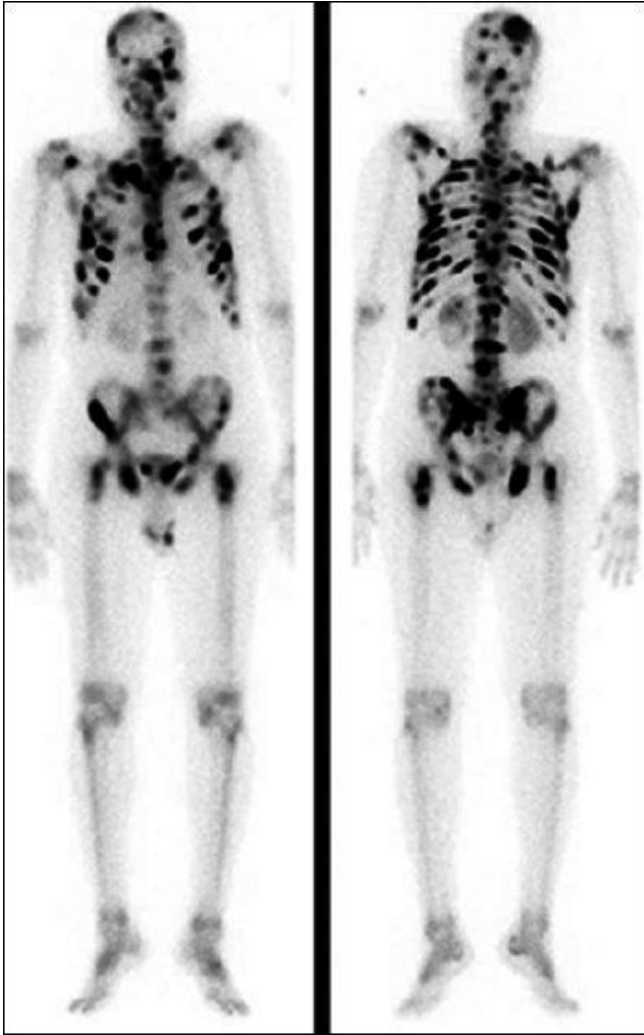




Bone Metastases and Pain

Graham Grove, 2025
(Updated from a 2015 talk)

Case (Isle of Wight, August 2015)

(First review, morning ward round following an overnight admission)

Profile:

- 89 year-old man, lives alone

PC:

- Severe pain in the left groin / hip

PMH:

- Prostate cancer
 - Gleason 3+3 diagnosed (2001) → hormone therapy
 - Rising PSA + bony metastases (January 2013) → hormone resistant cancer diagnosed
 - Pathological fracture of right neck of femur (November 2013) → total hip replacement
 - On abiraterone
- Aortic valve replacement – on warfarin
- Pacemaker + defibrillator
 - Inserted following an episode of broad-complex tachycardia
 - Removed in late 2013 due to an Infected lead
- Left distal femur fracture as a young man → treated with traction

Case

Current medications

- Digoxin
- Bisoprolol
- Ramipril
- Furosemide
- Regular paracetamol
- Abiraterone
- Prednisolone 10 mg daily
- Warfarin

Case

History of presenting complaint

- A few weeks of increasing pain in left hip, primarily when mobilizing
- Last 3 days, too painful to rise out of chair without help
- Severe pain over night lying in bed → called overnight GP service → reviewed by on-call GP → admitted directly to the hospice for pain management

Case 1

Examination findings of note:

- Heart rate 40 beats per minute
- Loud systolic murmur
- Pain in the left hip and knee on passive movement
- Vague tenderness around the left knee

Question

What do you think is going on?

What would you do?

Case

Assessment:

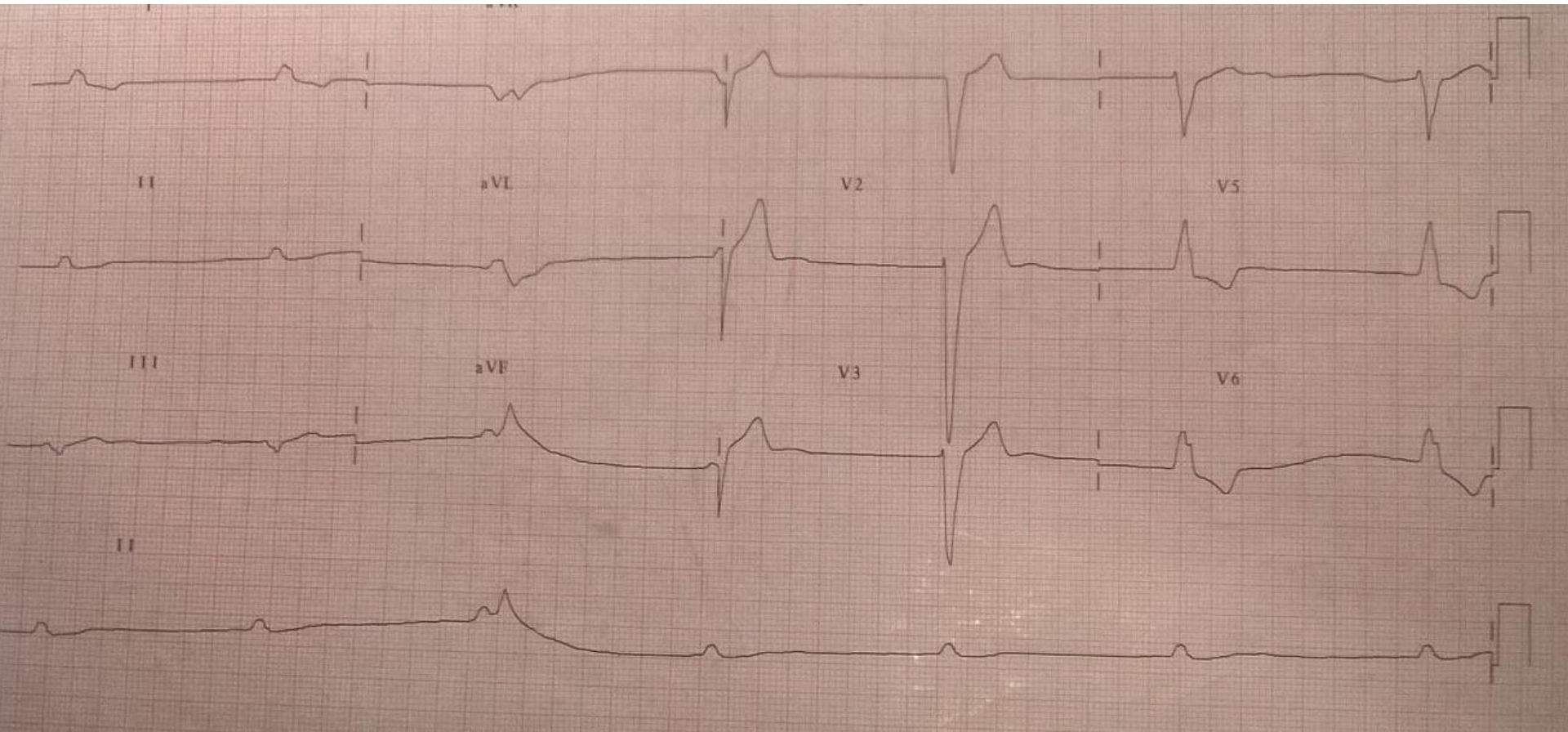
- Increasing pain probably due to femoral / pelvic metastases from progressive disease
- *(Note also, very bradycardic)*

Case

Plan:

- Oxycodone 2.5-5 mg orally hourly PRN
- X-ray of pelvic, left femur, left knee
- Nil weight bearing until x-ray reviewed
- ECG
- Stop digoxin / bisoprolol
- Bloods – PSA / Calcium / U&E / FBC / LFTs / digoxin level / INR

ECG



? Ventricular escape rhythm in the context of atrial fibrillation with complete heart block

Case

Blood results of interest:

- Digoxin level - 3.3
- PSA 118 (4 months earlier was 50)
- Creatinine 146
- Alb 27, Calcium 2.16
- INR 2.4
- Hb 95, MCV 88, Plt 218, WCC 7.9



Sclerotic metastasis in femoral shaft

Case

Management of pain:

- Review by orthopaedic surgeon requested
 - Pinning would be difficult given previous left distal femoral fracture
 - Relatively low fracture risk
 - Advised non-operative management
- Patient declined travelling to Portsmouth (required a ferry-trip) for radiotherapy
- Pain improved with analgesia and mobility improved with physiotherapy → discharged home 9-days post-admission

Case

Further progress

- Gradual decline in energy levels over the following 2 months
- Admitted to the hospice with haematuria + anaemia
 - Transfused + UTI treated
- Re-admitted a month later with dyspnoea, fever and hypotension
 - Treated for septic shock / pneumonia
 - Initially improved but then woke up 3-days post-admission with severe hip pain → left leg shortened and rotated
 - Decision made to withdraw treatment and focus on comfort care → died 4 days later peacefully

Painful bony metastases

At a glance...

Two main issues

- How do I control the pain?
- Will this fracture?

Managing the pain

At a glance...

Options:

- Basic analgesia (paracetamol) (weak evidence)
- NSAIDs and/or steroids (moderate evidence)
- Quick-acting opioids (especially prior to movement in cases of incident pain) (moderate evidence)
- Long-acting opioids (moderate evidence)
- Radiotherapy (strong evidence)
- Bisphosphonates (weak evidence for pain control)
- Other interventions
 - Vertebroplasties
 - Surgical stabilization
 - Calcitonin
 - Lidocaine infusions
 - Clonidine
 - Bone-seeking radio-isotopes

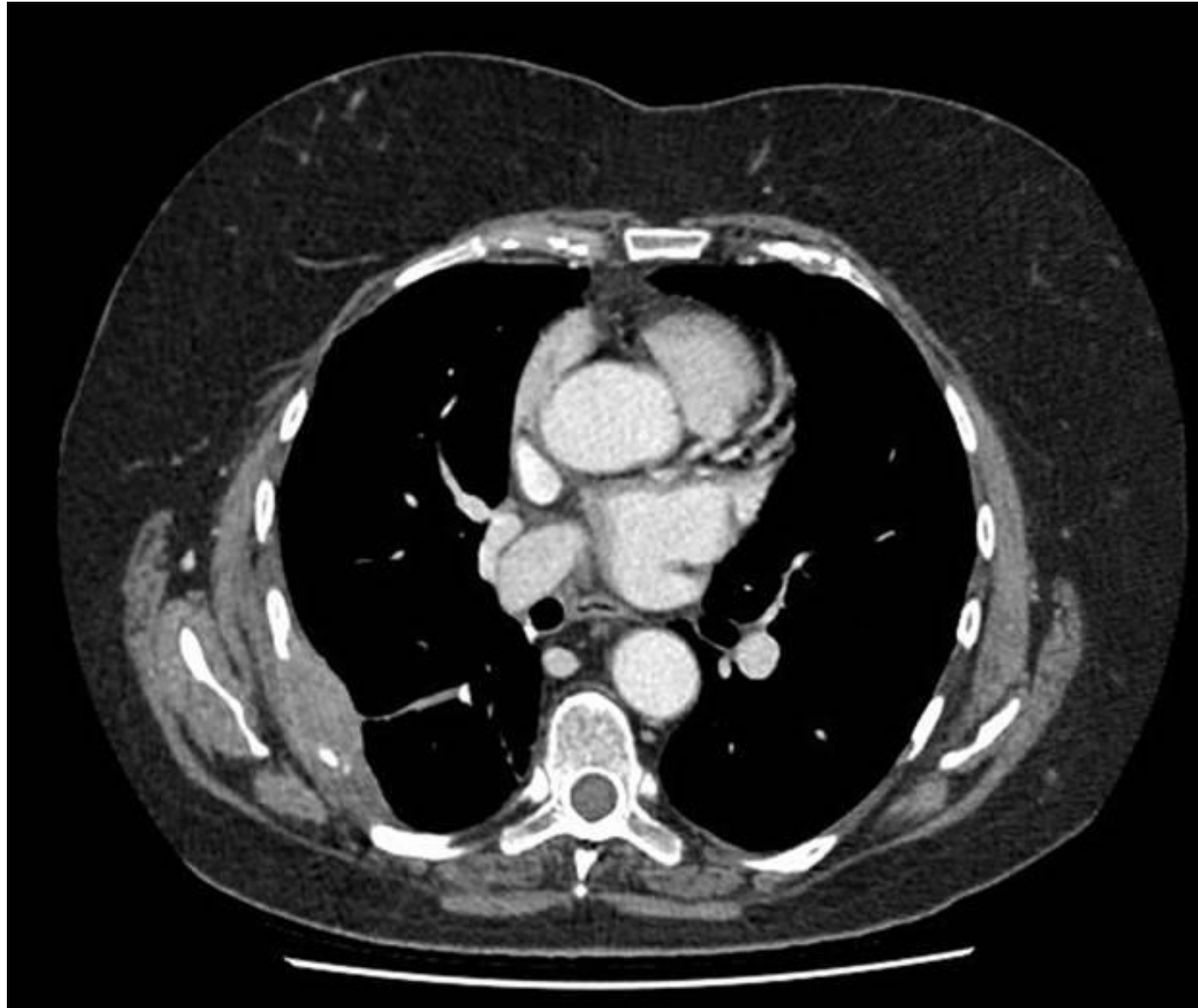
Bone metastases epidemiology

Bony metastases – very common (in metastatic cancer)

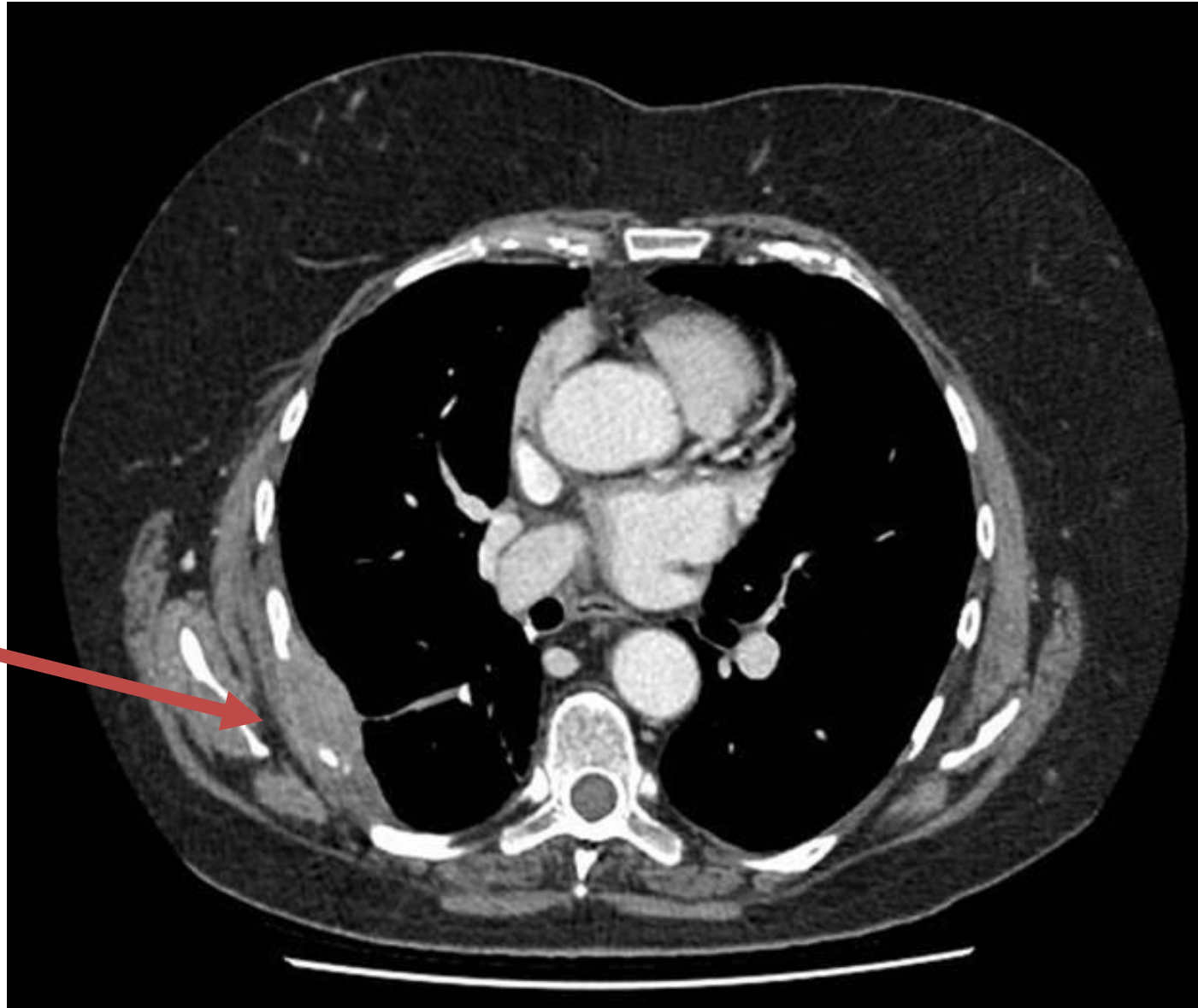
Bone → third most common site of metastatic disease (behind liver and lung)

In a patient with pain near a bone and a history of recent cancer – assume it's metastatic disease until proven otherwise

Past history of a lobectomy for lung cancer
Increasing pain for a few months
Told by oncologist that it was chronic pain post surgery



Past history of a lobectomy for lung cancer
Increasing pain for a few months
Told by oncologist that it was chronic pain post surgery



Recurrent cancer
eroding into the
rib and pleural

Bone metastases epidemiology

Any cancer can spread into the bone, but...

Bony metastases most common in:

- Breast cancer (20-40% of patients; 70% at post-mortem)
- Prostate cancer
- Lung cancer
- Renal cell cancer, bladder transitional cell cancer
- Thyroid cancer

Tumours that express certain adhesive molecule are more likely to metastasize to bone. Some molecules include:

- CXCR4
- Bone sialoprotein (in non-small cell lung cancer)
- Annexin II (in prostate cancer)

Pathophysiology

In general, bony metastases are classified as either

- Osteolytic (multiple myeloma)
- Mixed (most tumours)
- Osteoblastic (prostate and breast cancer)

Pathophysiology of pain:

Osteoclastic-mediated acidosis

Two main animal model techniques for replicating bone pain:

- Injection of malignant cells in left ventricle (with spread to multiple sites including bone)
- Injection of malignant cells directly into bone

Following injection →

- Rapid proliferation of tumour cells with replacement of marrow with tumour cells + inflammatory cells
- Proliferation of osteoclasts at the tumour-bone interface with destruction of bone
(tumour cells stimulate osteoclasts via various factors including Macrophage Inflammatory Protein [MIP1])
- Osteoclast activity correlates with bone pain



- Osteoclasts are differentiated from monocytes
- Osteoclasts resorb bone by maintaining an extracellular microenvironment of acidic pH

Pathophysiology of pain:

Nerve involvement

At least 3 mechanisms involved in pain

- Low pH
 - Some sensory neurons in bone are directly excited by protons (via acid-sensing ion channels)
 - TRPV1 (transient receptor potential vanilloid 1)
 - ASIC-3 (acid-sensing ion channel-3)
- Mechanical pressure
 - Some sensory neurons in bone are mechanosensitive
i.e. activated by minor mechanical stress in bones that have lost stability
- Cytokines
 - Some sensory neurons are activated by cytokines produced by inflammatory cells around the tumour including:
 - Prostaglandins
 - Bradykinin
 - Tumour necrosis factor alpha
 - Interleukin 1 and 6
 - Nerve growth factor (NGF)

Pathophysiology of pain:

Nerve involvement

Sensory and sympathetic neurons are present in

- Bone marrow
- Mineralized bone
- Periosteum

Direct damage to the nerve can occur via

- Direct invasion by tumour cells
- Ischaemia
- Fracture

Clinical Features

Background pain

- Dull ache
- Relatively localized
- Worse at night

Breakthrough pain

- Often predictable because occurs on weight bearing (incident pain)
- Throbbing exacerbations

Significant impact on quality of life due to:

- Pain
- Immobility

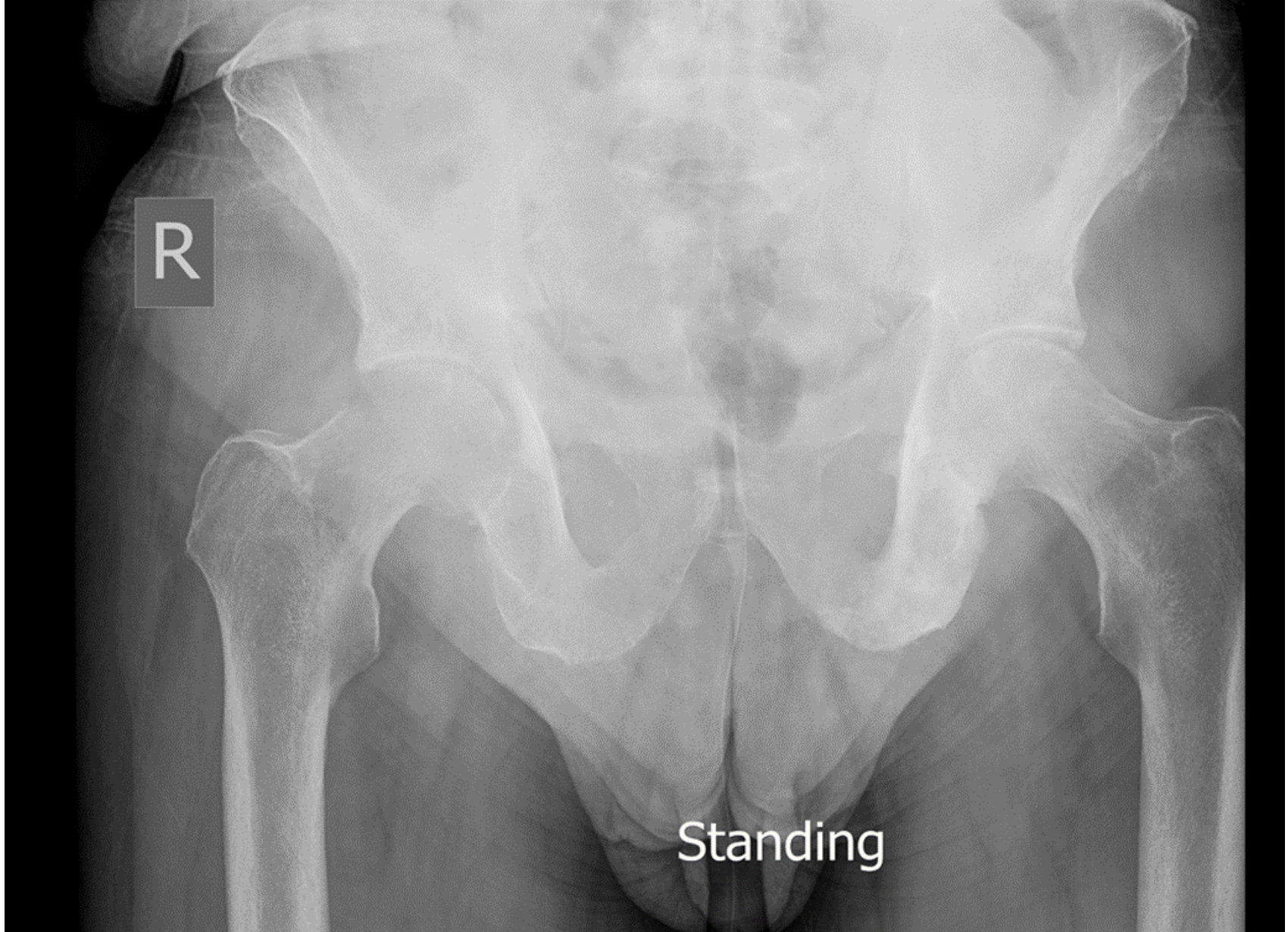
Investigations

Local imaging

- Plain film
- CT or MR imaging
- For back pain where spinal cord compression is suspected → urgent MRI

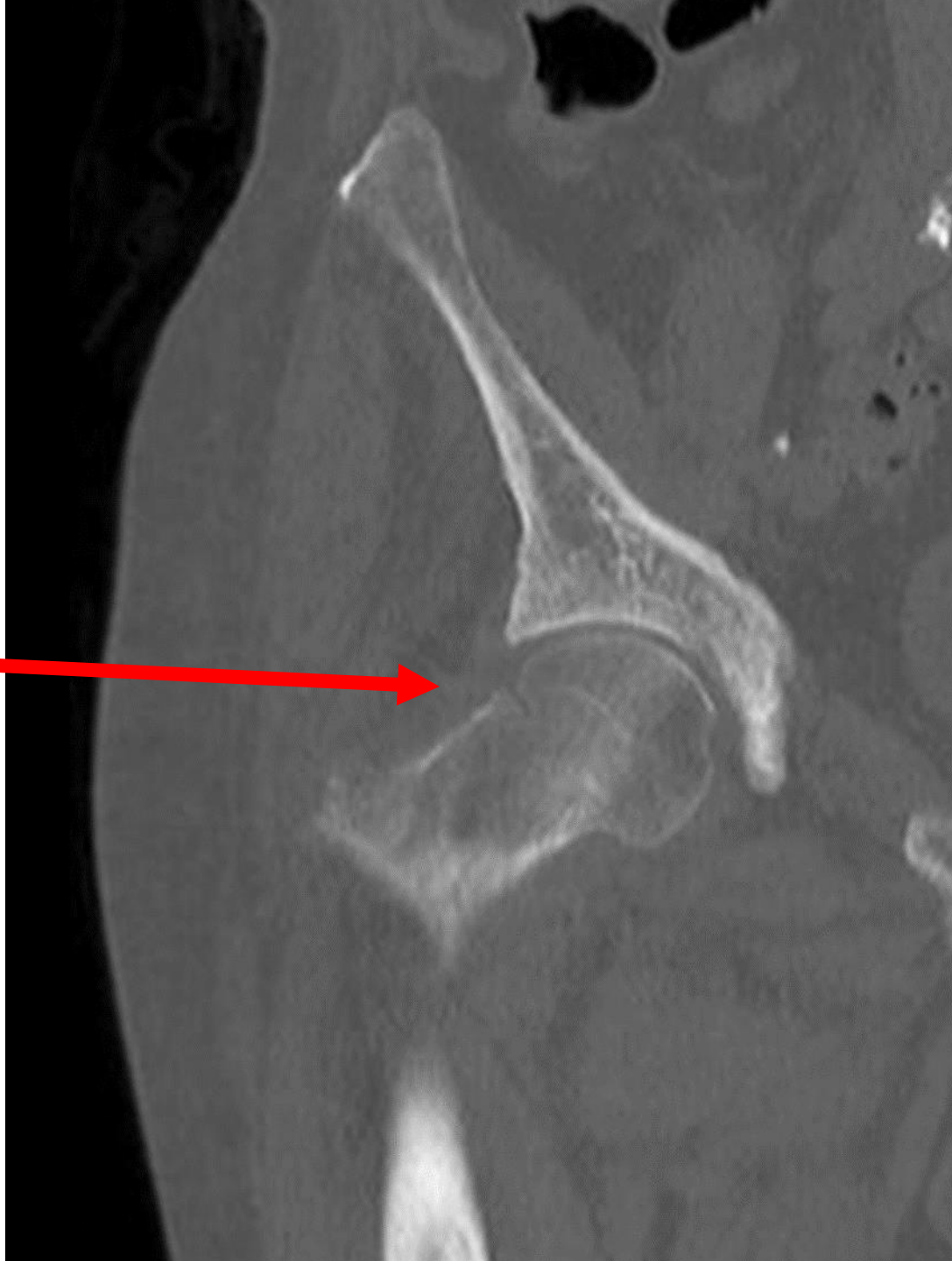
For whole-body evaluation

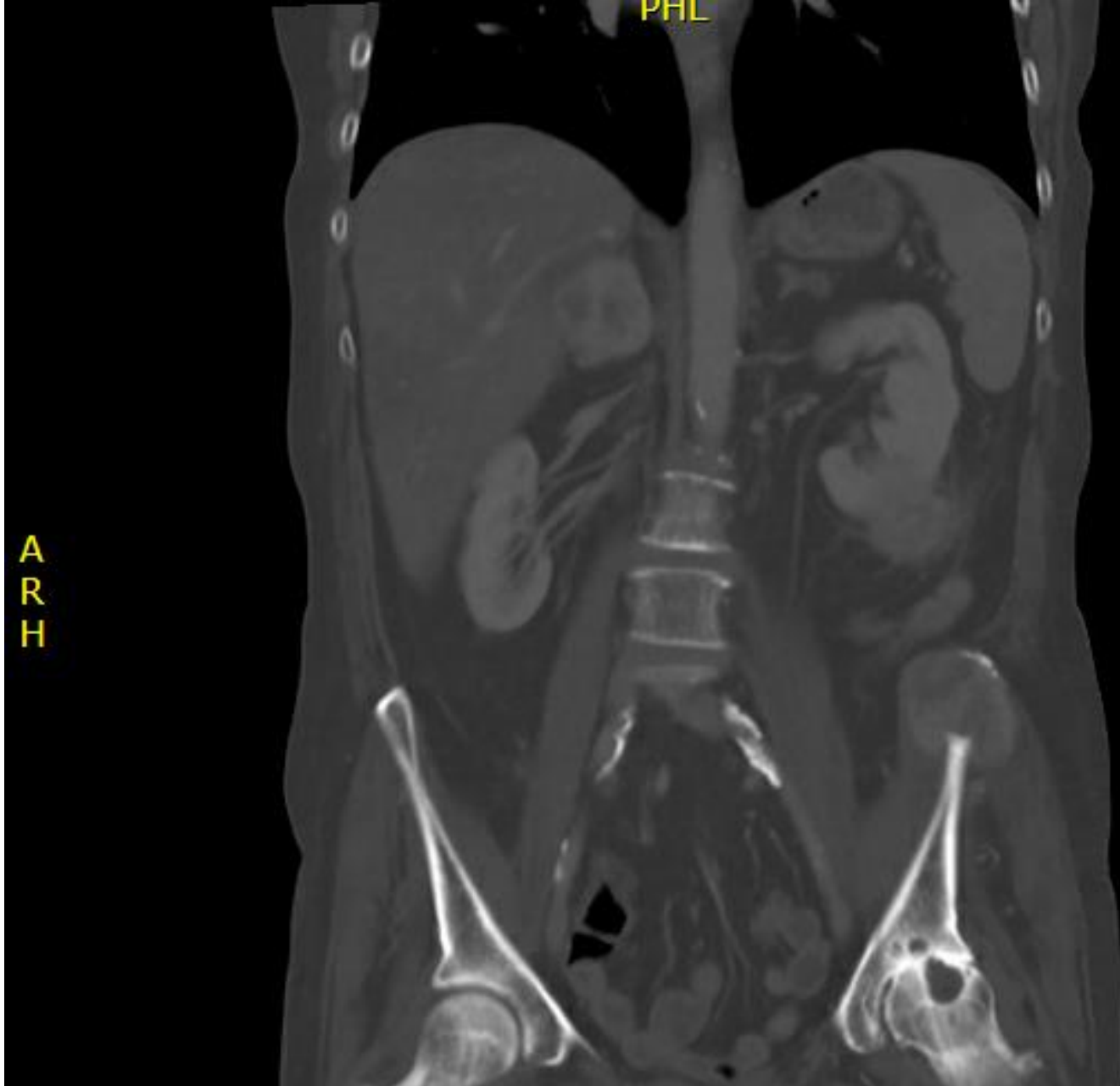
- Skeletal survey (for multiple myeloma)
- Whole body technetium bone scan (85% sensitive; 90% specific)
- FDG-PET scan (90% sensitive; 95% specific)
- Whole body MRI (DWIBS) (diffusion-weighted imaging background body signal suppression) (slightly less sensitive than WBBS and PET scan)



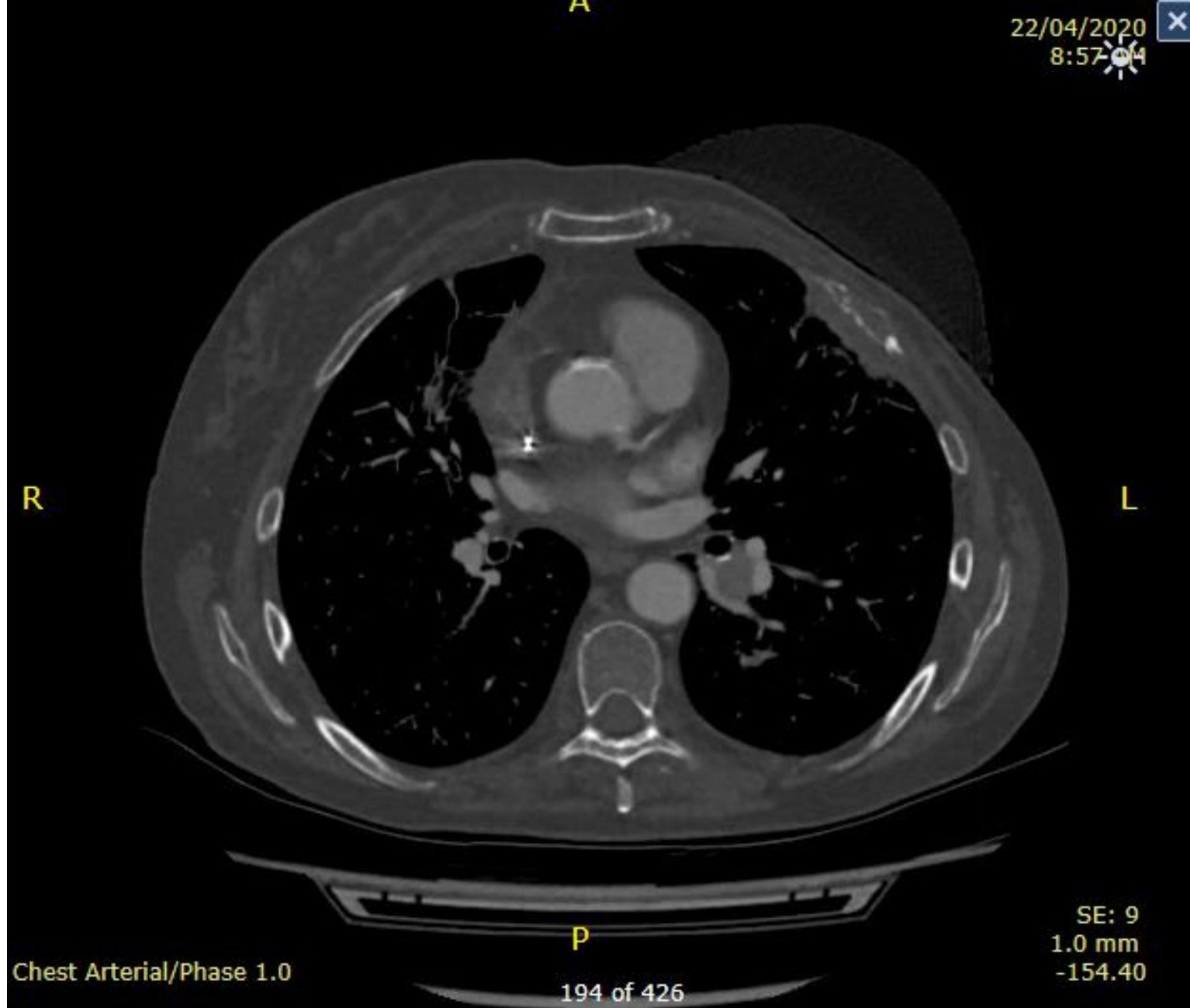
Pain on weight bearing
Reported as normal

Fracture

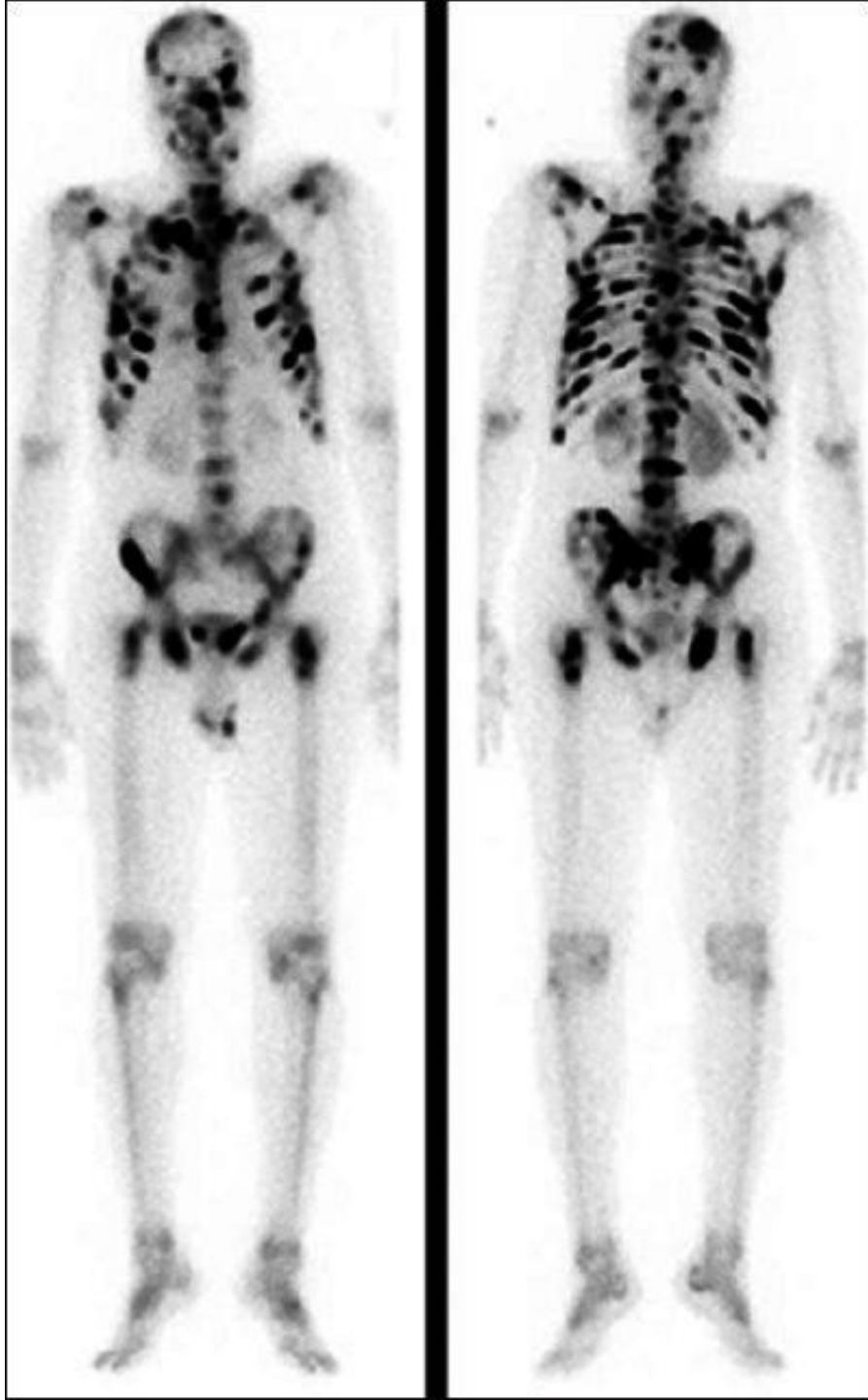




Left ilium erosive bone metastases



Left rib erosive lesion with fracture



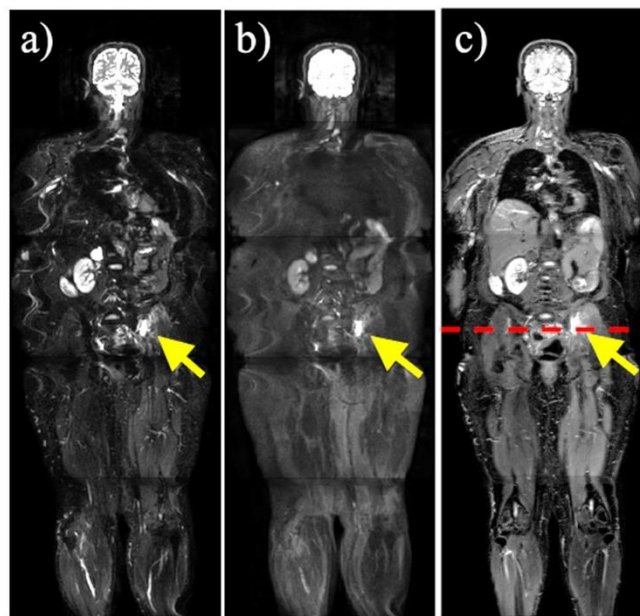
Multiple bony
metastases

DWIBS

b=0

b=800

DETECT



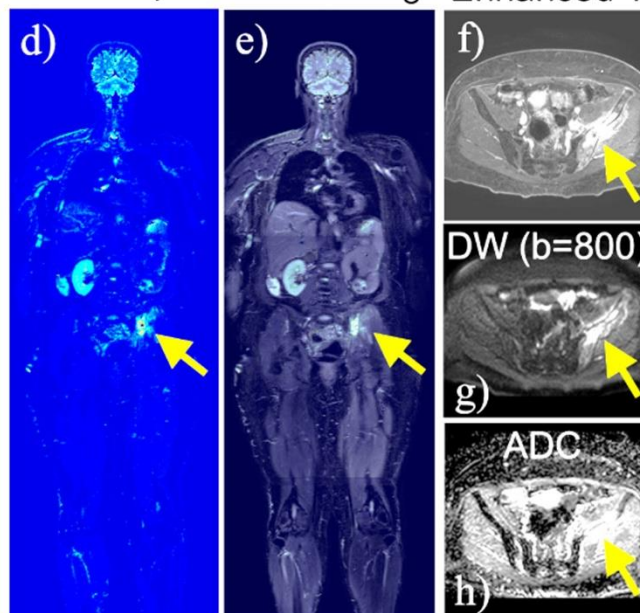
DETECT

Contrast-

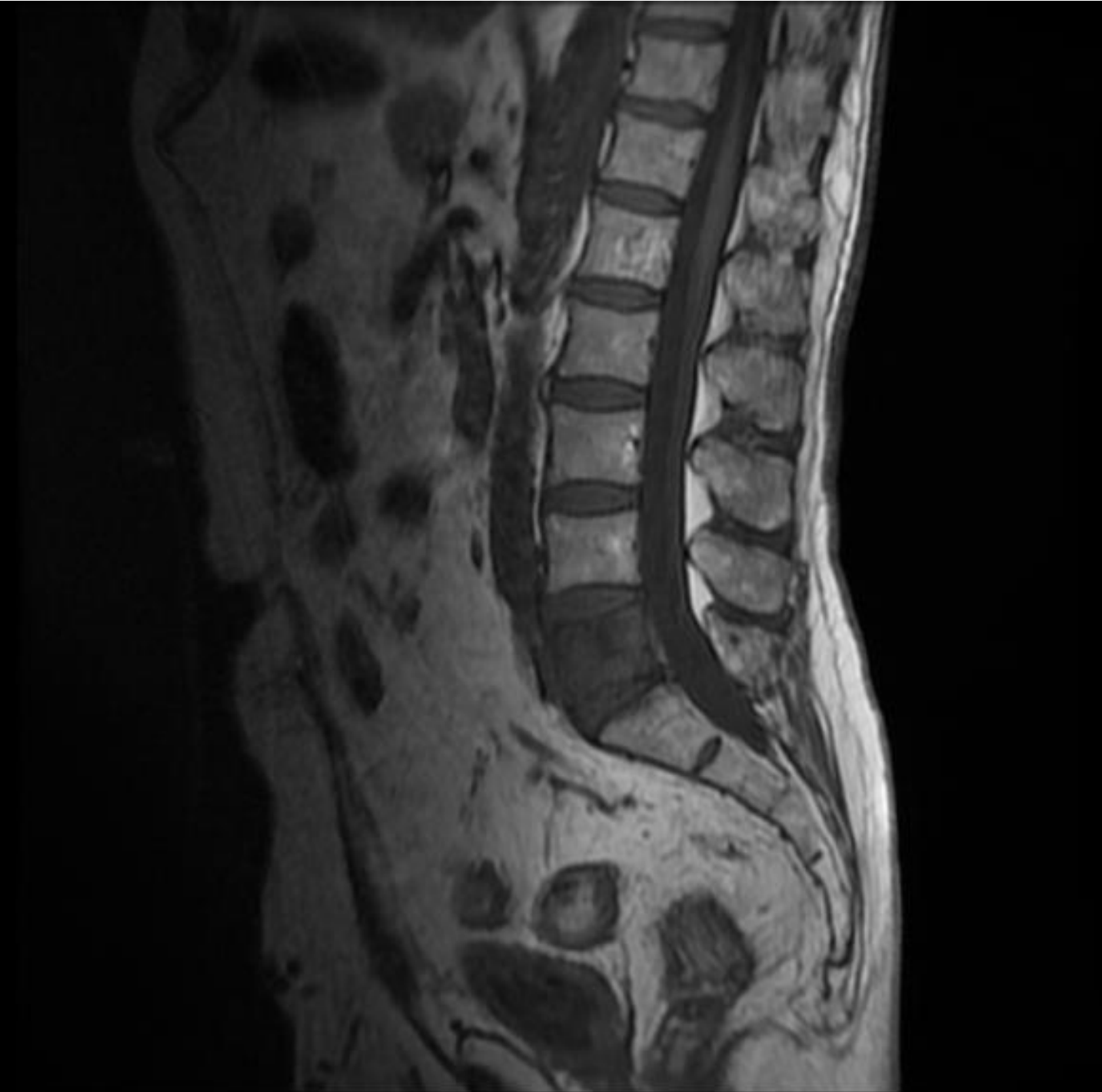
T2-map

Fused Image

Enhanced T1



Left ilium
metastasis



L5 metastases

Surgery

A key question to ask is: Will it fracture?

Particularly relevant for:

- Long bones (femur / humerus)
- Spine

→ Because prophylactic fixation may prevent fractures and suffering (and also reduce pain by providing mechanical support)

Mirels' Score

Mirels' Score ≥ 9 associated with a 33% fracture risk

Criteria	1 Point	2 Points	3 Points
Site	Upper Limb	Lower Limb	Peritrochanteric
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size	$< 1/3$	$1/3$ to $2/3$	$> 2/3$

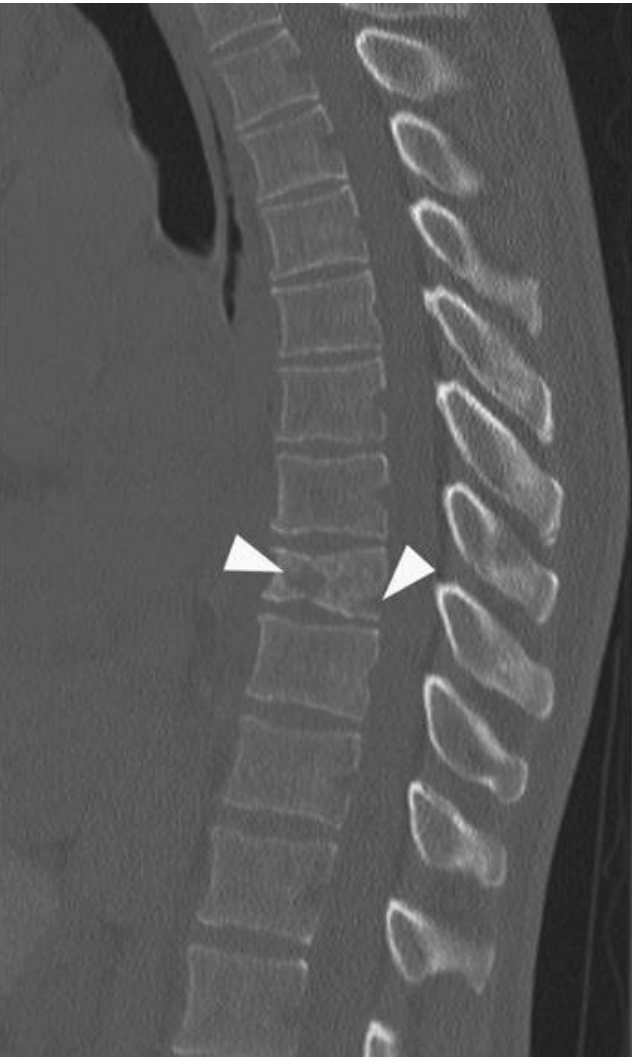


Spinal Instability Neoplasia Score

SINS > 7 →
generally
considered to
define a high
fracture risk

SINS Component	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain ^a	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements ^b	
Bilateral	3
Unilateral	1
None of the above	0

Vertebroplasties and Cement



- Helpful in acute fractures (< 4 weeks)
- Effective (immediately) in > 50%
- Radiologists often want both a CT scan and an MRI



Radiotherapy

Radiotherapy is typically the second line option for analgesia of bony metastases (if simple analgesia / opioids fails)

Treatment = Single 8 Gy fraction

Efficacy:

- 30% → complete analgesia
- 40% → partial analgesia
- 30% → no analgesia

Generally takes 2-4 weeks for analgesia effect

Anti-inflammatory agents *(NSAIDs and steroids)*

Randomized controlled trial of 3084 patients in 2004 →

Confirmed efficacy of **NSAIDs**

(No specific NSAID or COX-2 inhibitor more effective than another)

Randomized controlled trial in 1985

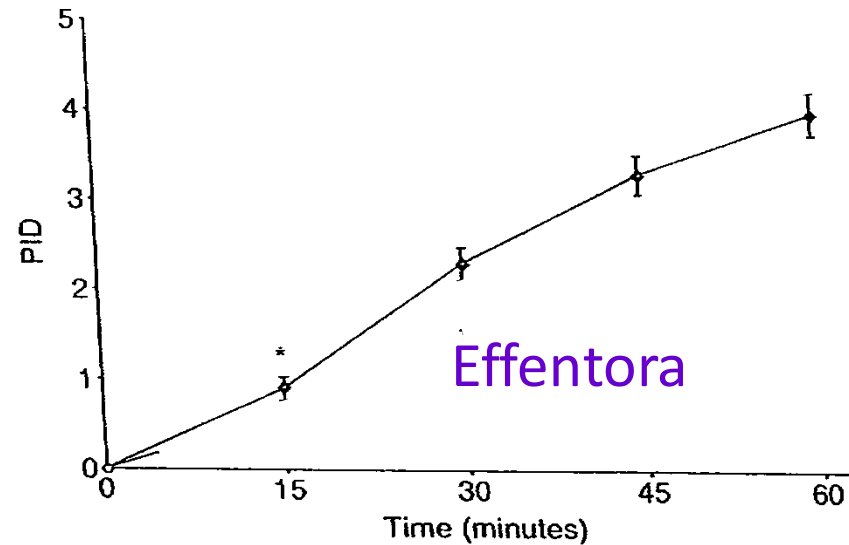
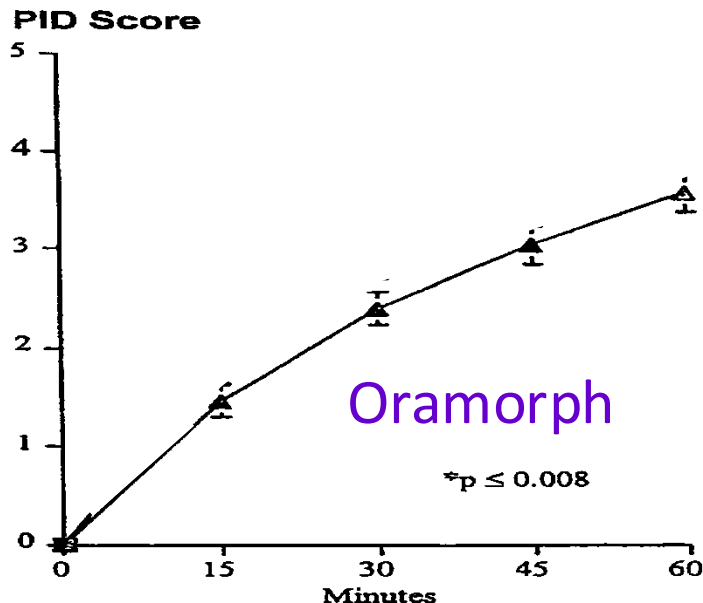
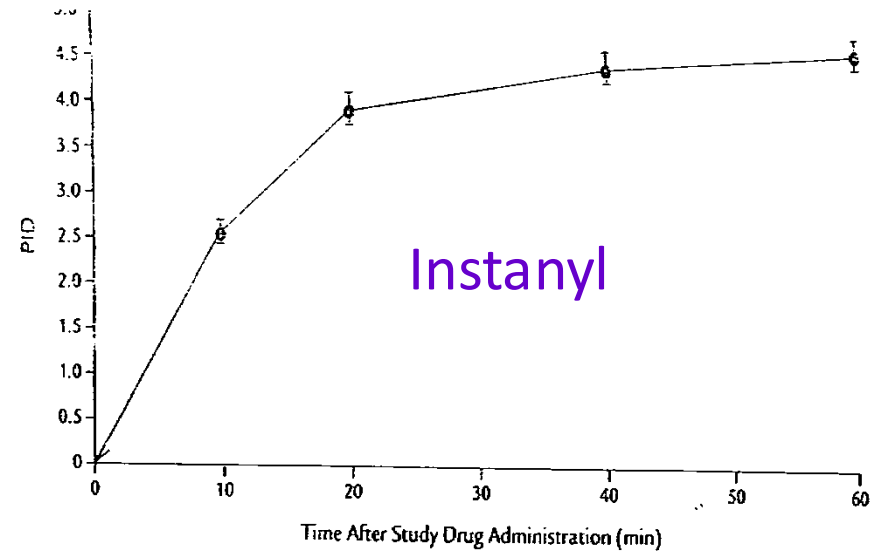
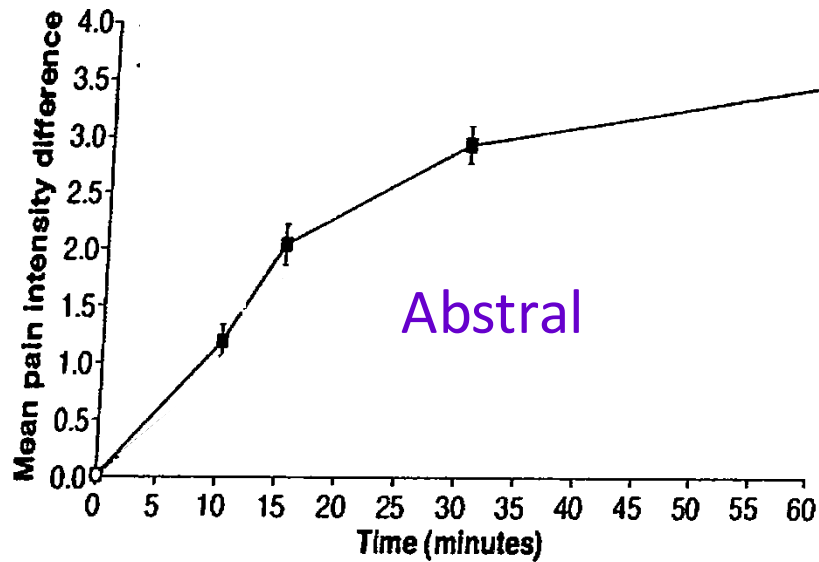
→ Confirmed **steroids** reduce bone pain in metastatic disease

Usual dose: dexamethasone 4-8 mg daily

Opioids and Incident Pain

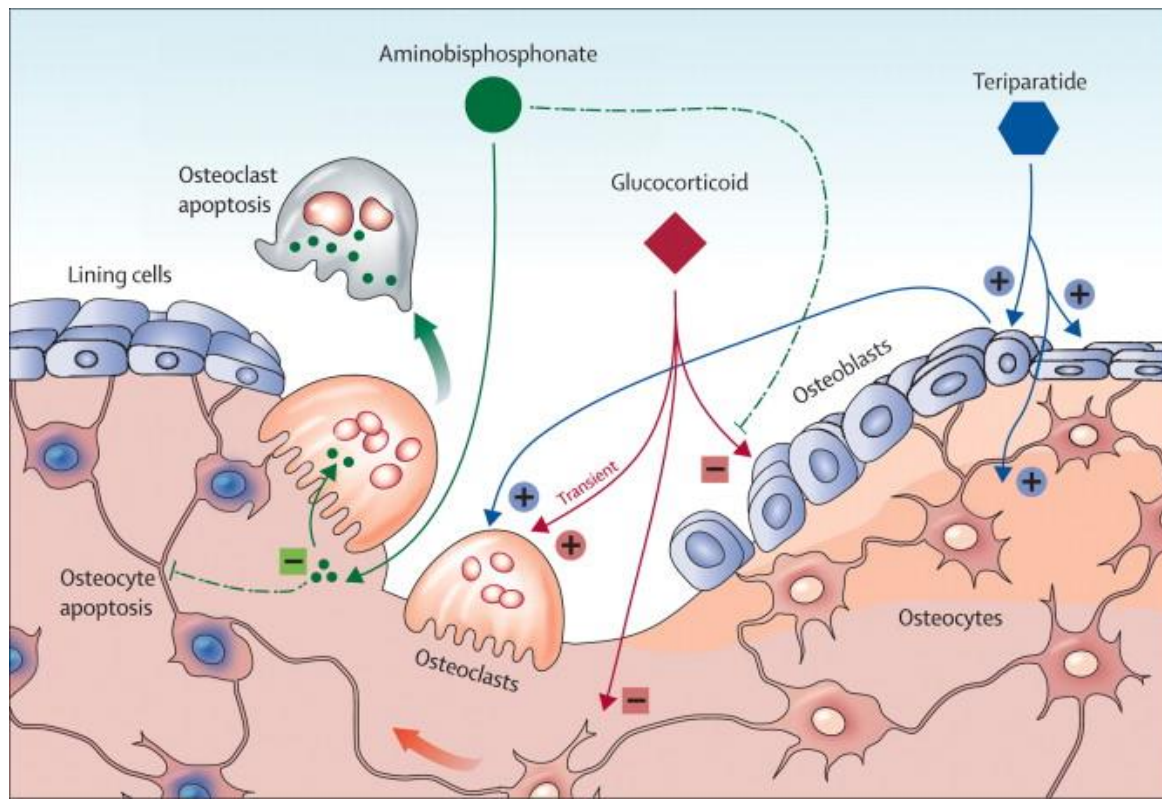
- Immediate release opioids effective for breakthrough pain
- A fast acting, rapidly cleared opioid is the logical best contender for incident pain, e.g.
 - Sublingual fentanyl 10 minutes prior to activity

Are PRN fentanyl products an advance?



Bisphosphonates

- Bisphosphonates bind to calcium ions in mineralized bone matrix
- Osteoclasts resorb bone (and bisphosphonates) via endocytosis
- Bisphosphonates then induce loss of function and apoptosis



Bone seeking radionuclide treatments

For widespread bony metastases causing pain

→ IV injection of radioactive isotopes (Strontium-89 or Radium-223) that localize to bone

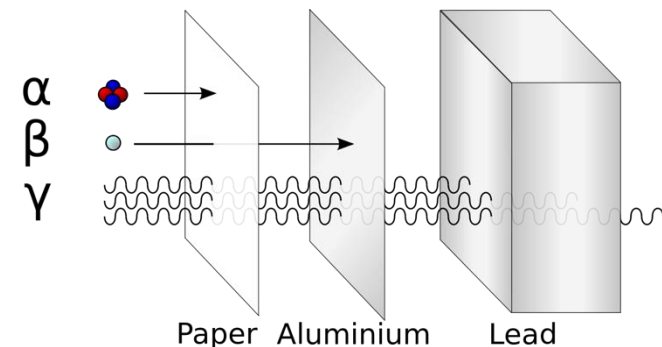
→ Pain relief in 40-90% of patients

Periodic Table

1 H Hydrogen				
3 Li Lithium	4 Be Beryllium			
11 Na Sodium	12 Mg Magnesi...			
19 K Potassium	20 Ca Calcium	21 Sc Scandium		22 Ti Titanium
37 Rb Rubidium	38 Sr Strontium	39 Y Yttrium		40 Zr Zirconiu
55 Cs Caesium	56 Ba Barium	57 La Lanthan...		72 Hf Hafnium
87 Fr Francium	88 Ra Radium	89 Ac Actinium		104 Rf Rutherford

Significant side effects

- Bone marrow failure with pancytopenia



What's on the horizon?

Suzetrigine

Mechanism

- Selective inhibitor of voltage-gated sodium channel NaV1.8 (primarily expressed on peripheral neurons)
(similar to lidocaine or mexiletine)

FDA approved; not currently approved in Australia

Current clinical indications:

- Severe acute back pain (post surgery) → comparable efficacy to low-dose opioids
- (Currently less evidence for chronic back pain)

Potential advantage of mexiletine / lidocaine

- Selective inhibitor (no known cardiac concerns)
- *Note: known serious adverse effects include – headache, confusion, incoordination, sudden visual loss*



Spinal Cord Compression

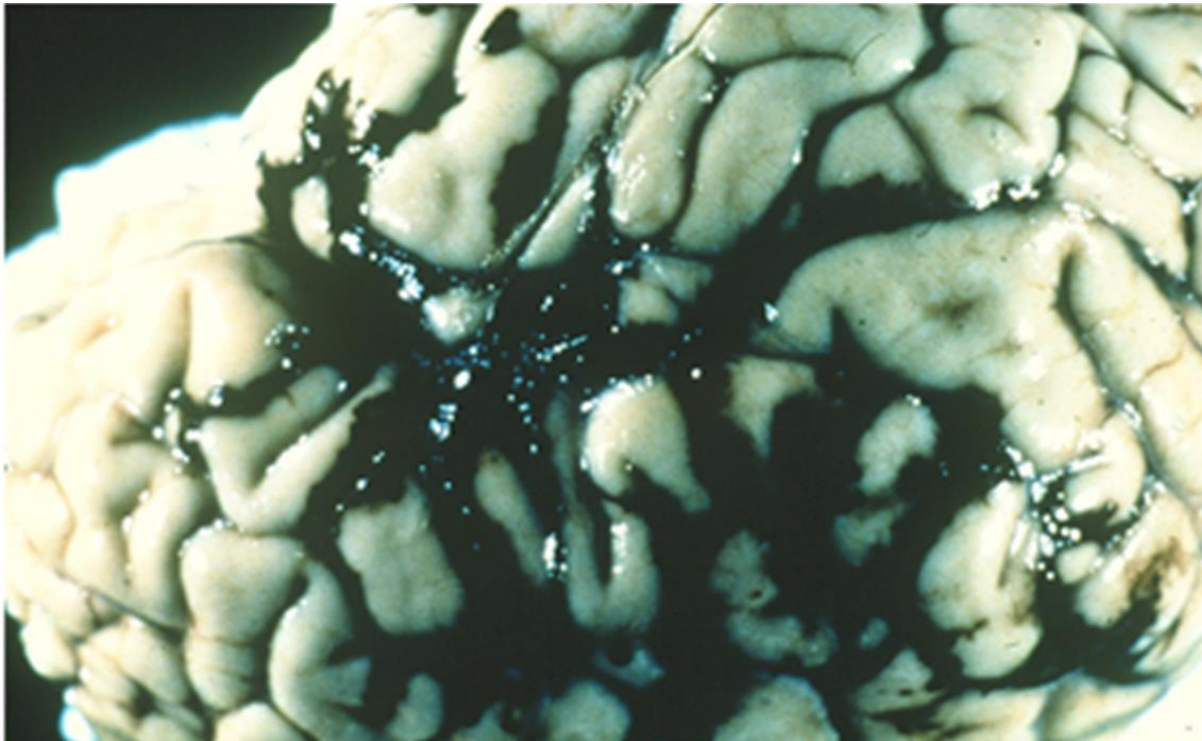
If suspected:

(and the patient's prognosis is possibly more than short weeks)

- Acts that day
- Dexamethasone 16mg daily
(or 8mg twice daily)
- Urgent imaging
(ideally an MRI)
(if MRI unavailable, CT scan)
- Discussion with radiation oncology +/- spinal surgery



Leptomeningeal spread



- Varied (often odd) presentations
- Difficult to diagnose
 - Either a lumbar puncture
 - OR MRI with gadolinium
- Typically indicates a poor prognosis (weeks to short months)
- Treatment - dexamethasone

Hypercalcaemia

Presents with

- Constipation
- Fatigue
- Confusion
- Worsened pain

Remember – check corrected calcium

Usually indicates progressive cancer and poor prognosis

Treatment often helps symptoms, so consider:

- Zoledronic acid 4mg IV infusion (dose reduce in renal impairment)
- (effect takes 3-5 days)

Bone marrow failure

Occurs with widespread bony metastases

Typical blood film

- Normocytic anaemia
- Low platelets
- Low white cell count
- Precursor cells
 - Myelocytes, metamyelocytes
 - Nucleated red cells present

Often indicates a poor prognosis

Usually a comfort care approach is appropriate, but if a decision to treat is made:

- ✓ Red cell transfusions give for symptomatic anaemia (typically when Hb < 80)
- ✗ Platelet transfusions usually not indicated (very short half-life) – may be an option for acute bleeding
- ✗ Broad-spectrum antibiotics (e.g. piperacillin/tazobactam)

Thank you!

- Comments or Questions?
- Mobile: 0406 813 044