

ADVANCED PROSTATE CANCER

The management and treatment options for secondary bone disease

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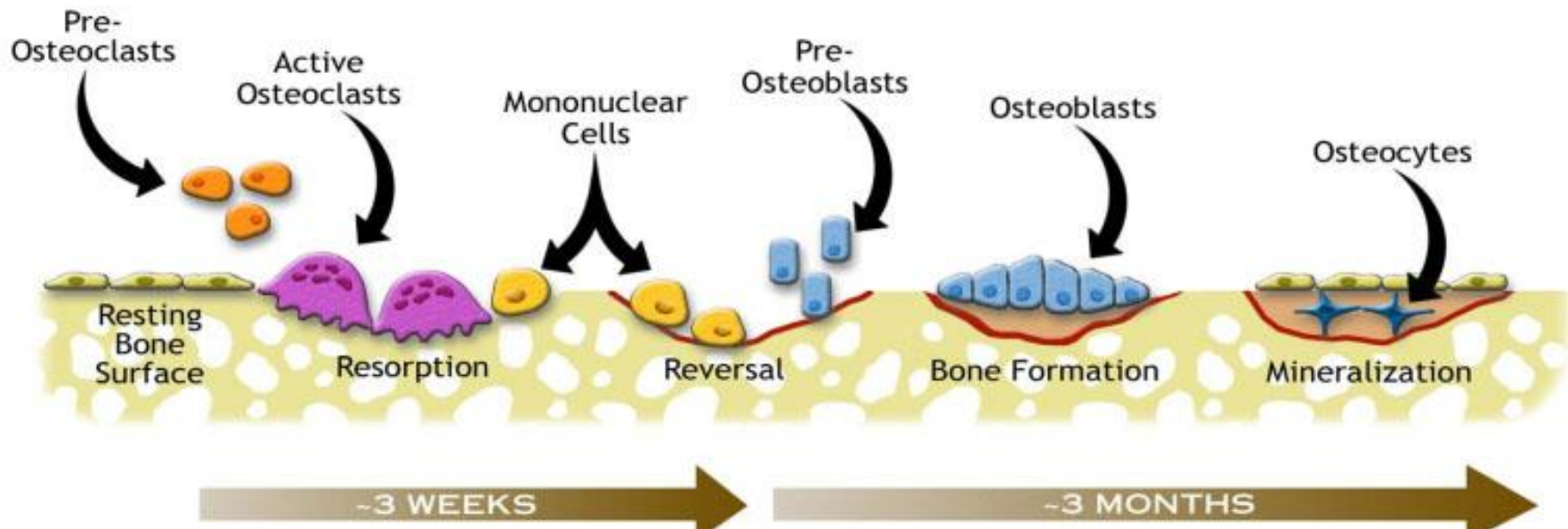
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AIMS

- Review bone metabolism
- Define SRE
- Detection of metastatic disease
- Management of metastatic disease

Bone metabolism

Bone Remodeling Cycle





OSTEOCLAST



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Diet
Hormone
Steroids

Smoking
Low BMI
Sedentary

Oestrogen
Testosterone
Exercise



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‘RANK’

RECEPTOR ACTIVATOR
OF NUCLEAR FACTOR- κ B



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Diagnosis of metastatic disease

- Asymptomatic diagnosis
 - PSA
 - Gleason score
 - Clinical Stage (T stage)



Prognostic grouping

- Low risk
 - PSA <10ng/ml
 - G6
 - T1/2
- Intermediate risk
 - PSA 10-20ng/ml
 - G7
 - T1/2
- High risk
 - PSA >20ng/ml
 - G8-10
 - T3/4



- MRI
 - Local staging
 - Spinal MRI in high risk (Not recommended NICE)
- Isotope bone scan
- CT abdomen pelvis
 - Abdominal nodes

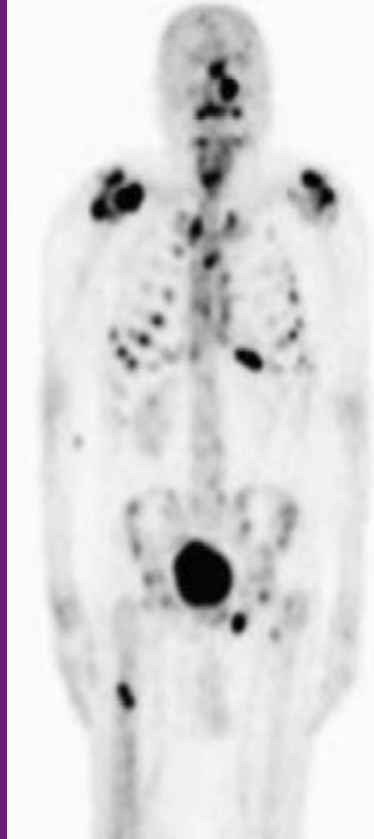


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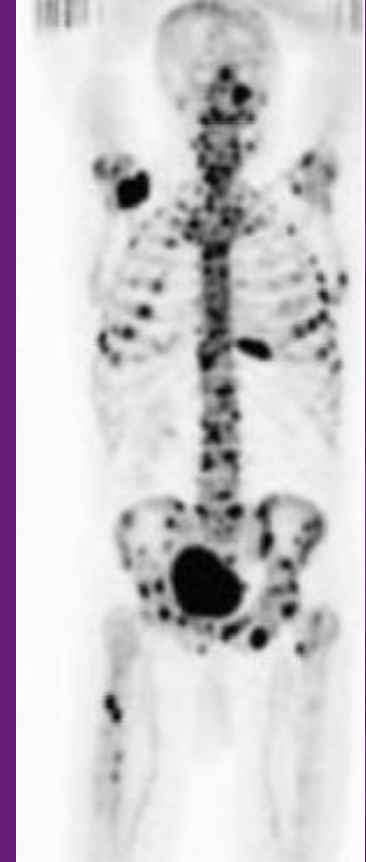




Tc 99



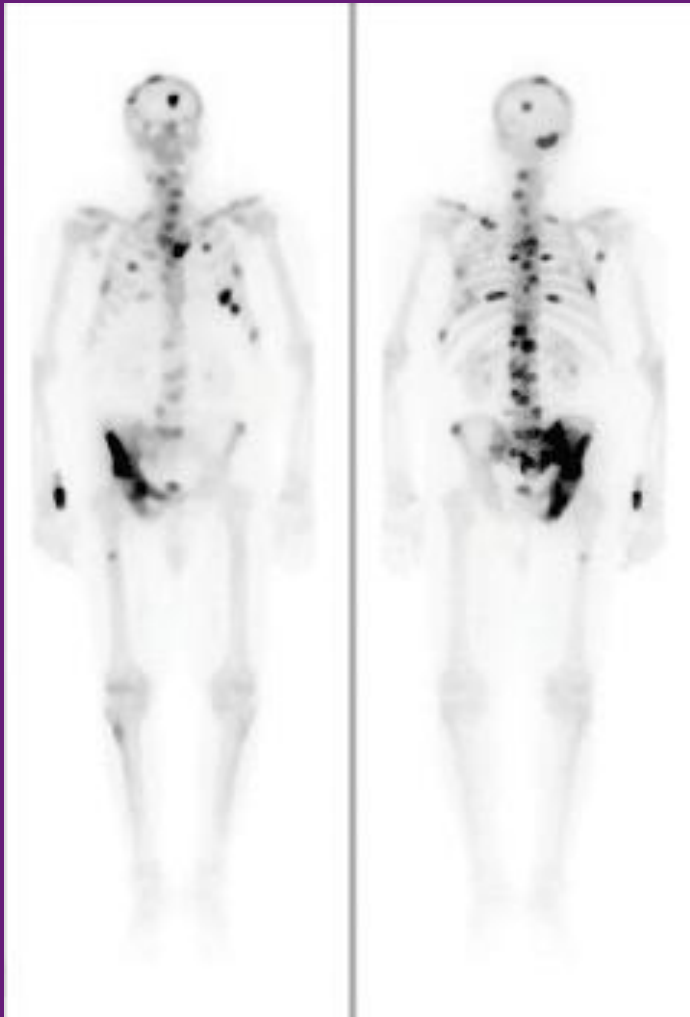
Multi field of view
SPECT

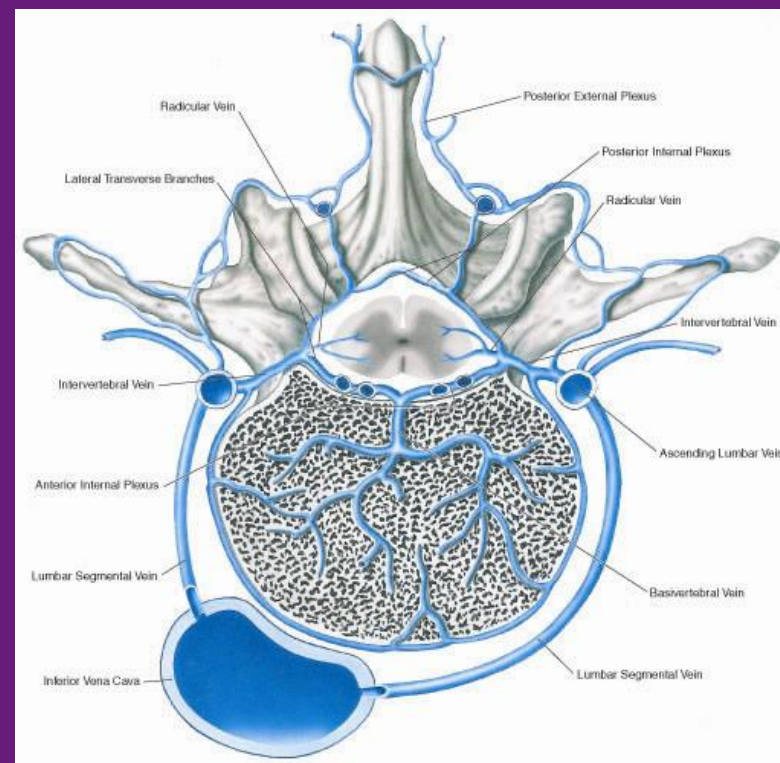
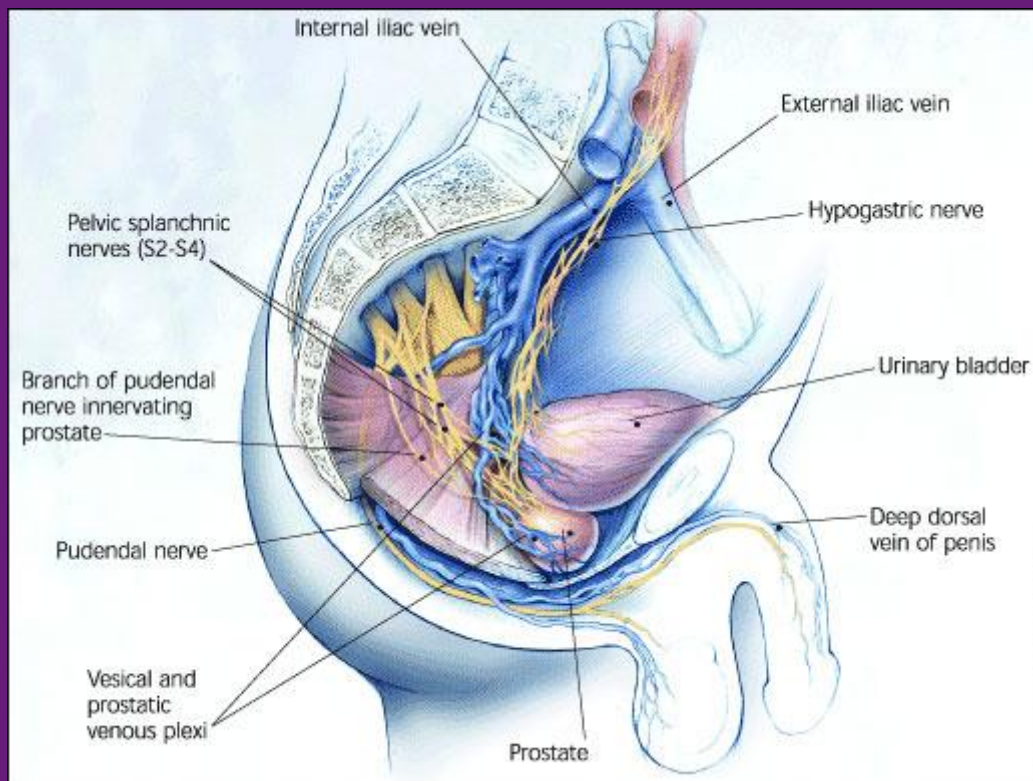


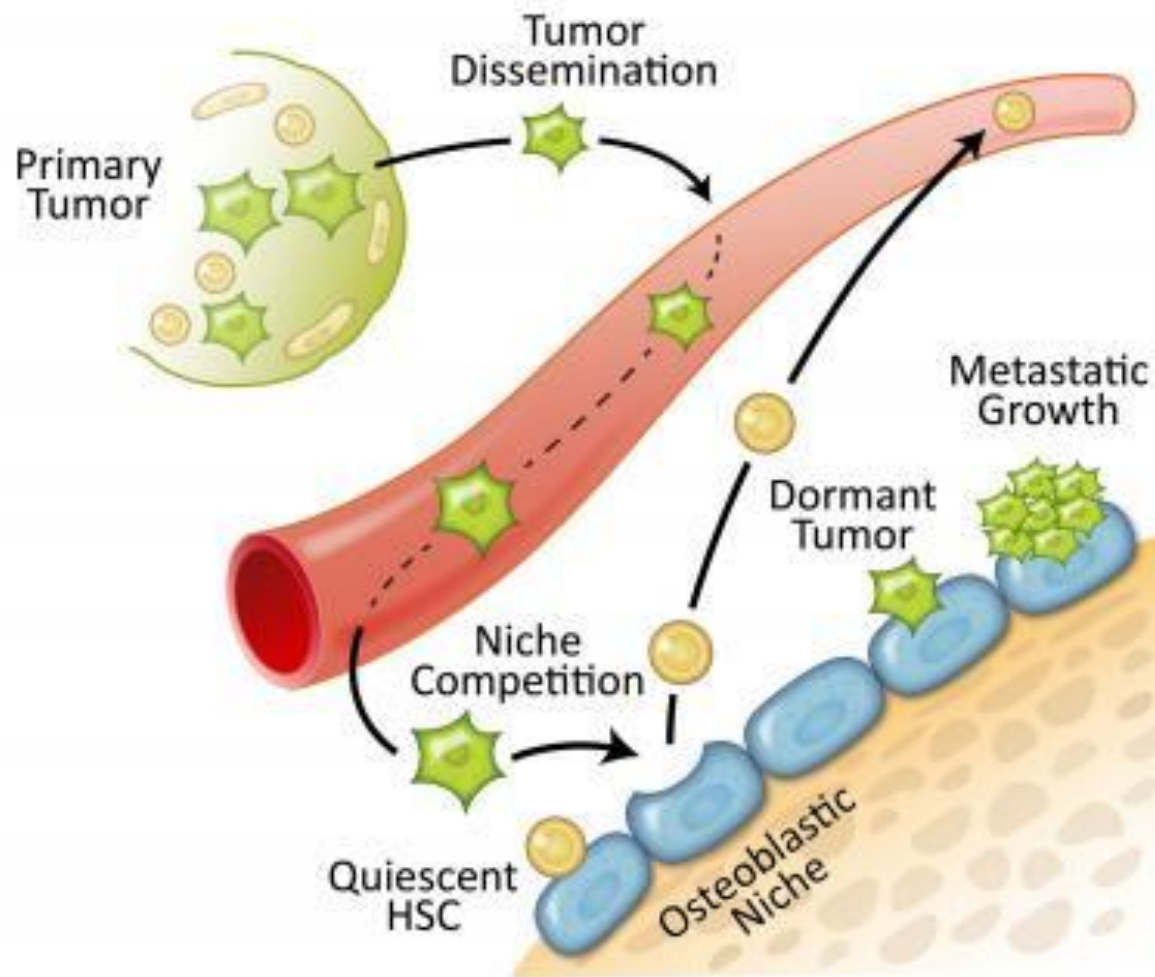
F-18 fluoride PET

- Symptoms?
 - Unexplained bone pain
 - Persisting >4weeks
 - Progressive in nature
- Alkaline phosphatase



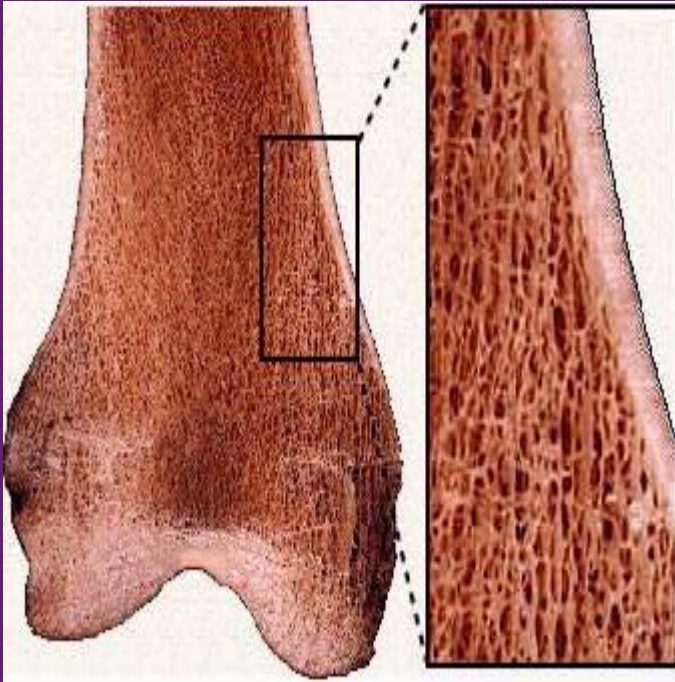






Prostate Metastasis

- Metastasis
 - High bone turnover
 - Activation of both Osteoclasts and Osteoblasts
 - Erosion of trabecular bone
 - Development of woven bone
 - Dense ('Sclerotic') but structurally weak
 - Limited number of disorganised collagen fibres



Lamellar



Woven

Bone Metastasis

- Pain
- Pathological fracture
- Spinal cord compression
- Marrow suppression
- Hypercalcaemia



Skeletal Related Events – “SRE’s”

- Defined as:
 - Pathological fractures
 - Spinal cord compression
 - Bone pain requiring palliative radiotherapy
 - Bone pain requiring orthopaedic surgery
- Effect on prognosis and Quality of Life

Treatment of metastatic disease

- Systemic therapy
- Focal therapy
 - Surgery
 - Radiotherapy
- Bone targeted therapy
 - Bisphosphonates
 - Denosumab
- Radionuclide therapy
 - Samarium
 - Radium 223 (Alpharadin)



Systemic therapies

- Androgen deprivation therapy
- Steroids
- Chemotherapy



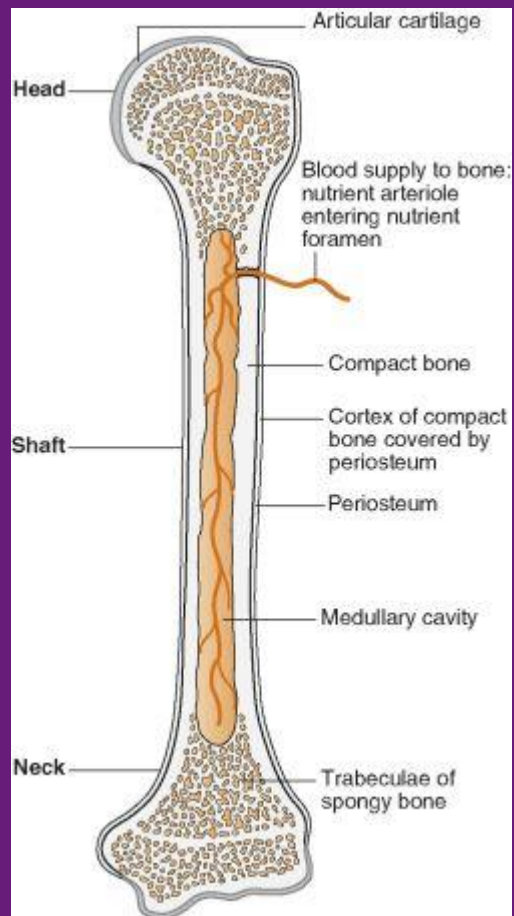
Systemic therapies

- Analgesics
 - WHO ladder
 - NSAID's
 - Neuroleptic
 - eg Gabapentin
- Palliative care team

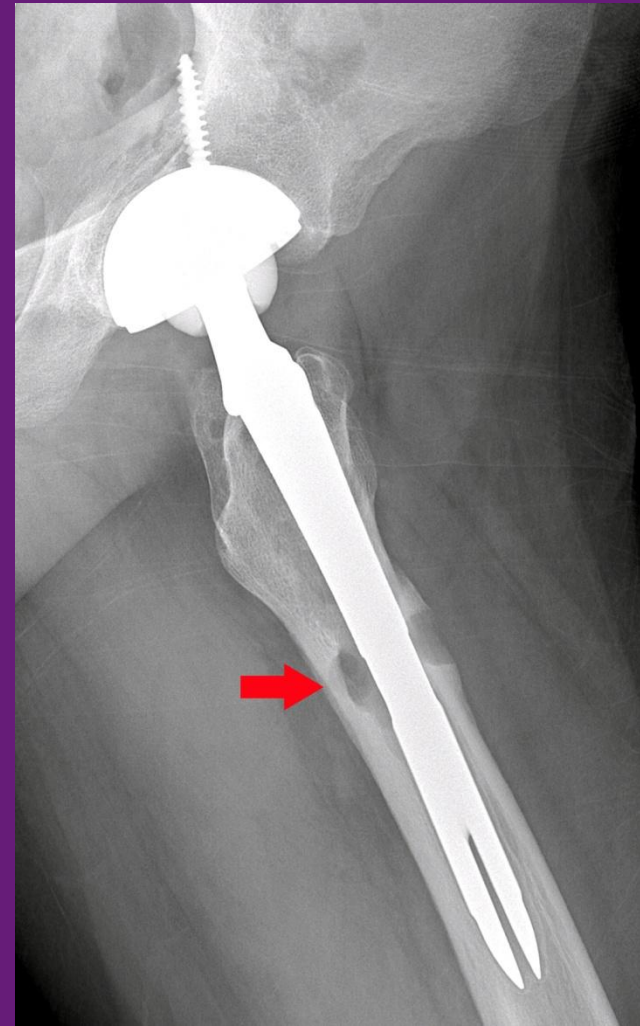


Surgery

- Aim of surgery
 - Prevent pathological fracture
 - Manage pathological fracture
- Risk of Pathological fracture
 - Lytic disease
 - Long natural history
 - 3 or more bone metastasis
 - Weight bearing areas (proximal femurs)



50% cortex destruction



>80% cortex destruction



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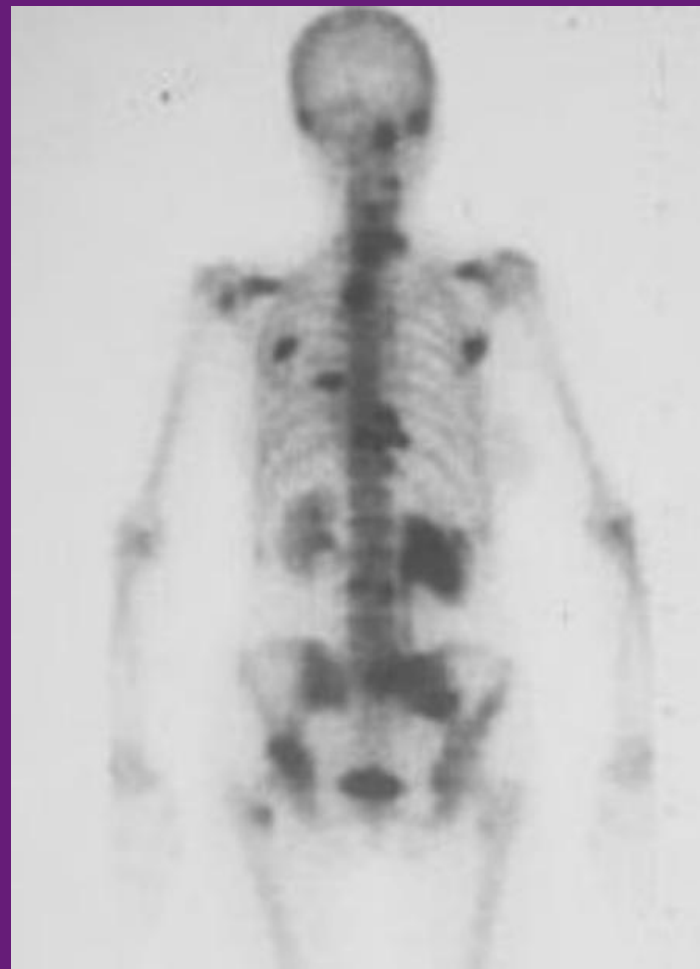
Radiotherapy

- Simple
- Pain free
- Effective





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Radiotherapy

- Benefit
 - 50-70% pain response
 - Generally take 5-7 days before effect noted
- Dose
 - 8Gy single fraction (53%)
 - 20Gy in 5 treatments over 1 week (61%)

Bisphosphonates

- Structurally similar to inorganic phosphate
- Rapidly incorporated into bone
- Inhibit osteoclasts
- May have a direct cytotoxic effect

Bisphosphonates

- Multiple drugs with various potency
 - Pamidronate
 - Zolendronate
- IV infusions
 - 4weekly



Bisphosphonates – side-effects

- Flare
 - Direct effect
 - T cell activation – acute phase reaction
- Hypocalcaemia
 - Calcium/Vit D supplementation
- Acute renal failure
- Osteo-Necrosis of Jaw (ONJ)



Bisphosphonates – ONJ

- ONJ (1-12%)
 - 60% associated with dental procedure while on bisphosphonates
 - Recommendation delay infusion until dental work completed
 - Impaired healing / Infection

Bisphosphonates – ONJ

- 3 criteria
 - Exposed bone persisting for more than 8 weeks
 - No history of radiation therapy to area
 - Previous bisphosphonate treatment.
- Presentation
 - Pain
 - Discharge
 - Halitosis



Bisphosphonates – ONJ





Bisphosphonates – ONJ

- Treatment
 - Withdrawal of bisphosphonates
 - Urgent maxillofacial/dental assessment
 - Resection/curettage
 - Antibiotic therapy
 - ? Hyperbaric oxygen therapy

Bisphosphonates

- ZOMETA 039 study
 - 643 PCA asymptomatic/mildly symptomatic men
 - Randomised to Zoledronic acid or control
 - SRE's
 - 33% vs 44% during 15months
 - Time to first SRE
 - 488days vs 321days
- NO significant improvement in OS

NICE CG58

- “Bisphosphonates should not be used for the prevention of bone metastases in men with prostate cancer.”
- “The use of bisphosphonates to prevent or reduce the complications of bone metastases in men with hormone-refractory prostate cancer is not recommended.”
- “Bisphosphonates for pain relief may be considered for men with hormone-refractory prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed.”
- “Bisphosphonates should not be used routinely to prevent osteoporosis in men with prostate cancer receiving androgen withdrawal therapy”.

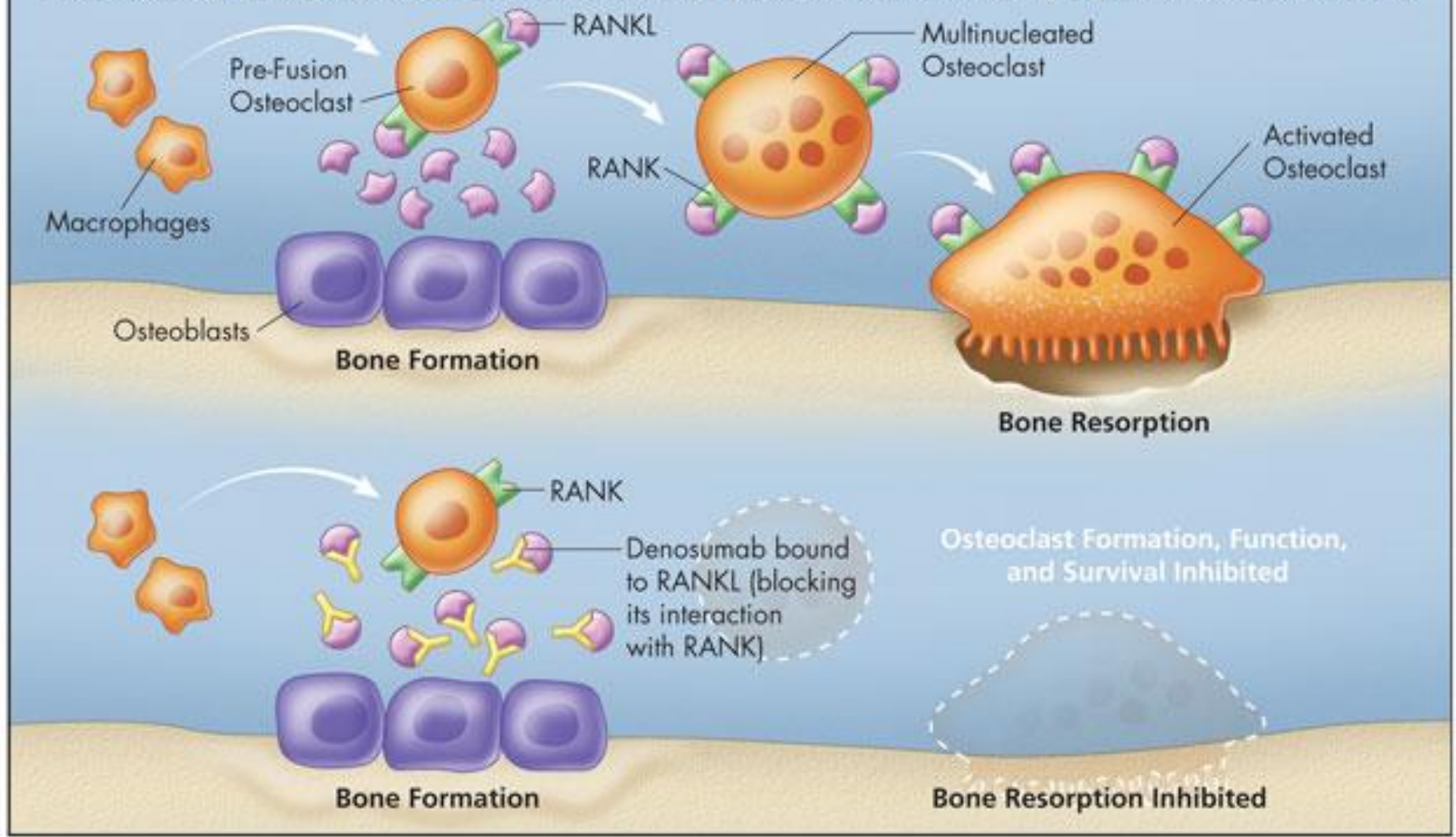
Denosumab

- Monoclonal antibody which binds to and inhibits RANKL
- Inhibition of osteoclast activation
- Administration
 - Osteoporosis s/c 6monthly



Figure 1:

Denosumab and Its Role in the Inhibition of Osteoclast Formation, Function, and Survival

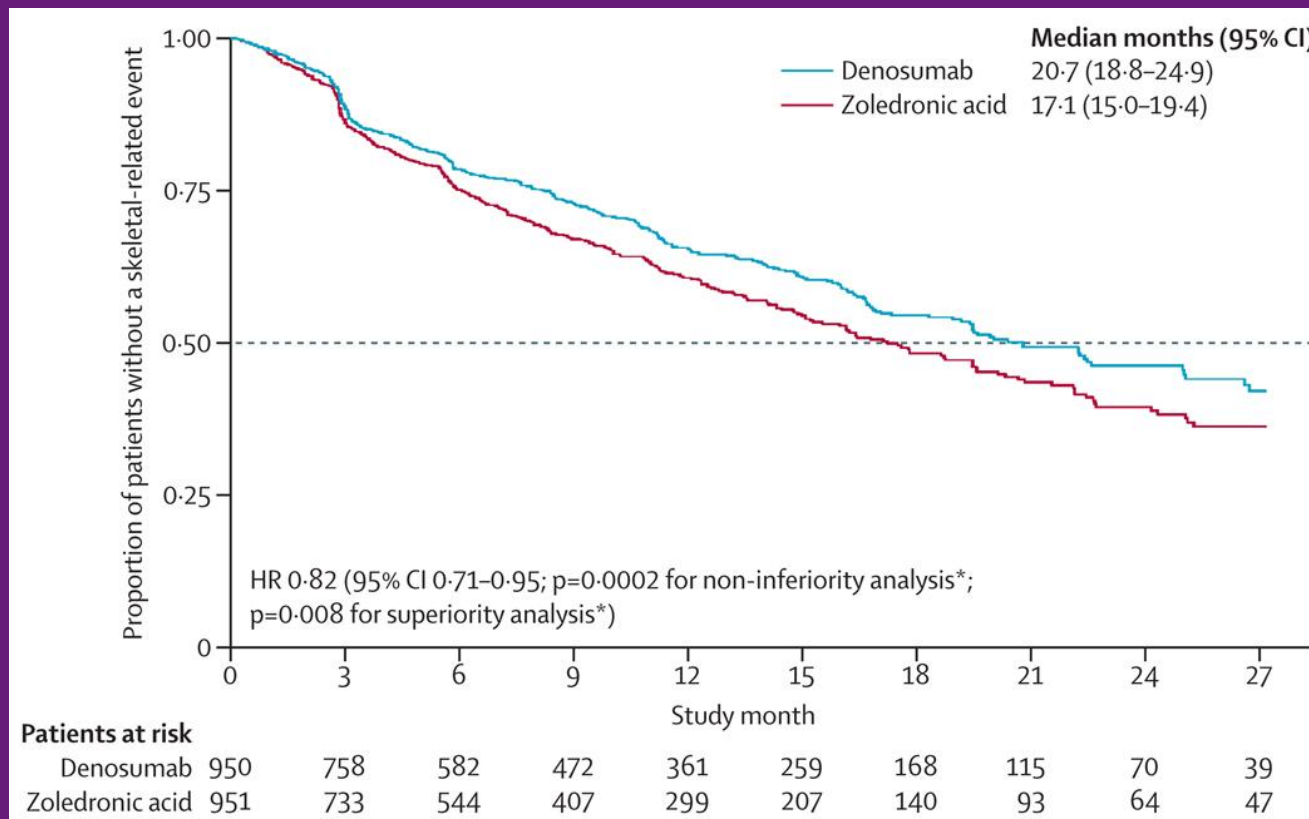


Denosumab – side-effects

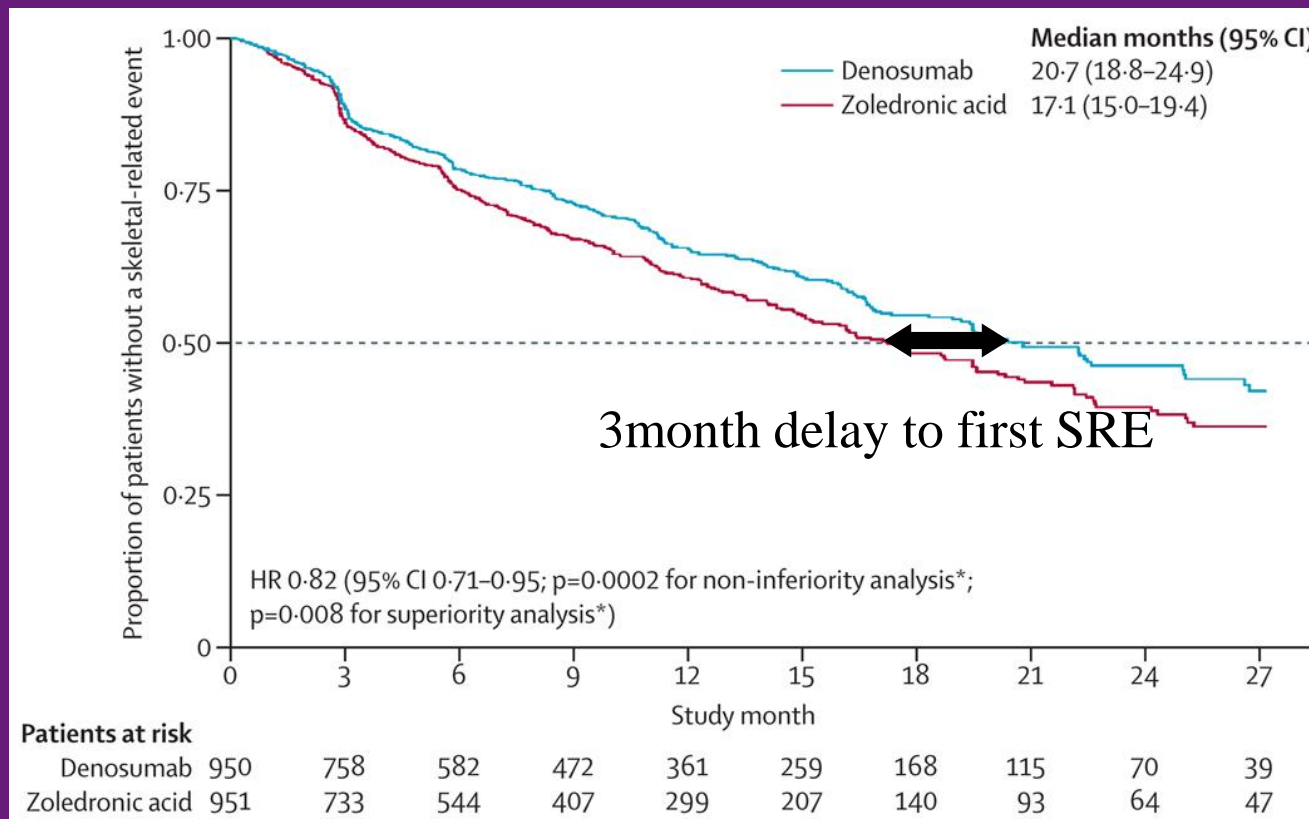
- Urinary/respiratory/skin infection
- Cataracts
- Constipation
- Rashes
- Joint pain
- Skin infection
- Hypocalcaemia
- ONJ



Denosumab versus zoledronic acid in men with Metastatic castration-resistant prostate cancer:



Denosumab versus zoledronic acid in men with Metastatic castration-resistant prostate cancer:



Denosumab versus zoledronic acid in men with Metastatic castration-resistant prostate cancer:

- ONJ
 - 22% vs 12%
- Hypocalcaemia
 - 13% vs 6%



NICE recommendation

- Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.

Denosumab - cost

- Total per patient over 1 year
 - Denosumab £22,000
 - (£12,200drug/£9,800administration)
 - Zoledronic acid £17,500
 - (£7,000drug/£10,500administration)



Radio nucleotide therapy

- Samarium¹⁵³ (Quadramed)
 - Radioactive compound bound to EDTA
 - Actively absorbed into areas of increased bone turnover
 - Release its radiation to surrounding area
 - ~ £5000 per treatment



Radio nucleotide therapy

- Samarium¹⁵³ (Quadramed)
 - Leucopenia – risk of infection
 - Anaemia
 - Thrombocytopenia – risk of bleeding
 - Nausea and vomiting
 - Dizziness, numbness/tingling.

Radio nucleotide therapy

- Samarium¹⁵³ (Quadramed)
 - 70% response rate
 - Approx 60days
 - 30% suitable for retreatment
 - Marrow suppression
 - No benefit in OS
 - Combination with other therapy?



Radio nucleotide therapy

- Alpharadin
 - Radium 223
- ALSYMPCA
 - ALpharadin in SYMptomatic Prostate CAncer

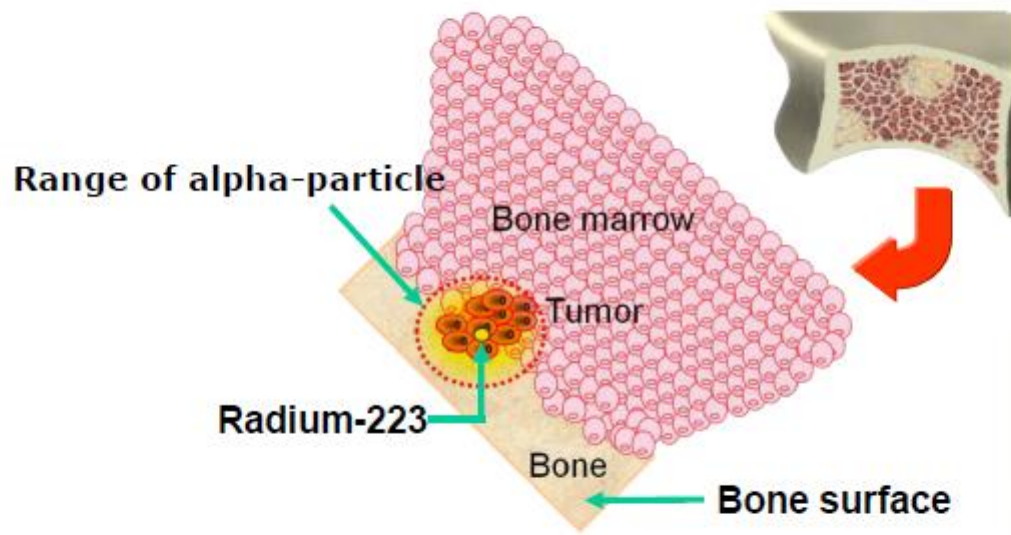


- hydrogen
- alkali metals
- alkali earth metals
- transition metals
- poor metals
- nonmetals
- noble gases
- rare earth metals



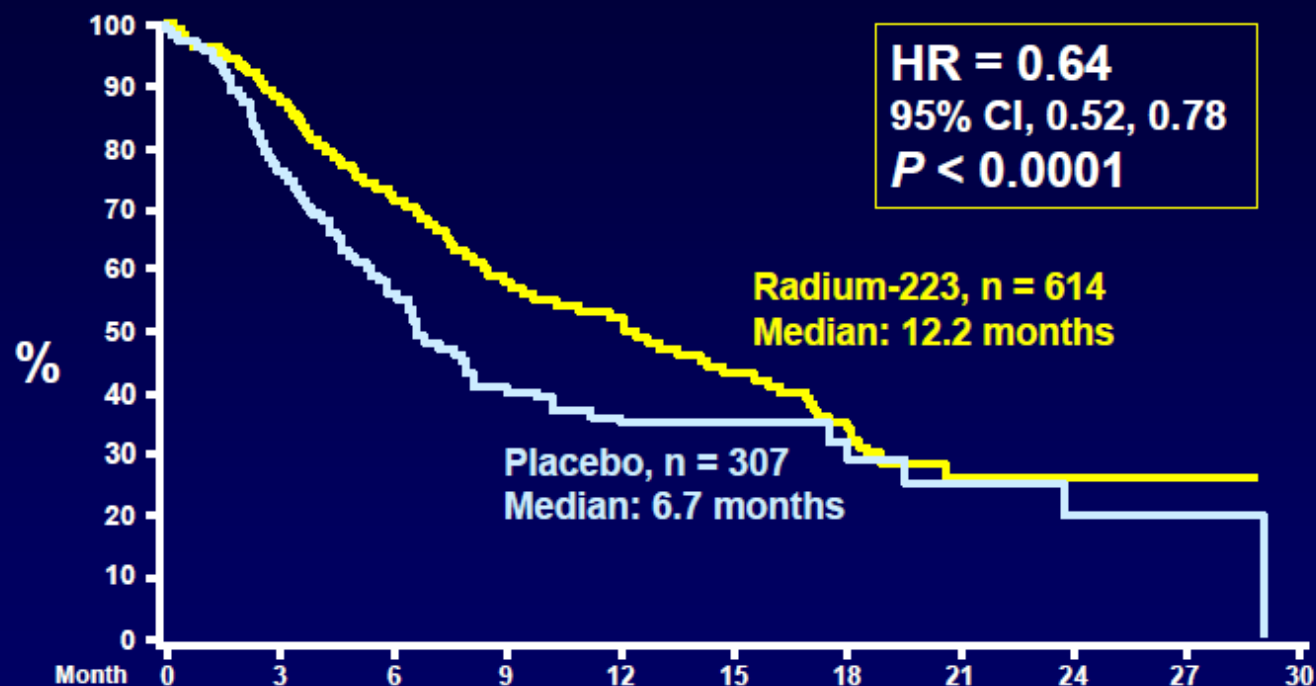
- hydrogen
- alkali metals
- alkali earth metals
- transition metals
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- noble gases
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Radium-223 Targets Bone Metastases



- Alpha-particles induce double-strand DNA breaks in adjacent tumour cells¹
 - Short penetration of alpha emitters (2-10 cell diameters)
= highly localised tumour cell killing and minimal damage to surrounding normal tissue

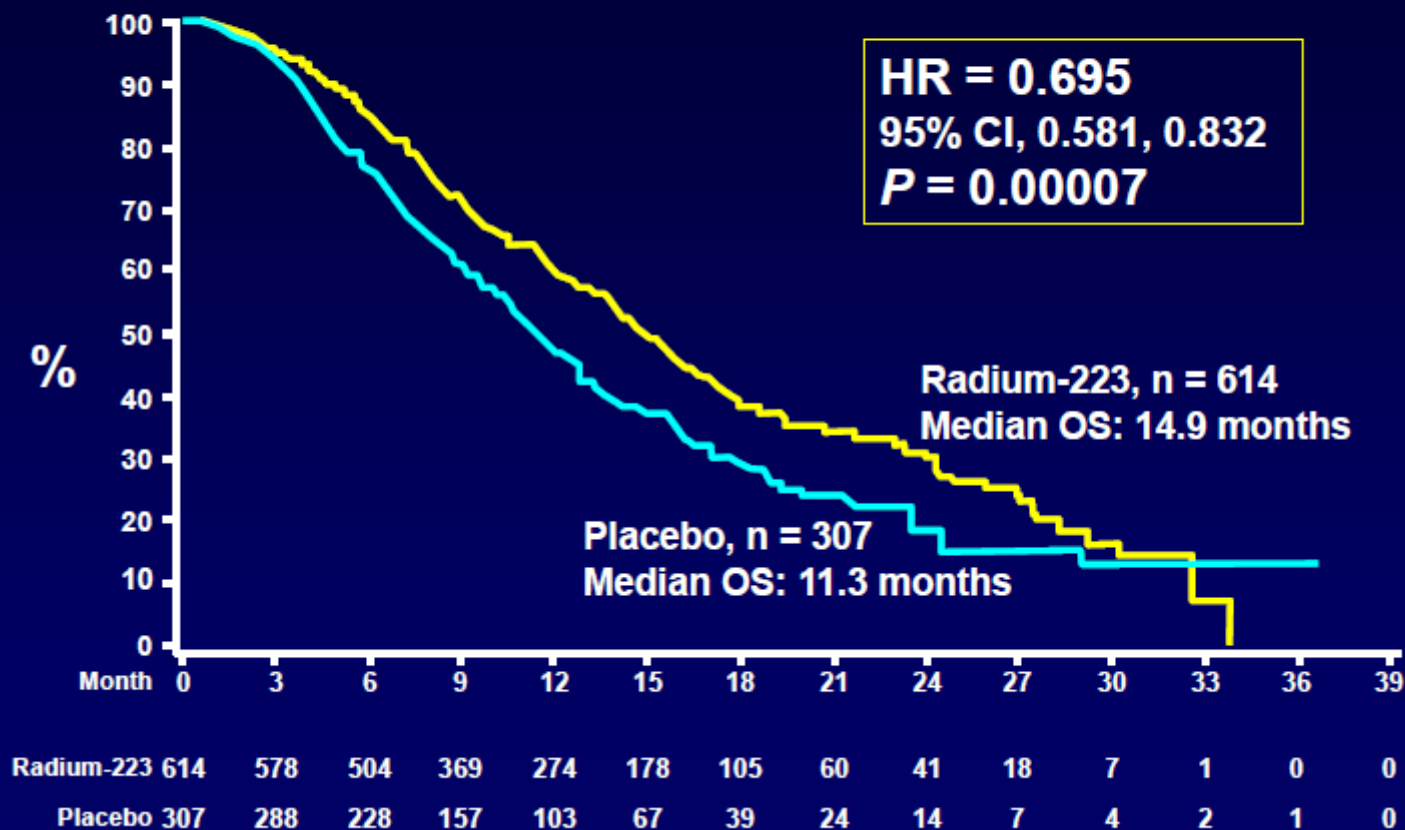
ALSYMPCA Updated Analysis Time To First SRE*



Radium-223	614	487	332	193	125	62	31	8	8	1	0
Placebo	307	207	108	51	33	17	8	6	3	1	0

*Provisional data

ALSYMPCA Updated Analysis Overall Survival



Alpharadin – side effects

- Bone pain
 - 43% vs 58% placebo
- Diarrhoea
 - 22% vs 13%
- Nausea
 - 34% vs 32%
- Vomiting
 - 17% vs 13%
- Constipation
 - 18% both groups

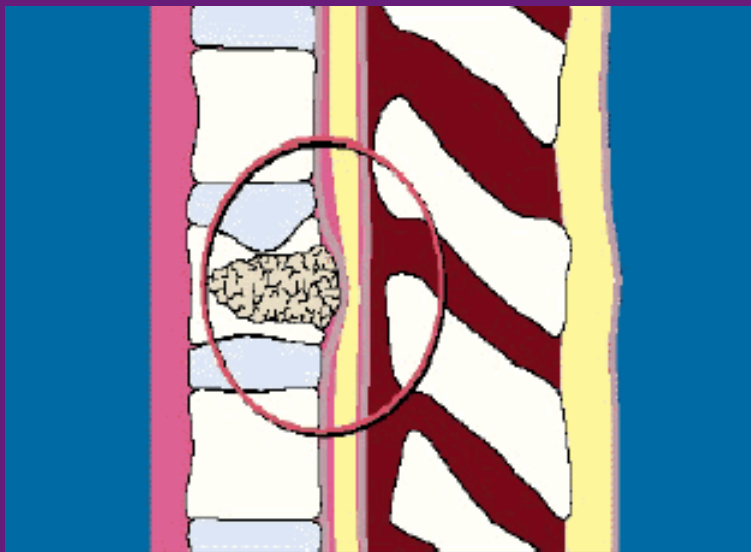


- Approval awaited
- NICE ?



Malignant spinal cord compression





MSCC

- 3-5% of pt with metastatic cancer will develop MSSC
- NI ~ 120 per year
- Approx 30 (20%) of those will have PCa

Signs and Symptoms

- Pain
- Motor Deficit
- Sensory Deficit
- Autonomic deficit



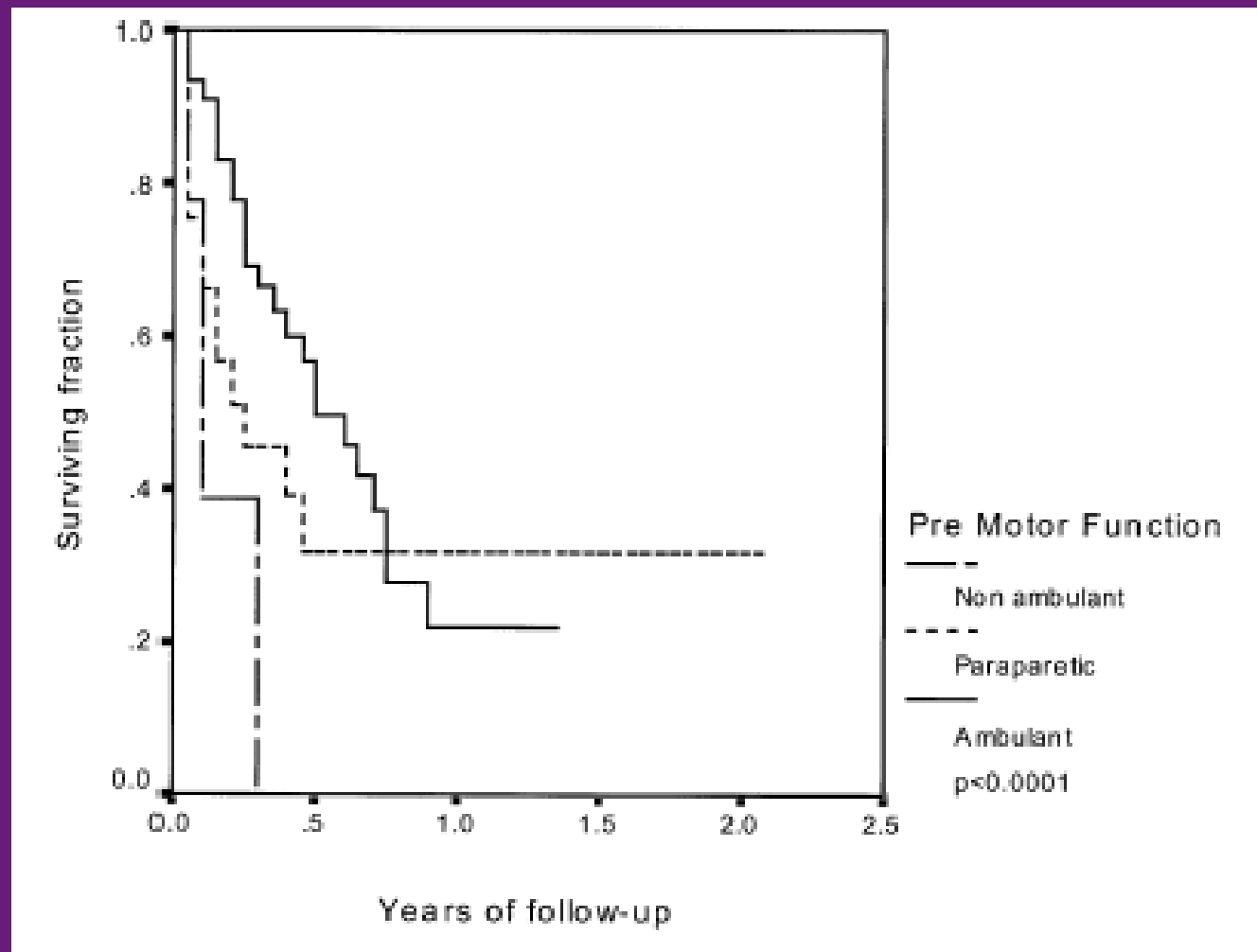
Signs and Symptoms

- Pain (85%)
 - Localised
 - Increasing intensity
 - Radicular/gripping
 - Mechanical
- Motor Deficit (65%)
 - Strongest predictor of outcome
- Sensory Deficit (20%)
 - Subtle
- Autonomic deficit (up to 50%)
 - Late sign, often associated with motor deficit and rarely recovered

MSCC management

- MRI within 24hours if neurological symptoms
- Steroids + PPI
- Surgery + RT
- Radiotherapy
- PCT
- Systemic therapy options





Summary

- Bone metastasis are common in prostate cancer
 - Systemic therapy
 - Focal therapy
 - Bone targeted therapy
 - Radionucleotide therapy
- MSCC – early detection and treatment