies
• Choice: Jamshidi, trephine, surgical biopsy
  • Aim at center of the lesion
  • Take multiple biopsies
  • Cytology can help (20 or 18G)
Clinical Staging

- Palpate and aspirate regional lymph nodes
- Complete blood count
- Serum chemistry (ALP?)
- Urinalysis
- Thoracic radiographs
  - <10% overt metastasis
  - >90% micrometastasis
- Advanced imaging studies
Canine Osteosarcoma

Advanced Imaging-CT scans
Canine Osteosarcoma

Additional Staging Diagnostics??

- Bone Survey Radiography
  - Expensive and time consuming
  - LaRue et al, JAVMA 1986 & Straw et al, JAVMA 1989
    - 4% metastases on chest radiographs only
    - 6.4% metastases on radiographic bone survey

- Bone Scintigraphy (nuclear medicine scan)
  - Extremely sensitive, but not very specific
    - Must follow-up with high-detail radiographs of any suspicious lesion on scintigraphy
    - Results debatable
      - Helpful Parchman et al, VetSurg 1989
      - Not helpful Berg et al, JAVMA 1990
Canine Osteosarcoma

Distal tibia OSA

Rib metastasis
Canine Osteosarcoma

Prognostic factors

• Age
  – < 5 years of age = worse
    • Spodnick et al, JAVMA ‘92

• Metastatic disease
  – Lung, Lymph node
    • Hillers KR et al, JAVMA 2005
      4.4% LN +, Median DFI/Surv 48d/59d

• Large tumor size & Proximal Humerus
  – Bergman et al, JVIM 1996; McMahon et al, JVIM 2011

• Weight (> 40 kg = worse)
  • Function of BSA (body surface area) dosing??
  • Bergman et al, JVIM 1996, Moore et al, JVIM 2007
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Prognostic factors

• Alkaline Phosphatase
  – *Ehrhart et al, JAVMA 1998*
    • Inc total ALP = 170d dfi (vs. 366d)
    • Inc total ALP = 177d survival (vs. 495d)
  – *Garzotto et al, JVIM 2000*
    • Found liver ALP to also be prognostic
    • Inc plasma ALP pre-Rx = worse prognosis
      Multivariate predictor of outcome
  – *Moore et al, JVIM 2007*
    • Inc serum and/or bone ALP = worse prognosis
  – *Liptak et al, Vet Surg 2008 (Rib OSA)*
    • Inc ALP = 210 days vs Normal ALP = 675d

Monocyte & Lymphocyte Counts

– *Sottnick et al, JVIM 2010*
  • Inc monocytes or lymphocytes before Rx = POORER prognosis
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ALP

Ehrhart et al, JAVMA 1998
Prognostic factors

- % tumor necrosis (RT, Chemo)
- Quantitative bone scintigraphy
- Infection of allografts

Pathology based:
- Grading system
  - Microvessel density/Grade
- Cox-2 expression
  - High Exp 86 d
  - Neg Exp 423 d

Mullins et al. JVIM 2004
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Prognostic factors

– P53 Status (Tumor Suppressor Gene)
  • Mutant p53 = 81d MST (P = .026)
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Treating Osteosarcoma

• Prognosis without therapy
  – Quality of life concerns

• Conventional treatment
  – Amputation with systemic chemotherapy
  – Limb-spare with chemotherapy
  – Median survival time ~ 10-14 months

• Amputation alone
  – Does not address metastatic disease
# Canine Osteosarcoma

Adjuvant to definitive therapy of primary tumor

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival</th>
<th>Disease Free 1 Year</th>
<th>Disease Free 2 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation Alone</td>
<td>4 months</td>
<td>&lt;10%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Amp + Doxorubicin</td>
<td>7-10 months</td>
<td>40%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Amp + Platinum (Cis or Carbo)</td>
<td>9-13 months</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Amp + Platinum + Doxorubicin</td>
<td>9-13 months</td>
<td>40-50%</td>
<td>???%</td>
</tr>
</tbody>
</table>
Canine Osteosarcoma

Standard of Care Therapy
Axial OSA

- Medium to large breeds more common but when smaller dogs get OSA, more often axial
- Middle-age to older
- ♀ > ♂ (2:1)
- Common sites: maxilla, mandible, ribs, pelvis, spine, nasal, cranium
- Signs and Hx vary with location
Canine Axial Osteosarcoma

Diagnosis

• Similar as with app. OSA
• Advanced imaging
• Fluoroscopy or CT-guidance for biopsies
Behavior and prognosis

- More of a local problem
- Less metastatic?
- Ribs vs mandibular vs others?
- Surgical resection, XRT, CTX
- Palliative XRT
- Aminobisphosphonates
- Analgesic therapy
Canine Osteosarcoma

Palliative Treatments Options

• Most, but not all dogs are candidates for amputation

• The rational institution of effective palliative options for dogs suffering from OSA requires an understanding of:
  – Cancer pain physiology
  – Malignant osteolytic process
  – Mechanism of action of pharmacologic agents
Canine Axial Osteosarcoma

Bone Pain:

- Significantly impacts quality of life
- Behavioral and activity changes
- Malignant osteolysis activates
  - Peripheral nociceptors
    - Periosteum, bone, and soft tissues
    - Unmyelinated C fibers
    - Peripheral stimulus processed by central nervous system as PAIN
Reducing Malignant Bone Pain

• Indirect:
  – Target and kill osteoclasts
  – Reduce the ability of cancer cells to induce osteoclastogenesis
  – Alter RANKL/OPG axis

• Direct:
  – Target and kill cancer cells
  – Radiation therapy and systemic chemotherapy
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Palliative Treatment Options

• Megavoltage radiation therapy
  – Delivery of large doses of radiation (8-10 Gy)
  – Infrequent intervals
    • Weekly for 4 consecutive weeks
    • Days 0,7,14,21
  – Primarily to kill tumor cells
    • Directly reduces malignant osteolysis
    • Also kill osteoclasts
• 75% of dogs will have significant pain relief lasting from 2-7 months
Canine Osteosarcoma

Palliative Treatment Options

- $^{153}$Samarium-EDTMP (Quadramet)
  - Emits gamma photons (imaging)
  - Emits beta particles (therapeutic)
  - Binds to areas of active bone turnover
  - Radioactive half-life-approximately 48 hours

- Advantages
  - Multifocal and diffuse
  - Specificity
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Palliative Treatment Options

• $^{153}$Samarium-EDTMP (Quadramet)
  – Effective for managing malignant bone pain

• Completed study (U of Missouri)
  – Combination of carboplatin with Sm-153 for management of OSA-induced bone pain

• Ongoing study (CSU)
  – Localized limb perfusion prior to limb spare
  – Enhancement of tumor necrosis
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Palliative Treatment Options

• Stereotactic Radiosurgery
  • Delivery of very high and focal dose of megavoltage radiation therapy
  • Minimizes normal tissue damage
  • Traditionally used for management of brain tumors in children
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Palliative Treatment Options

• Bisphosphonates
  • Analogues of Ppi
  • Potency depends on $R_2$ group
  • Aminobisphosphononates = more potent
  • Used to decrease the effects of post-menopausal osteoporosis in women
Canine Osteosarcoma

Bone Turnover

Resorption

NTx
CTx
TRAP
Pyd
Dpd

Formation

BALP
Osteocalcin

Osteoclastic activity
(Osteoclasts)

Osteoblastic activity
(Osteoblasts)
Canine Osteosarcoma

Palliative Treatment Options


- 41 dogs received q4weeks pamidronate
- 50% may benefit from therapy, with 25% having durable responses (>4 months)
- No statistical evidence that higher dose provides better pain control (1mg/kg vs 2mg/kg)
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OSA Palliation: Standard of Care

• Palliative Radiation Therapy
• Pamidronate
  – 1mg/kg q 4 weeks
• NSAIDs (Rimadyl, Deramaxx, Piroxicam, Galliprant)
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Questions??
BREAK