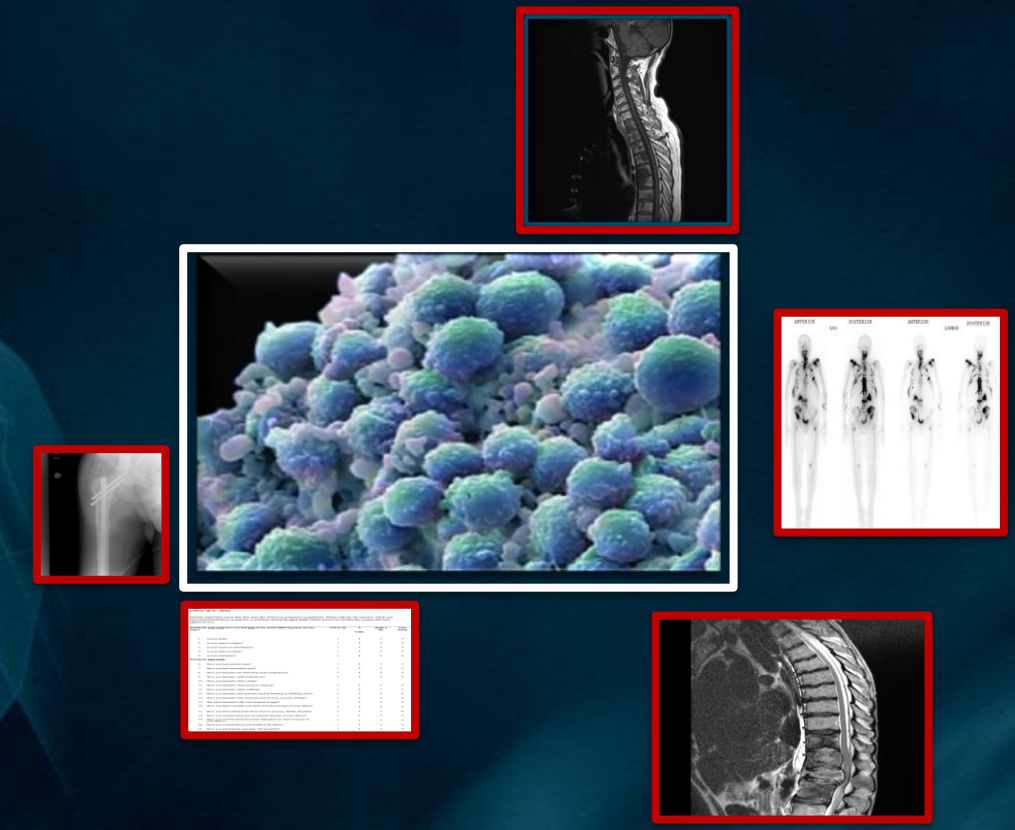
Metastases & The Bone Environment

Advanced Prostate Cancer



Lawrence Drudge-Coates

Uro-Oncology Clinical Nurse Specialist & Hon Lecturer
King's College Hospital NHS Foundation Trust

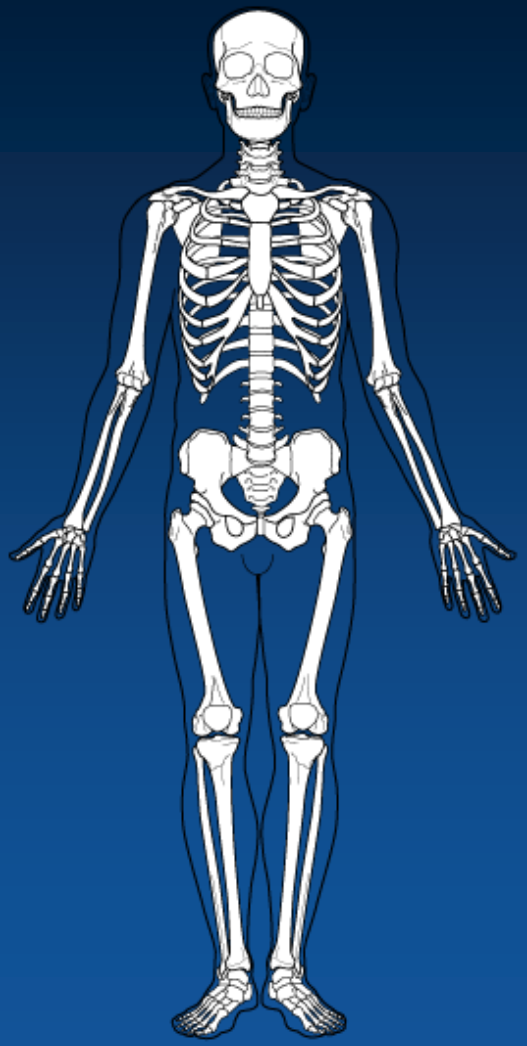
Functions of the Skeleton

Structural support
For heart, lungs and marrow

Protection of internal organs
From mechanical damage, particularly the brain, heart and lungs

Attachment of muscles
Bones act as levers for muscles, allowing voluntary movement

Mineral storage
The skeleton is the largest depot for minerals in the body; 99% of calcium, 85% of phosphorus and 50% of magnesium are stored in the bones



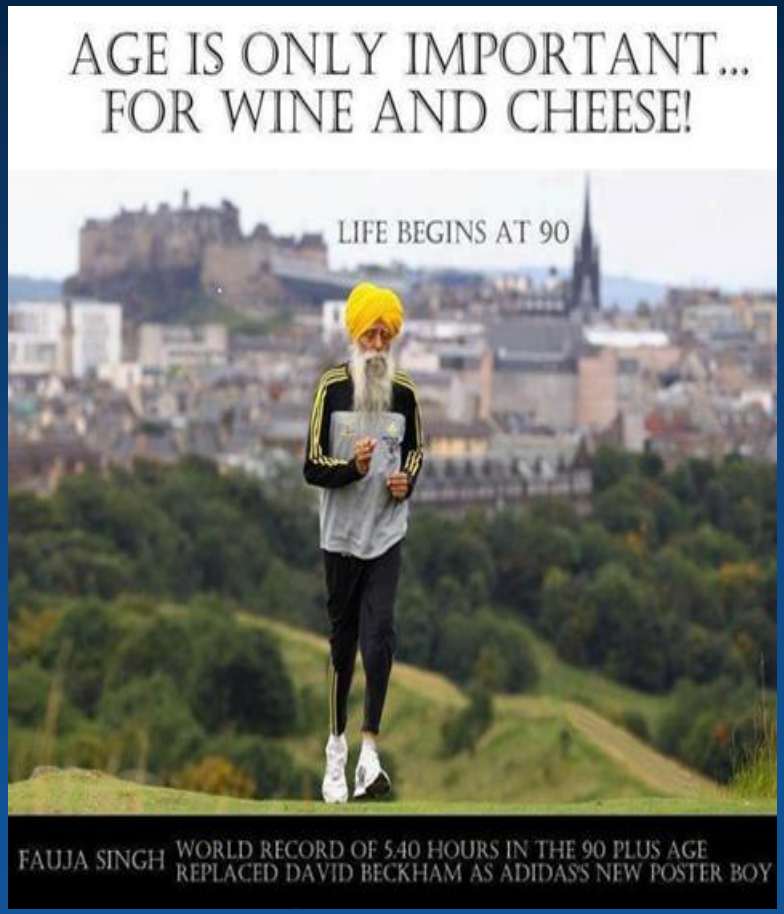
Production of blood cells
Red bone marrow produces blood cells in a process known as haematopoiesis

Storage of fatty acids
Yellow bone marrow contains a reserve of fat for consumption during starvation states

Acid-base balance
Bone buffers the blood against excessive pH changes by absorbing or releasing alkaline salts

Detoxification
Bone tissues can store heavy metals, such as lead, which can be gradually released and excreted

Fauja Singh – a.k.a “Turban Tornado”

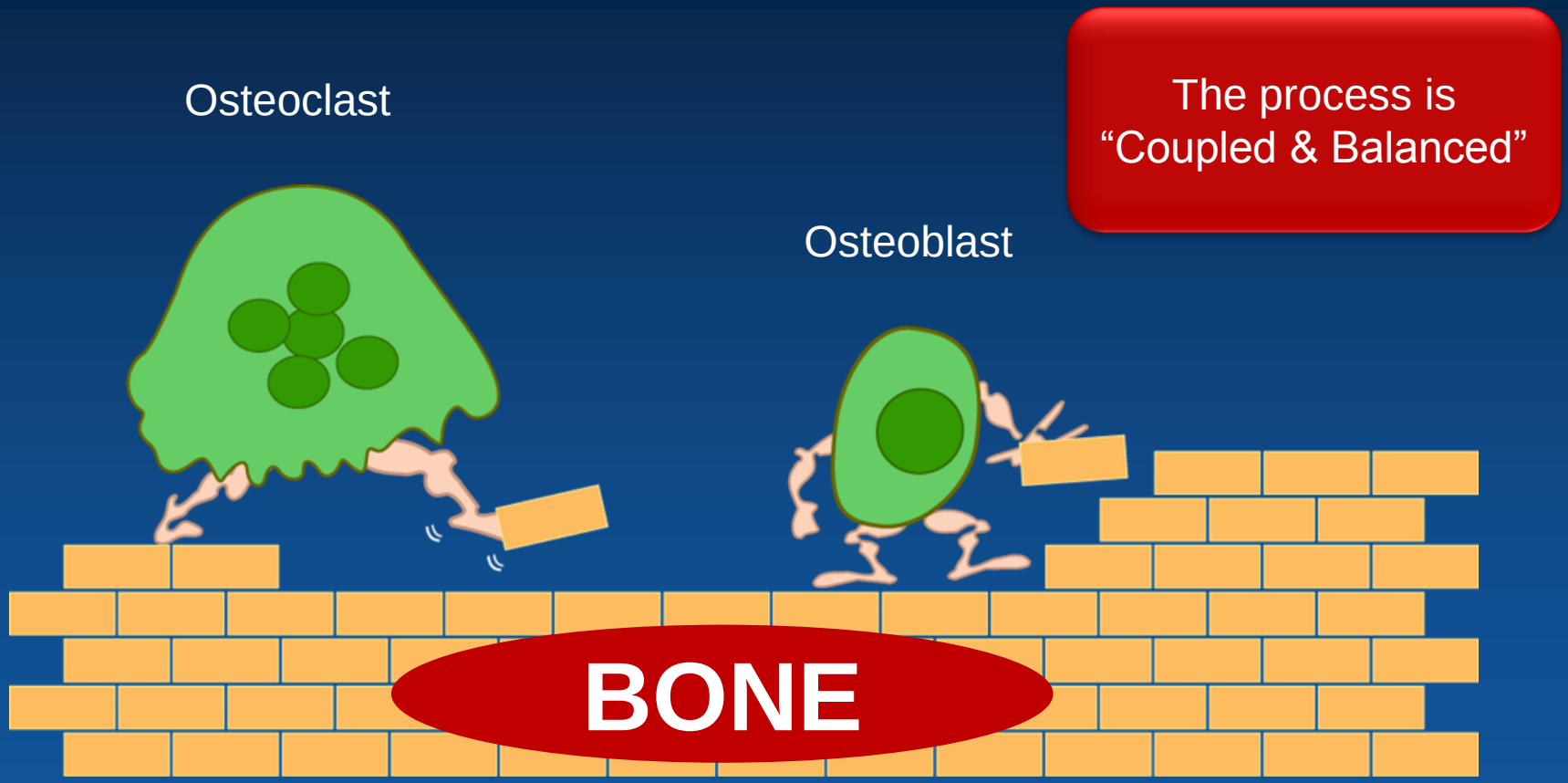


Bone Remodeling

Bone Remodeling

- Continuous throughout life
- Maintained by tightly coupled balance between osteoblastic and osteoclastic cell activity
  - Osteoblasts: cells that produce bone
  - Osteoclasts: cells that break down bone
- Ensures skeletal integrity
- Maintains mineral homeostasis

Normal bone remodeling: Old/damaged bone Is removed by osteoclast activity and replaced by osteoblast activity



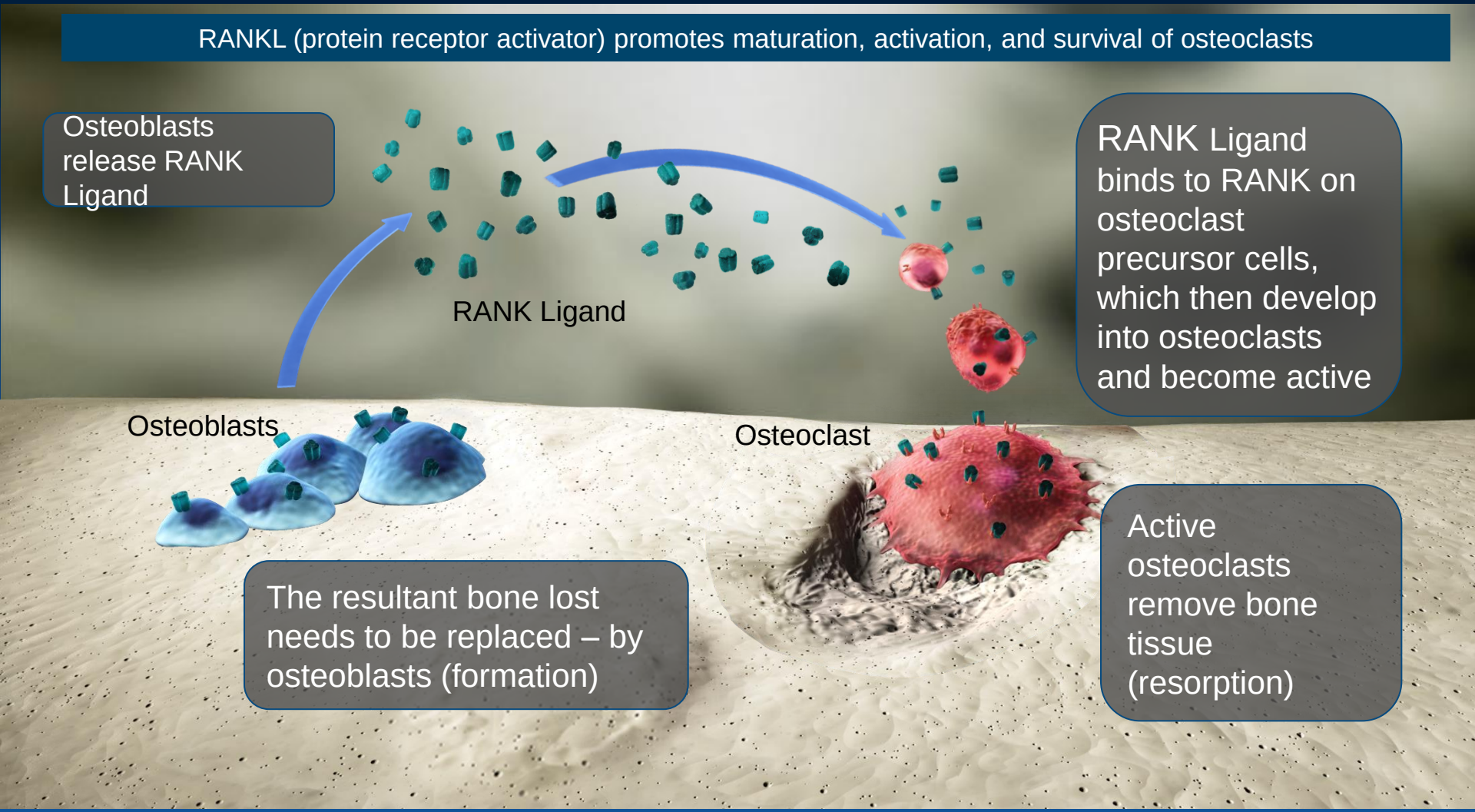
Adapted from Prof GR Mundy, Vanderbilt University

Bone Remodeling

Normal bone remodeling is tightly regulated & balanced

(The RANK Ligand pathway is key in local regulation of bone remodeling)

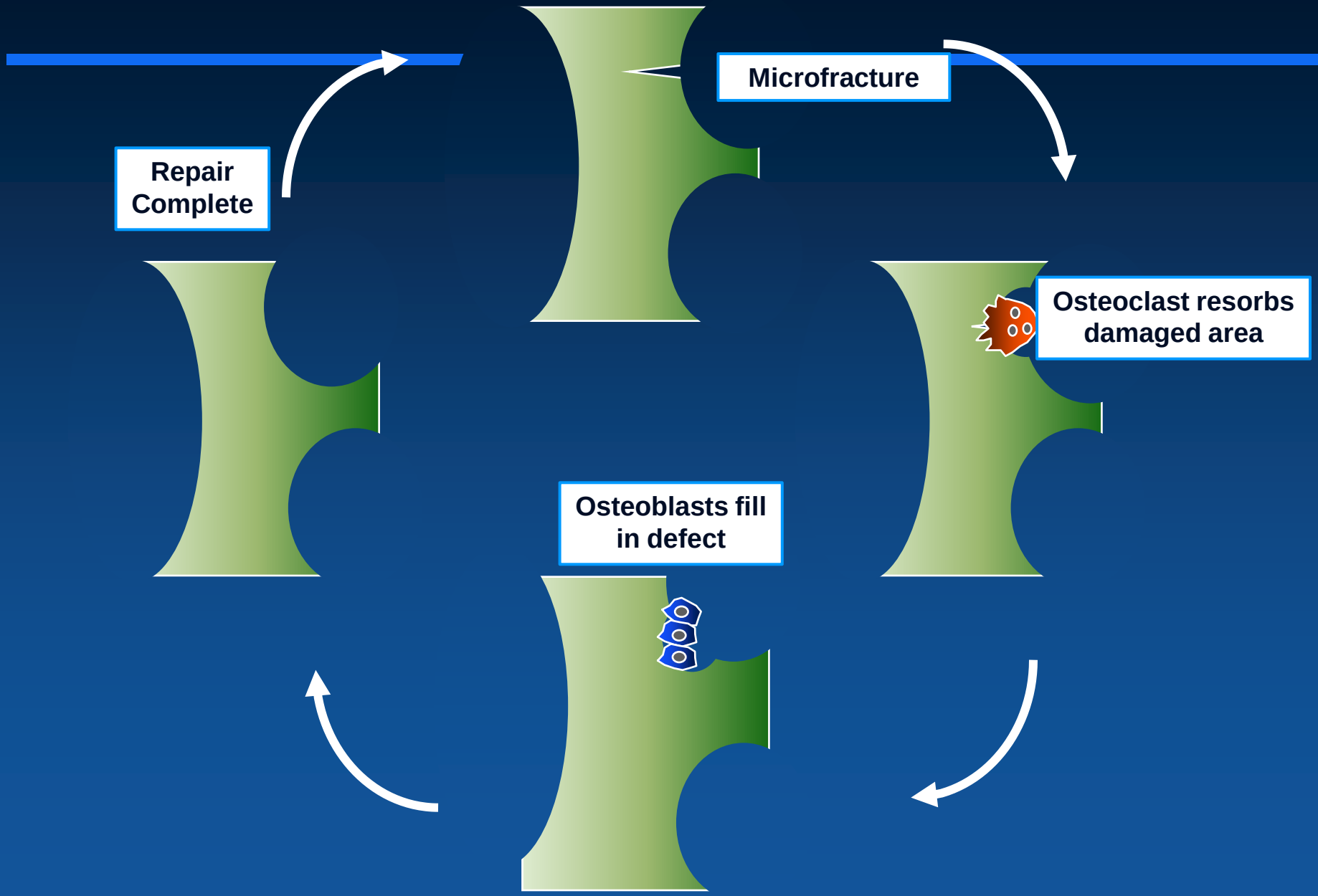
RANKL (protein receptor activator) promotes maturation, activation, and survival of osteoclasts



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

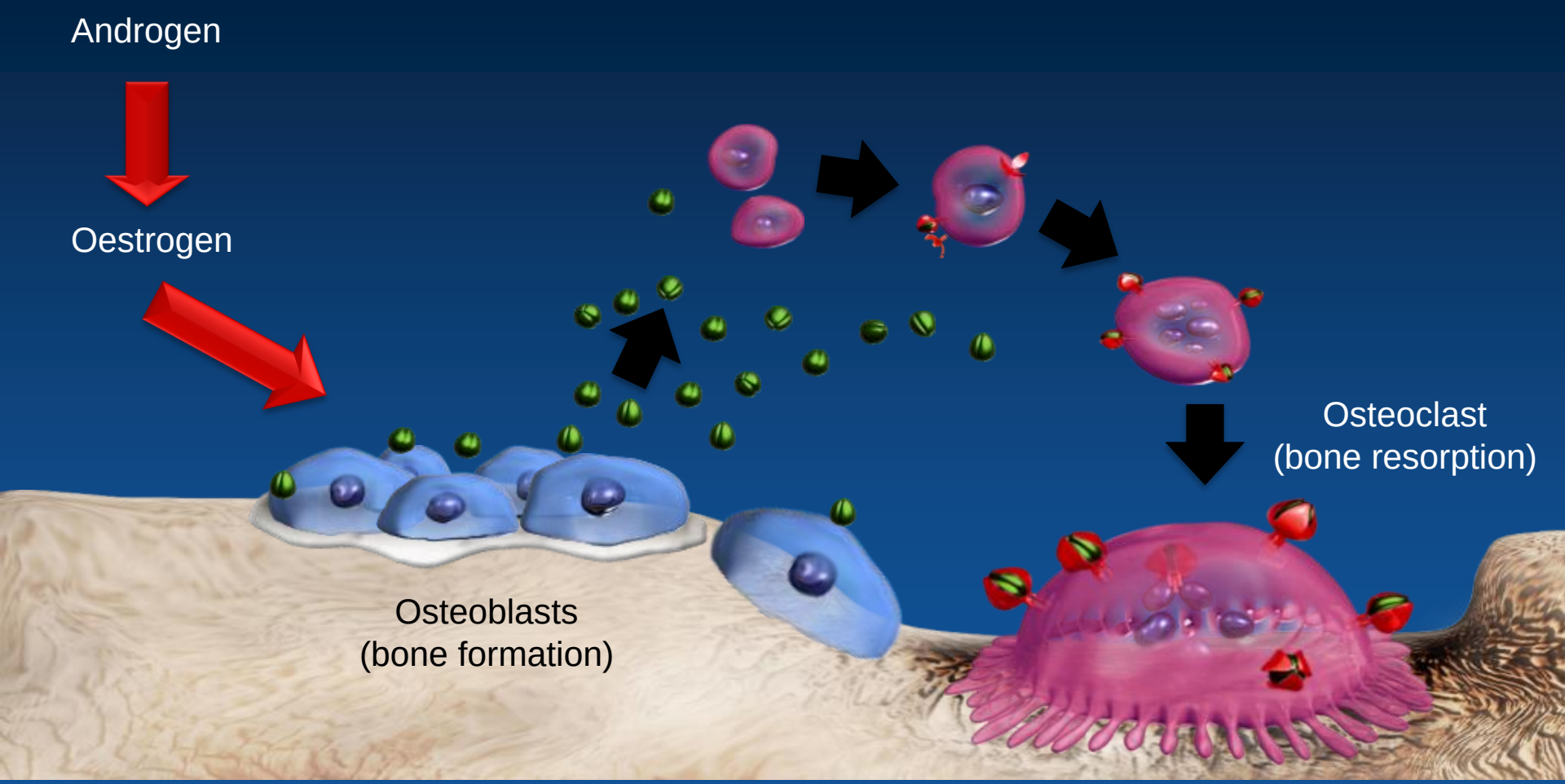
RANK, receptor activator of nuclear factor κ B

The Fracture Cycle



Cancer Therapy Induced Bone Loss (CTIBL)

Androgen is a key mediator of bone formation

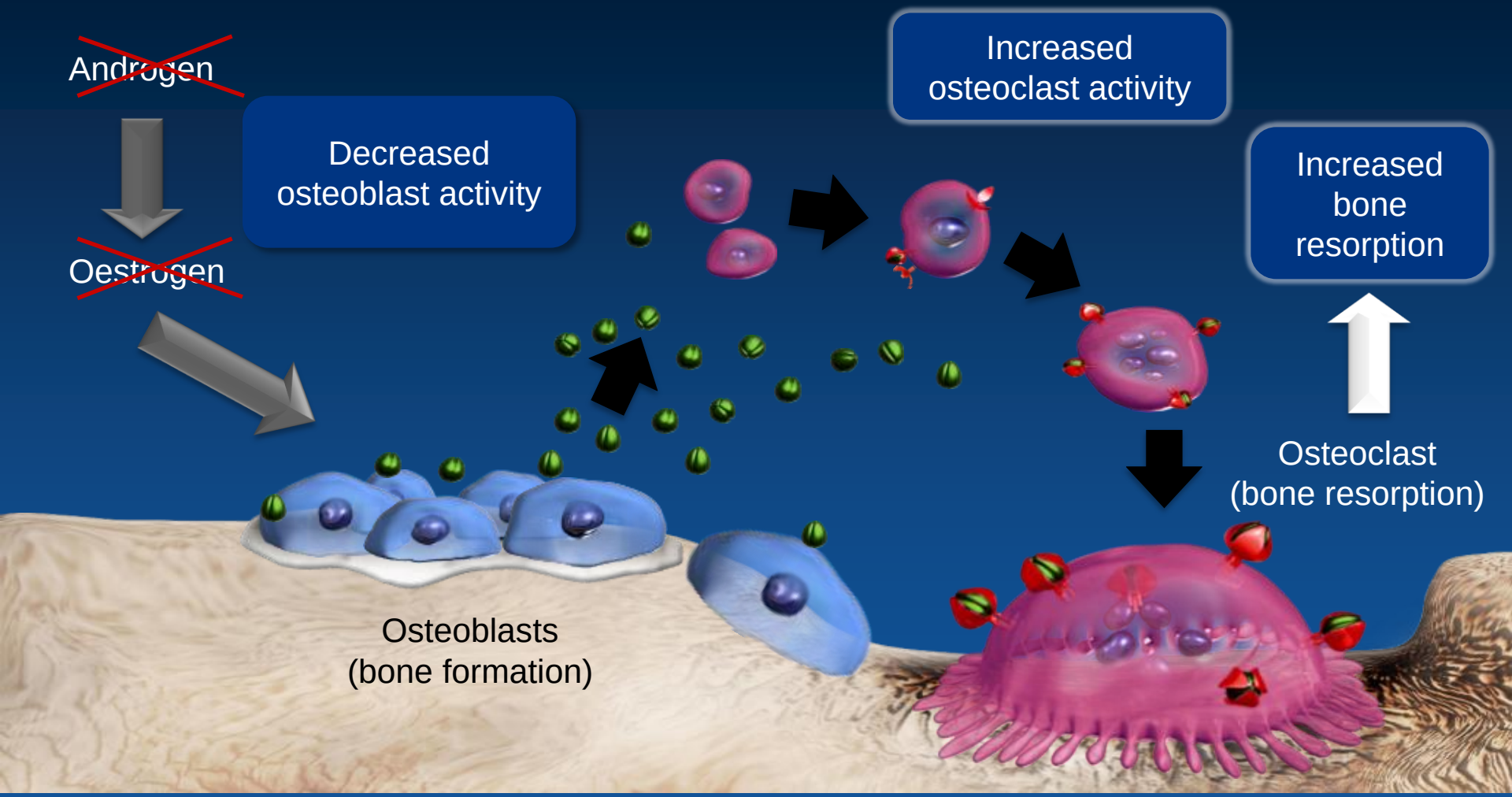


Adapted from Boyle WJ *et al*. *Nature* 2003;423:337–42. Lewiecki. *Exper Opin Biol Ther* 2006;6:1041-50.

= RANK = RANK ligand

RANK, receptor activator of nuclear factor κ B

ADT reduces osteoblast activity and increases bone resorption by osteoclasts

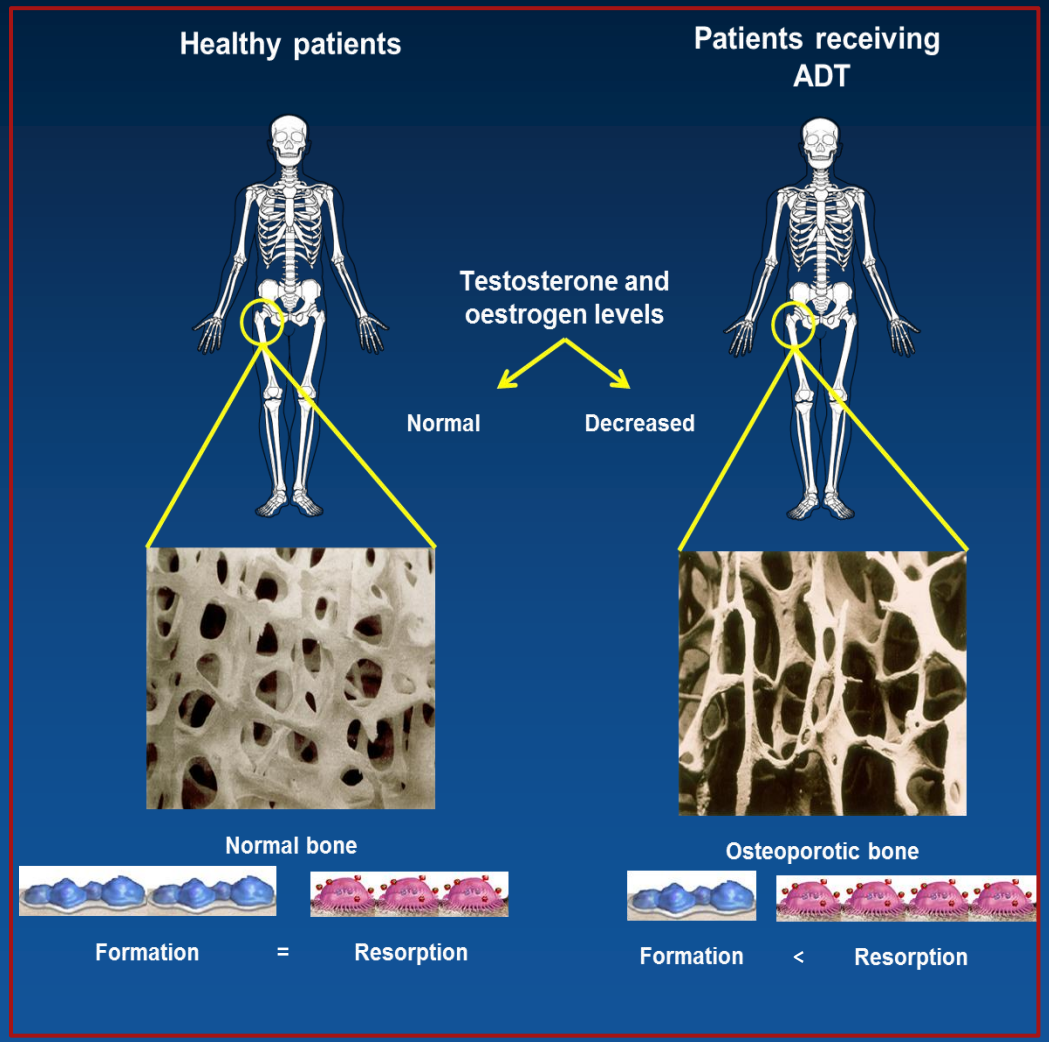


Adapted from Boyle WJ *et al*. *Nature* 2003;423:337–42. Lewiecki. *Exper Opin Biol Ther* 2006;6:1041-50.

= RANK = RANK ligand

ADT, androgen-deprivation therapy; RANK, receptor activator of nuclear factor κ B

Pathophysiology of the development of cancer treatment-induced bone loss



EAUN e-learning bone health course (2013)

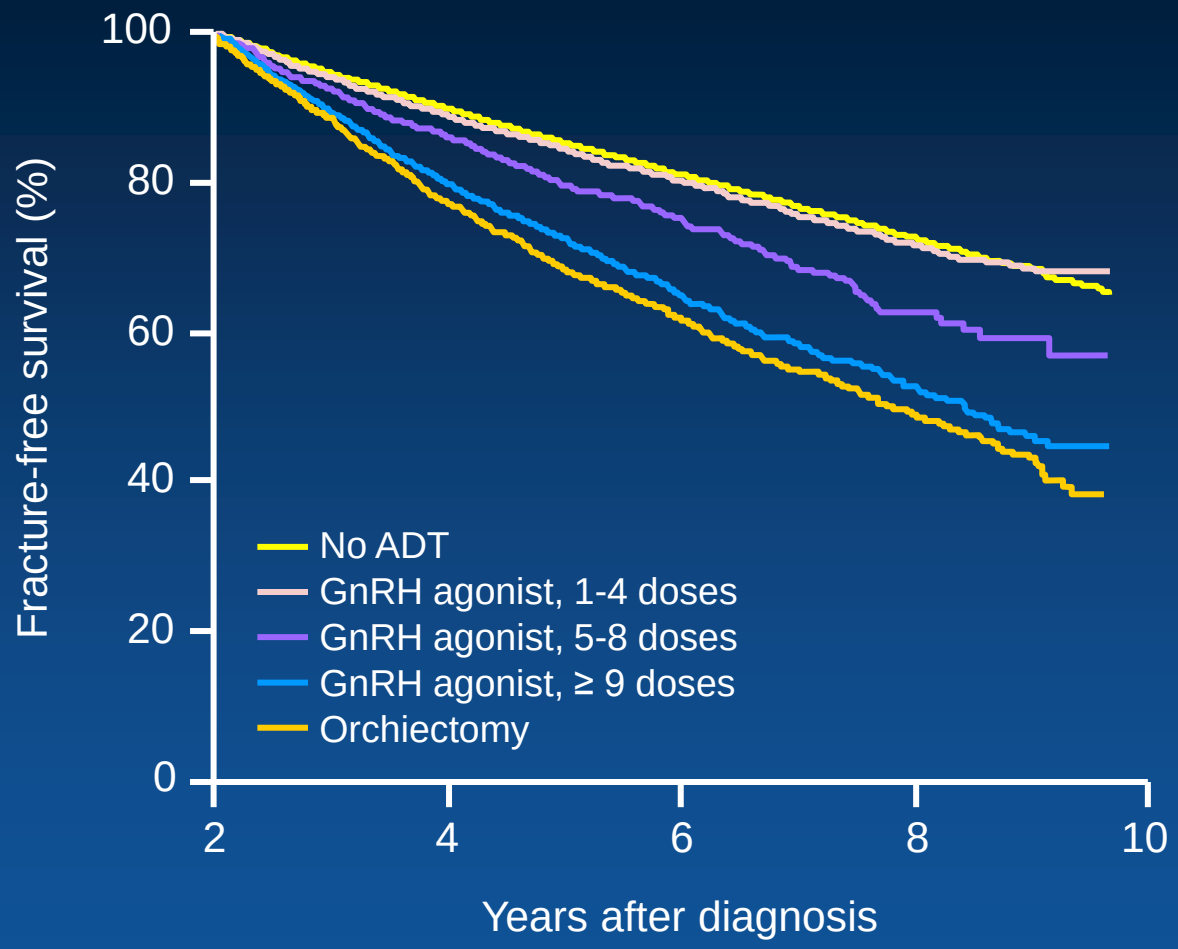
- Androgen deprivation therapy (ADT) results in increased bone resorption through:
  - Increased osteoclast formation, mediated by RANK Ligand
  - Increased osteoblast apoptosis
  - Down-regulation of OPG production
- Increased osteoclast activation leads to a decrease in bone mineral density
- Overall, ADT results in more bone resorption than formation, placing prostate cancer patients at greater risk of osteoporosis and fractures

Prevalence of Osteoporosis at Baseline and Under ADT in Prostate Cancer: Cross-Sectional Data

Duration of ADT (yr)	Patients (%)		
	Osteoporosis	Osteopenia	Normal
None	35.4	45.2	19.4
2	42.9	39.3	17.8
4	49.2	34.4	16.4
6	59.5	29.7	10.8
8	65.7	28.5	5.7
10	80.6	19.4	0

Morote J, et al. Urology. 2007;69:500-504.

Prostate cancer: Risk of fractures increases with longer duration of ADT

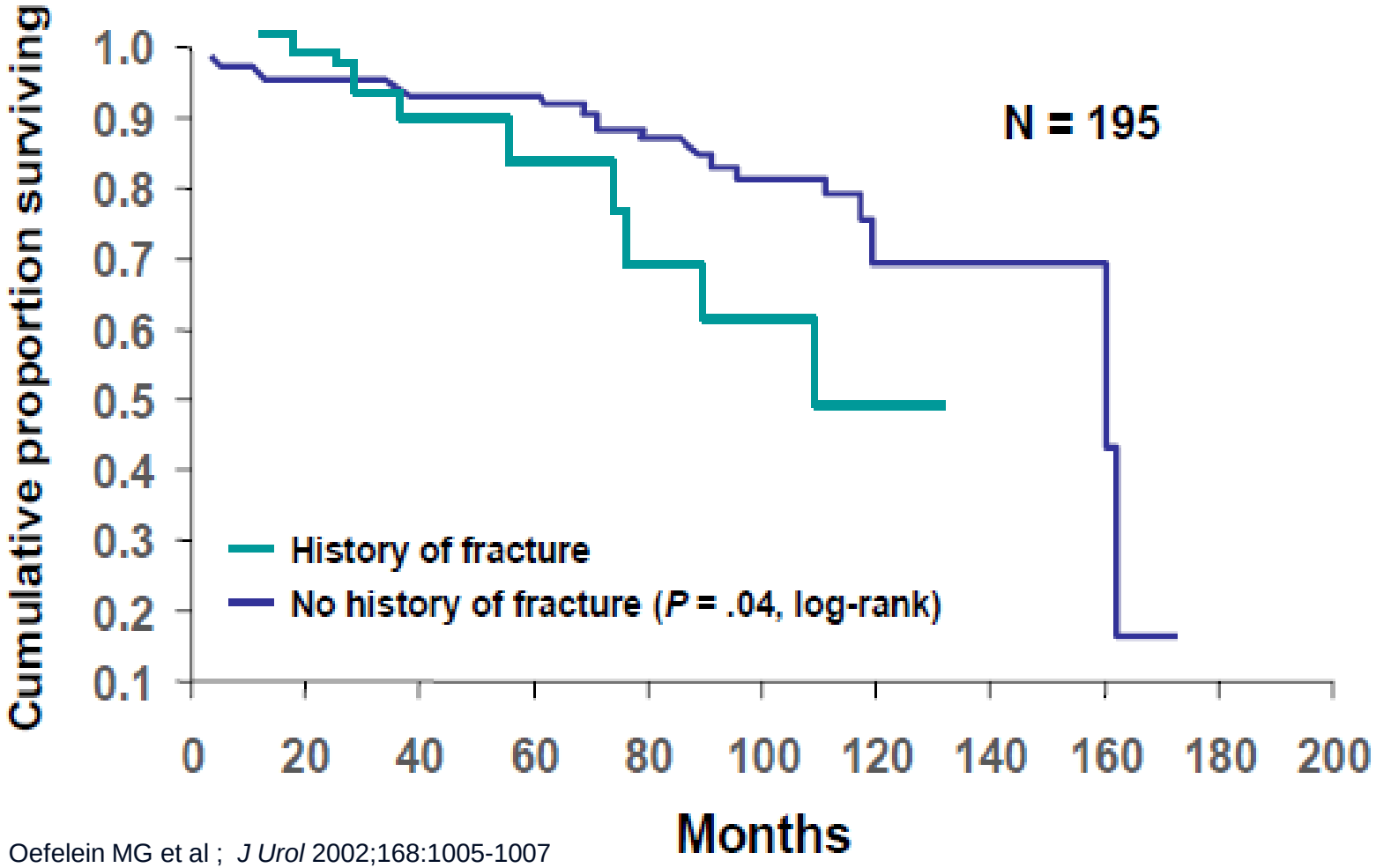


Of men surviving at least five years after diagnosis, 19.4% of those who received ADT had a fracture, compared with 12.6% of those who did not receive ADT ($p<0.001$)

GnRH, gonadotropin-releasing hormone

Shahinian VB, et al. N Engl J Med 2005;353:154-64.

Fractures Negatively Correlate With Overall Survival in Prostate Cancer Patients



Oefelein MG et al ; *J Urol* 2002;168:1005-1007

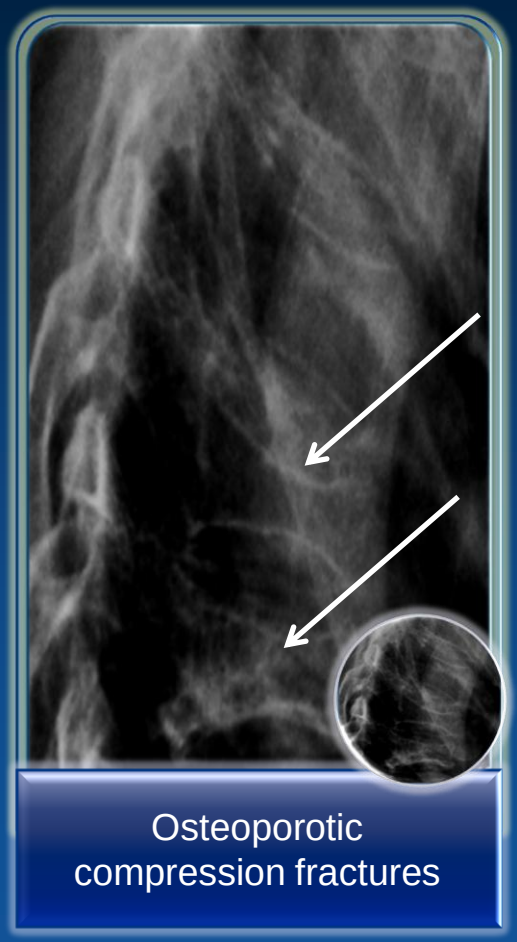
Consequences of Hip Fractures

- 1-yr mortality in men is ~ 30% to 35%

- Hip fracture affects life expectancy dramatically
  - Ages 60-69 yrs: 11.5 yrs of decreased life expectancy
  - Ages 70-79 yrs: 5 yrs of decreased life expectancy

Forsen L, et al. Osteoporosis Int. 1999;10:73-78. Schurch MA, et al. J Bone Miner Res. 1996;11:1935-1942.
Cree M, et al. J Am Geriatr Soc. 2000;48:283-288. Center JR, et al. Lancet. 1999;353:878-882.

Vertebral (spine) & Hip fractures



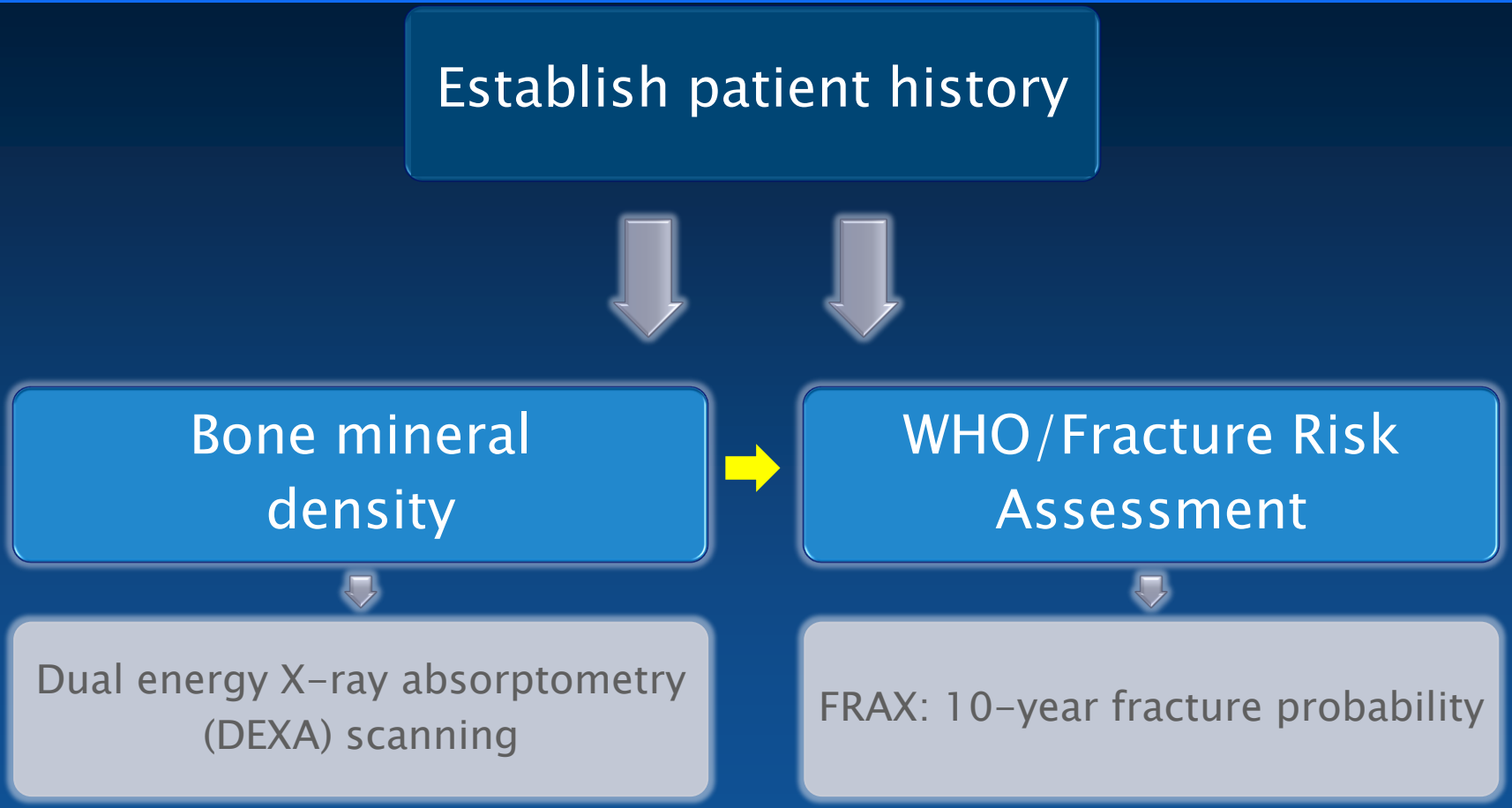
Osteoporotic compression fractures

Osteoporotic compression fracture with “wedge” deformity

Osteoporotic fracture of the left femur

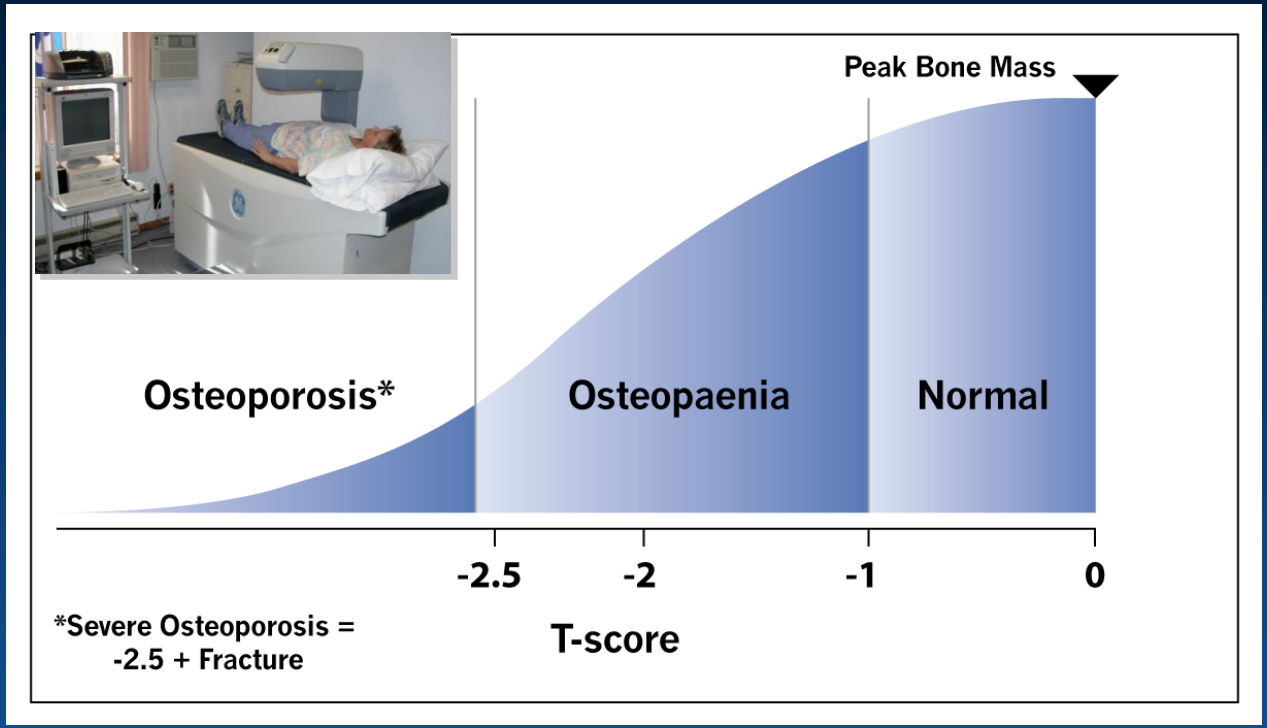
Images supplied courtesy of Lawrence Drudge-Coates

Assessment tools



WHO Fracture risk assessment tool. Available at: http://www.shef.ac.uk/FRAX

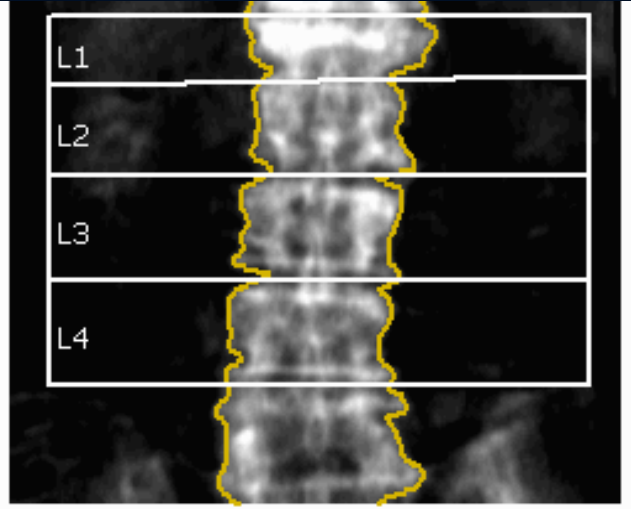
T-score: Interpreting DEXA results



T-score

The number of standard deviations that separate the patient from the mean value of a healthy population - Every unit decrease associated with 10 -12 % loss of bone density

World Health Organisation.1998



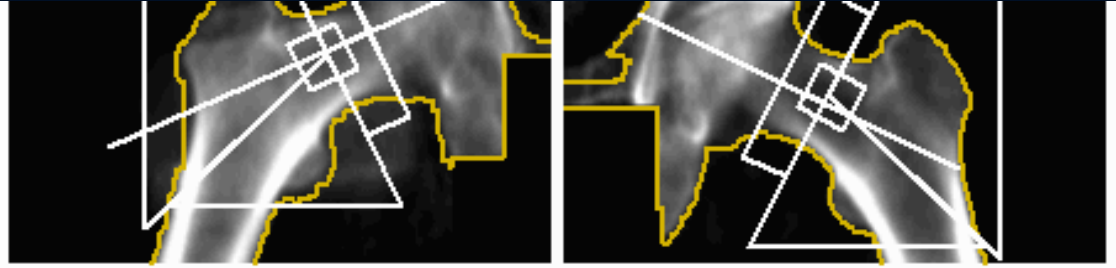
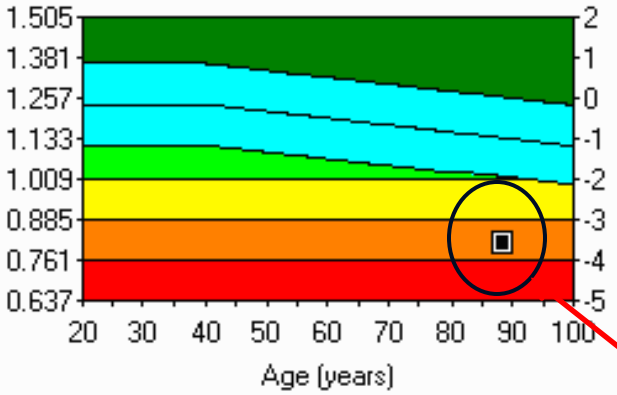


Image not for diagnosis

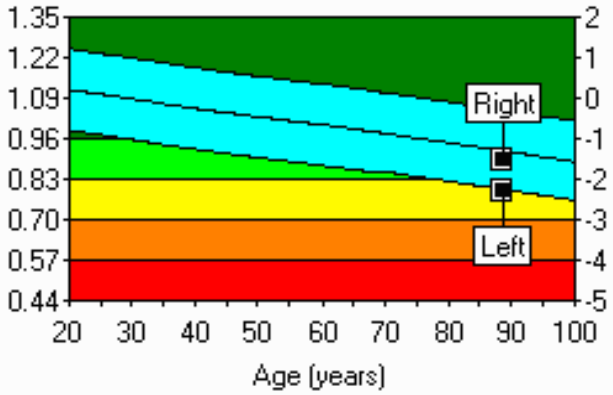
HAL chart results unavailable

Image not for diagnosis

Densitometry Reference: AP Spine L2-L4



Densitometry Reference: DualFemur Total



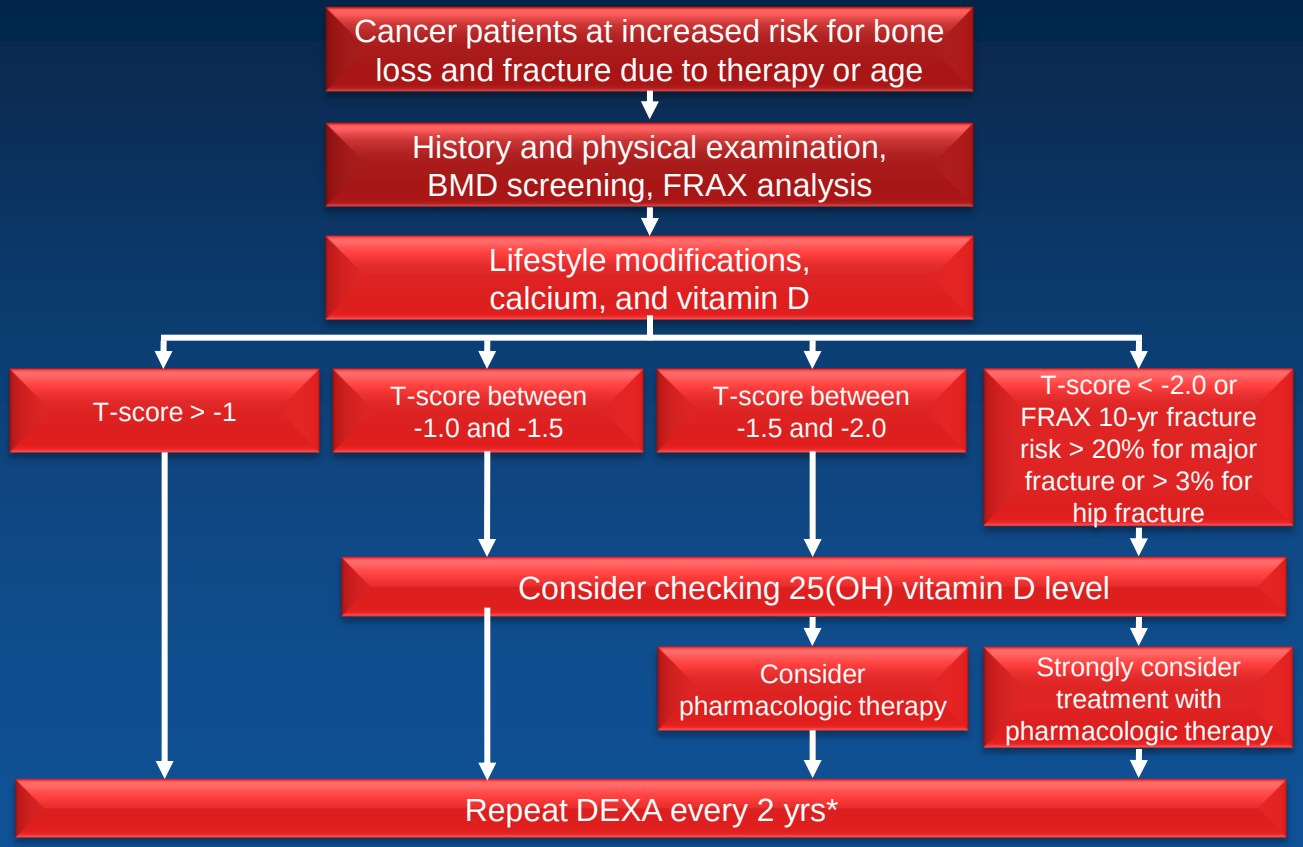
Region	BMD [1] (g/cm²)	Young-Adult [2,7] T-Score	Age-Matched [3] Z-Score	WHO Classification [11]
AP Spine L2-L4	0.808	-3.6	-2.8	-
DualFemur Total				
Left	0.792	-2.3	-1.0	-
Right	0.898	-1.5	-0.2	-
Mean	0.845	-1.9	-0.6	-
Difference	0.105	0.8	0.8	-

Recommendations to Prevent ADT-Induced Bone Loss

- Men older than 50 yrs: calcium 1200 mg/day and vitamin D3 800-1000 IU/day
- DXA scan monitoring
- Treat osteoporosis with bisphosphonates (alendronate or zoledronic acid)
- Consider treating patients with osteopenia and other risk factors (FRAX)
  - 10-yr probability of hip fracture ≥ 3%
  - 10-yr probability of major osteoporosis-related fracture ≥ 20%
- Encourage cardiovascular and weight-bearing & resistance exercise
- Limit alcohol and caffeine consumption
- Smoking cessation

National Osteoporosis Foundation Guidelines(2010)

Management of Bone Health in Patients With Cancer



*In selected cases, longer or shorter intervals may be considered. If a major change in patient risk factors or a major intervention occurs, repeating DEXA at 1 yr is reasonable.

Gralow JR, et al. J Natl Compr Canc Netw. 2009;7(suppl 3):S1-S32.

FRAX assessment tool: 10-year probability of fracture

"In the absence of a prostate cancer specific algorithm, we advocate the use of FRAX for men receiving ADT"

Saylor & Smith (2010)

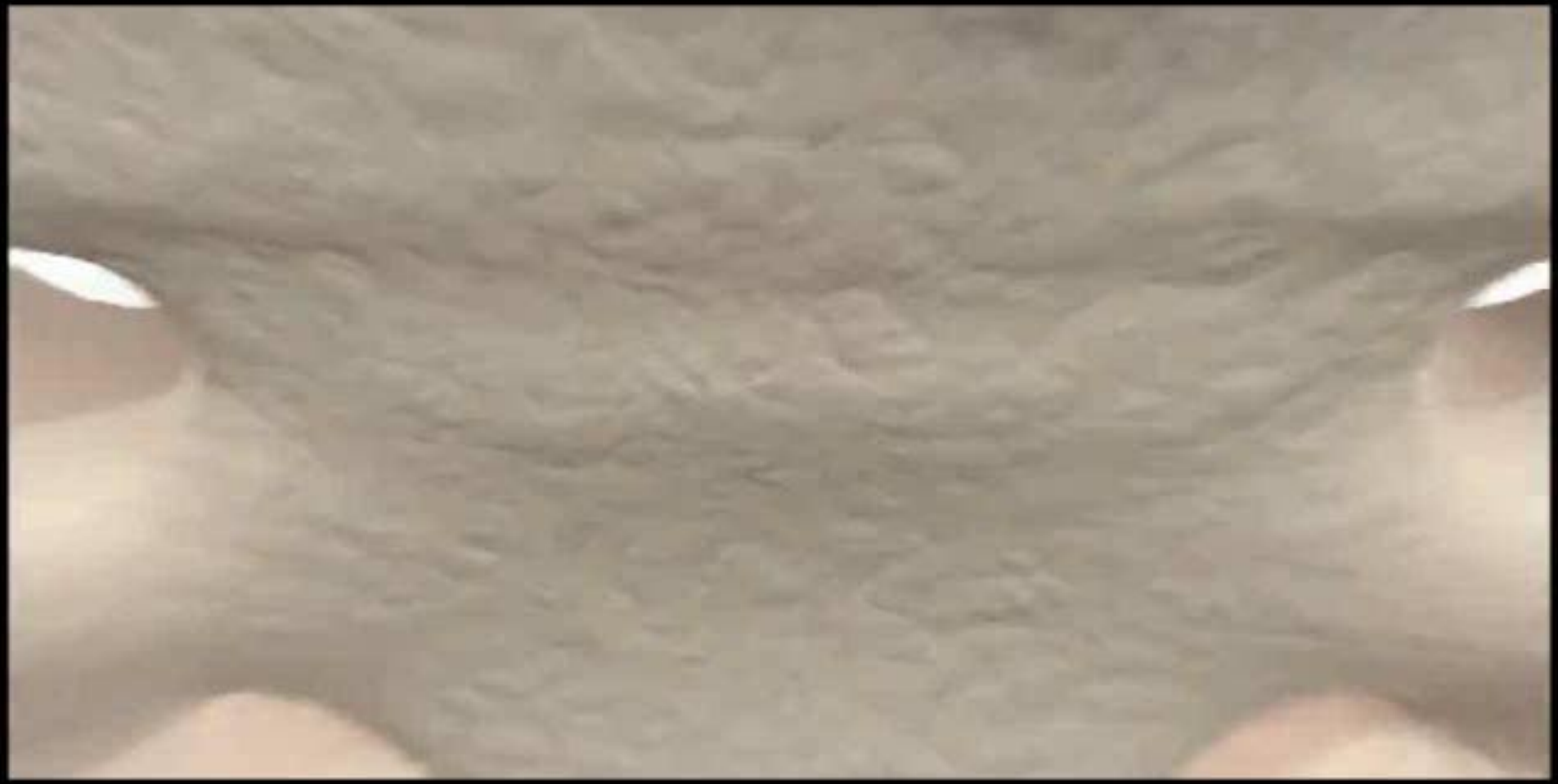
Since FRAX was not designed specifically for men receiving ADT, important clinical factors unique to men receiving ADT may not be accounted for and the risk of fracture may be underestimated. Further work is needed to refine risk assessment in this vulnerable population.

Saylor & Smith (2010)

WHO Fracture risk assessment tool. Available at: http://www.shef.ac.uk/FRAX Saylor P & Smith M (2010) Prostate Cancer and Prostatic Diseases. 13; 20-27. Adler et al *Osteoporosis Int (2010)*; 21(4): 747-53

Bone Metastases & Cancer Induced bone loss (CIBL)

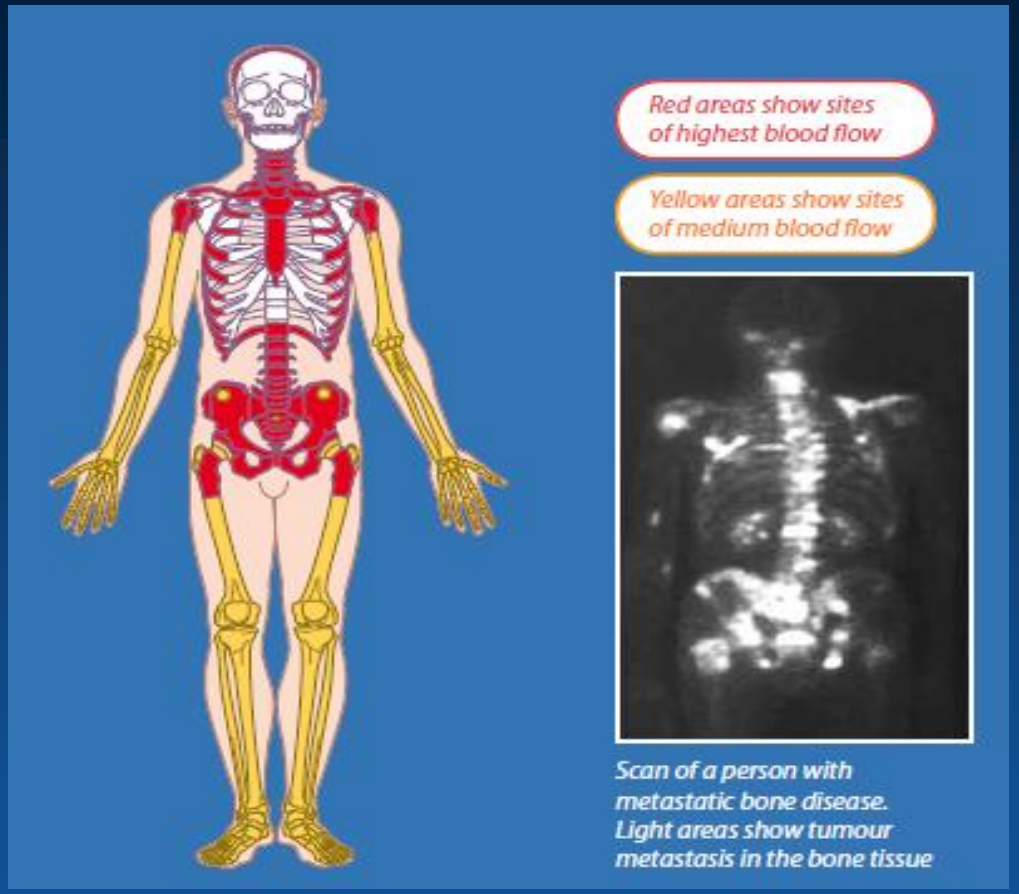
Steps in Bone Metastasis – “Seed and Soil”



Sites of bone metastasis

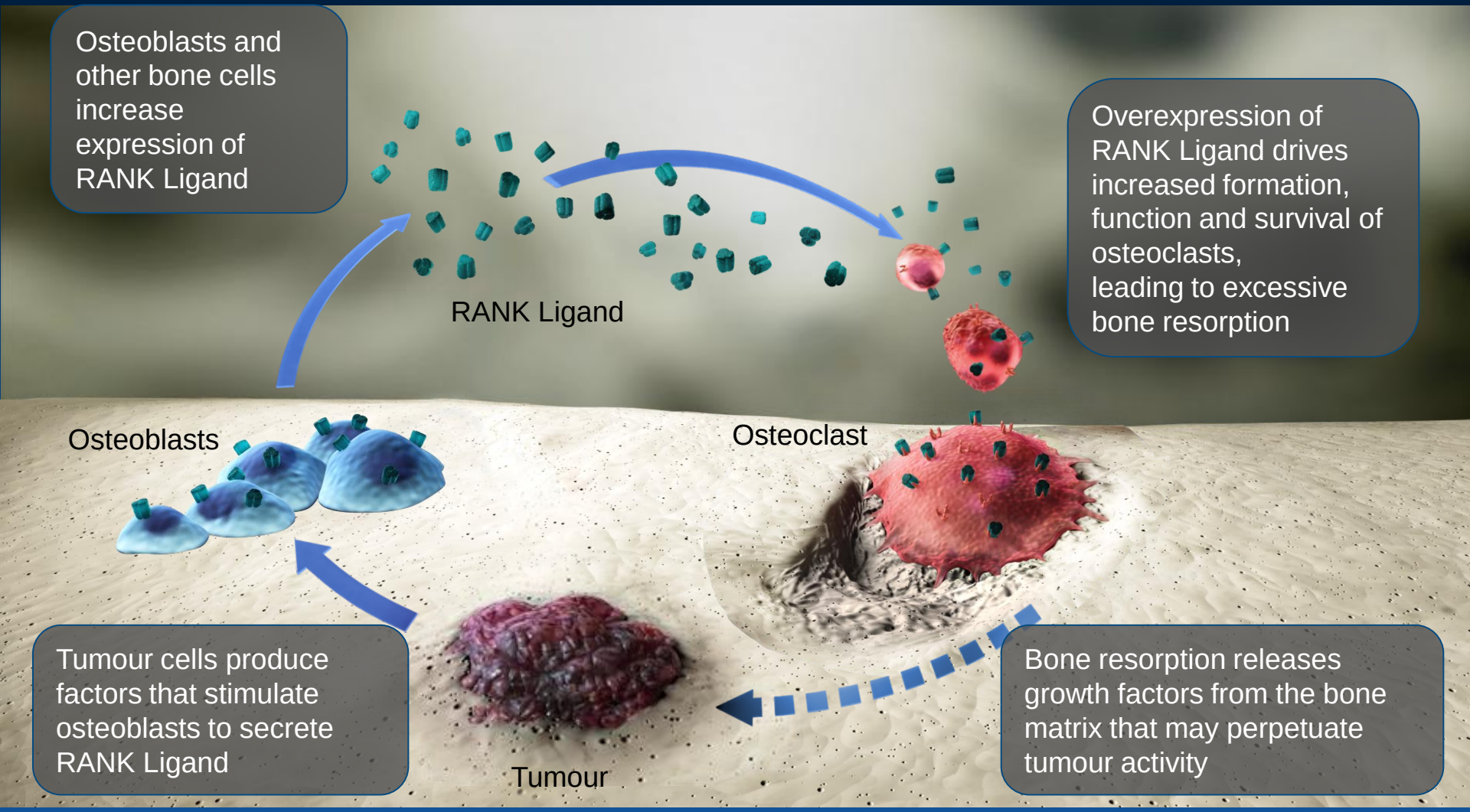
The most common sites of bone metastasis are:

- Spine
- Pelvis
- Ribs
- Skull
- Upper arm
- Long leg bones



American Academy of Orthopaedic Surgeons. Available at : http://orthoinfo.aaos.org/topic.cfm?topic=A00093
Mundy GR. Cancer 1997;80(Suppl 8):1546-56.

A vicious cycle of bone destruction in the presence of tumour cells

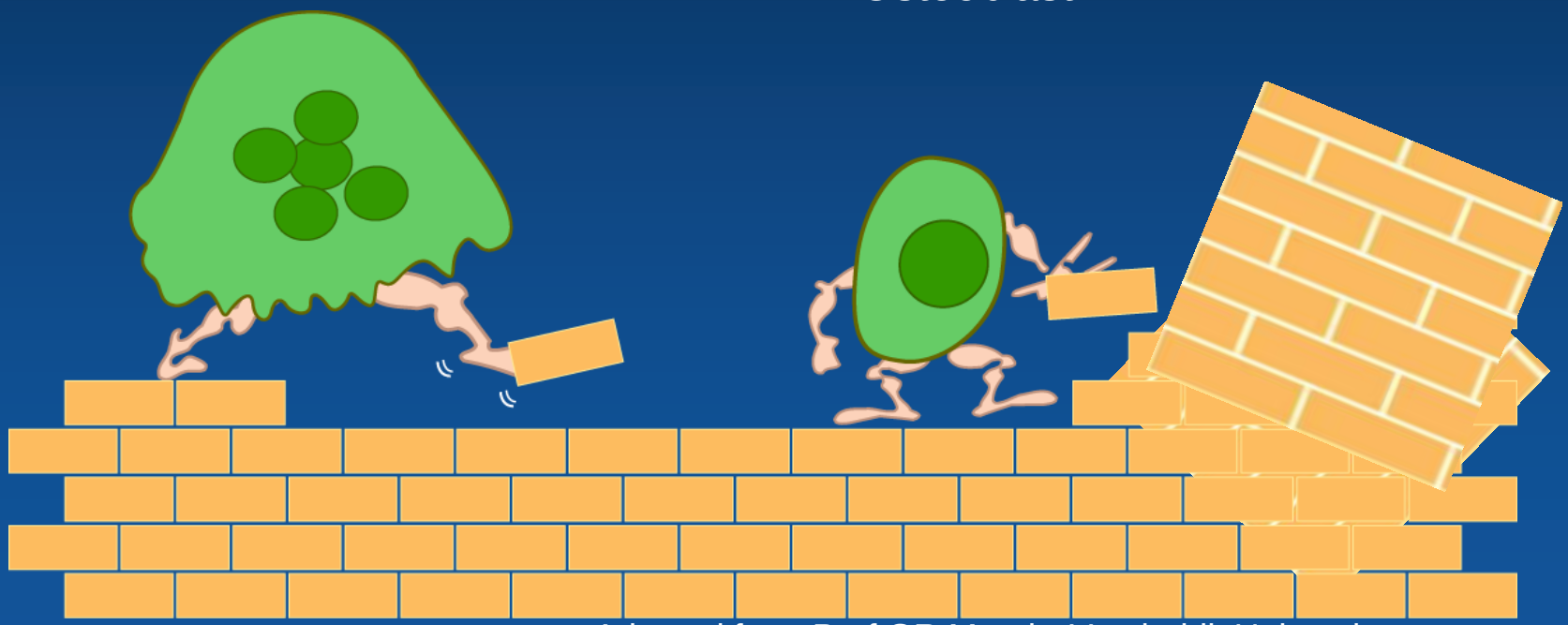


Adapted from Roodman GD. N Engl J Med 2004;350:1655–64;
Mundy GR. Nat Rev Cancer 2002;2:584–93.

- In metastatic prostate cancer –
  excessive irregular bone Is laid down by osteoblastic activity stimulated by the tumour”

Osteoclast

Osteoblast



Adapted from Prof GR Mundy, Vanderbilt University

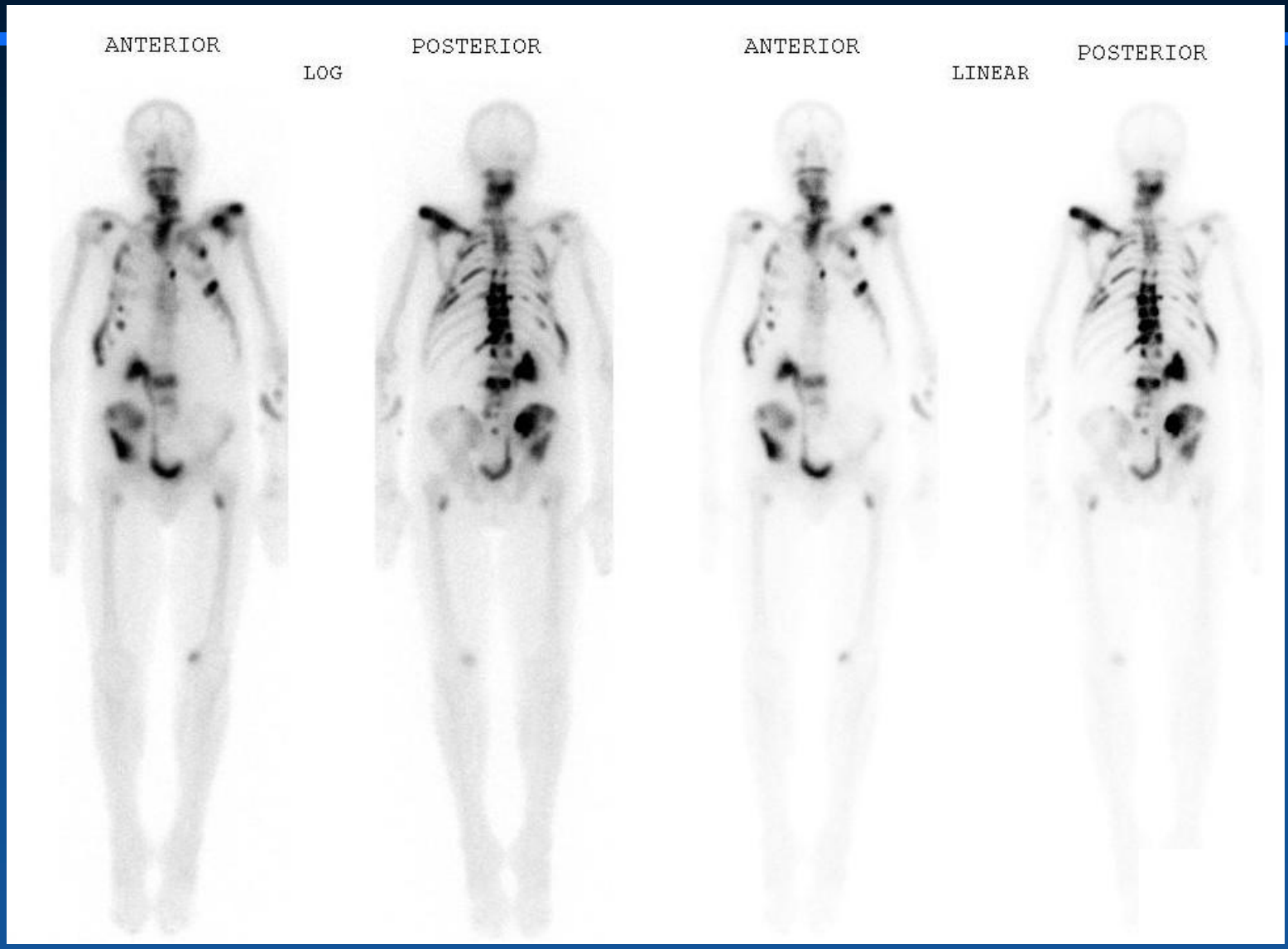
Abnormal Osteoblastic activity in prostate cancer

Bone metastases : Osteoblastic & Osteolytic

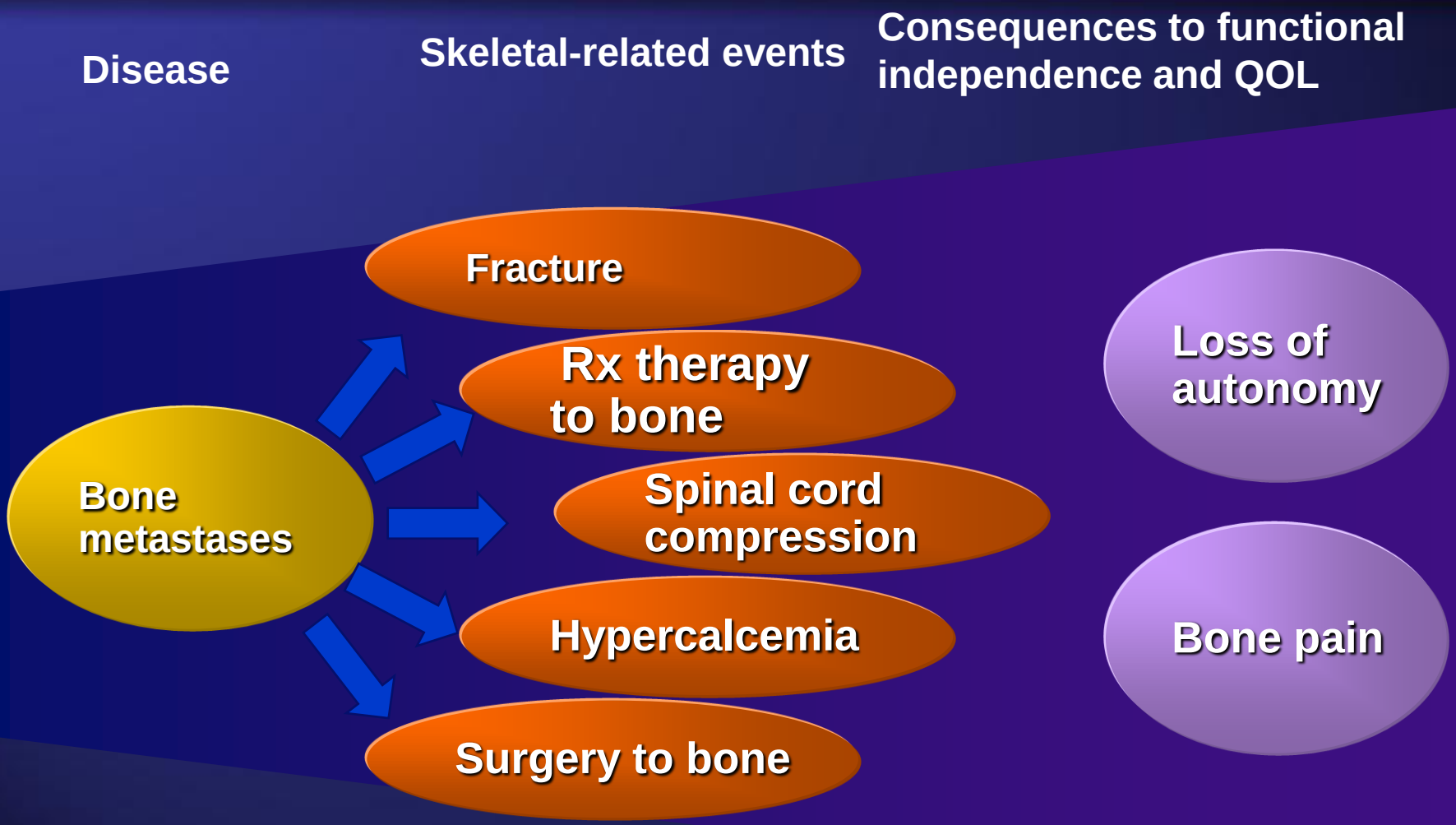
- Bone metastases are identified according to their radiographic appearance
- Osteoblastic lesions are referred to as sclerotic & Osteolytic lesions referred to as lytic

X-ray of the pelvis and femurs showing multiple Osteoblastic (Sclerotic) metastases from prostate cancer

X-ray of the right tibia showing Osteolytic destruction (Lytic) from metastatic renal cancer


ANTERIOR
POSTERIOR
LOG
ANTERIOR
POSTERIOR
LINEAR

Bone Metastases Have Debilitating Consequences



QOL = Quality of life.

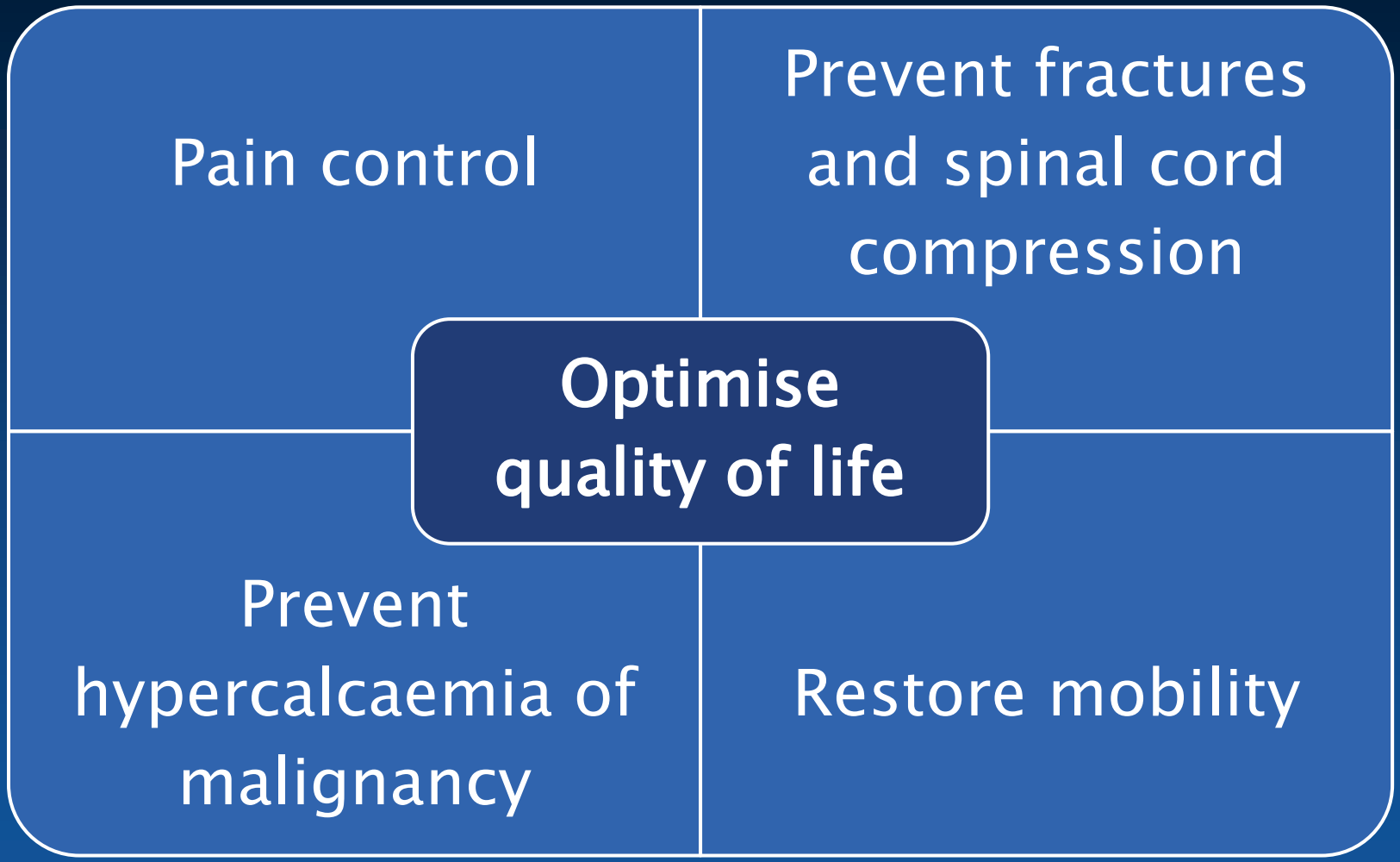
Bone metastasis/bone lesions lead to skeletal-related events (SRE)

	Breast cancer (24 months)	Prostate cancer (24 months)	Lung/other solid tumours (21 months)
Pathological fractures	52%	25%	22%
Hypercalcaemia of malignancy	13%	1%	4%
Spinal cord compression	3%	8%	4%
Radiation to bone*	43%	33%	34%
Surgery to bone**	11%	4%	5%

* Usually given for pain
** Usually a result of fracture

Lipton A, et al. Clin Adv Hematol Oncol 2009;7(5 Suppl 11):1-30. Reprinted with permission from Clinical Advances in Hematology and Oncology.

Goals of management



Reich CD. Clin J Oncol Nurs 2003;7:641-6.

Bone Pain

Pathophysiology of pain in Bone Metastases

- Bone metastases may lead to pain via several mechanisms
- A significant portion of the pain is related to the process of bone resorption

Nociceptor-sensory neuron responding to potentially damaging stimuli by algesic mediators	▪ Cytokines, prostaglandin, E, bradykinin, serotonin, or substance P(neurotransmitter related to the sensation of pain)
Involvement of pain-sensitive structures	▪ Involvement or invasion, stretching, or compression of the nerves and vasculature and periosteum ▪ Microfractures of various joint structures
Mechanical instability	▪ Mechanical instability of “weakened bone” or intraosseous pressures (> 50 mm Hg)

Smith HS. Pain Physician. 2011;14:E373-405

Pain type & assessment in Metastatic Cancer

- Types of pain
  - Intermittent, chronic, breakthrough, incident, end-of-dose failure
- Assessment
  - Location
  - Radiation
  - Quality
  - Associated symptoms
  - Time
  - Provoking/relieving
  - Intensity/duration

Faiman B. Cleve Clin J Med. 2010;77:273-278. Siemionow K, et al. Cleve Clin J Med. 2008;75:557-566.

Presentation of bone pain

Bone issue	Type of pain
Bone metastasis/bone lesions	• Usually dull and constant with increased intensity at night or with weight bearing • Tends to develop gradually and becomes move severe within weeks to months
Pathological fracture	• Acute and sharp with a specific focal point
Spinal cord compression	• Initially localised, and typically increases in intensity over time • May become more radicular if lumbosacral spine involved • Bilateral, gripping girdle discomfort if thoracic epidural lesions

Reich CD. Clin J Oncol Nurs 2003;7:641-6; Prasad D & Schiff D. Lancet Oncol 2005;6:15-24

Anaemia Incidence

- Approximately 30% of men with prostate cancer with metastasis to the bone have anaemia at the time of diagnosis.

- The most common sites of spread — spine, pelvis, ribs, skull, upper arm, and long bones of the leg — correspond to areas of bone marrow that produce high levels of red blood cells.

Albers et al 2001. Eur Urol; 39 1-8

Causes

Androgen deprivation

- Testosterone required for the enhancement of erythropoietin formation in the kidney.

Marrow replacement

- Replacement of normal marrow with cancer cells, bone marrow infiltration –. Disease progression.

Radiotherapy, Chemotherapy, Radiopharmaceuticals

- Myelosuppression – bone marrow suppression

Haematuria

Poor nutrition

Albers et al 2001. Eur Urol; 39 1-8. Nalesnick et al 2004.Rev Urol; 6(1),1-4

Management

- In patients with limited bone marrow reserve, blood transfusions may be the only effective treatment of anaemia associated with prostate cancer.
- Erythropoietin - severe anaemia due to cancer treatment (chemotherapy), and also where given blood transfusions cannot be given

Szucs et al. 2011. Oncology: 81(1); 45-49. Bokemeyer et al. 2010 Eur J Cancer: 43(2); 258-70.

Pathological fracture

- Signs and symptoms
  - Pain
  - Weakness
  - Gait disturbances

- Pathological fractures can be slow to heal and lead to surgery and rehabilitation

Lipton A, et al. Clin Adv Hematol Oncol 2009;7(5 Suppl 11):1-30;
Image courtesy of Lawrence Drudge-Coates, King's College Hospital, London

Mirels Metastatic Fracture Risk Assessment

	Score		
	1	**2**	**3**
Site	Upper limb	Lower limb	Peritrochanter
Pain	Mild	Moderate	Mechanical**
Lesion	Blastic	Mixed	Lytic
Size	< 1/3	1/3 – 2/3	> 2/3

- Score of 7/12 associated with a low risk of fracture
- Score of 8/12 associated with a 15% risk of fracture
- Score of 9/12 associated with a 33% risk of fracture 9 or more should be used to indicate the need for prophylactic fixation.

Mirels H. Metastatic disease in long bones. Clin Orthop Rel Res. 1989;249:256-264.

Hypercalcaemia of malignancy (HCM)

- Abnormal elevation of serum calcium associated with malignant tumours
- Approximately 20%-30% of cases in patients with cancer.
- Primarily due to increased bone resorption and release of calcium from bone and inadequate renal calcium clearance.
- Major mechanisms by which this can occur:
  - Osteolytic metastases with local release of cytokines (including osteoclast activating factors).
  - Tumour secretion of parathyroid hormone-related protein (PTHrP).
  - Tumour production of 1,25-dihydroxyvitamin D (calcitriol).

Stewart AF .N Engl Med 2005;352:373. Clines et al. Endoc Relat Cancer 2005; 12: 549.

Recognising HCM

Signs and symptoms

- Anorexia
- Nausea and vomiting
- Thirst
- Confusion
- Constipation
- Lethargy/fatigue
- Muscle weakness (cramps)

Severity

- Depends on:
  - Plasma calcium level
  - How rapidly calcium rose
  - General condition of the patient

Always check a serum calcium for cancer patients with unexplained vomiting, thirst, polyuria or confusion. Neurological manifestations occur in over 50% of patient

Grill V & Martin TJ. Rev Endocr Metab Disord 2000;1:253-6.

Management

- The treatment of choice is an intravenous bisphosphonate infusion.
- Drugs promoting hypercalcemia (thiazide diuretics, lithium, ranitidine, cimetidine, vitamins A and D and preparations containing calcium) should be withdrawn
- Assess hydration state clinically and according to U&E!!!!!!! Commence IV fluids, 3-5 litres sodium chloride 0.9% per 24 hours if dehydrated.

Pamidronate:

Corrected Calcium	Pamidronate dose	Administration
Up to 3.0 mmol/l	30mg	250ml Sodium Chloride 0.9% over 30 minutes
3.0 – 3.5 mmol/l	60mg	250ml Sodium Chloride 0.9% over 1 hour
3.5 – 4.0 mmol/l	90mg	500ml Sodium Chloride 0.9% over 90 minutes

After Pamidronate, calcium will start to fall after approximately 2 -3 days and normalisation is usually achieved within 3-7 days. Dose can be repeated at 3 - 4 week intervals.

The total dose of pamidronate may be administered either as a single infusion or in multiple infusions over 2 – 4 consecutive days.
The maximum dose per treatment course is 90mg for both initial and repeated courses.

Dosage in renal failure (SPC): Pamidronate should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. It is recommended that for patients with established or suspected renal impairment, the infusion rate should not exceed 20mg/hour.

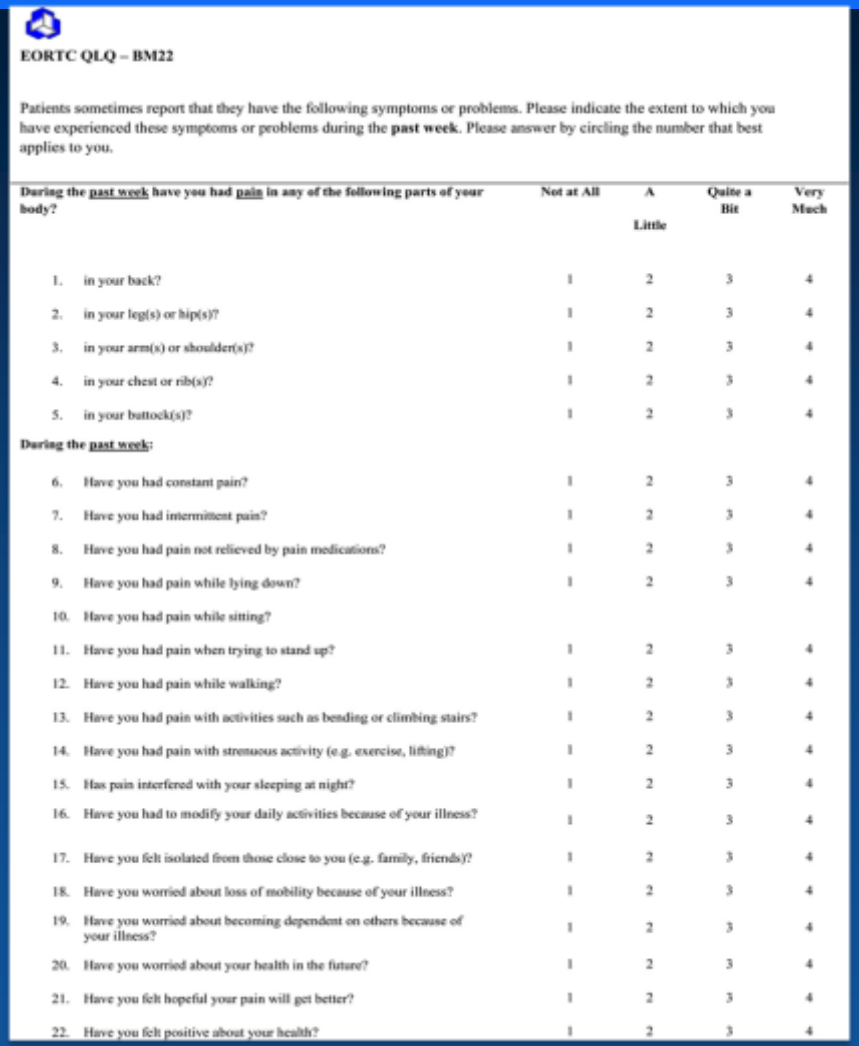
Assessment strategies for suspected spinal cord compression

Back pain (83-96% cases)	Motor deficits (Hrs-days: wks/mths)	Sensory deficits (40-90% cases)	Autonomic dysfunction (late stages**)
Onset	**Onset**	**Onset**	**Urinary frequency**
Location	**Weakness**	**Numbness**	**Urinary retention**
Intensity	**Location**	**Tingling**	**Incontinence**
Quality	**Heaviness/stiffness**	**Parasthesia**	**Constipation**
Localised or radicular	**Ambulation problems**	**Sensation of touch**	**Poor sphincter tone**
Aggravating factors	**Gait disturbances**	**Sensation of temperature**	**Sexual dysfunction**
Alleviating factors	**Falls**	**Loss of position sense**	
	Paralysis	**Hyper-reflexia**	

Lowey SE. Home Healthcare Nurse 2006;24:439-46. Drudge-Coates L & Rajbabu K. Int J Palliat Nurs 2008;14:110-6.

Assessing quality of life

- Developed specifically to assess quality of life in bone metastases
- Based on published literature, patient and HCP interviews, and quantitative and qualitative data analyses
- Has been tested across different countries
- Contains physical and psychosocial assessment components



EORTC QLQ – BM22

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the **past week**. Please answer by circling the number that best applies to you.

During the past week have you had pain in any of the following parts of your body?	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
1. in your back?	1	2	3	4
2. in your leg(s) or hip(s)?	1	2	3	4
3. in your arm(s) or shoulder(s)?	1	2	3	4
4. in your chest or rib(s)?	1	2	3	4
5. in your buttock(s)?	1	2	3	4
During the past week:				
6. Have you had constant pain?	1	2	3	4
7. Have you had intermittent pain?	1	2	3	4
8. Have you had pain not relieved by pain medications?	1	2	3	4
9. Have you had pain while lying down?	1	2	3	4
10. Have you had pain while sitting?				
11. Have you had pain when trying to stand up?	1	2	3	4
12. Have you had pain while walking?	1	2	3	4
13. Have you had pain with activities such as bending or climbing stairs?	1	2	3	4
14. Have you had pain with strenuous activity (e.g. exercise, lifting)?	1	2	3	4
15. Has pain interfered with your sleeping at night?	1	2	3	4
16. Have you had to modify your daily activities because of your illness?	1	2	3	4
17. Have you felt isolated from those close to you (e.g. family, friends)?	1	2	3	4
18. Have you worried about loss of mobility because of your illness?	1	2	3	4
19. Have you worried about becoming dependent on others because of your illness?	1	2	3	4
20. Have you worried about your health in the future?	1	2	3	4
21. Have you felt hopeful your pain will get better?	1	2	3	4
22. Have you felt positive about your health?	1	2	3	4

Chow E, et al. *Eur J Cancer* 2009;45(7):1146–52.

Planning Bone Health Care

- Assessing need and setting goals
  - Enhance quality of life
  - Maintain maximum bone health
  - Prevent complicating factors
  - Be prepared for future challenges
- Implementation and evaluation
  - Develop an index of suspicion to facilitate early intervention
  - Prepare caregivers to manage chronic care issues
  - Educate, reassure, and support


Thank you!