Comprehensive treatment for metastatic bone disease

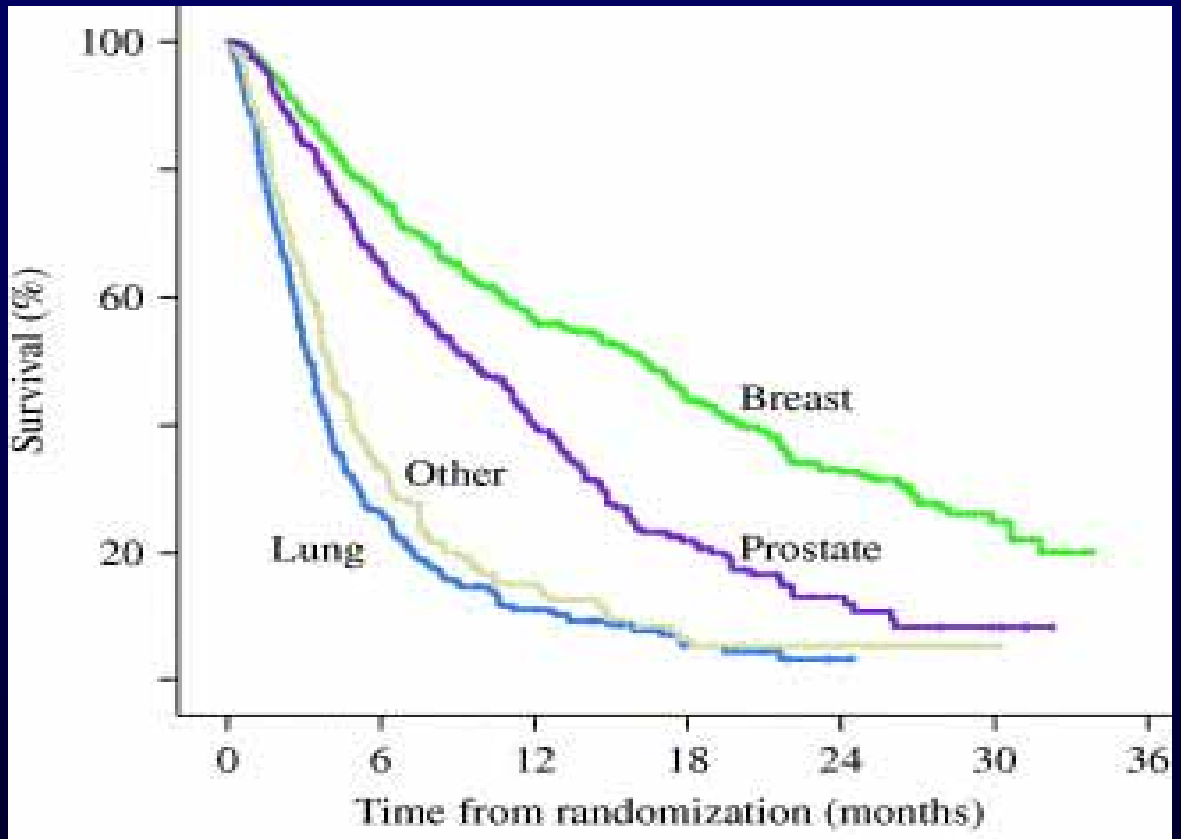
P J Hoskin
Mount Vernon Cancer Centre
Northwood
Middlesex
UK

MVH

UCL

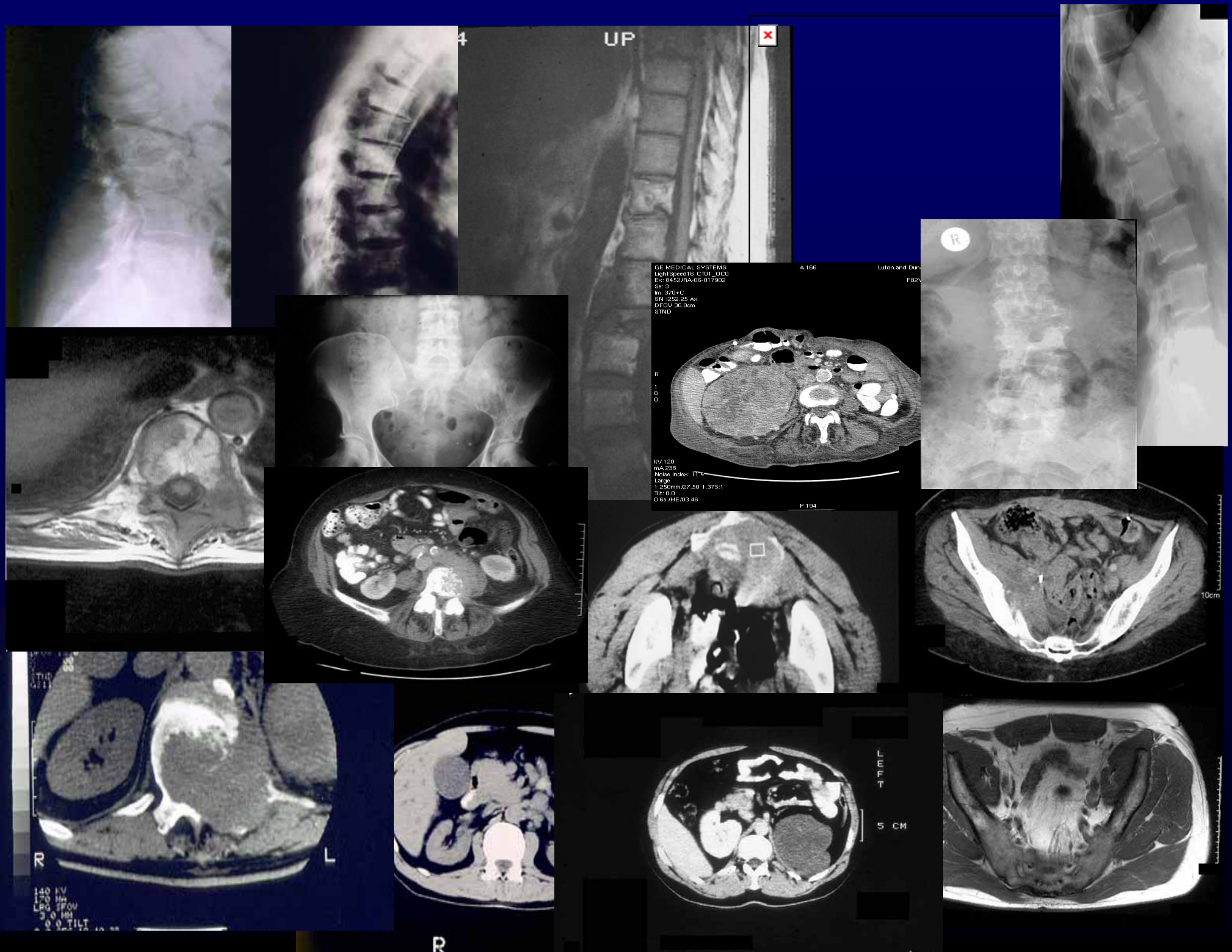
Survival and primary site in bone metastases

[Van der Linden et al 2006]



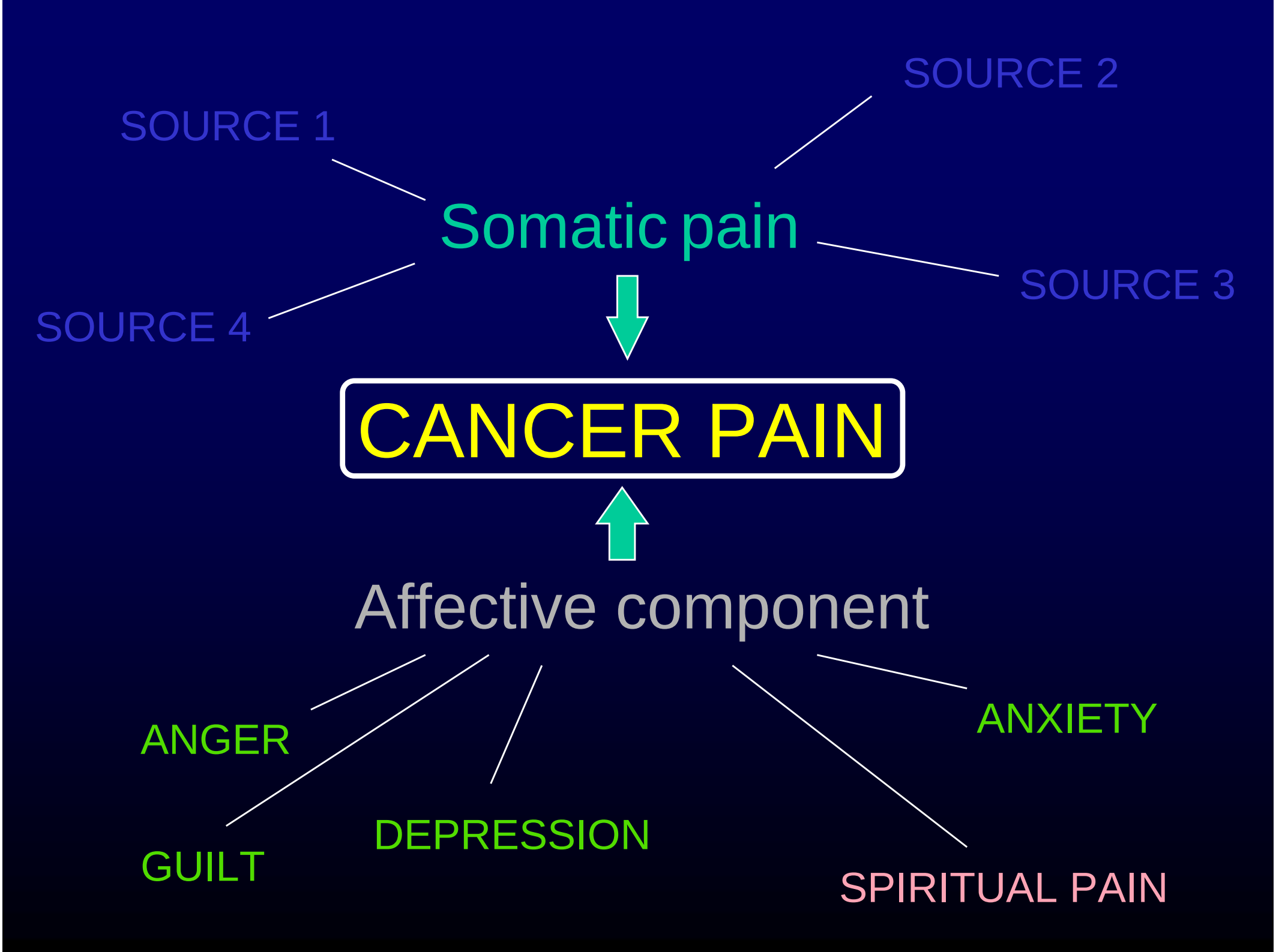
Number of patients 'at risk'

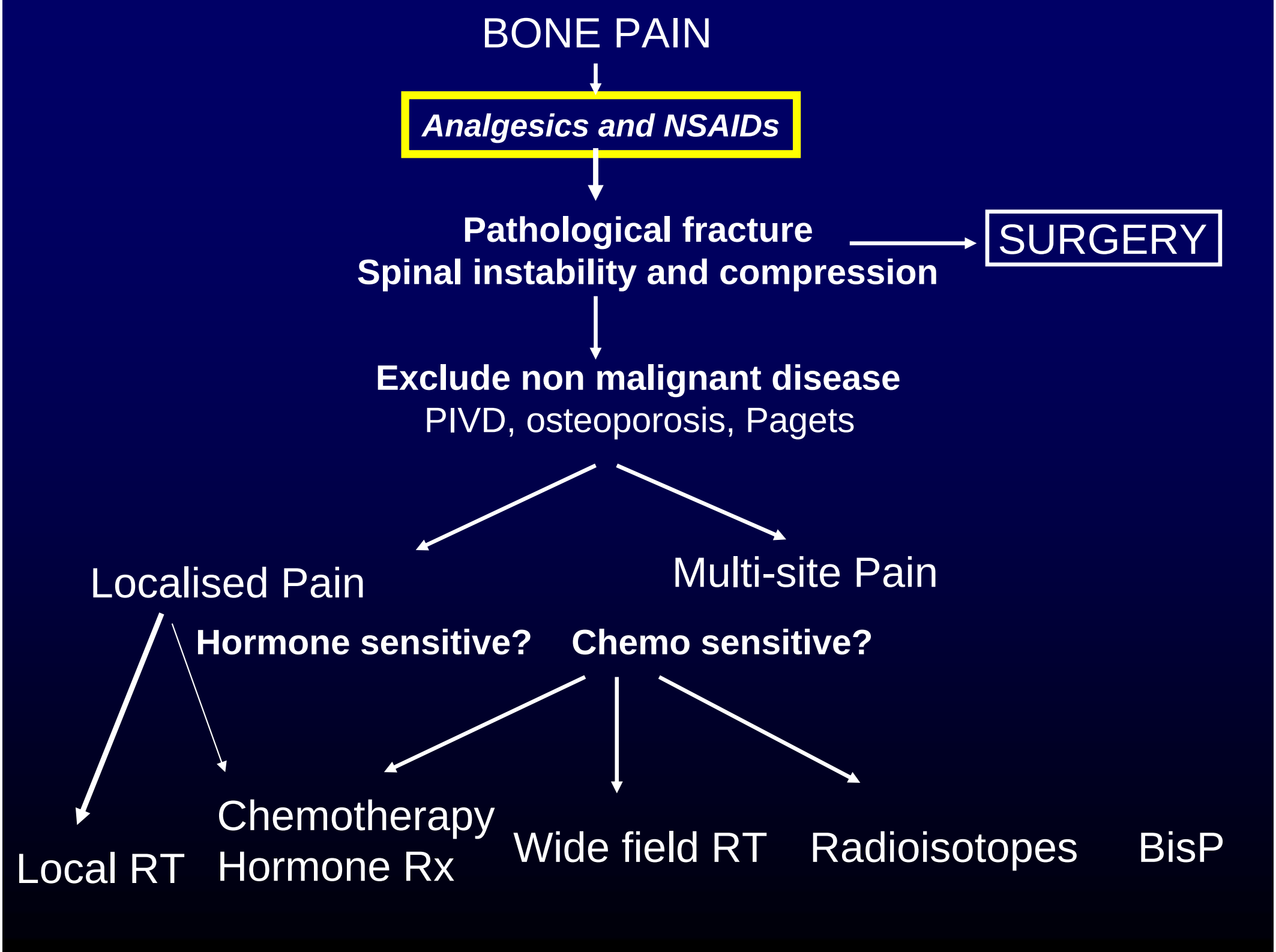
Breast	451	320	209	123	66	19
Prostate	267	165	81	34	9	-
Lung	287	74	26	6	-	-
Other primaries	152	46	17	6	-	-


UP
GE MEDICAL SYSTEMS
LightSpeed16 CT01_0C0
Ex: 8452/RA-05-017302
Se: 3
Im: 370+C
SN 252.25 Ax
DFOV 36.0cm
STND
A 166
kV 120
mA 238
Noise Index: 11.4
Large
1.250mm/27.50 1.375:1
Tilt: 0.0
0.6s /HE/03.46
P 194
R
L
LEFT
5 CM
10cm

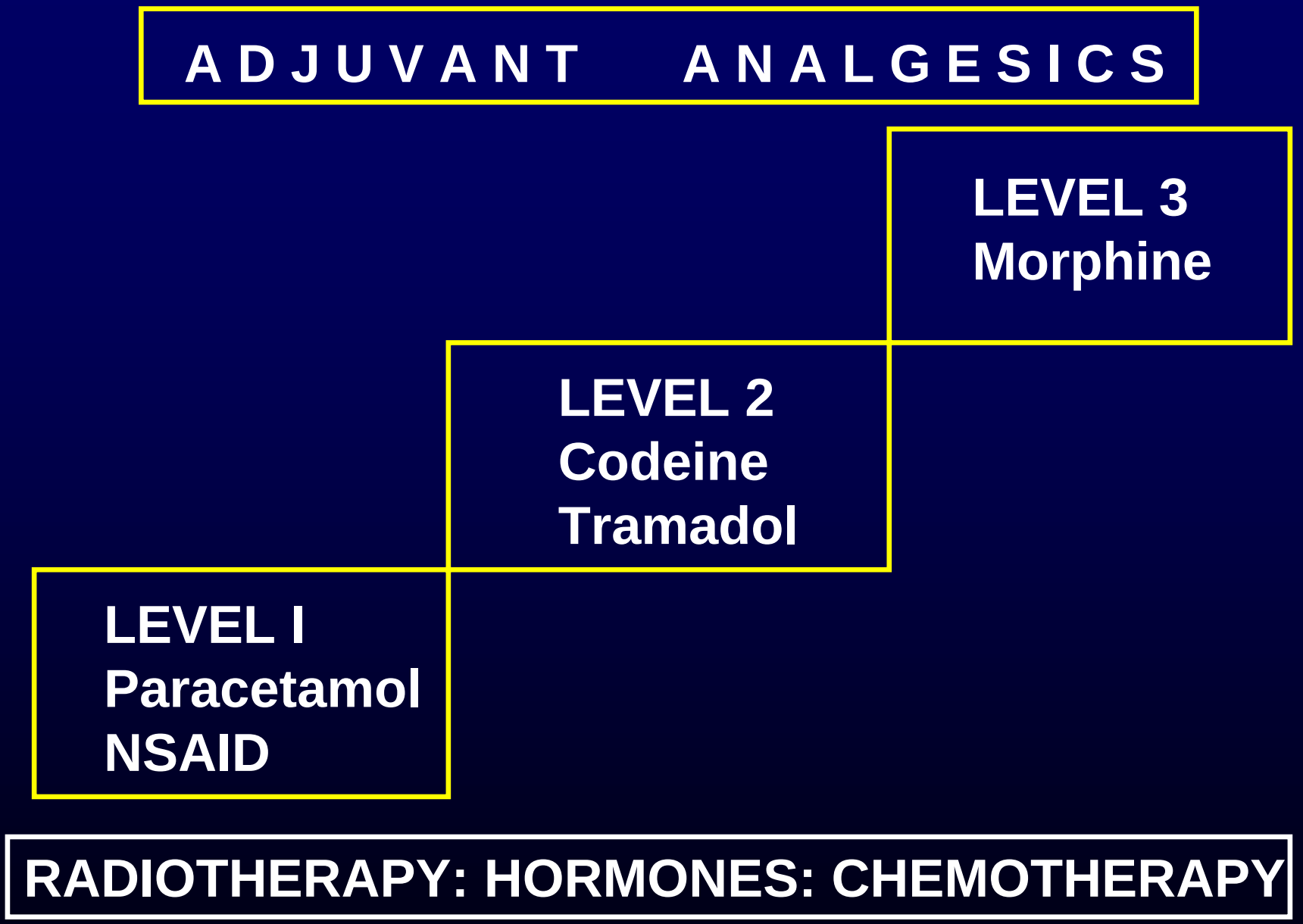
Metastatic bone pain

- Background pain
- Spontaneous pain
- Incident pain
- Incidental pain


SOURCE 2
SOURCE 1
Somatic pain
SOURCE 3
SOURCE 4
CANCER PAIN
Affective component
ANGER
ANXIETY
GUILT
DEPRESSION
SPIRITUAL PAIN


BONE PAIN
Analgesics and NSAIDs
Pathological fracture
Spinal instability and compression
SURGERY
Exclude non malignant disease
PIVD, osteoporosis, Pagets
Localised Pain
Multi-site Pain
Hormone sensitive?
Chemo sensitive?
Local RT
Chemotherapy
Hormone Rx
Wide field RT
Radioisotopes
BisP

Analgesic ladder



Metastatic bone pain: the evidence NSAIDs

- Single agent data: 20% RR [Coombs et al 1979]

- Meta-analysis [Eisenberg et al 1994]
- 25 RCTS; 16 drugs; 15,445 patients

TWO included analgesic efficacy data for metastatic bone pain

(i): single dose X over study with Ketoprofen: 34-55%RR

(ii):multiple dose study of Naproxen

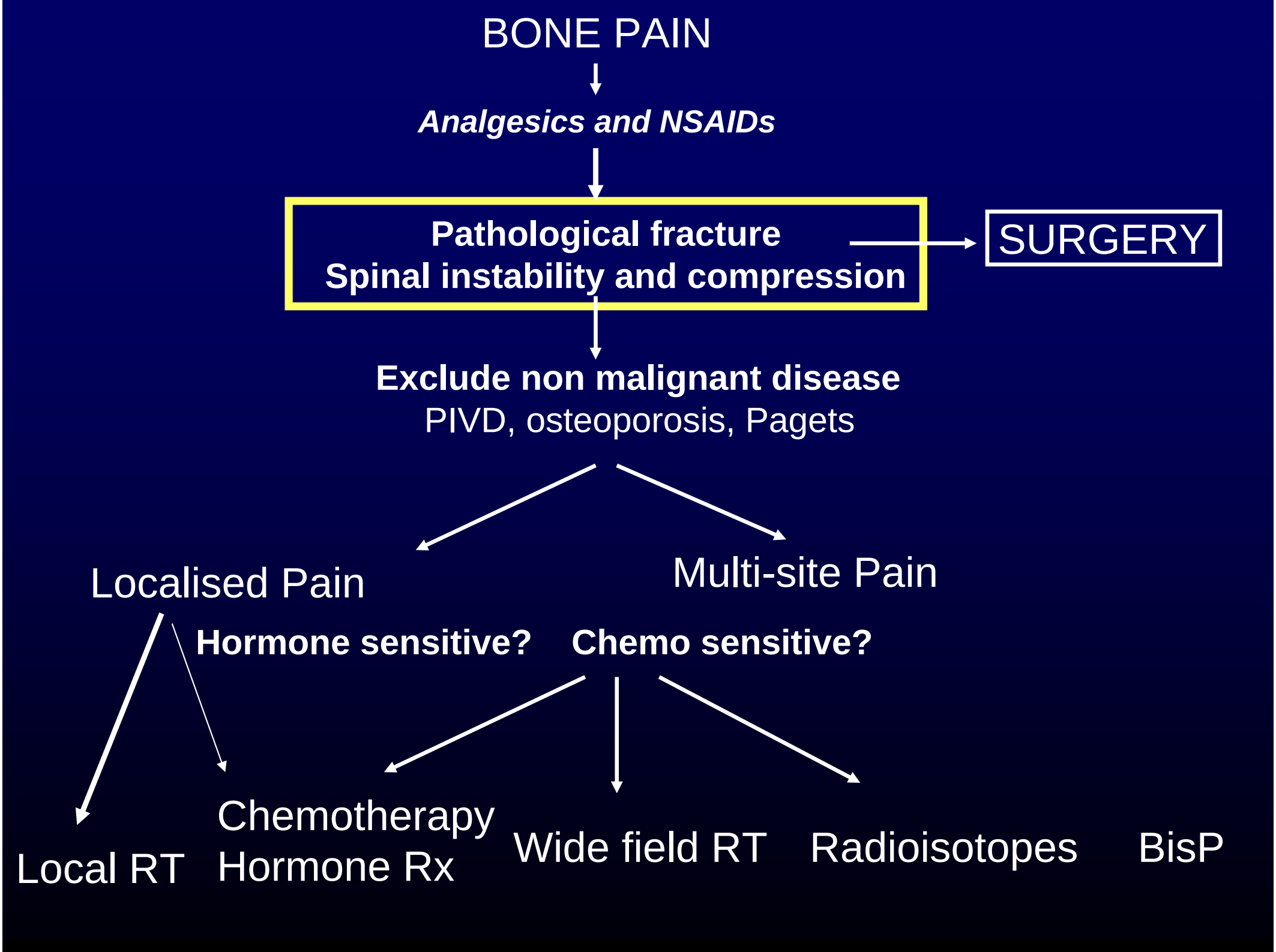
275mg vs 550mg: 23-33%RR

Opioids in metastatic bone pain

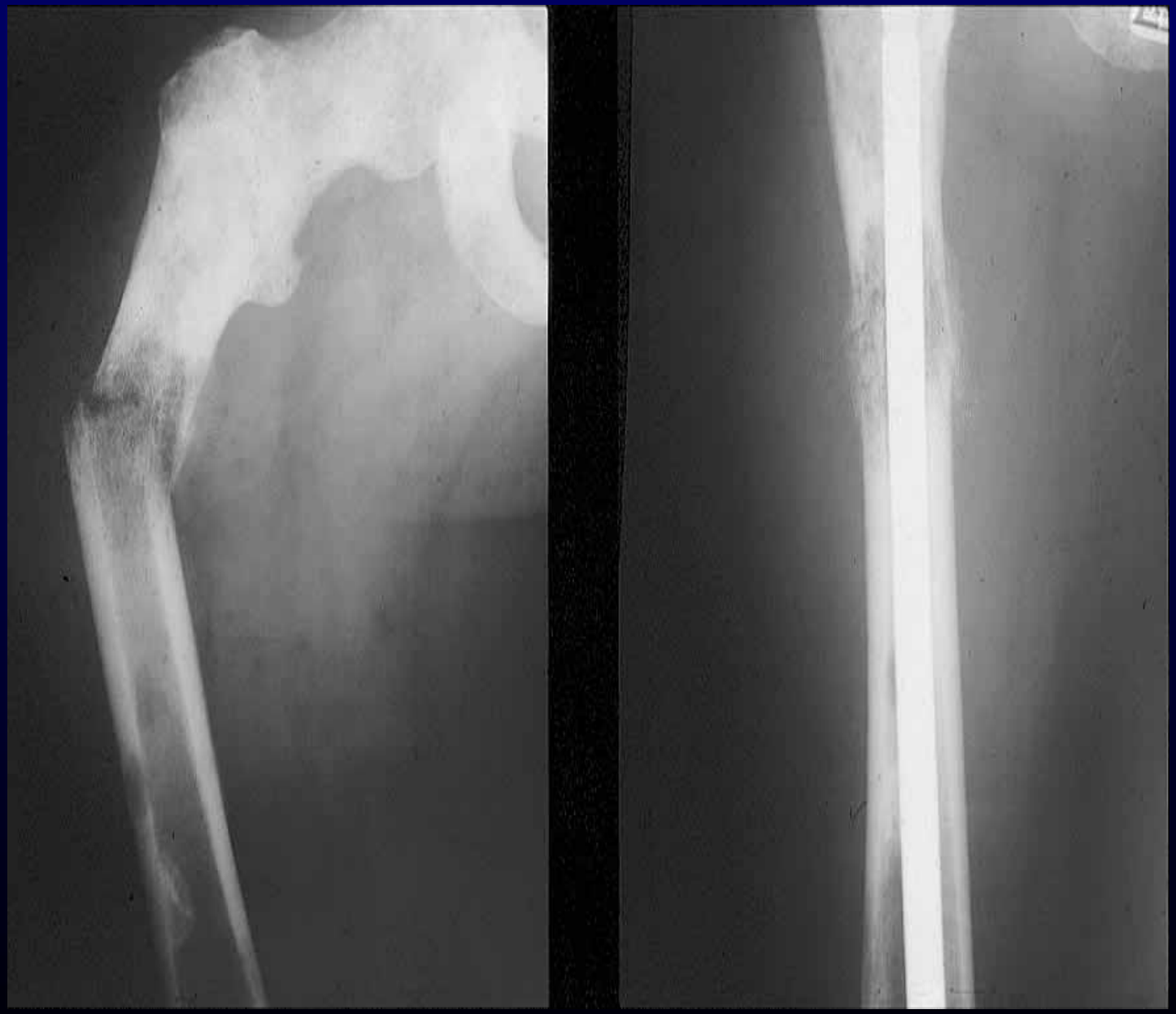
- Experimental evidence in bone pain models for both μ and δ opioid mediation on bone pain responsive to morphine[Urch et al 2005, Brainin-Mattos et al 2006]
- Clinical evidence for morphine efficacy in bone pain less strong: dose titration beyond rest pain relief reduces incident pain but increased toxicity [Mercadente et al 2004]

Optimisation of opioid therapy in bone metastases [Mercadente et al 2004]

	T0	T1	T2	T3	Tend
Basal pain	5.3	1.7	1.6	1.0	2
Incident pain	9.2	4.8	4.5	6.7	4.6
Opioid dose		102	118	130	125
N&V	1	5	8	3	3
Drowsiness	0	2	0	4	1

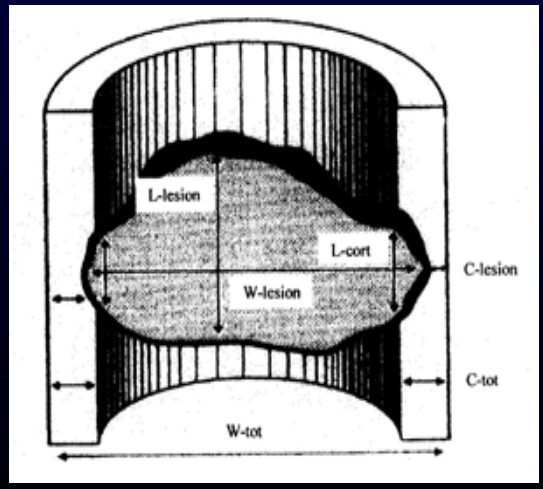

BONE PAIN
Analgesics and NSAIDs
Pathological fracture
Spinal instability and compression
SURGERY
Exclude non malignant disease
PIVD, osteoporosis, Pagets
Localised Pain
Multi-site Pain
Hormone sensitive?
Chemo sensitive?
Local RT
Chemotherapy
Hormone Rx
Wide field RT
Radioisotopes
BisP

Metastatic bone pain: the evidence surgery

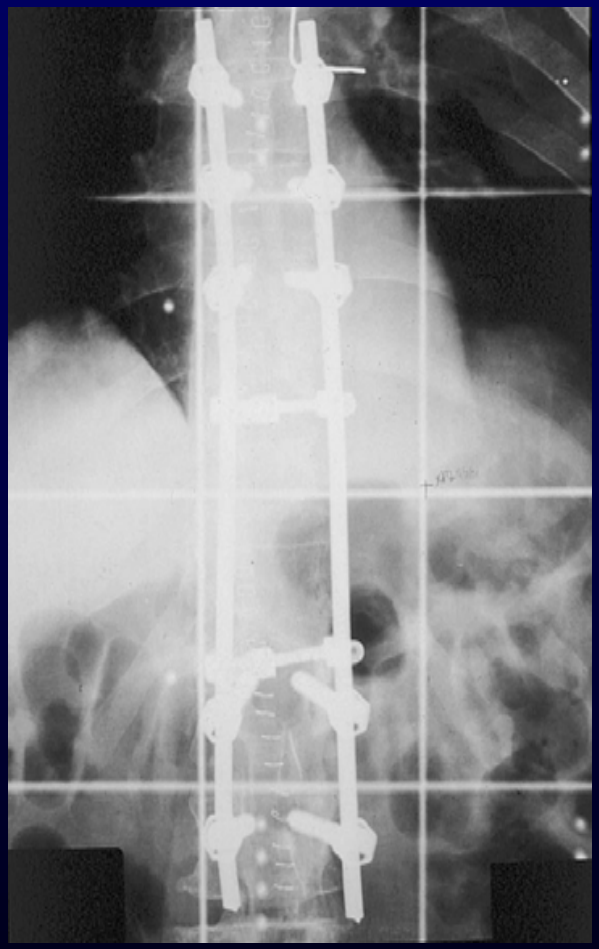


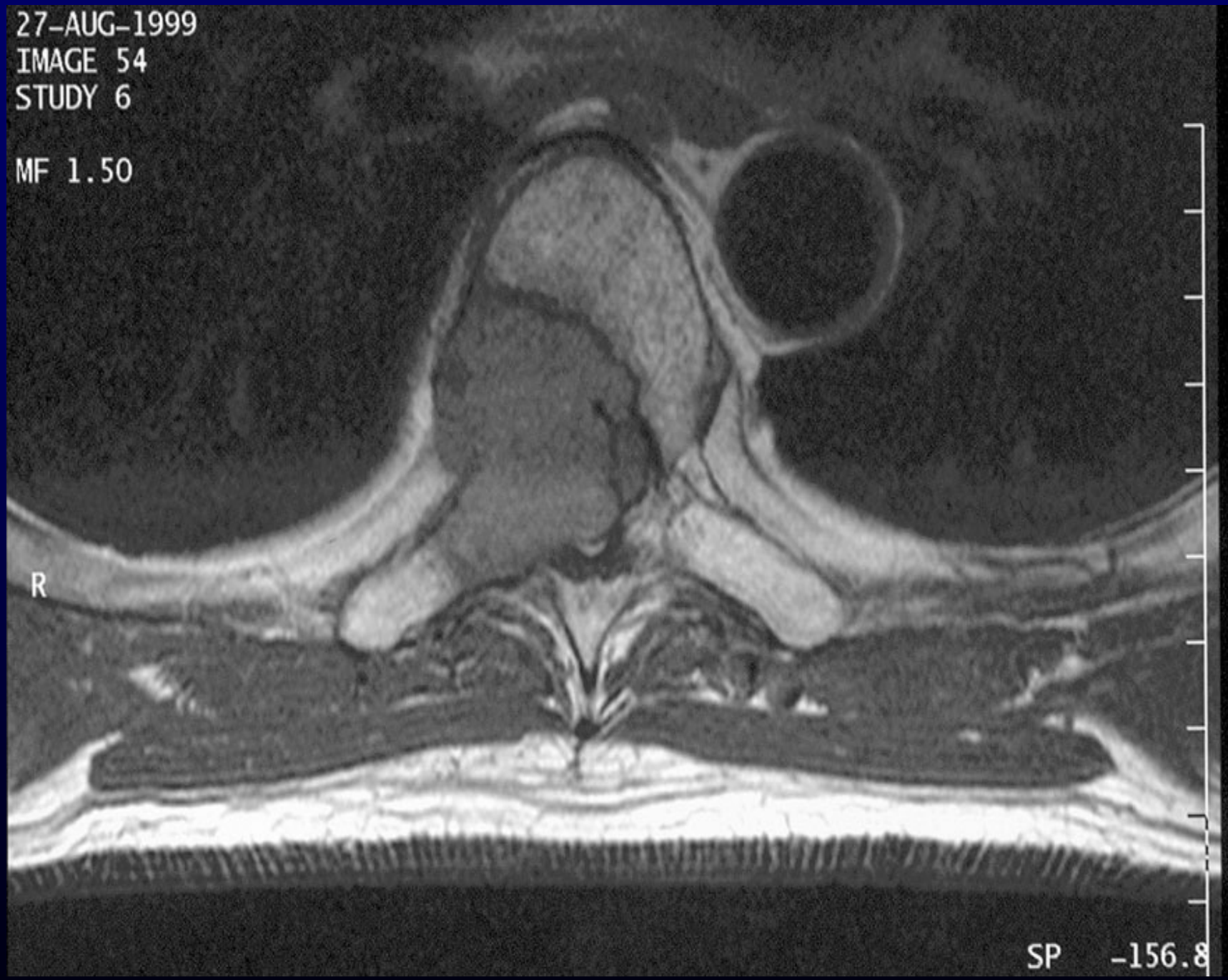
Radiological predictors for pathological fracture

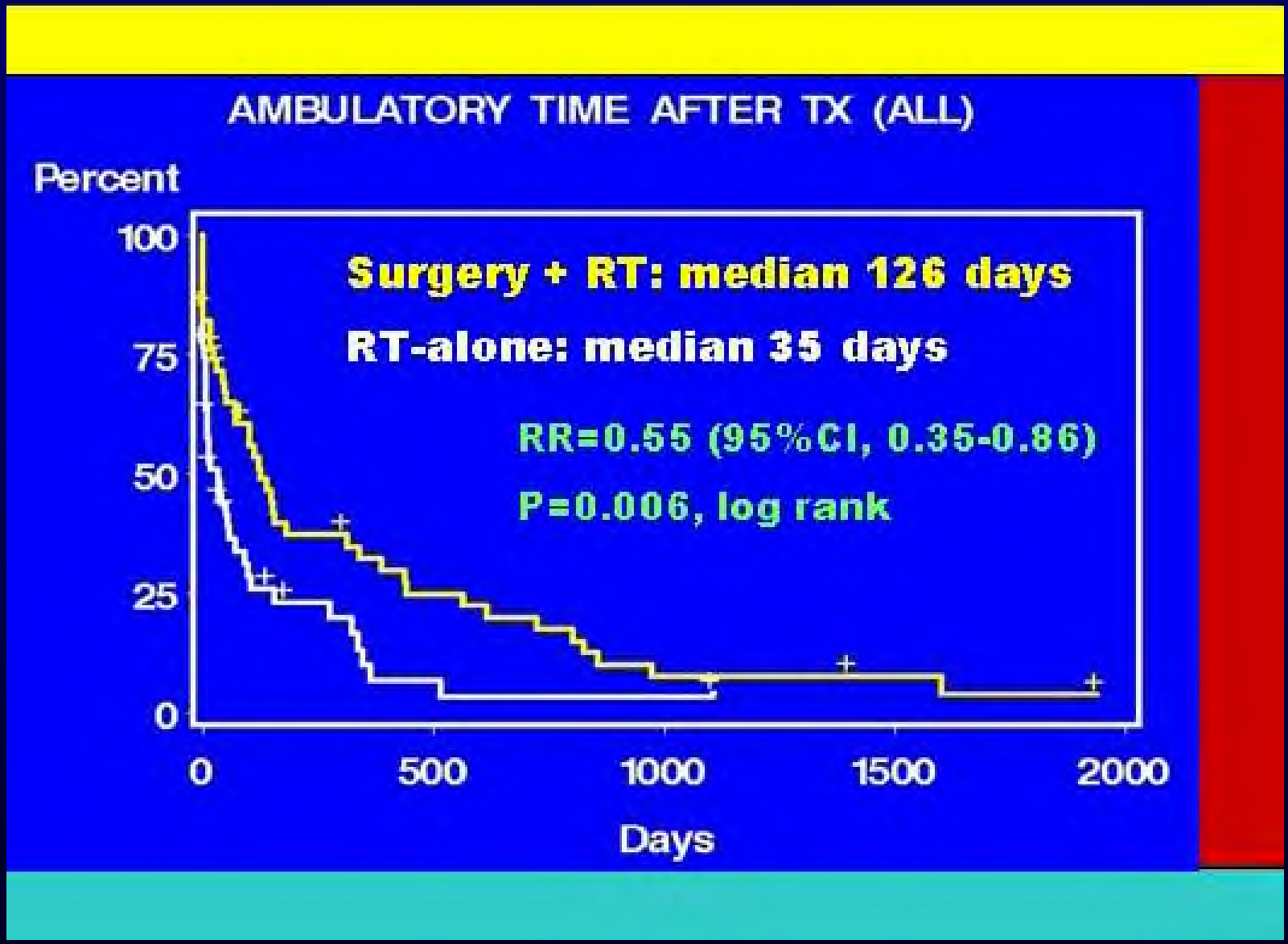
- Univariate analysis of risk factors
  - Solitary vs multiple vs diffuse: NS
  - Osteoblastic vs osteoclastic: NS
  - Proximal vs shaft vs distal: NS
  - Medial vs central vs lateral: NS
  - radiographic parameters:
    - all NS except
    - L-cort 29mm vs 42mm: p=0.001



Bone metastases:surgery

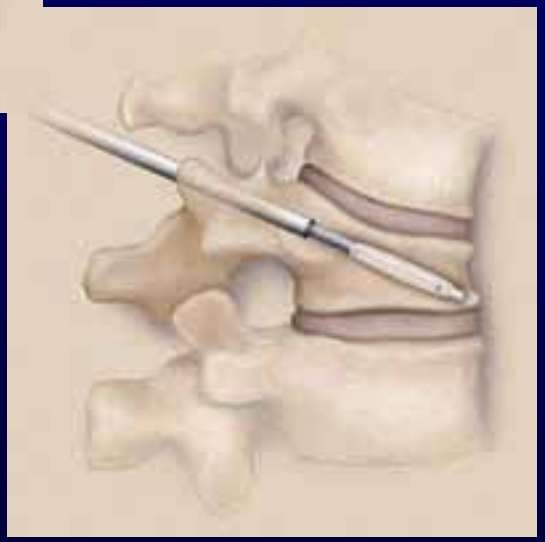


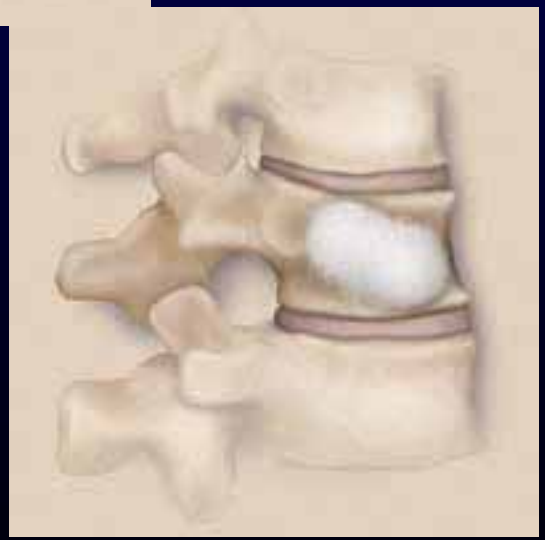

27-AUG-1999
IMAGE 54
STUDY 6
MF 1.50
R
SP -156.8



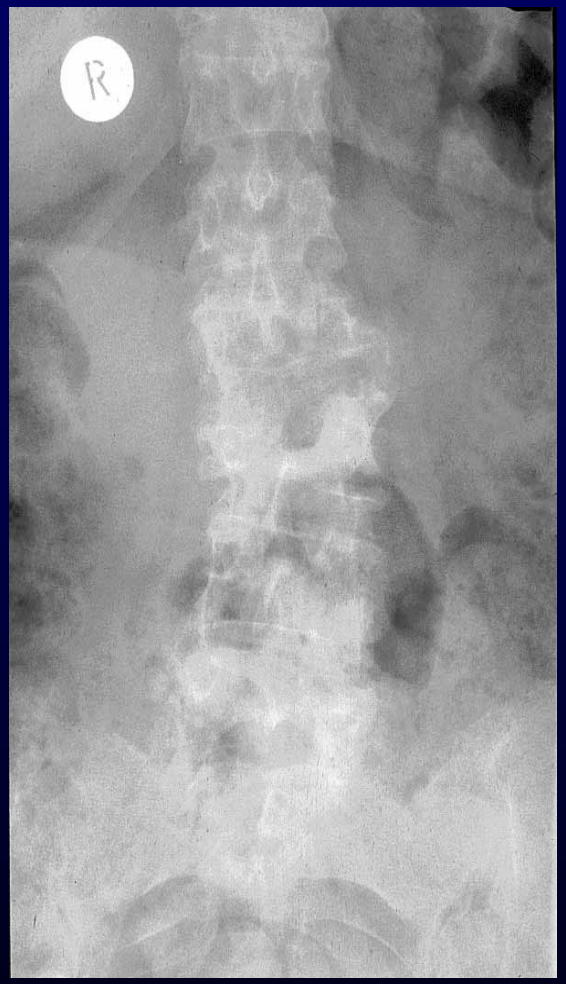
Patchell et al ASCO 2003

Balloon Kyphoplasty





Bone metastases:neuropathic pain



Neuropathic pain

Radiotherapy

Opioids

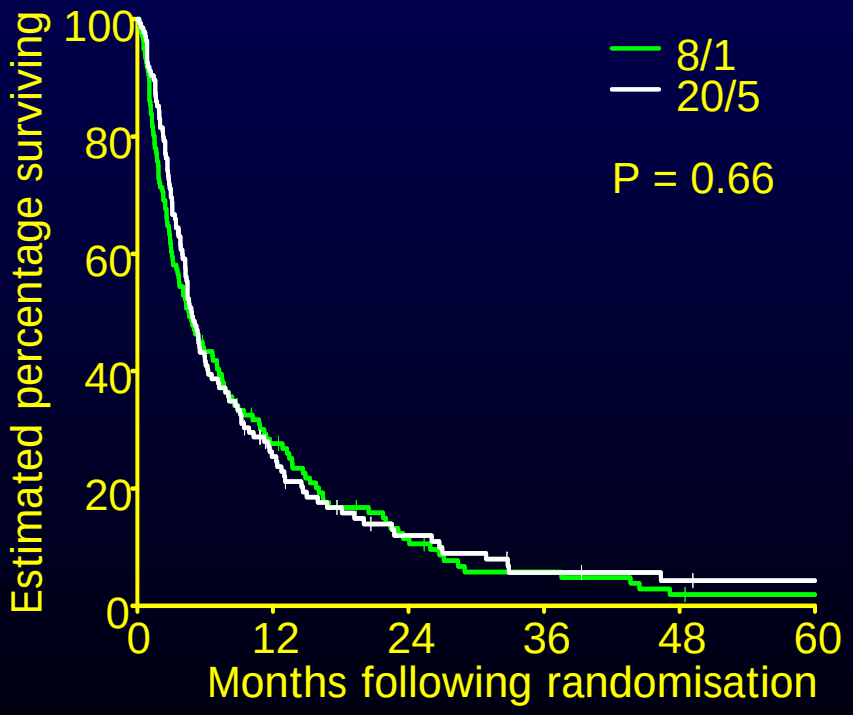
Gabapentin

Neuropathic bone pain

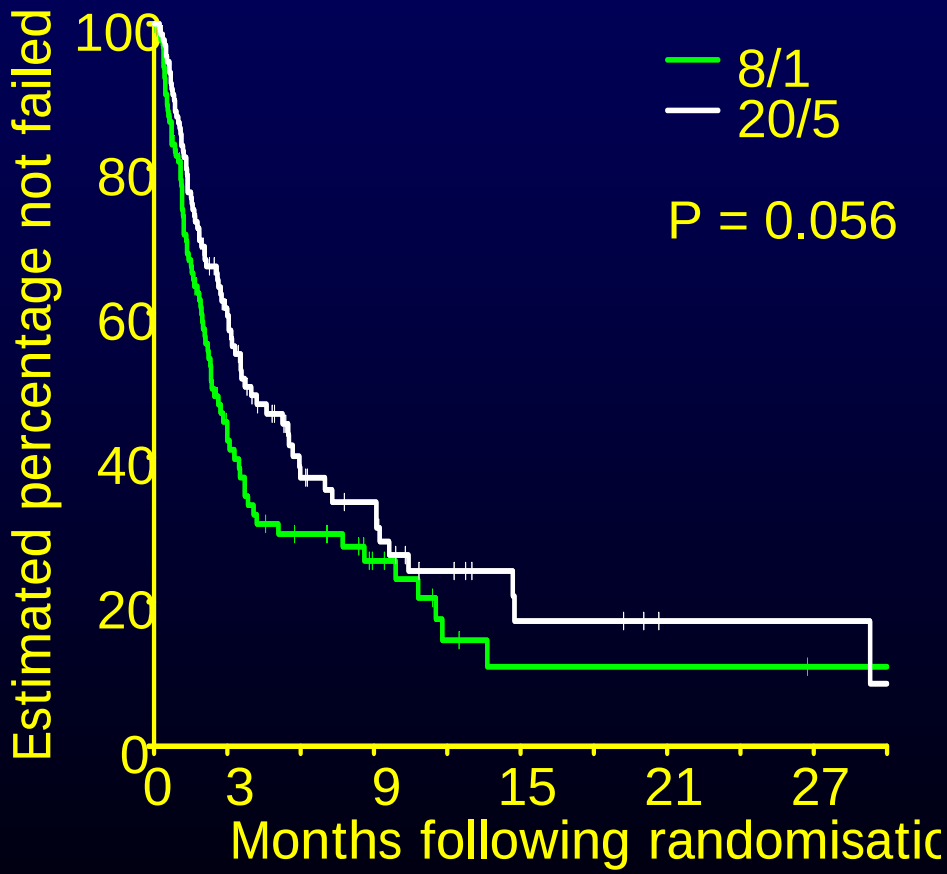
Roos et al 2005

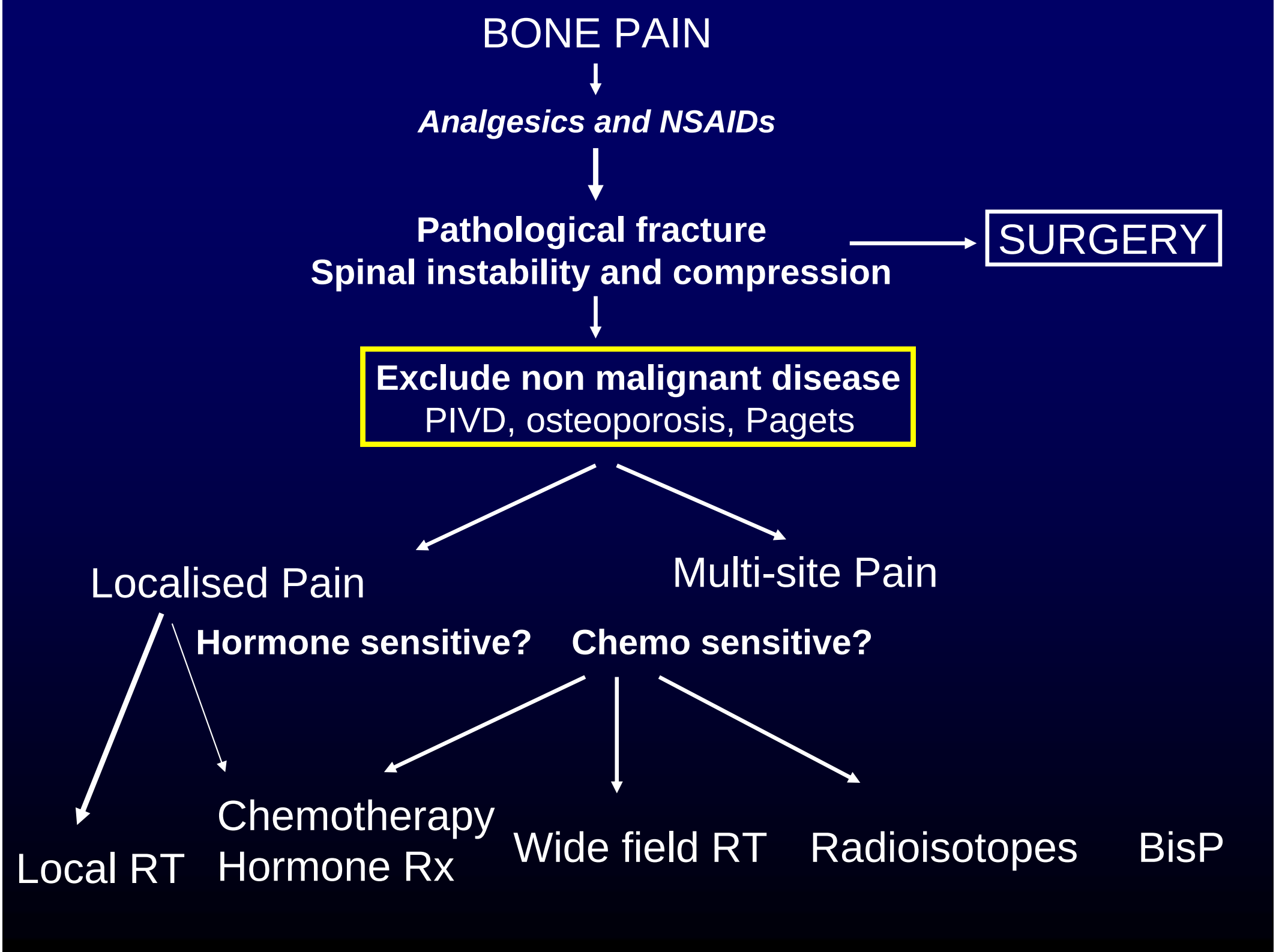
Overall RR: 57%
Complete response: 30%

survival

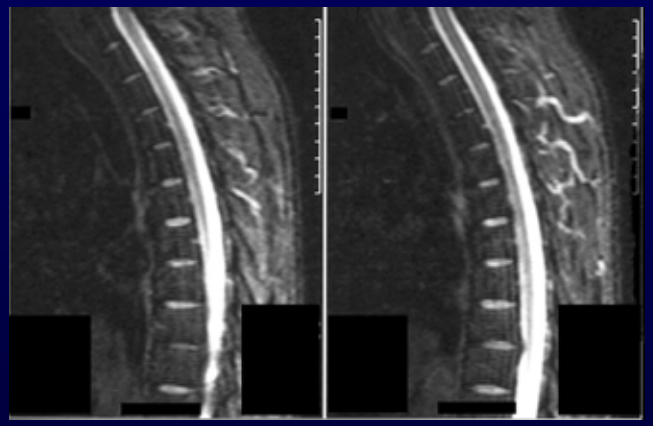


TTF

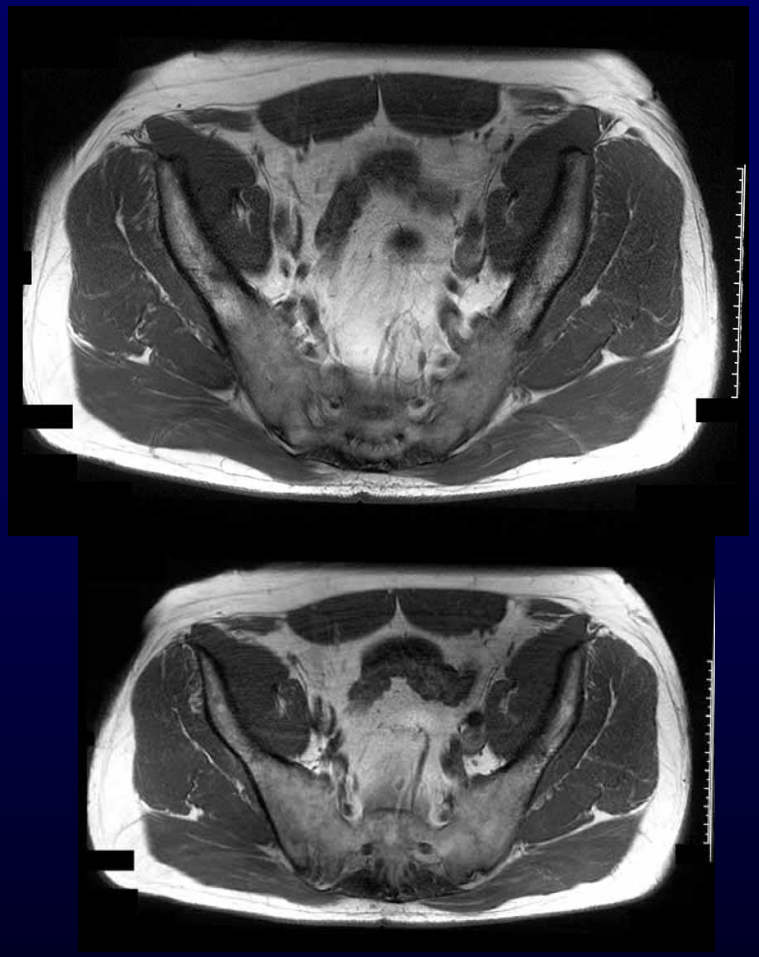



BONE PAIN
Analgesics and NSAIDs
Pathological fracture
Spinal instability and compression
SURGERY
Exclude non malignant disease
PIVD, osteoporosis, Pagets
Localised Pain
Multi-site Pain
Hormone sensitive?
Chemo sensitive?
Local RT
Chemotherapy
Hormone Rx
Wide field RT
Radioisotopes
BisP

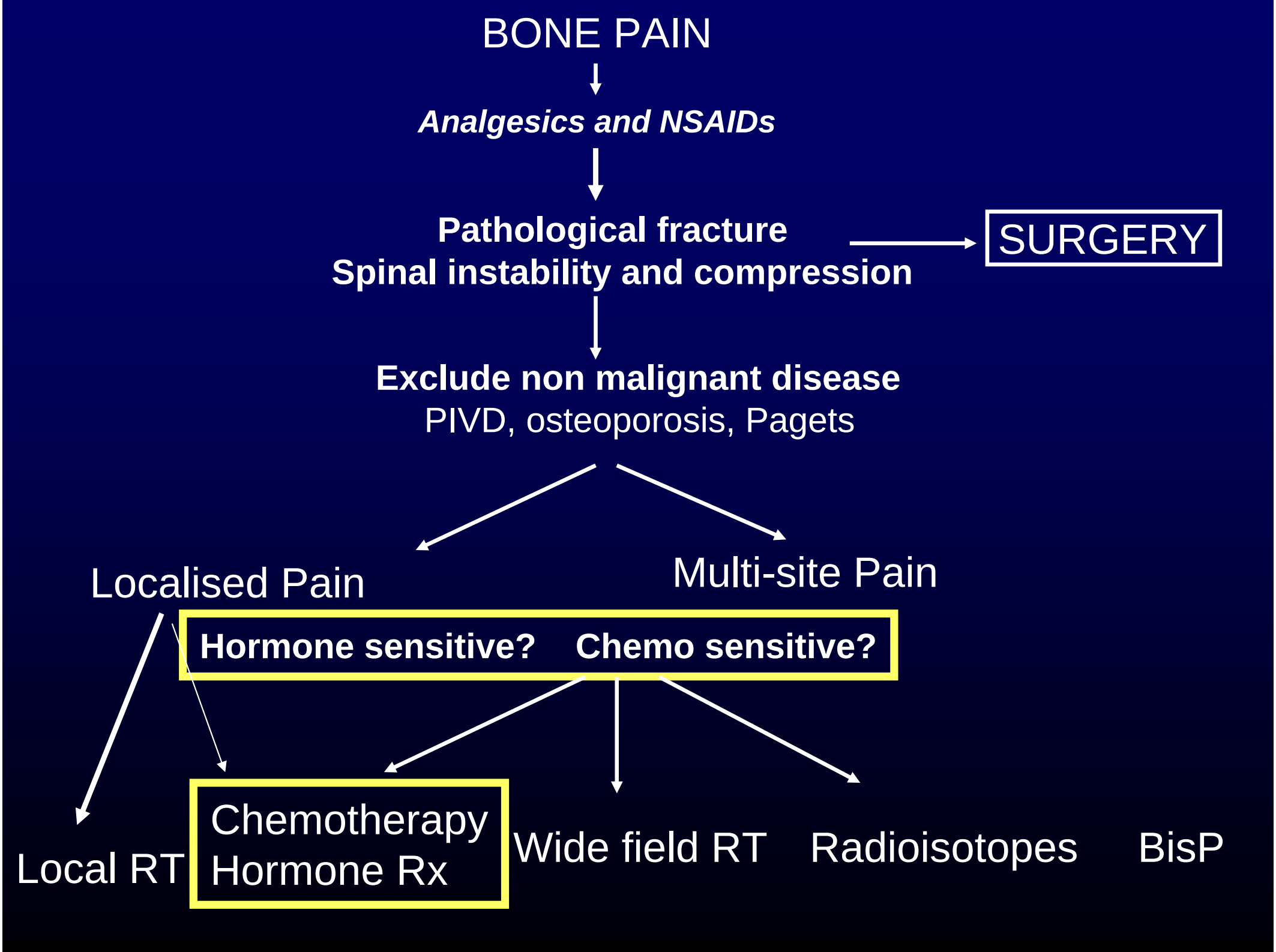
Benign causes

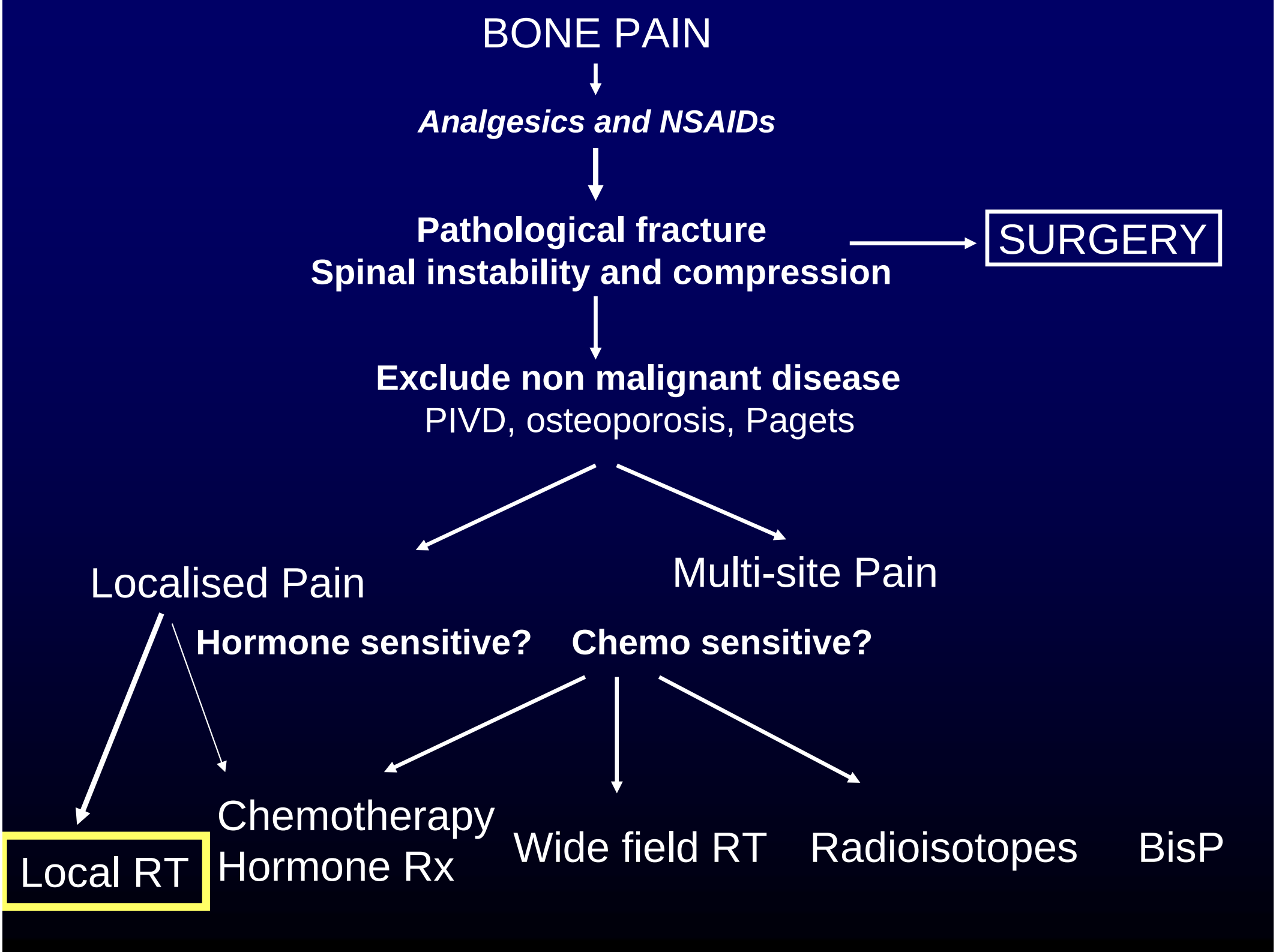


PIVD and spasm



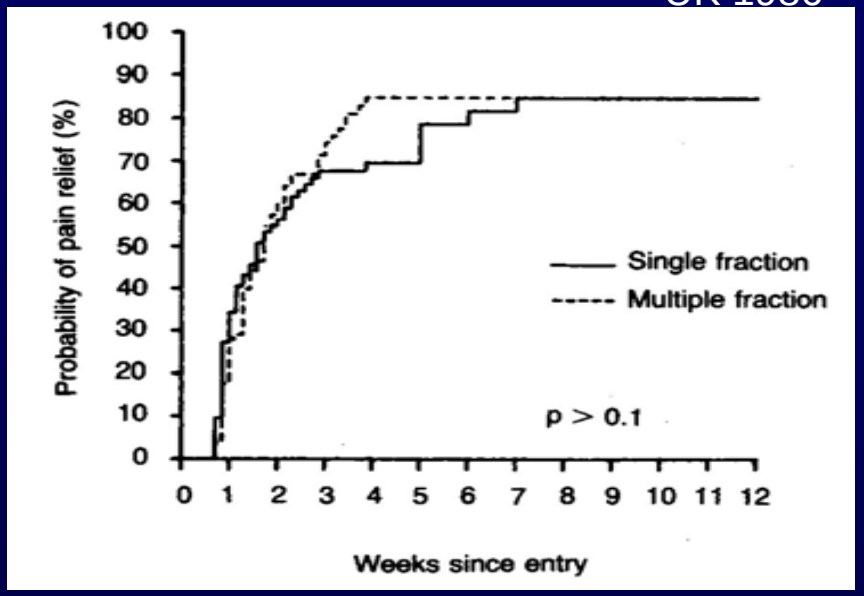
Ankylosing spondylitis


BONE PAIN
Analgesics and NSAIDs
Pathological fracture
Spinal instability and compression
SURGERY
Exclude non malignant disease
PIVD, osteoporosis, Pagets
Localised Pain
Multi-site Pain
Hormone sensitive?
Chemo sensitive?
Local RT
Chemotherapy
Hormone Rx
Wide field RT
Radioisotopes
BisP

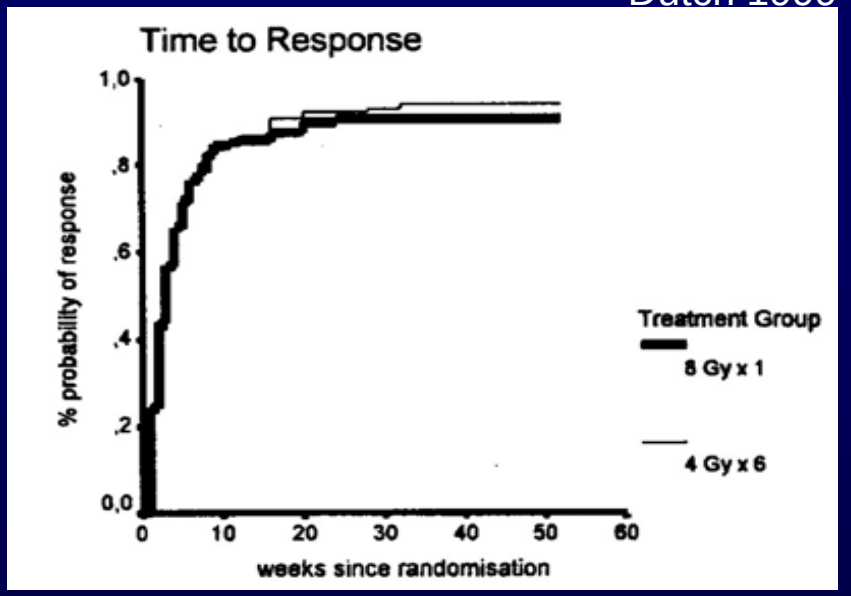

BONE PAIN
Analgesics and NSAIDs
Pathological fracture
Spinal instability and compression
SURGERY
Exclude non malignant disease
PIVD, osteoporosis, Pagets
Localised Pain
Multi-site Pain
Hormone sensitive?
Chemo sensitive?
Local RT
Chemotherapy
Hormone Rx
Wide field RT
Radioisotopes
BisP

Radiotherapy for metastatic bone pain

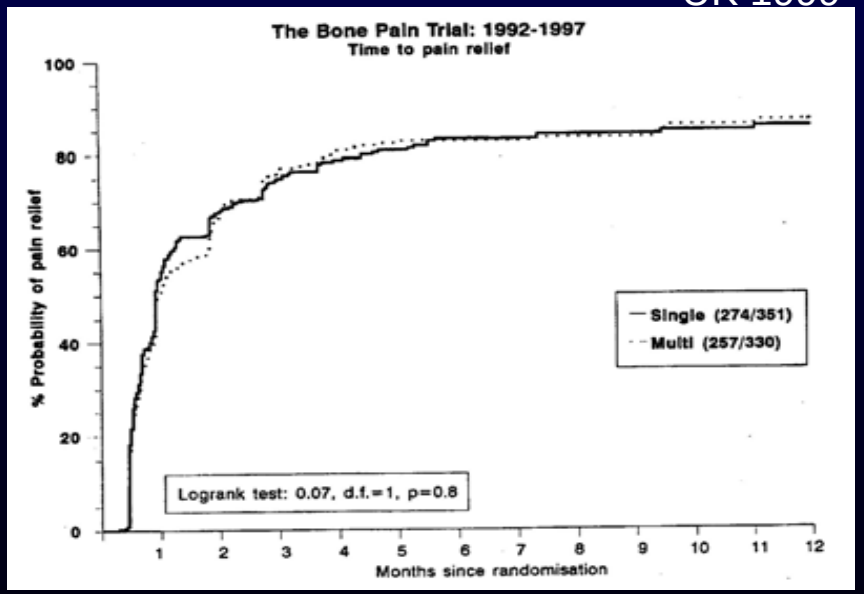
UK 1986



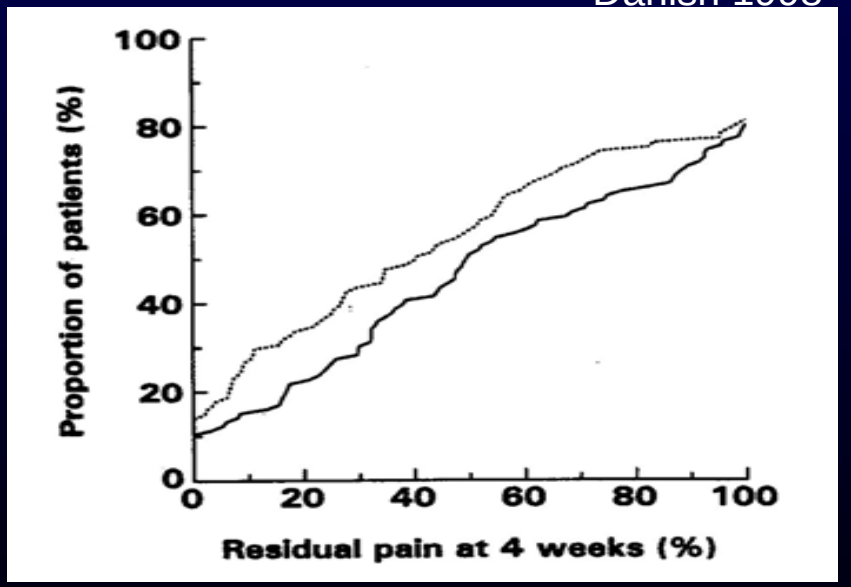
Dutch 1999



UK 1999



Danish 1998



Cochrane review of radiotherapy for metastatic bone pain

[McQuay et al 1997]

- 13 trials identified:
  - 8 local external beam fractionation studies
  - 1 hemibody fractionation study
  - 4 isotope studies

- NNT:
  - CR: 3.9 (3.5-4.4)
  - PR: 3.6 (3.2-3.9)

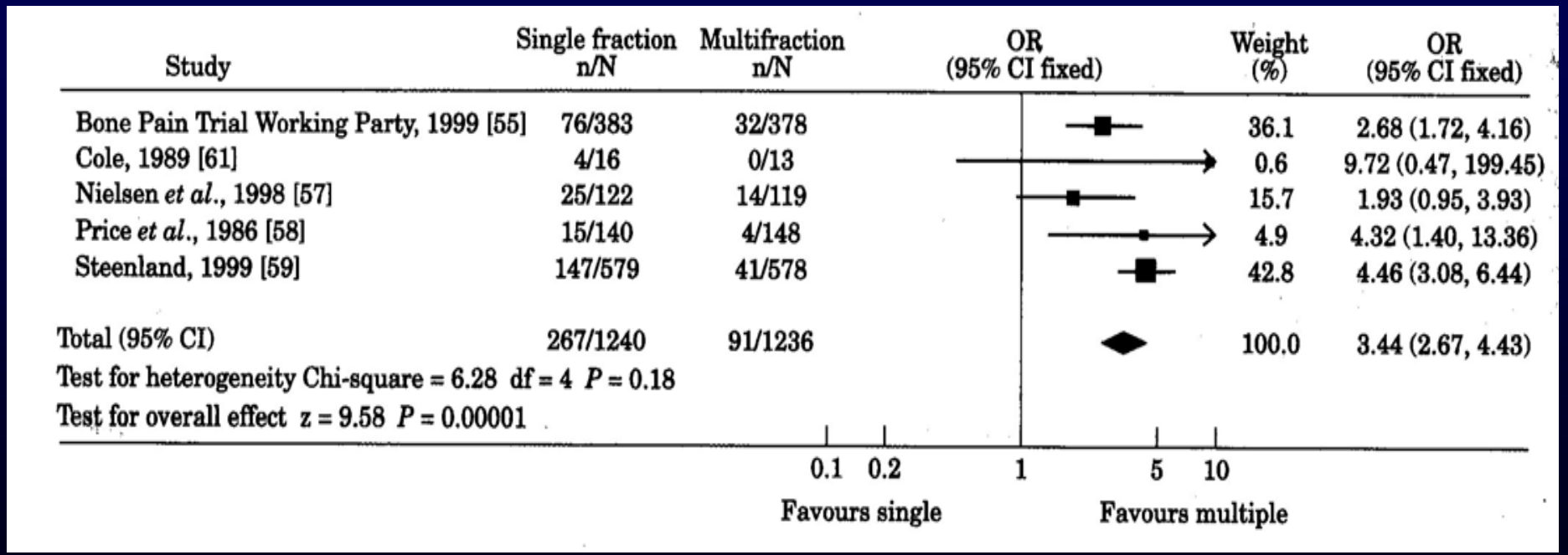
An overview of the overviews [Roos 2003]

	Wu	Sze
Date	July 2002	March 2003
Trials	8	12
Patients	3260	3508
Overall response		
Multi#	58.7%	59%
Single	62.1%	60%
CR		
Multi#	32.3%	32%
Single	33.4%	34%

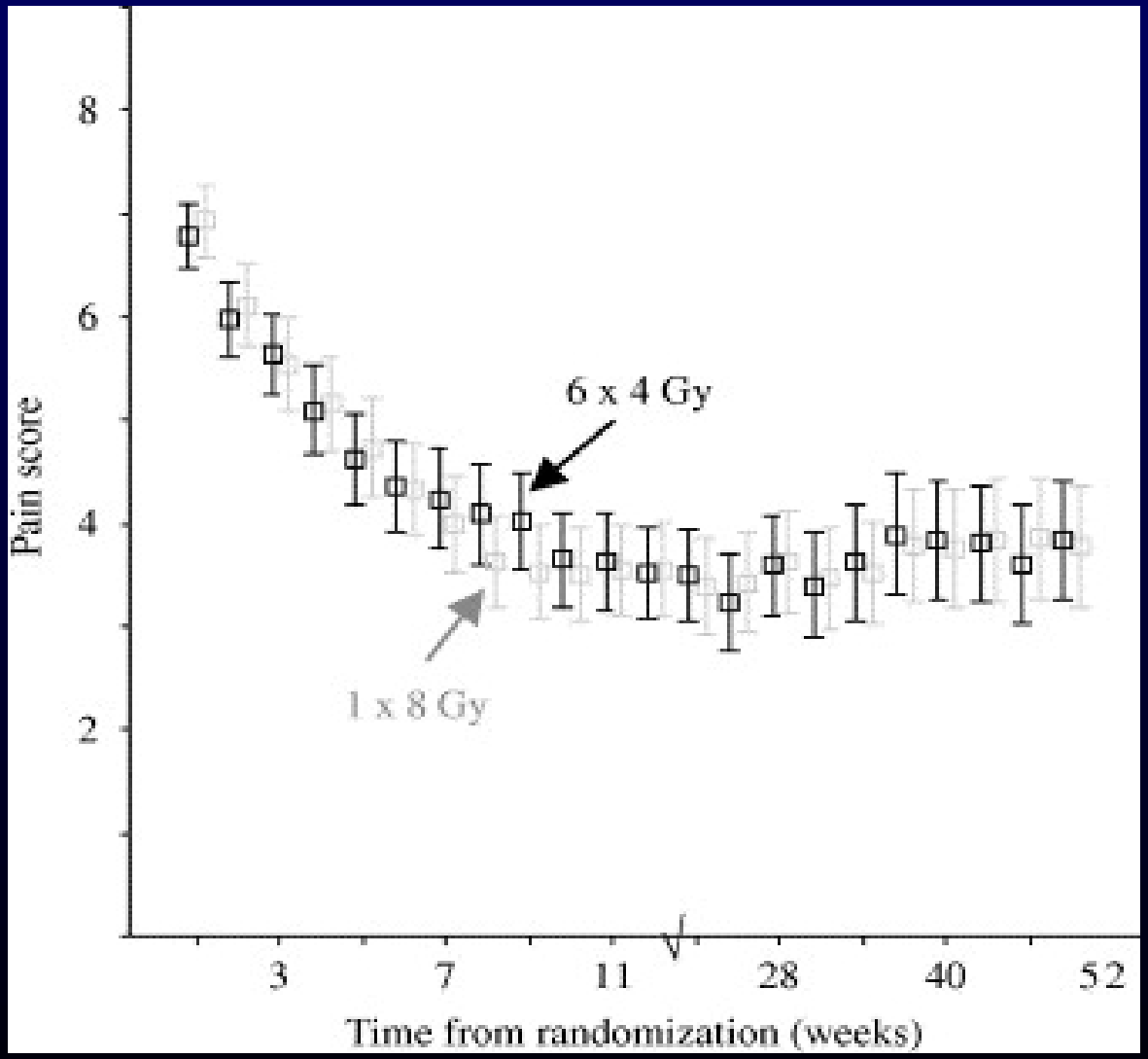
Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

[Sze et al 2003]

Retreatment rate



Pain response in long term (>52 weeks) survivors after radiotherapy for metastatic bone pain [van der Linden et al 2006]



Local RT for metastatic bone pain

- Effective
- Low dose, single treatments
- Durable 1 year
- No increased complications
- Independent of primary tumour histology

The placebo

Clinac® Accelerators: Clinac 23EX with MLC-120 and PortalVision™

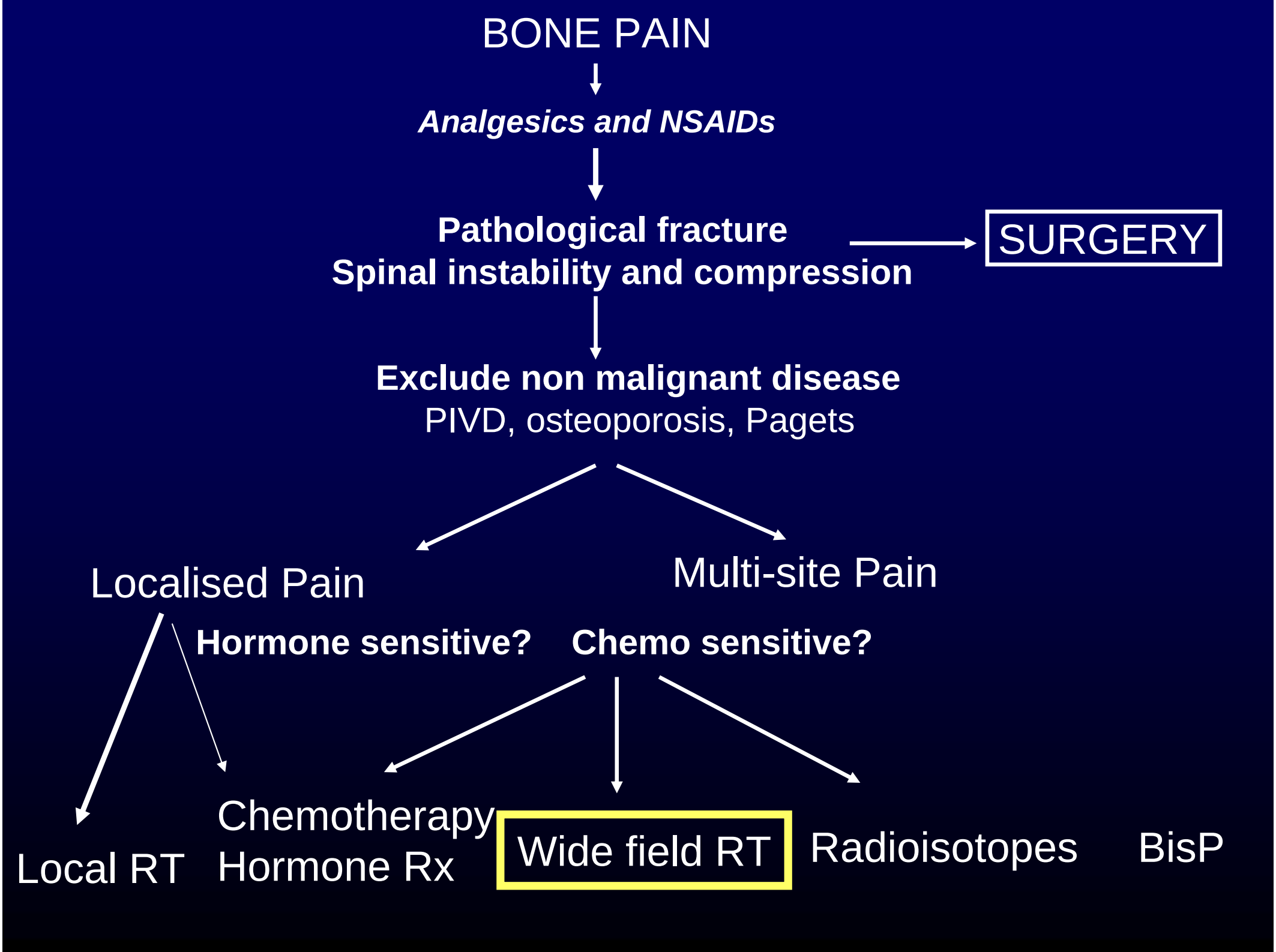
Sham radiotherapy in musculoskeletal disorers

- *Goldie et al 1970*
  - 399 patients: 205 - RT 600R
    194 - SHAM RT
  - Response:

    RT: 68% SHAM: 64%

- *Valtonen et al 1975*
  - 127 patients: 64 - 75 - 250R
    63 - SHAM RT
  - Response:

    RT: 59% SHAM: 65%


BONE PAIN
Analgesics and NSAIDs
Pathological fracture
Spinal instability and compression
SURGERY
Exclude non malignant disease
PIVD, osteoporosis, Pagets
Localised Pain
Multi-site Pain
Hormone sensitive?
Chemo sensitive?
Local RT
Chemotherapy
Hormone Rx
Wide field RT
Radioisotopes
BisP

Bone Scintigraphy in Cancer Patients

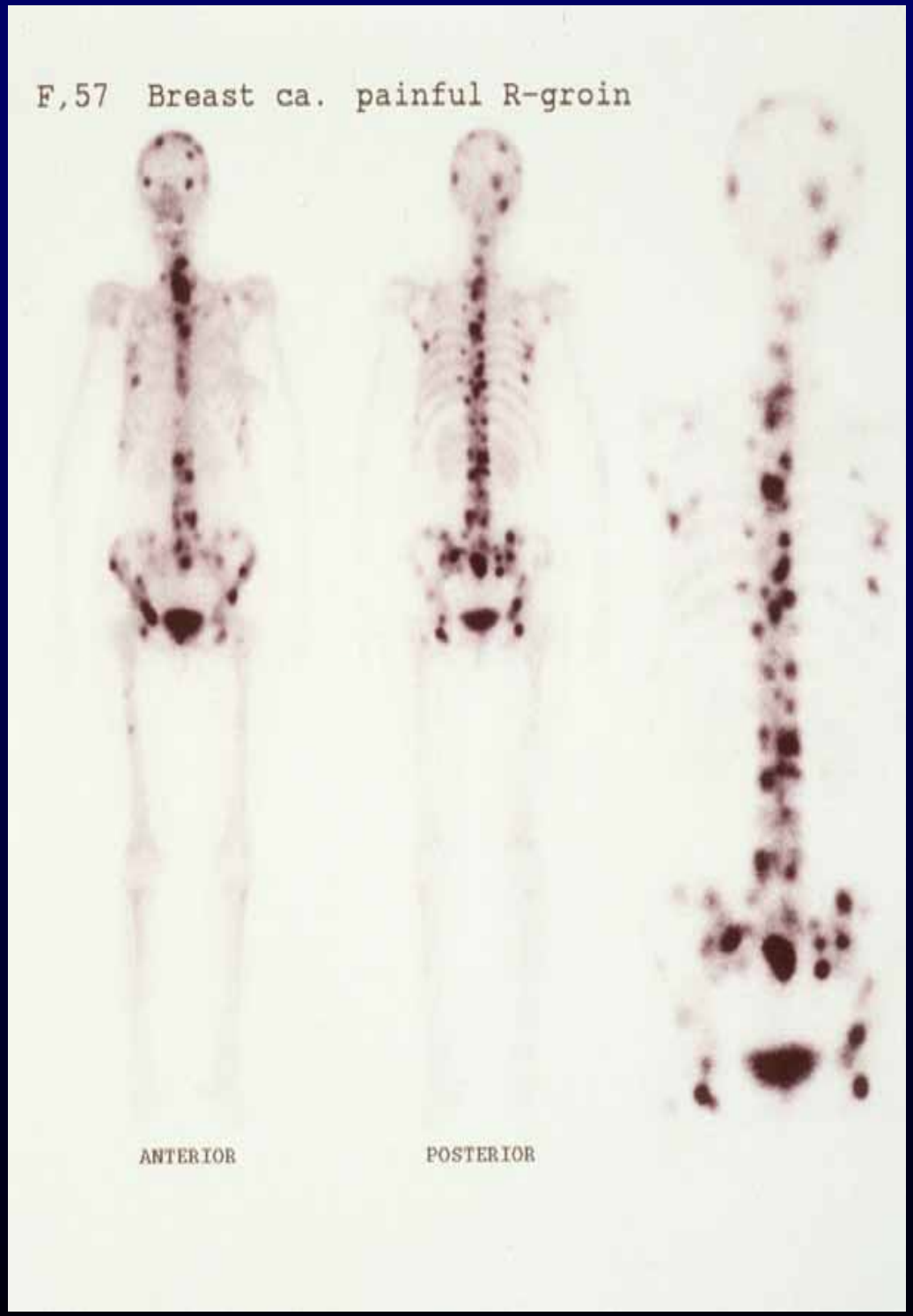
Appearances of bone metastases:

multiple hot spots (85%)
- “superscan” (10%)
- cold (photopenic) lesions (2%)
- normal (false negative) scan (<3%)

Solitary hot spot:

occurs in 7% of patients with met’s
- in spine: 80% metastasis
- in ribs: 1-17% metastasis

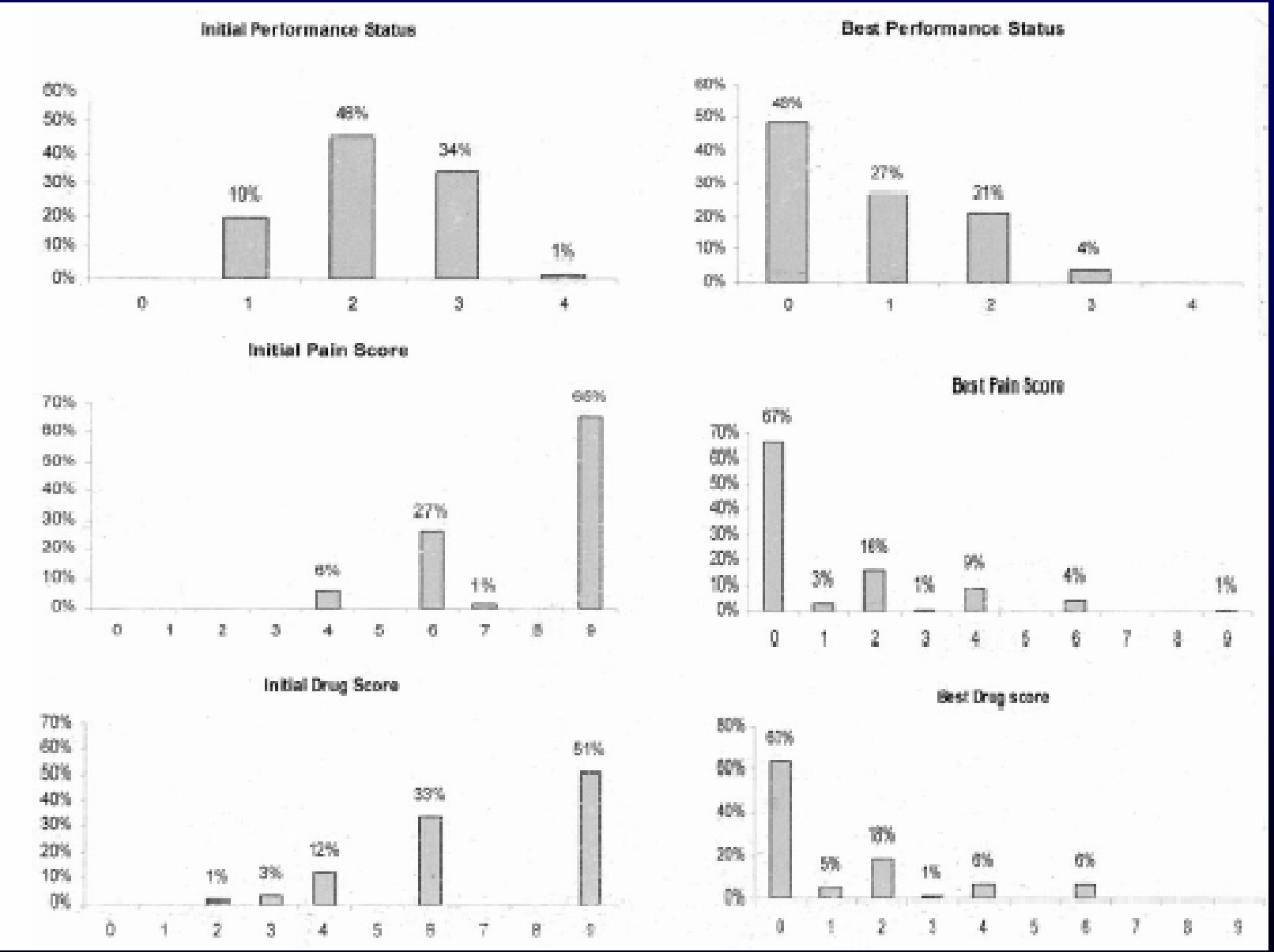
(McNeil 1984)



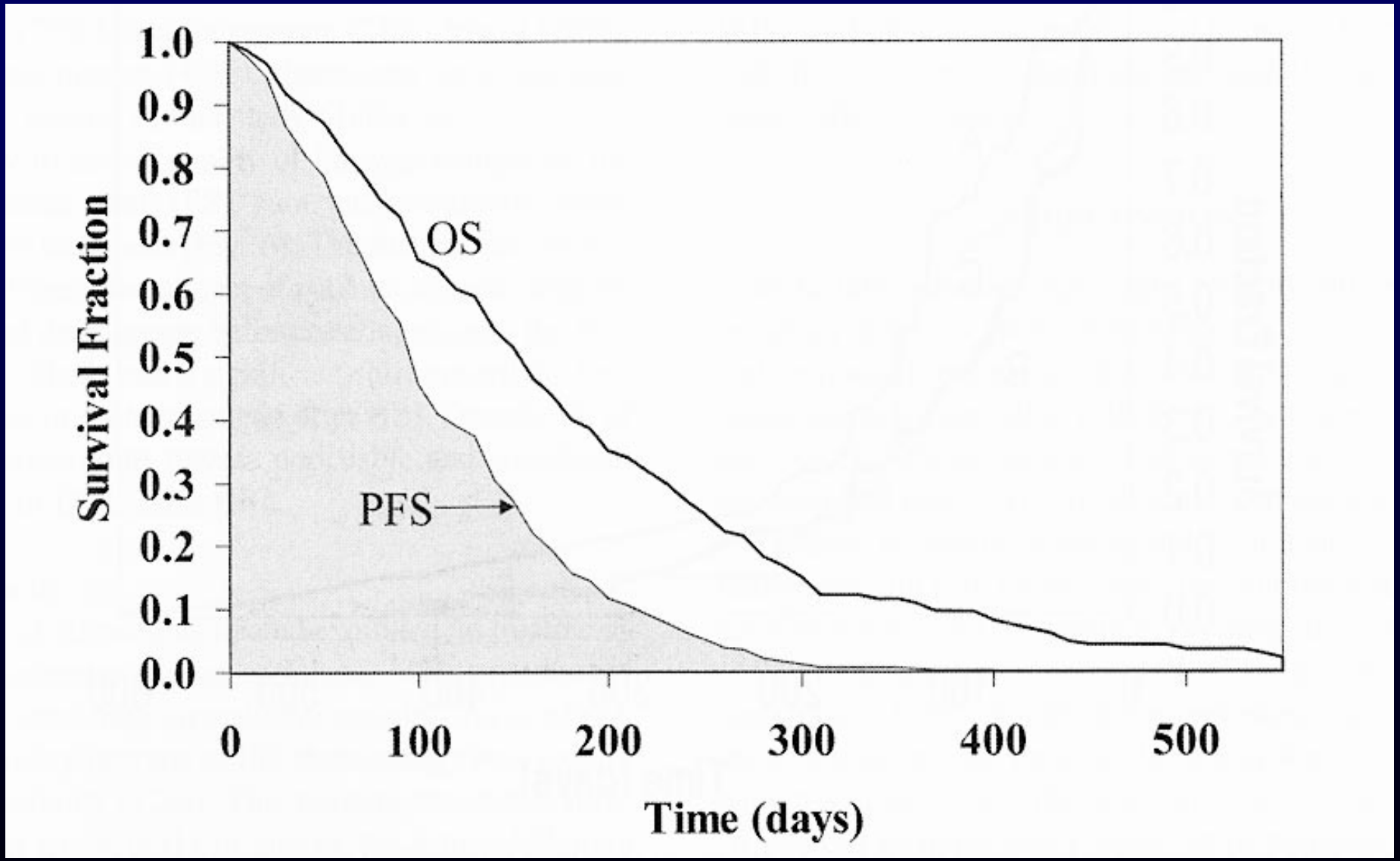
Bone metastases

- Hemibody radiotherapy
  - Salazar et al IAEA 2001
  - 156 patients
  - Brazil, Cameroon, Pakistan, Peru, Spain, USA
  - HBI
    - 15Gy/5f/5d
    - 8Gy/2f/2d
    - 12Gy/4f/2d

Hemibody radiotherapy [Salazar et al 2002]

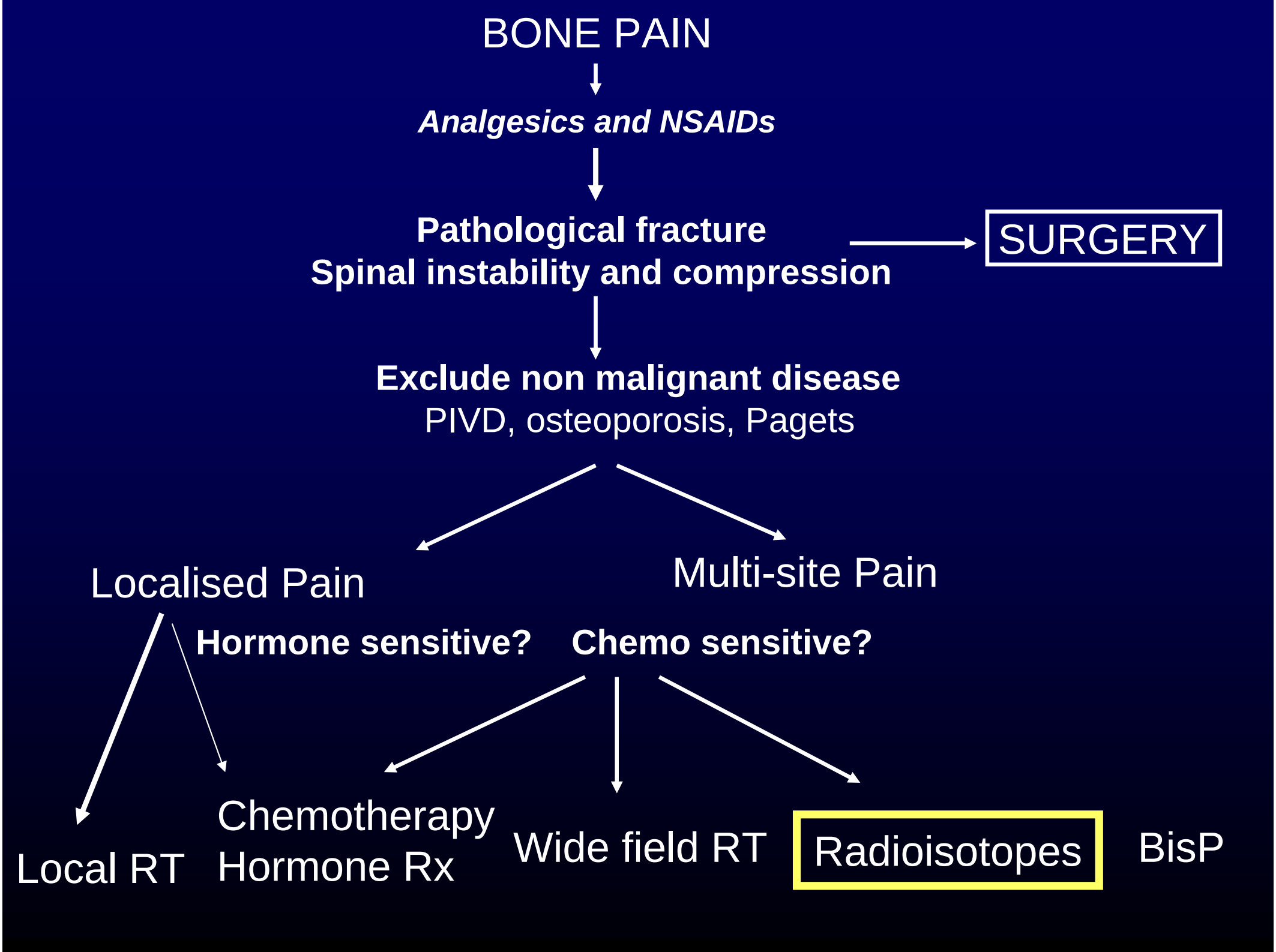


Hemibody radiotherapy [Salazar et al 2002]



Hemibody radiotherapy [Salazar et al 2002]

	Grade 3/4 toxicity	
	UHBI	LHBI
15Gy/5f	13%	4%
8Gy/2f	23%	11%
12Gy/4f	11%	12%
Overall	16%	9%


BONE PAIN
Analgesics and NSAIDs
Pathological fracture
Spinal instability and compression
SURGERY
Exclude non malignant disease
PIVD, osteoporosis, Pagets
Localised Pain
Multi-site Pain
Hormone sensitive?
Chemo sensitive?
Local RT
Chemotherapy
Hormone Rx
Wide field RT
Radioisotopes
BisP

Radionuclide bone therapy

Indications:

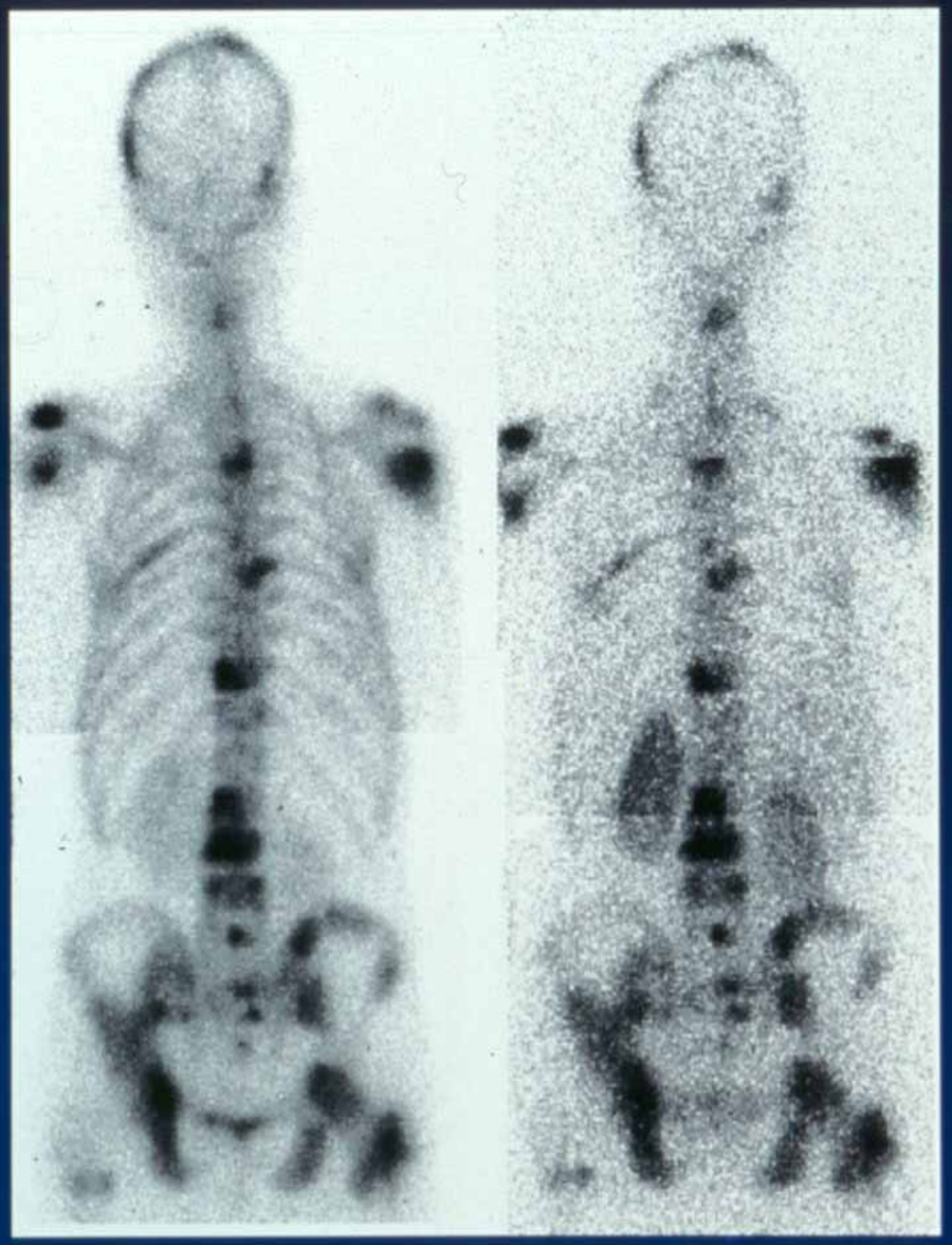
painful skeletal metastases from
- prostatic carcinoma
- breast carcinoma
- other tumors with intense uptake around metastases on bone scan

Contraindications:

- myelosuppression
- impaired renal function
- spinal cord compression
- pregnancy
- continued breast feeding
- lack of understanding or ability to cooperate with radiation safety guidelines

Caution:
urinary incontinence!

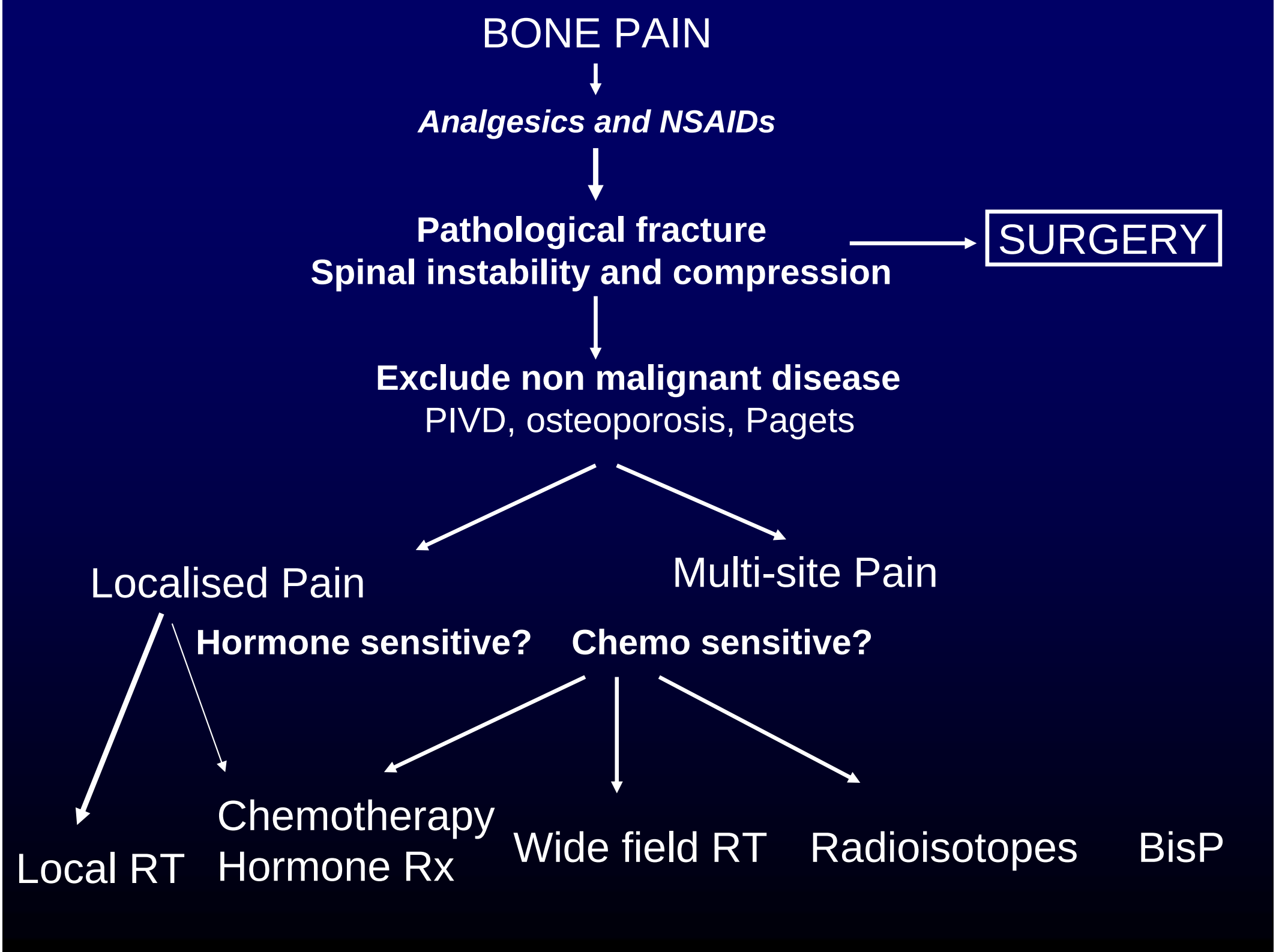
Targetted radiation



Courtesy Dr. J. de Klerk NKI

Radioisotope therapy: the disadvantage

1 patient dose	Cost, including taxes and transport (NL)
Sr-89 chloride 148 MBq	€ 1630
Re-186 HEDP 1420 MBq	€ 1021.60
Sm-153 EDTMP 3900 MBq	€ 1295
P-32 orthophosphate 370 MBq	€ 450
W-188/Re-188 generator 1 Ci	US$ 10,000 **(exclusive)**
EXTERNAL BEAM 1#	100 euro


BONE PAIN
Analgesics and NSAIDs
Pathological fracture
Spinal instability and compression
SURGERY
Exclude non malignant disease
PIVD, osteoporosis, Pagets
Localised Pain
Multi-site Pain
Hormone sensitive?
Chemo sensitive?
Local RT
Chemotherapy
Hormone Rx
Wide field RT
Radioisotopes
BisP

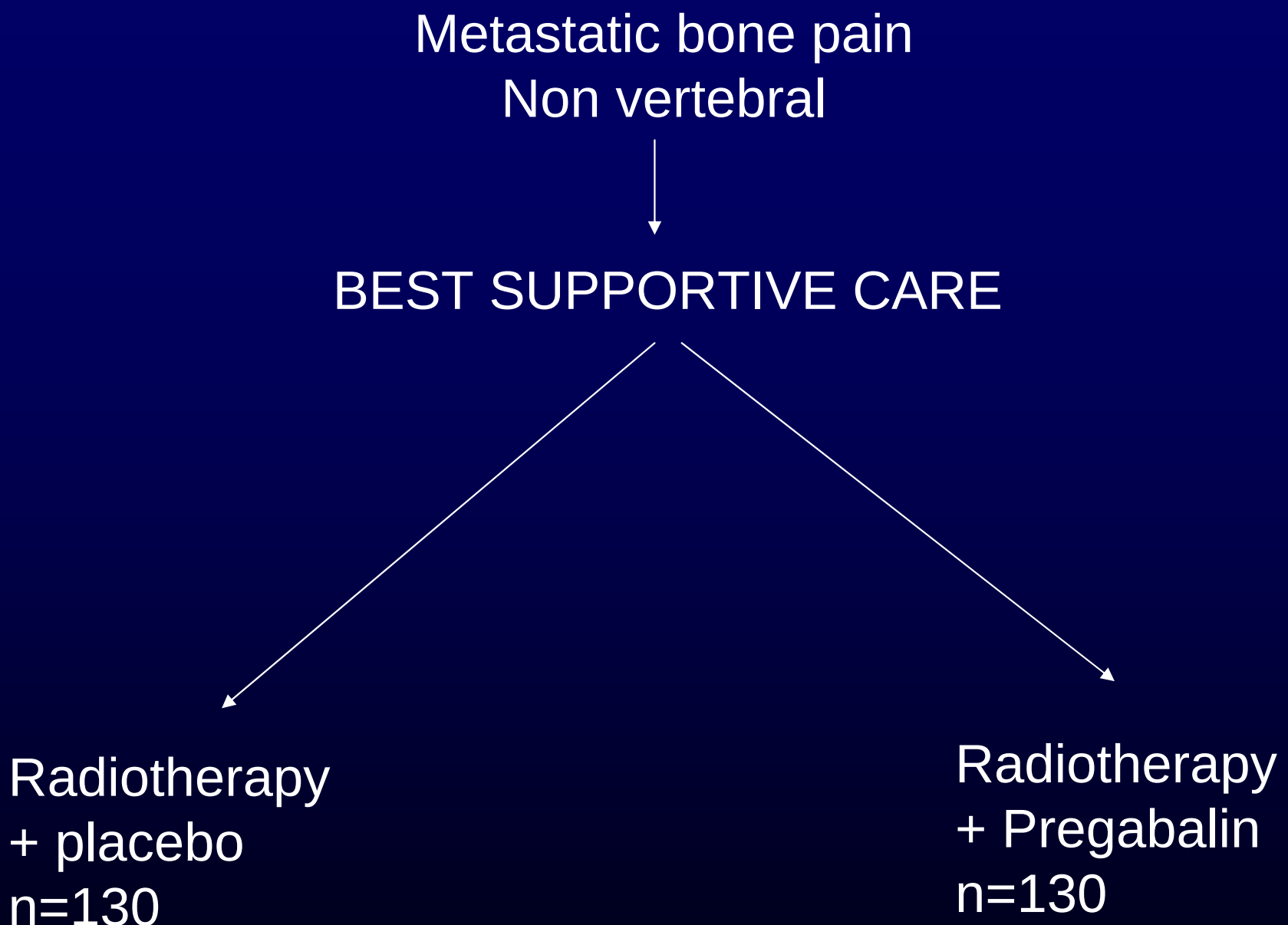
New approaches for metastatic bone pain

- Novel RT/drug combinations
- MR guided Focussed Ultrasound
- Novel inhibitors of osteoclast activation

Neurophysiology of bone pain

- Ongoing central sensitization
- Behavioural hyperalgesia and allodynia parallels altered neuronal response
- Mediated through NMDA receptor and neurotransmitter glutamate

Double-blind randomised controlled trial of pregabalin versus placebo in conjunction with palliative radiotherapy for malignant bone pain.


Metastatic bone pain
Non vertebral
BEST SUPPORTIVE CARE
Radiotherapy
+ placebo
n=130
Radiotherapy
+ Pregabalin
n=130

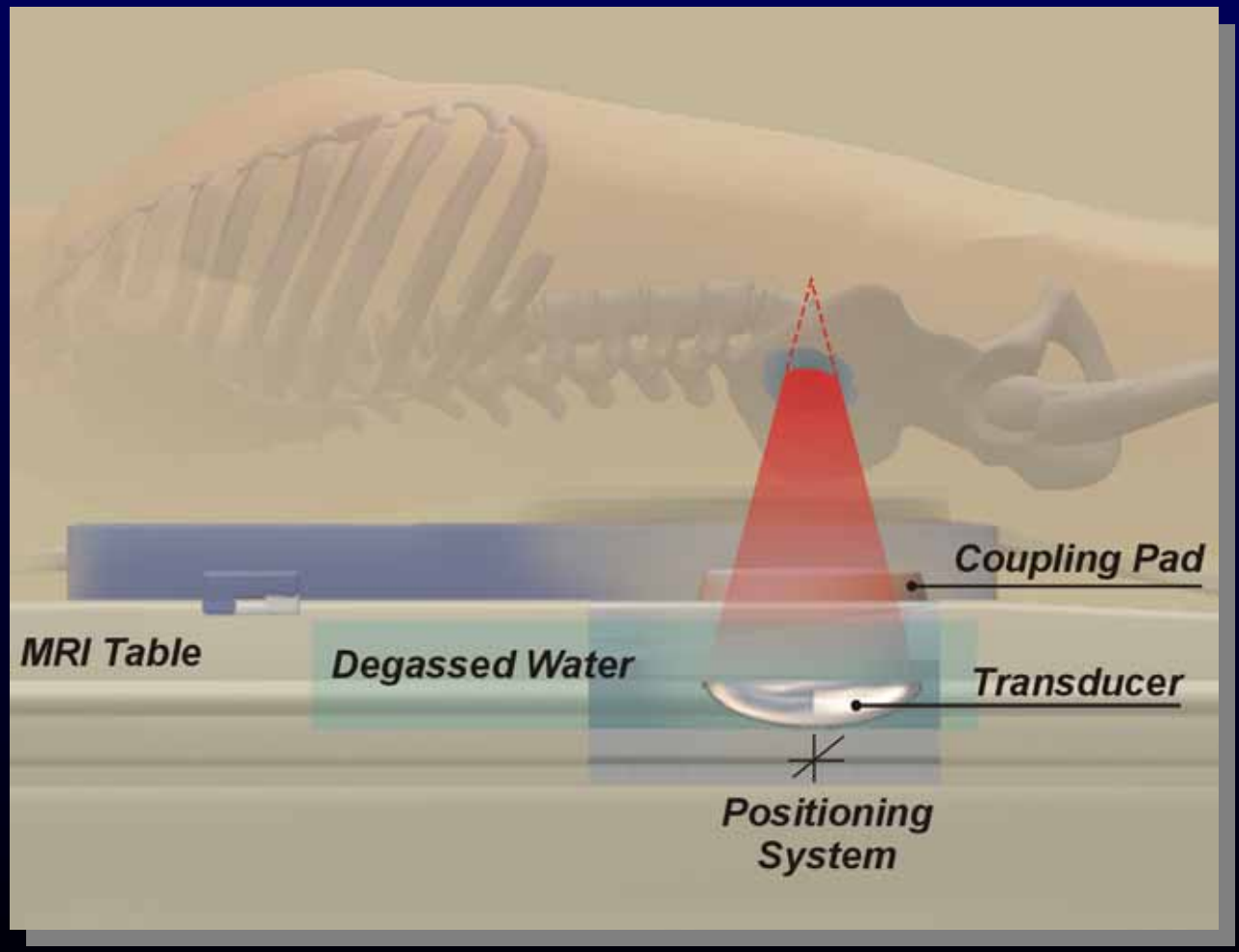
New approaches for metastatic bone pain

- Novel RT/drug combinations
- MR guided Focussed Ultrasound
- Novel inhibitors of osteoclast activation

Non ionising radiation

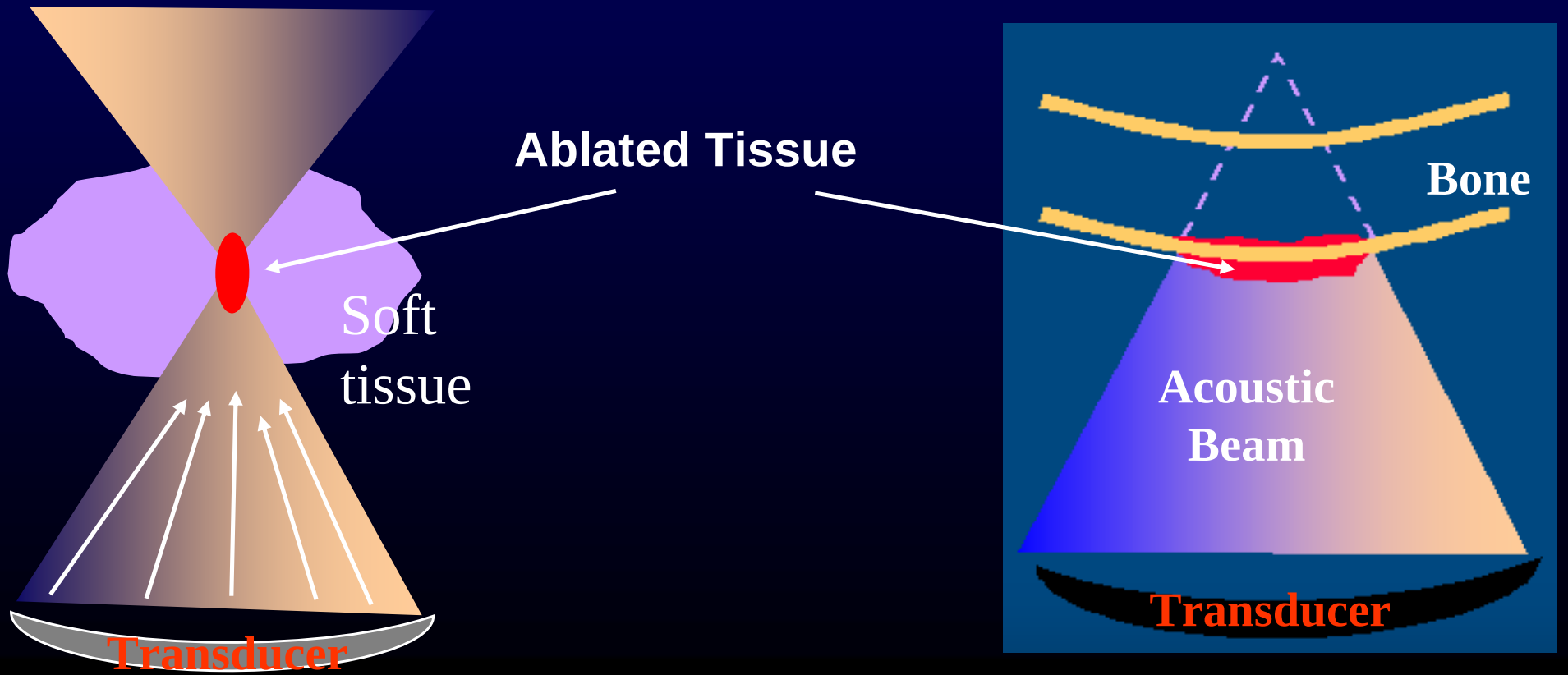
MR guided Focussed Ultrasound

MRgUS



MRgFUS for Palliation of Bone Metastases

- Treatment principles
  - Bone heating is used to ablate the adjacent periosteum
  - Palliation achieved by the ablation of the bone periosteum, which is the sensory origin of the pain



MRgFUS for Palliation of Bone Metastasis

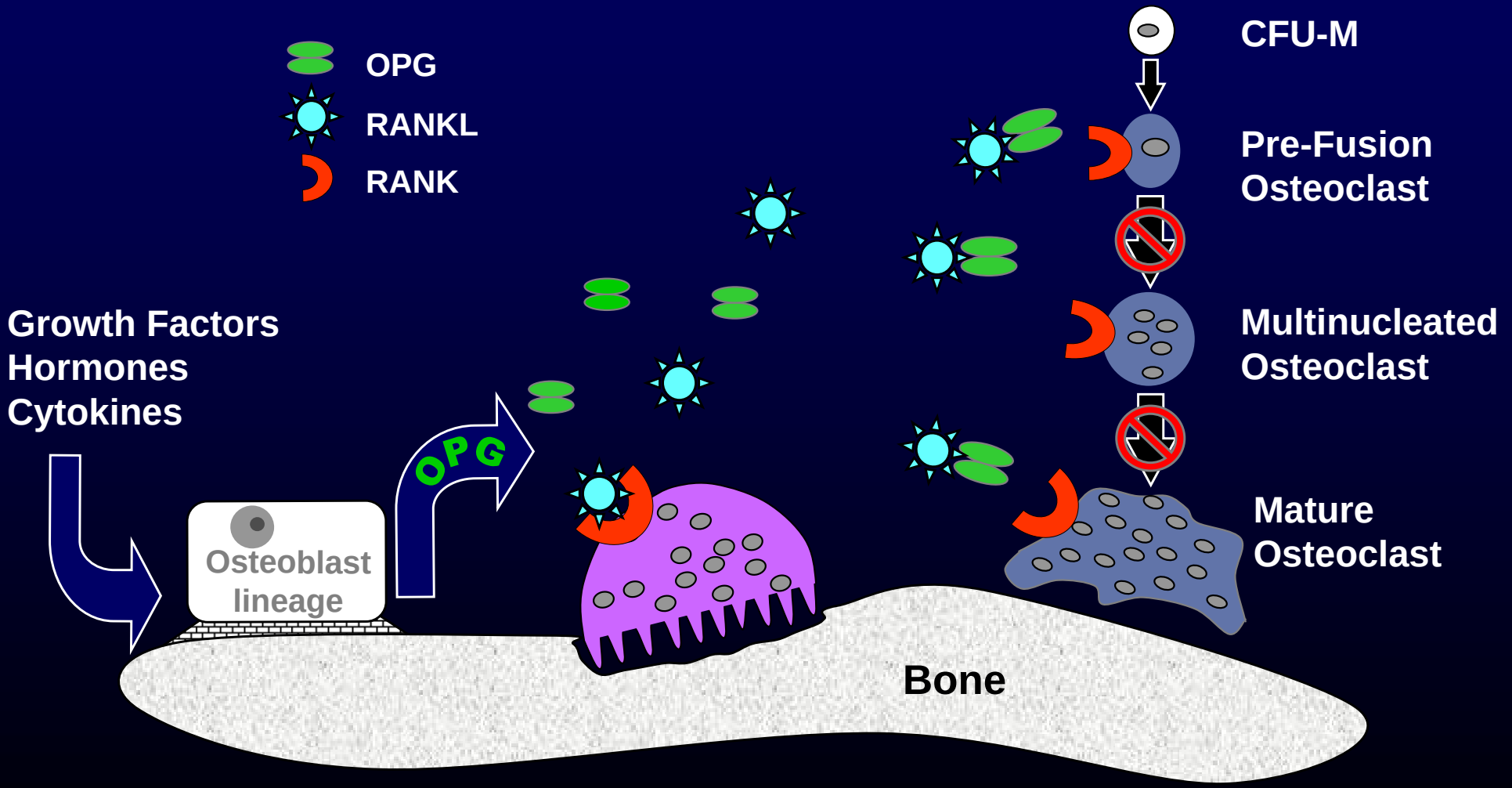
- Clinical results
  - 11 treatments in 9 patients
  - No significant device related adverse event
  - Only one patient failed to tolerate treatment
  - All treated patients with follow-up data have reported reduction of pain and / or medication dosage
  - Follow-up of up to 6 months

New approaches for metastatic bone pain

- Novel RT/drug combinations
- MR guided Focussed Ultrasound
- Novel inhibitors of osteoclast activation

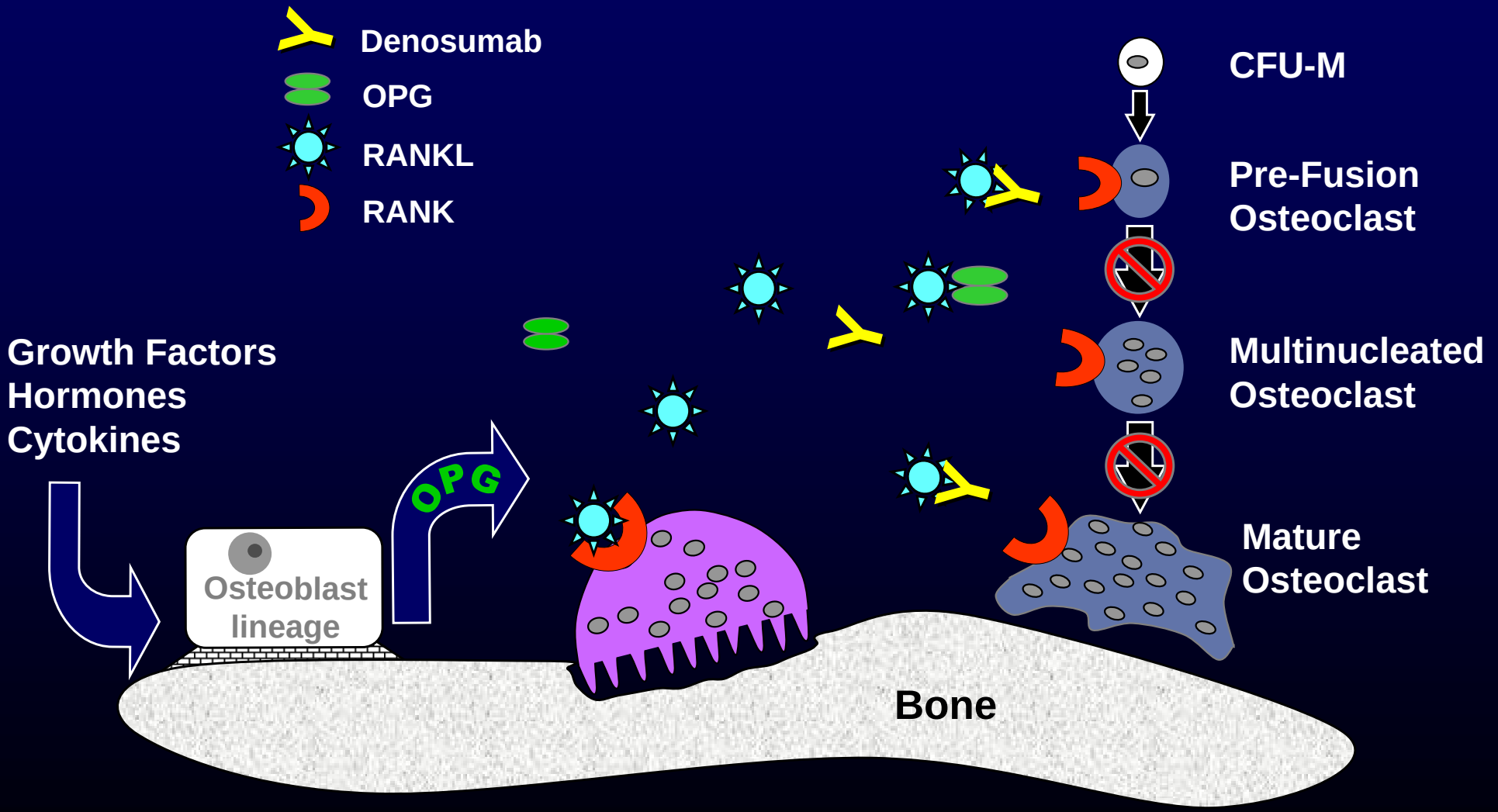
RANK Ligand is antagonised by Osteoprotegerin (OPG) binding

Osteoclast Formation, Function and Survival Inhibited by OPG

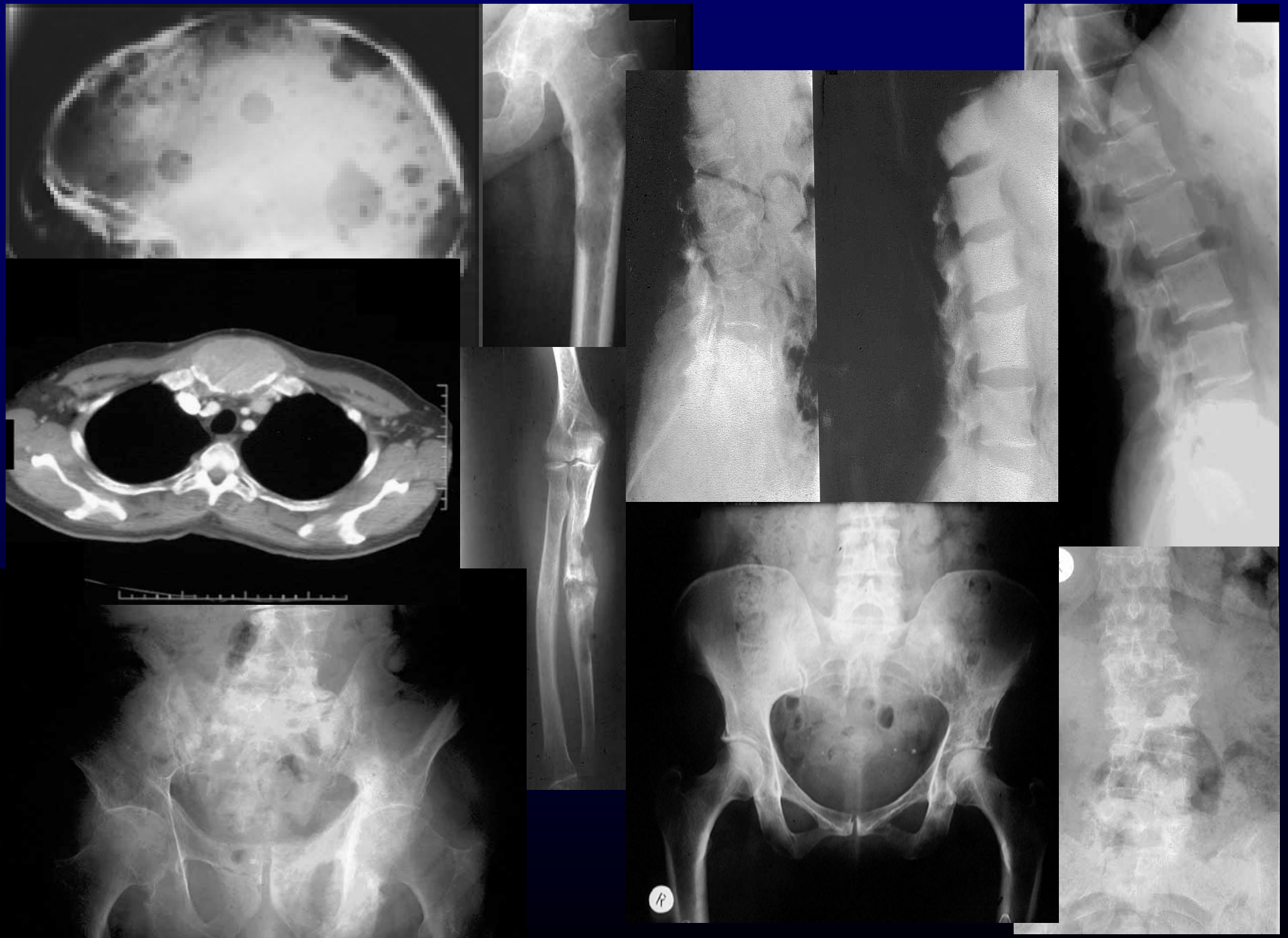


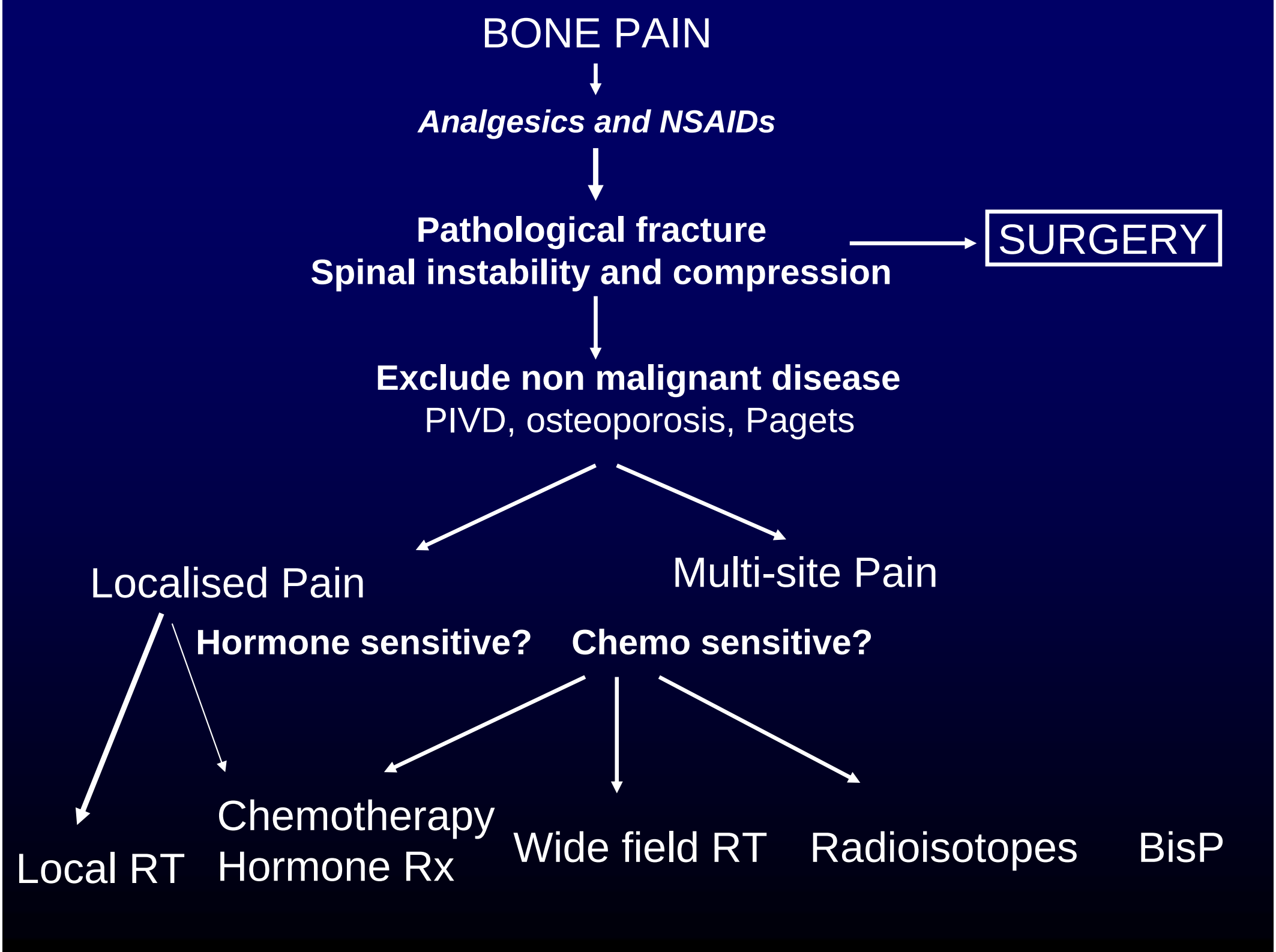
Adapted from Boyle WJ et al. *Nature.* 2003;423:337-42.

Mechanism of Action for Denosumab



Adapted from Boyle WJ et al. *Nature.* 2003;423:337-42.




BONE PAIN
Analgesics and NSAIDs
Pathological fracture
Spinal instability and compression
SURGERY
Exclude non malignant disease
PIVD, osteoporosis, Pagets
Localised Pain
Multi-site Pain
Hormone sensitive?
Chemo sensitive?
Local RT
Chemotherapy
Hormone Rx
Wide field RT
Radioisotopes
BisP