

Radiotherapy of canine osteosarcoma

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Pain

- Inflammatory pain/nociceptive pain
- Neuropathic pain



Cancer Induced Bone Pain (CIBP)

- CIBP is a unique and specific pain state
 - Mixed pain (inflammatory pain and neuropathic pain)
 - Distinct unique cell modulations in peripheral tissues and neurochemical changes at the spinal cord level
- One of the most difficult pain conditions to treat
- Needs multimodal treatment approach due to the variety of pain triggering events

Events

Induces a severe inflammatory infiltrate

Cancer cells secrete growth factors and cytokines



Paracrine interaction between tumour and nerve endings → nociceptor activation

Growth factors: *NGF - hyperinnervation*

Cytokines: *TNF, IL-1, IL-6, chemokines, prostanoids,*
Induce inflammatory and neuropathic

endothelins
pain

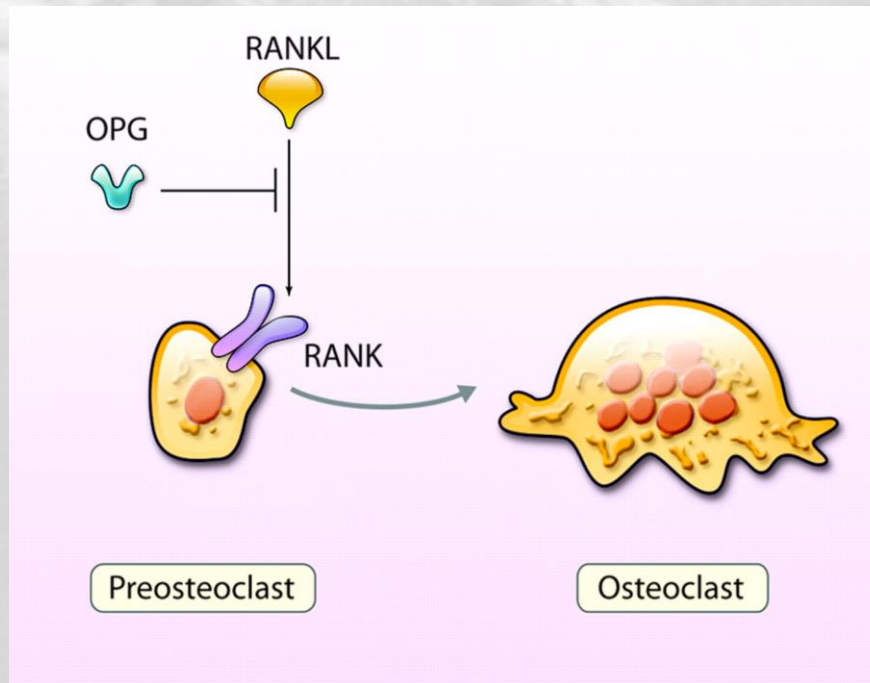
Prostanoids: Pro-inflammatory substances produced by activation of COX

Induce inflammatory pain

Events

Induces a severe inflammatory infiltrate

Alters the osteoclast/osteoblast balance



Events

Induces a severe inflammatory infiltrate

Alters the osteoclast/osteoblast balance

Tumour cells/invading T-cells secrete RANK-L and sequester osteoprotegrin (OPG)

Increased number of osteoclasts compared to osteoblasts



Increased bone resorption



Stimulation of nociceptor-rich endosteum and periosteum → Pain

Events

Induces a severe inflammatory infiltrate

Alters the osteoclast/osteoblast balance

Decreased local pH

Cancer cells generate an acidic microenvironment

Accumulation of acidic metabolites, ischemia, apoptosis and phagocytosis



- Directly sensitizes nociceptors in bone
- Increases bone resorption rate by osteoclasts



Pain

Events

- Induces a severe inflammatory infiltrate
- Alters the osteoclast/osteoblast balance
- Creates neuroma-like structures

NGF



Sprouting and reorganization of nerve fibers in the periosteum



Increased nerve fiber density (neuroma-like structures)



Pain

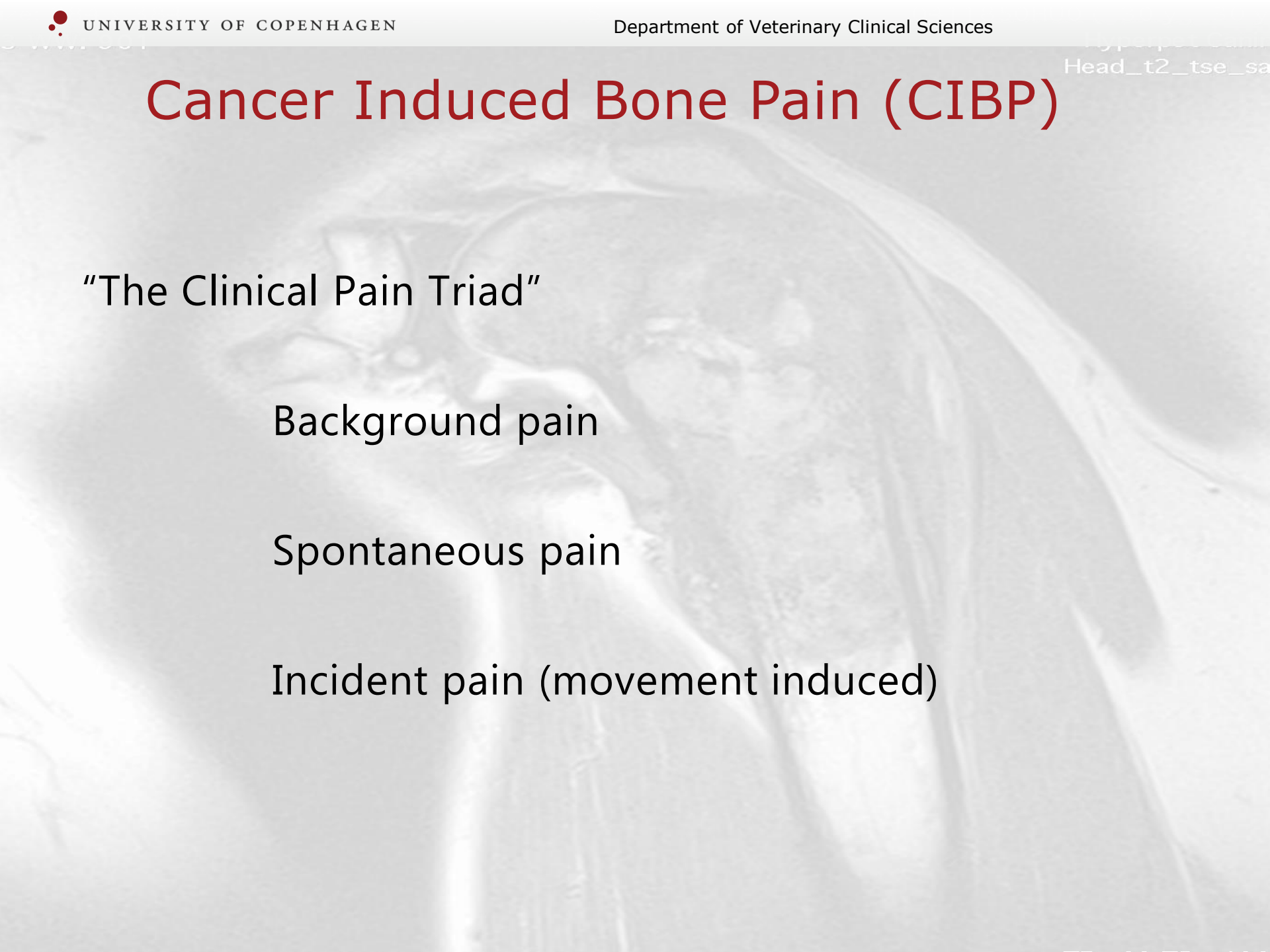
Cancer Induced Bone Pain (CIBP)

“The Clinical Pain Triad”

Background pain

Spontaneous pain

Incident pain (movement induced)



Multimodal treatment of CIBP

- Systemic analgesia: NSAIDs, Opioids, Gabapentin
- Radiotherapy
- Bisphosphonate
- Chemotherapy
- Surgery
- Local anesthetics



Radiotherapy - CIBP

- External beam radiation (teletherapy)
 - megavoltage radiation units
 - linear accelerators (LINAC) – energy > 1MeV
- Ionizing radiation
 - photons (gamma rays)
 - electron beams
- Beam is shaped
 - focused treatment area
- Fractionation



Mechanisms of pain relief

Unknown

Targets malignant cells (G2, M phase)

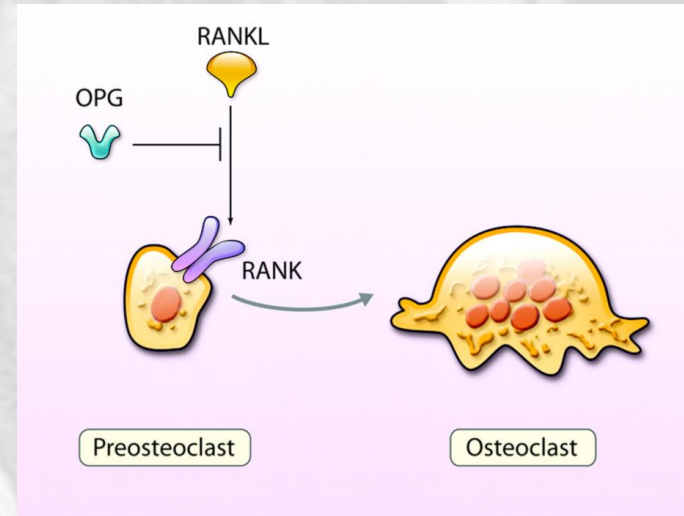
Apoptosis



Decreased RANK-L and cytokines

Decreased tumour burden

Decreased NGF (neuroma-like structures)



Radiotherapy protocols

- Palliative treatment

Goal: pain relief
 reduce acute side effects

- Definite treatment

Goal: potential cure or long-term survival
 reduce late-onset side effects

Palliative radiotherapy

1-4 fractions of 6-10 Gy

Complete or partial response in 74-93%
(Force plate gait analysis 67%)

Duration 53-130 days

Retreatment is possible

Co-administration of chemotherapy and/or bisphosphonate increase the response rate and duration

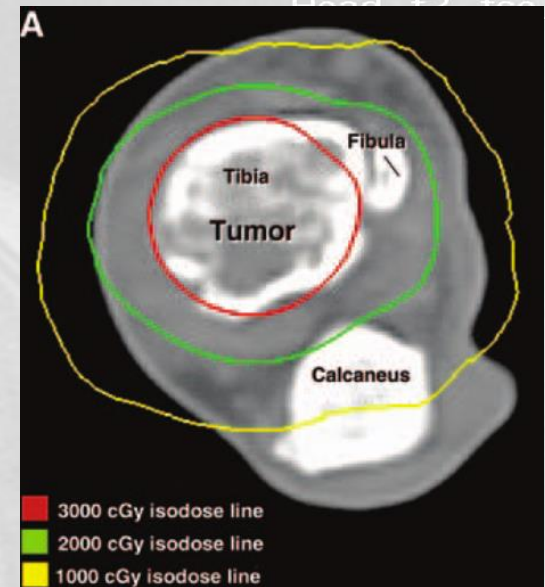


Stereotactic radiotherapy

1 fraction of 30 Gy
(+/- chemotherapy)

MST 363 days (range 145-763 days)*

Limitations: Large tumour size (> 5 cm diameter)
Large lytic component



* Farese JP, Milner R, Thompson MS, Lester N, Cooke K, Fox L, et al. Stereotactic radiosurgery for treatment of osteosarcomas involving the distal portions of the limbs in dogs. J Am Vet Med Assoc. 2004;225(10):1567-72, 1548.

Radiotherapy – side-effects

- Reduces the energy absorptive capacity
- Fragility of bone increases
- Acute side effects
 - Dermatitis
 - Leukotrichia
 - Hypotrichia
- Late side-effects
 - Osteonecrosis/osteitis
 - Tumour induction



Outcome

Treatment	Median Survival Time	1 year survival rate
No treatment	Weeks	
Amputation	3 – 5 months (Stage III 2 months)	11 %
Amputation + Carboplatin x 4 Amputation + Cisplatin x 6	11 months 13 months	35 % 56 %
Chemotherapy + Palliation	?	
Stereotactic Radiotherapy + Chemotherapy	12 months	