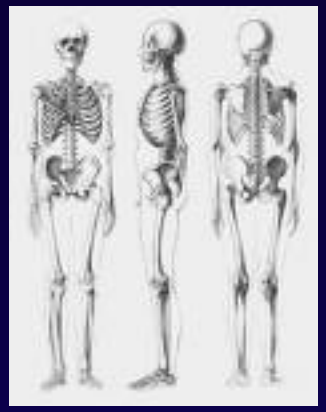

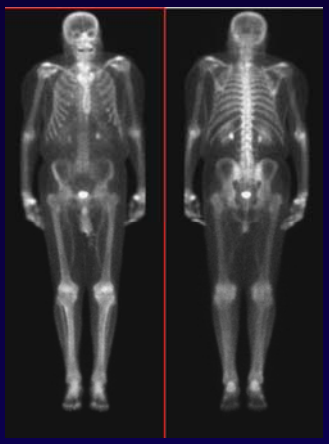

Advances in Treatment of Bone Metastasis

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Department of Breast Medical Oncology

THE UNIVERSITY OF TEXAS
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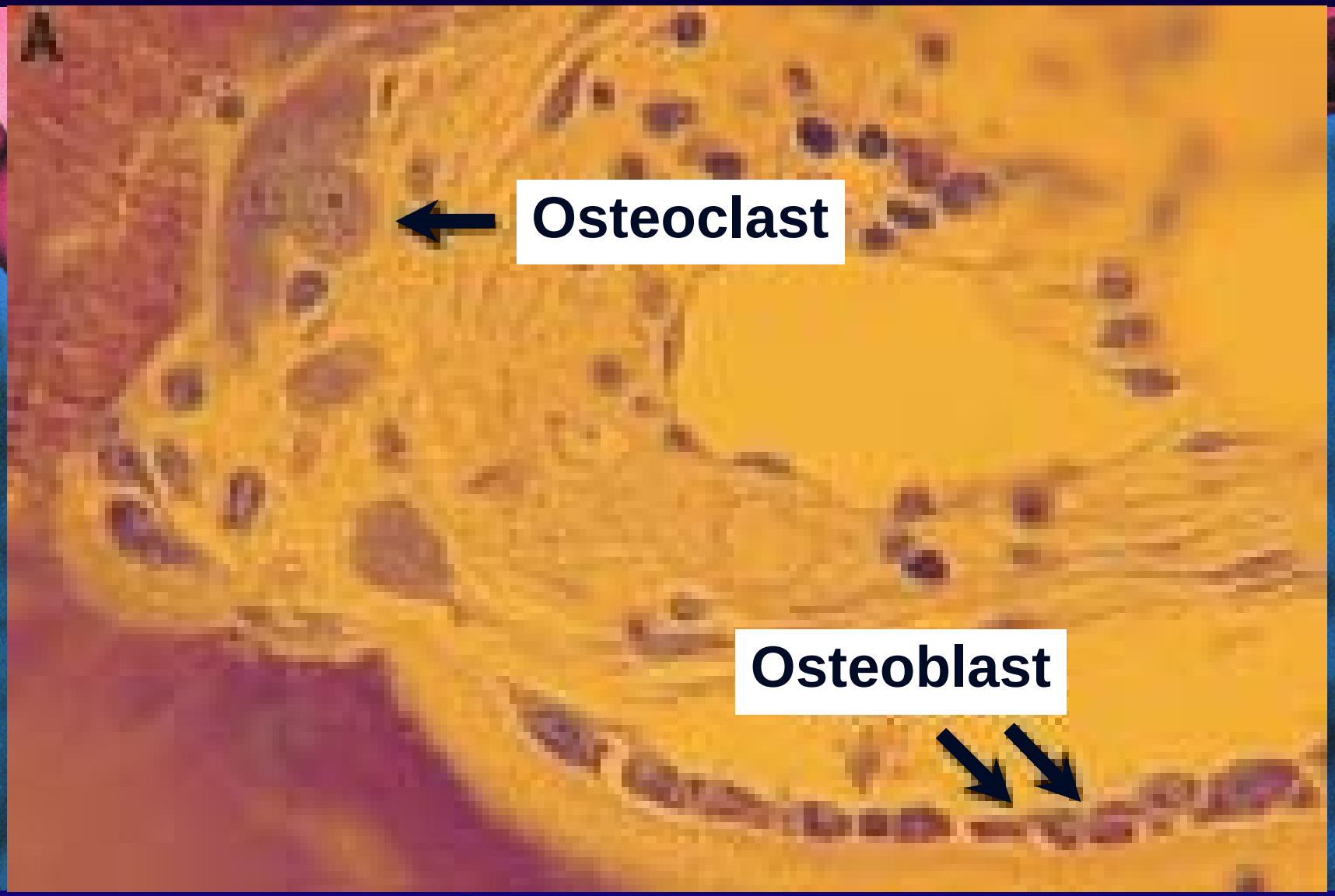
CANCER CENTER

Objectives

- Physiology of Bone
- Pathophysiology of Bone Metastasis
- Treatment of Bone Metastasis
  - Bisphosphonate (no talk)
  - Non-bisphosphanate treatment
- Assessment of Treatment Response of Bone Metastasis
- Cancer-induced bone loss
- Advances in Treatment
- Summary

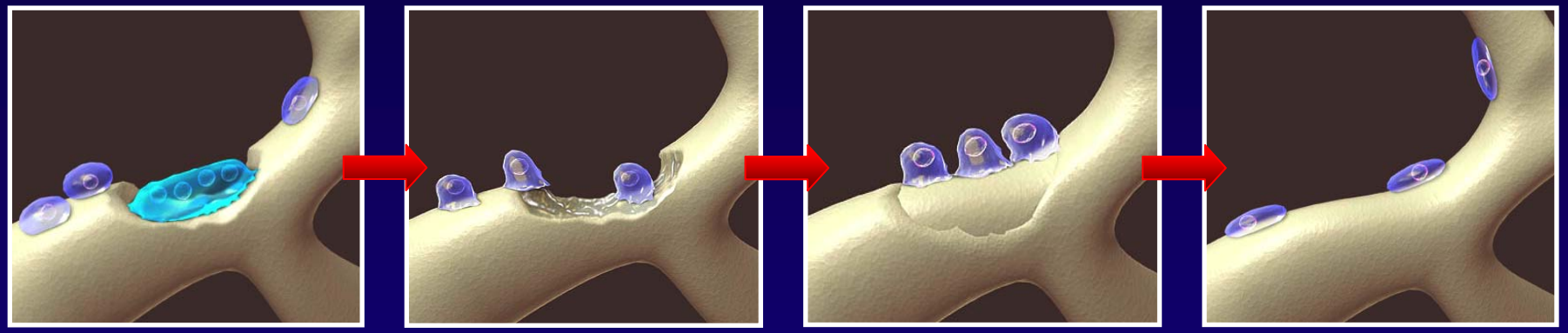
What are Normal Functions of Bone?

- Supports network for muscles/tendons
- Protects internal organs
- Creates blood cells
- Stores calcium and phosphorous
- Buffers numerous metabolic processes



NEJM 350;16, 2004

Normal Bone Turnover: Bone Breakdown and Bone Formation Are in Equilibrium



Resorption

Osteoclasts break down bone mineral and matrix, creating an erosion cavity

Reversal

Mononuclear cells prepare bone surface for new osteoblasts to begin building bone

Formation

Osteoblasts form a matrix to replace resorbed bone with new bone

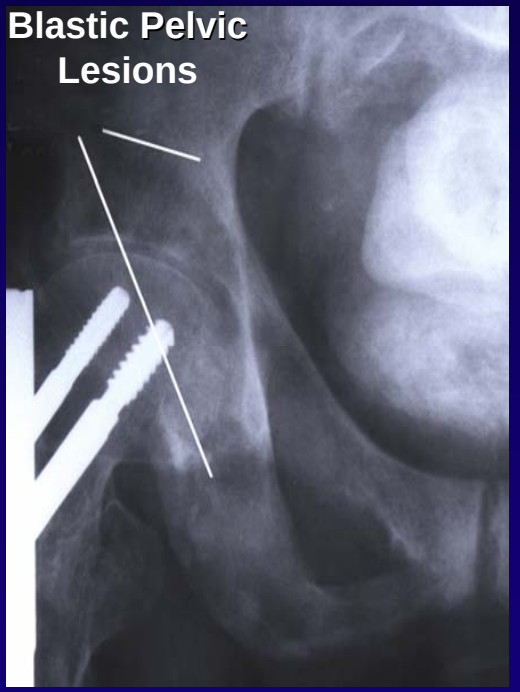
Resting

A prolonged resting period follows until a new remodeling cycle begins

Bone Metastasis:
A Significant Complication of Cancer

"Bone metastasis is a catastrophic complication for most patients with cancer. Not only does it cause intractable pain and . . . fracture after trivial injury, spinal cord compression, and hypercalcemia, it also signifies that the malignant process is incurable."

Gregory R. Mundy, MD

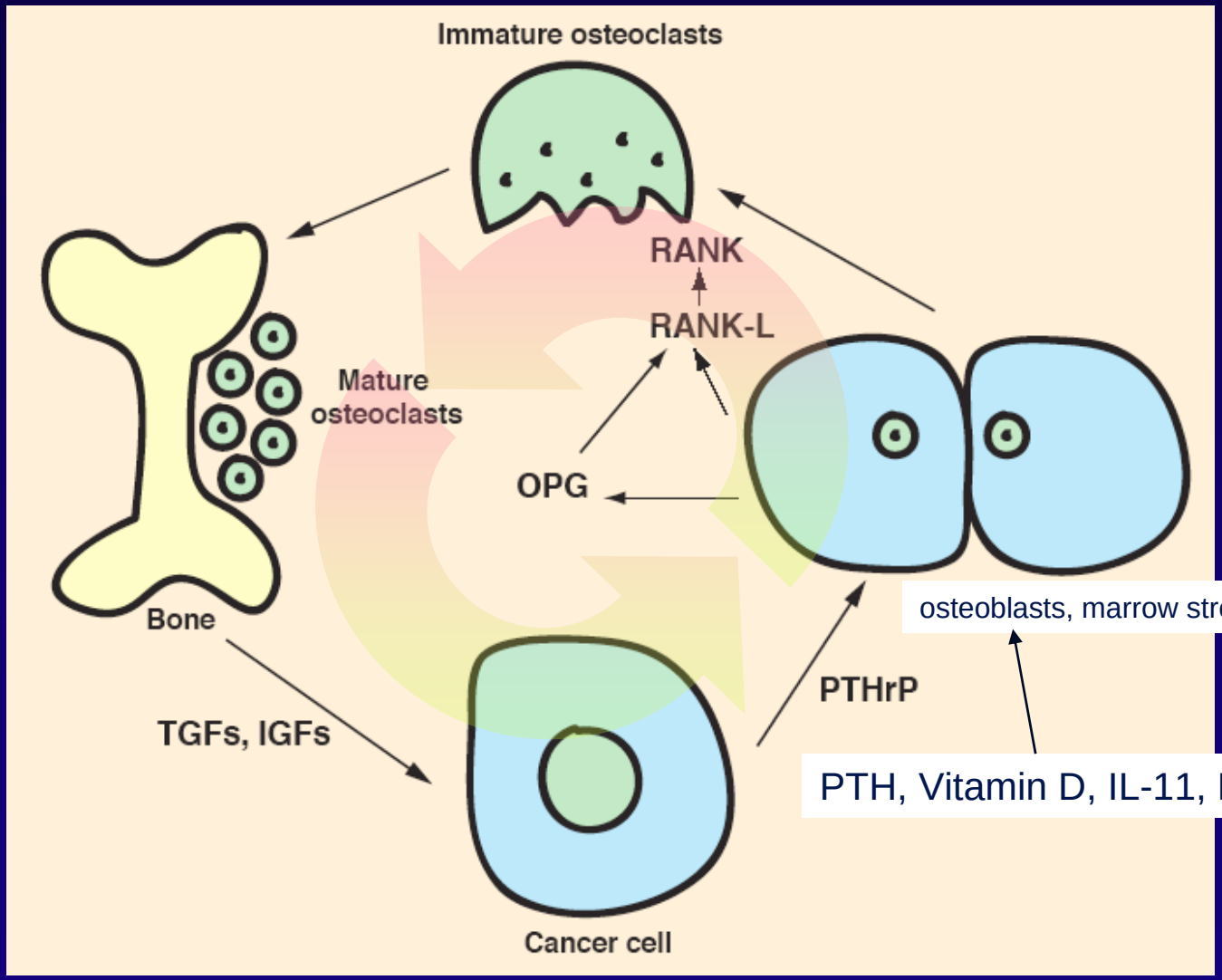


Cancer 80 (Suppl 8):1546-1556, 1997

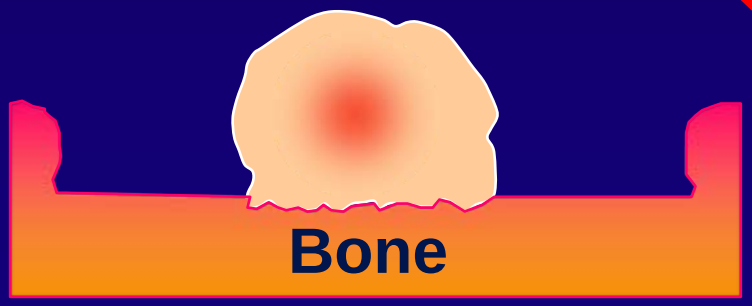
Type of Bone Metastasis

- **Osteolytic: dominant activity of osteoclasts**
- **Osteoblastic: dominant activity of osteoblasts**
- **Mixed: No dominance between lytic and blastic.**

Pathogenesis of Bone Metastasis



Consequences of Increased Bone Resorption



Hypercalcemia

Increased bone resorption

Fracture

Impaired mobility

Bone pain

Cord compression, nerve root damage, bone marrow suppression

C

Treatment of Bone Metastases

Rapid Decision needed to be made

- Surgery
- Radiation Therapy
- Analgesics

Decision needed to be made

- Bisphosphanate
- Diet and Life Style
- Systemic Treatment for Metastatic Breast Cancer

Surgery

- **Objective: Prevent pathological fractures, or spinal cord compression**
- **When:**
  - **Perform surgery before fracture.**
  - **30 mm axial cortical involvement in weight bearing area (osteolytic) → needs surgery**
- **Method:**
  - **Make sure that you are not missing other impending pathological fracture.**
  - **Pathological fracture → stabilization (nail or rod), internal fixation**
  - **Surgery followed by external-beam radiation**

External Beam Radiation Therapy

- **Objectives: palliation of symptoms**
  - **Pain control (within 24-48 hours)**
  - **Bone lesion stabilization**
  - **Delay pathological fracture, spinal cord compression**
- **Methods:**
  - RT dose of at least 30 Gy in 10 fractions
  - Short course RT dose should be considered in patients with short life expectancy
- Side effects: BMS, nausea/vomiting, diarrhea

Radiopharmaceutical

- Objective: Pain control
- Methods
  - Strontium chloride 89, Samarium 153
  - Response takes up to 3 weeks
  - Indicated for those who can survive more than 3 M
- Side Effects
  - 20% may have flare pain
  - Bone marrow suppression

Patient Education (Learn about)

- Fracture prevention, pain management, and maintenance of daily activities.
- Drugs available to minimize bone loss.
  - bisphosphonates
  - non pharmaceutical measures, maintaining body weight, increasing non–weight-bearing exercise, minimizing caffeine and alcohol intake, and stopping smoking
- Risks of falls and developing individualized
- Programs to increase physical stability are critical.
- Pain is a part of metastatic disease and that it can be controlled. To prevent undertreatment.
  - Many patients prefer to avoid strong opioids like morphine due to the fear of addiction.
  - Some patients express a desire to reserve the use of opioids in case pain worsens over time.

Patients are under-treated for Bone Metastasis

Due to Physicians

Due to Patients

Due to Family Members

Issues related addressing bone tumor response

- What is true response?

  Bone structural change?

  ....sclerotic change of lytic lesion….

  Metabolic change?

  ....activity down of hot spot….
- No reliable response criteria.
- Breast cancer patient with bone only metastasis will be excluded from the patient eligibility.

Response criteria for bone tumor response

- UICC (International Union Against Cancer;1977)
  → based on XR.
- WHO (World Health Organization; 1978)
  → based on XR and SS.
- RECIST (Response Evaluation Criteria in Solid Tumors Group;2000)
  → does not cover bone lesions

The reality is that most of oncologist using CT and/or MRI for the assessment of bone tumor response without published criteria.

↓

Standardized criteria, which include CT, MRI, and PET/CT are needed.

UICC and WHO criteria for the treatment response

	UICC*1 Only cover **XR**	WHO *2 Only cover **XR** and **SS**
Complete Response	Disappearance of all known disease Lytic lesions should have radiologic evidence of calcification	Complete disappearance of all lesions on X-ray or scan for at least 4weeks
Partial Response	Objective improvement in evaluable or non measurable lesions At least 50% decrease in size of measurable lesions No new lesions and progressive lesions	Partial decrease in size of lytic lesions, recalcification of lytic lesions, or decreased density of blastic lesions for at least 4 weeks
No Change (Stable Disease)	Unchanged Less than 25% increase or less than 50% decrease in size of measurable lesions	“no change” at least for 8 week
Progressive Disease	Mixed; some lesions persist while others progress, or new lesions appear Failure; some or all lesions progress and/or new lesions appear No lesions regress	Increase in size o f existent lesions or appearance of new lesions

*1:Br J Cancer 38, 1978 *2:WHO handbook, 1979

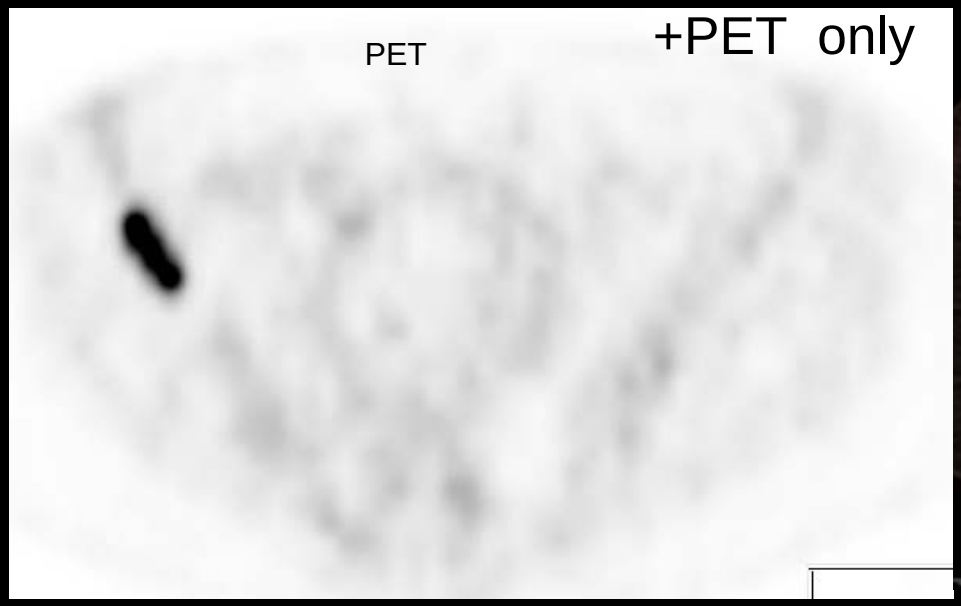
New criteria for the treatment response (MDA criteria)

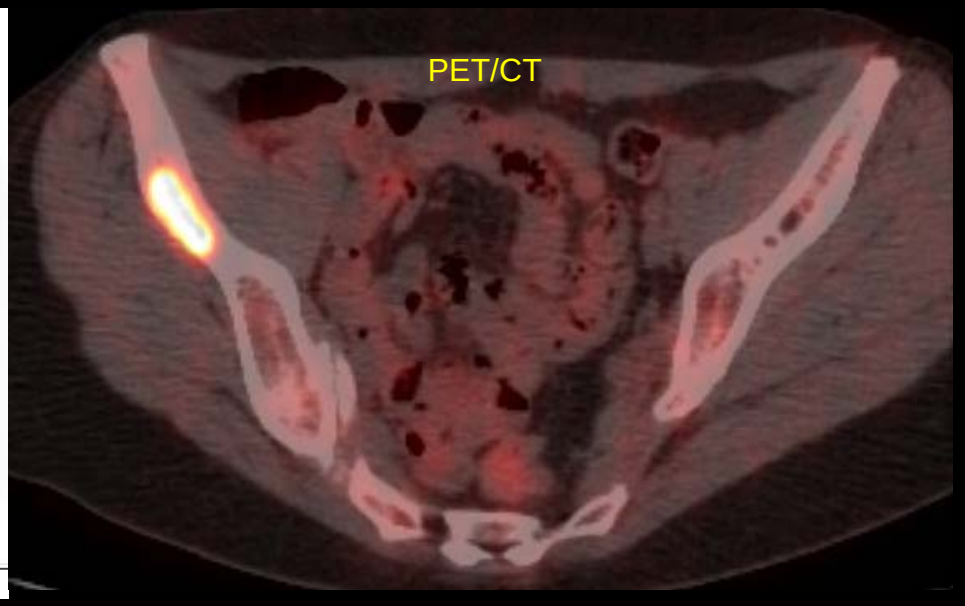
Complete Response	Complete fill-in or sclerosis of lytic lesion on XR and CT Disappearance of hot spots or tumor signal on SS, CT or MRI Normalization of osteoblastic lesion on XR and CT
Partial Response	Sclerotic rim about initially lytic lesion or sclerosis of previously undetected lesion on XR or CT Partial fill-in or sclerosis of lytic lesion on XR or CT Regression of measurable lesion on XR, CT or MRI Regression of lesion on SS (exclude rapid regression) Decrease in blastic lesion on XR or CT
Stable Disease	No change in measurable lesion on XR, CT or MRI No change in blastic lesion on XR, CT or MRI No new lesion on XR, SS, CT or MRI
Progressive Disease	Increase in size of any existing measurable lesions on XR, CT or MRI New lesion on XR, SS, CT or MRI (exclude flares) Increase in activity on SS (exclude flares) or blastic/lytic lesion on XR or CT

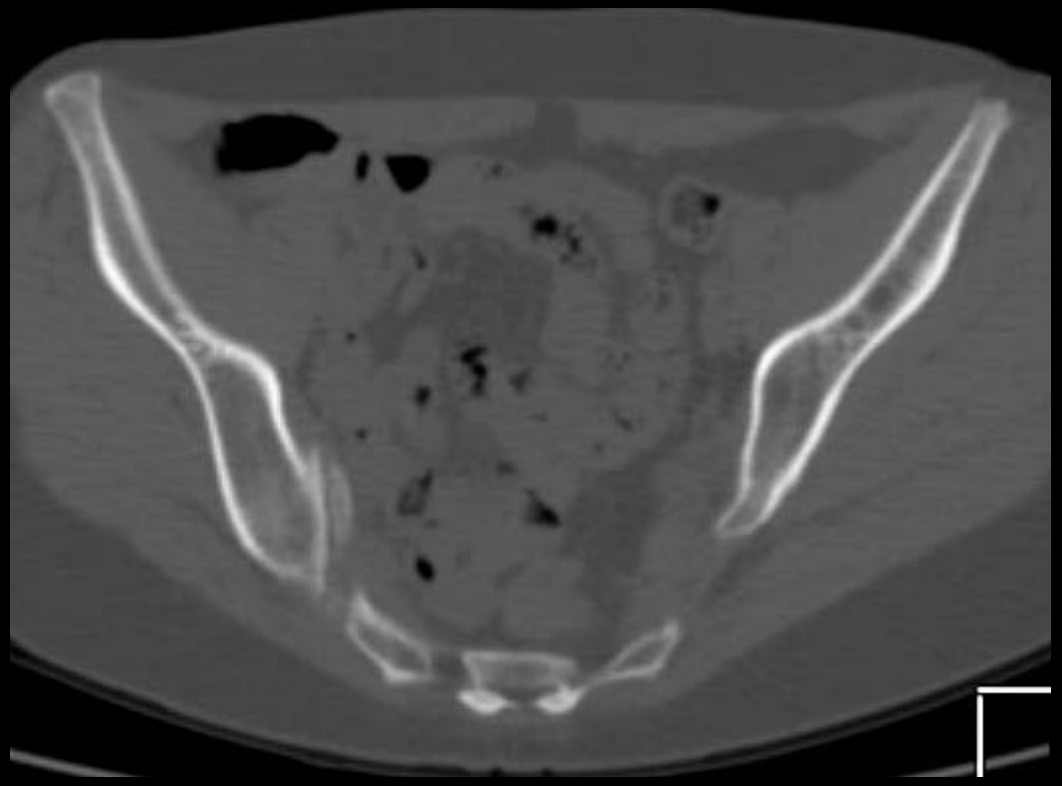
Hamaoka, Ueno. J Clin Onco: 22, 2942 2004

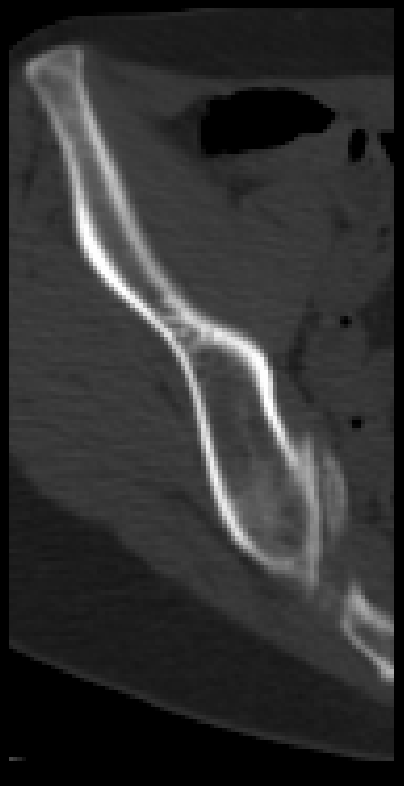
Imaging diagnosis of bone metastasis

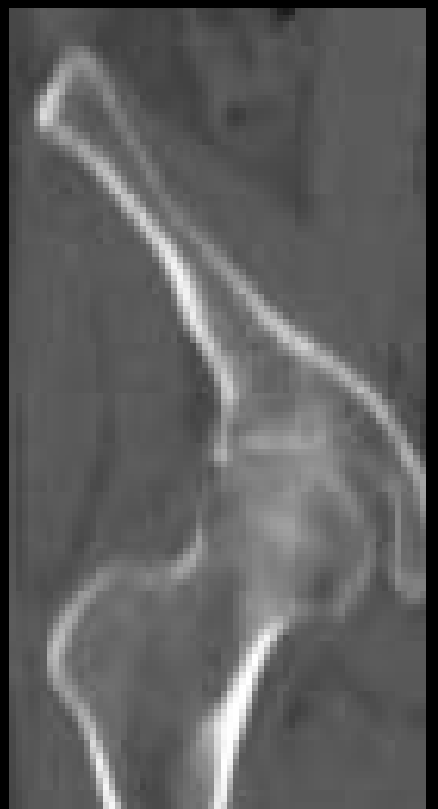
Diagnostic imaging	Pros	Cons	Examination order and purpose
SS	High sensitivity (62-100%) Whole body	No anatomic detail Low specificity	1: Screening
XR	Bone anatomic detail Low cost	Low sensitivity (44-50%) Local bone image	2: Diagnosis
CT	High sensitivity (71-100%) Bone and tumor anatomic detail	Local image	3: Diagnosis
MRI	High sensitivity (82-100%)	Local image No signal in bone High cost ($ 1700 for total spine)	3: Diagnosis


PET
+PET only

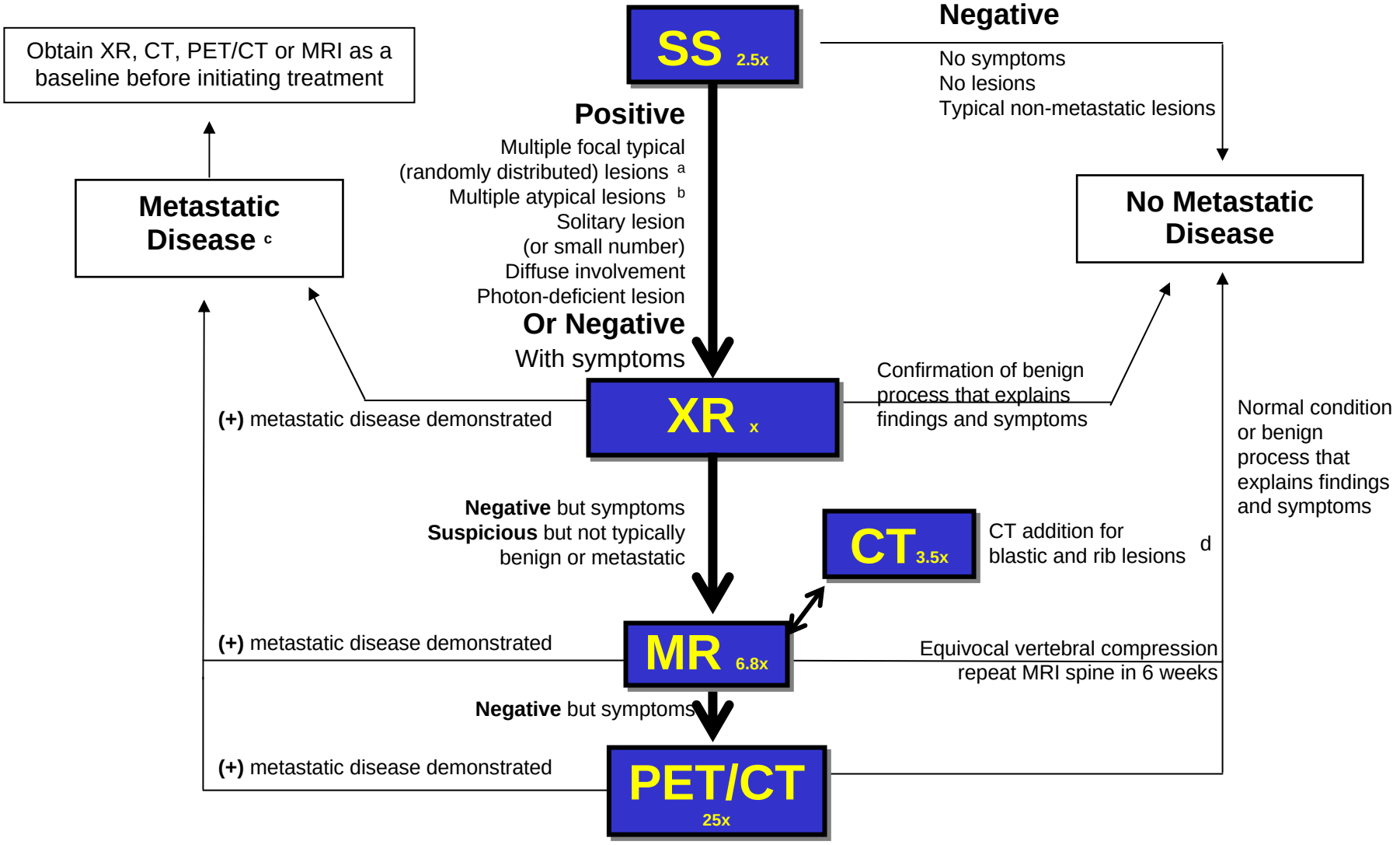

PET/CT







Algorithm for Bone Metastasis



a These lesions can be diagnosed as "metastatic disease". However, XR images are needed as a baseline for future assessment of bone tumor response and complications like pathologic fracture.

b Can be caused by metabolic disease (osteoporosis, Cushing's syndrome, osteomalacia), trauma, arthritis, inflammatory disease (osteomyelitis), Paget's disease, or infarction.

c Bone biopsy may be required for confirmation.

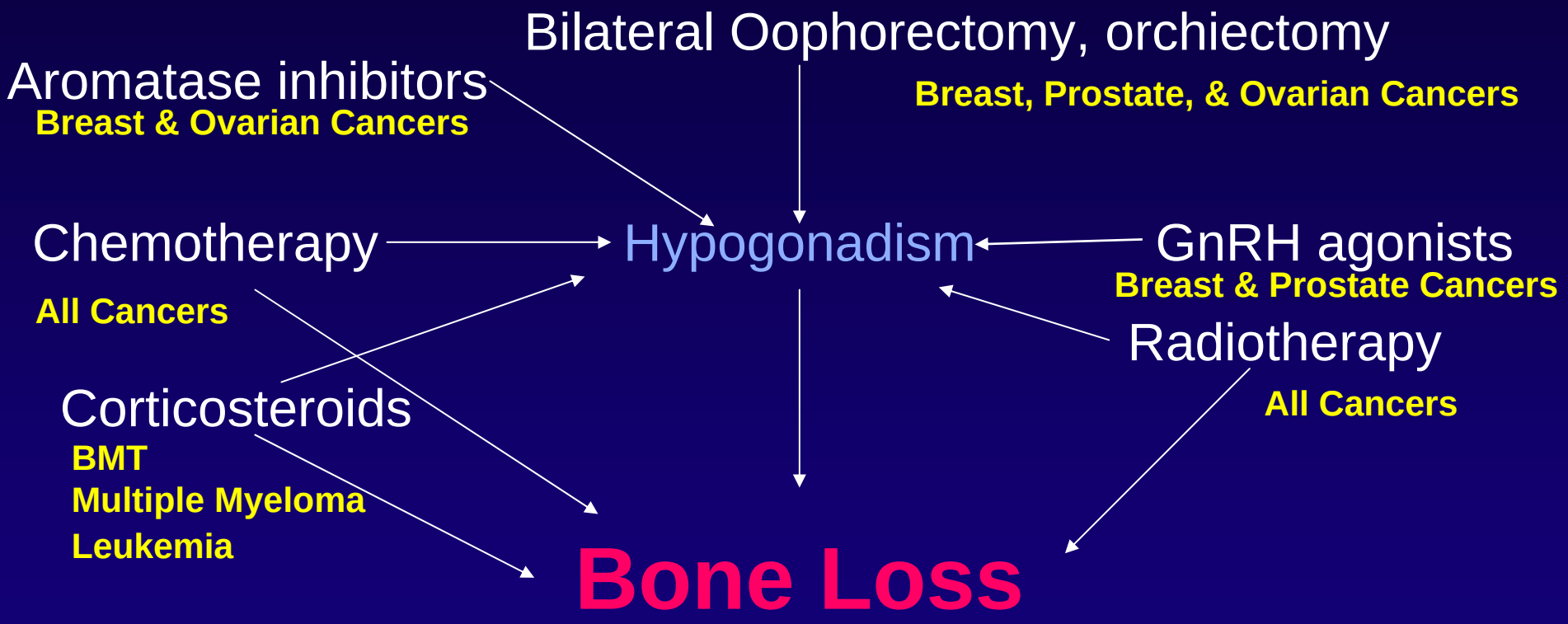
d CT is indicated for lesions in weight-bearing , chest-wall or complex structure bones, and MRI is indicated for spinal lesions.

We continue to improve our ability to assess Tumor Response in Bone Metastasis

Due to Imaging Technology

Due to Response Criteria

Causes of Cancer Treatment Induced Bone Loss (CTIBL)



Pfeilschifter J and Diel IJ. J Clin Onco 2000;18:1570-159

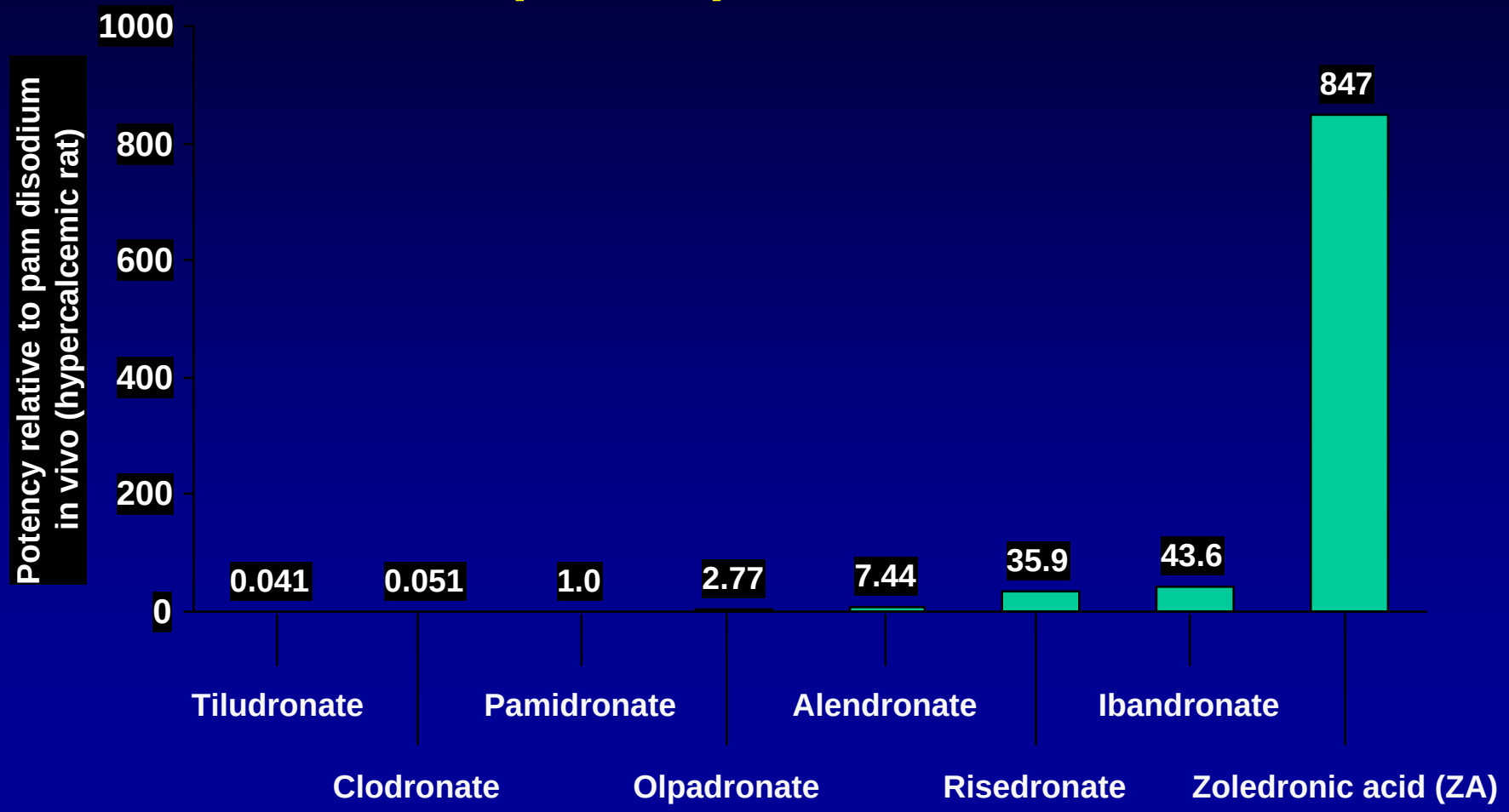
BMD

- BMD is compared with “young normal” (optimal or peak density of a 30-year-old healthy adult)
- Standard deviation (SD): the difference between patient’s BMD and that of a healthy young adult
  - For every 1 SD decrease, there is a relative risk of fracture increase of 1.5- to 2.5-fold

Diagnosis	T Score
Normal	>-1
Low bone mass (Osteopenia)	-1 to -2.5
Osteoporosis	≥-2.5
Severe osteoporosis	≥-2.5 and ≥1 fracture

National Osteoporosis Foundation; 2002.

Relative Potency of Bisphosphonates



Green JR. *J Bone Miner Res*. 1994;9:745-751.

Treatment of Bone Loss

BMD increase up to 10%

- Bisphosphonates
  - Alendronate (Fosamax) Oral
  - Risedronate (Actonel) Oral
  - Pamidronate (Aredia) IV
  - Zoledronic acid (Zometa) IV
  - Ibandronate
  - Clodronate
- In randomized clinical trials, bisphosphonates have achieved greater increases in BMD than other treatments

Summary and Conclusions

- Cancer treatments cause bone loss in women and men
- Bone loss is associated with an increase risk of fracture and can be identified early
- Bone complications are debilitating, painful and negatively impact on QOL
- Zoledronic acid prevents bone loss and increase BMD
- Further study with zoledronic acid will optimize treatment strategies to protect bone

Need to recognize bone loss is a major problem in cancer treatment

If you are going to control or cure cancers for long-term, you need to think about bone loss prevention

Some thoughts

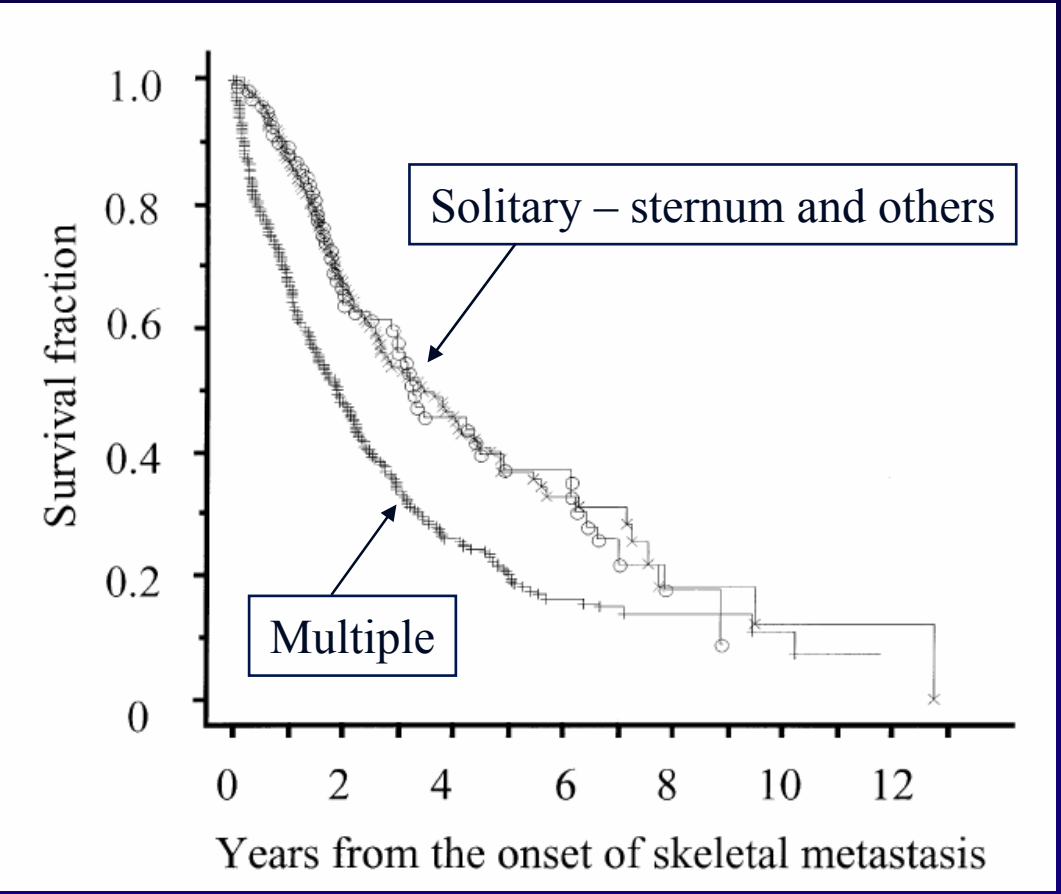
- **Can we cure bone only metastatic disease?**
  - **Oligometastasis**
  - **Multiple bone metastasis**
- **Can we develop drugs that target bone metastasis?**
  - **Mechanism**
  - **Potential new drugs**

Background of Oligo bone metastasis

- Initial presentation, about 18% of breast cancer patients had disease only in the bone. Survival is better in patients with bone only disease:
  - **bone only H.R. 1.0;**
  - **bone & other organs H.R. 1.4,**
  - **other organs initially H.R. 2.5, p < 0.001)**
- Solitary metastasis in 20-40% of patients with bone only disease
  - **The spine and sternum were common sites**
  - **5 year survival**
    - **Initial solitary bone (with or without other organ metastasis) : ~38%**
    - **multiple bone metastases: ~20%**
  - **~ 56% eventually develop additional bone metastasis.**

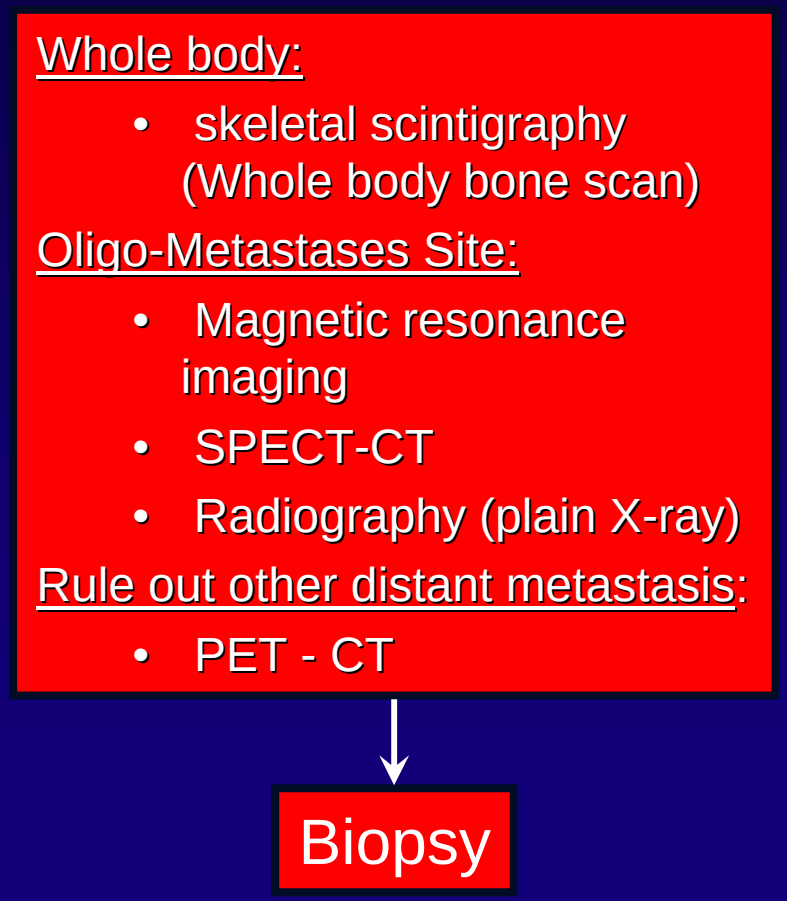
James, et al. Br J Cancer 89, 2003
Boxer, et al., J Nucl Med **30**, 1989
Koizumi, et al., Ann Oncol **14**, 2003

Solitary vs Multiple Bone Metastasis



(Koizumi, *Annals of Oncology*, 2003)

Treating Oligo-metastasis
Study Schema: Initial Evaluation



Treating Oligo-metastasis Study Schema: Treatment Plan

CTV 45 Gy (3 Gy x 15 fx) + GTV 60 Gy (3 Gy x 20 fx)

27 Gy (9 Gy x 3 fx) allowed for vertebrae only

Biopsy →

Evaluation by:
Multidisciplinary Clinic
1. Orthopedic Surgeon
2. Radiation Oncologist
3. Medical Oncologist
4. Radiologist

→ **Definitive Surgical Resection**

→ **Surgical Fixation and RT**

→ **Definitive Radiation Therapy**

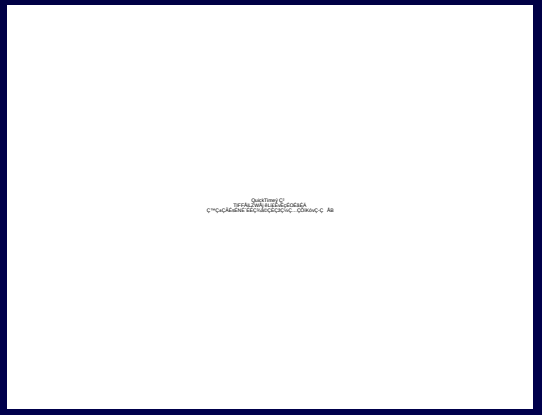
- No Chemotherapy
- Give endocrine therapy and trastuzumab in appropriate patients

Follow-up at 1 M, then q3M:
1. MRI
2. PET-CT

Determine the PFS after definitive local therapy

Phase II Study of ^{153}Sm-EDTMP Followed by Autologous Peripheral Blood Stem Cell Transplantation for Breast Cancer Patients with Bone Only Metastases (2006-0349)

- ^{166}Ho-DOTMP, 2 out of 6 pt had no progression for > 5 y, minimum toxicities
- Eligibility: bone only metastatic breast cancer
- Treatment: ^{153}Sm-EDTMP with autologous stem cell transplant
- Eradication of bone only disease by high-dose radiation targeting only the bone



Some thoughts

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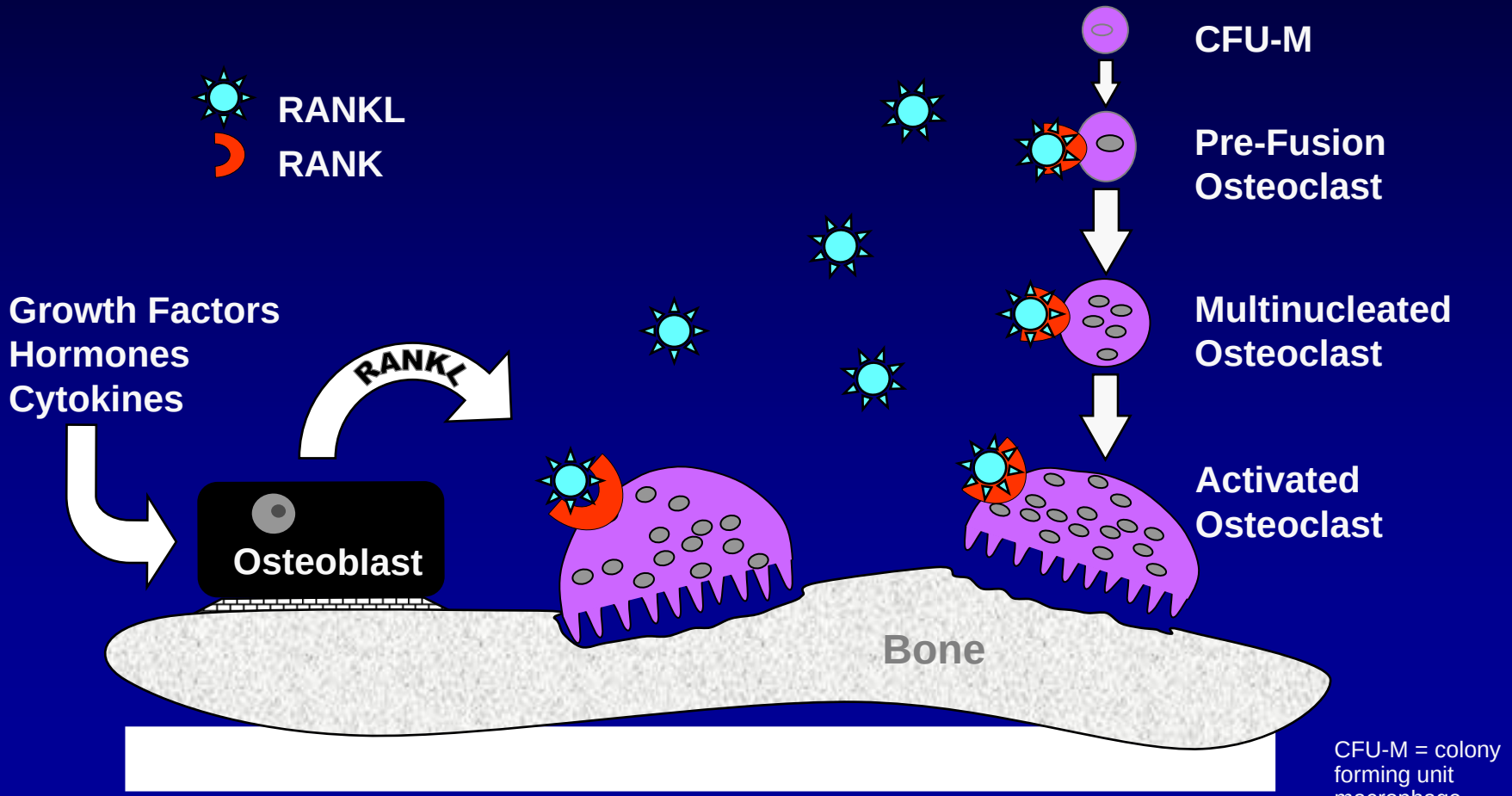
  - **Oligometastasis**
  - **Multiple bone metastasis**
- **Can we develop drugs that targets bone metastasis?**
  - **Mechanism**
  - **Potential new drugs**

What Is Denosumab?

- Fully human monoclonal antibody
  - Lower risk of allergic reactions
  - Stable PK profile
- IgG_2
- High affinity for human RANK ligand
  - Kd 3×10^{-12} M
- Does not bind to TNFα, TNFß, TRAIL, or CD40L

Bone Resorption is Dependent on RANKL

RANKL is the primary mediator of osteoclast formation, function and survival

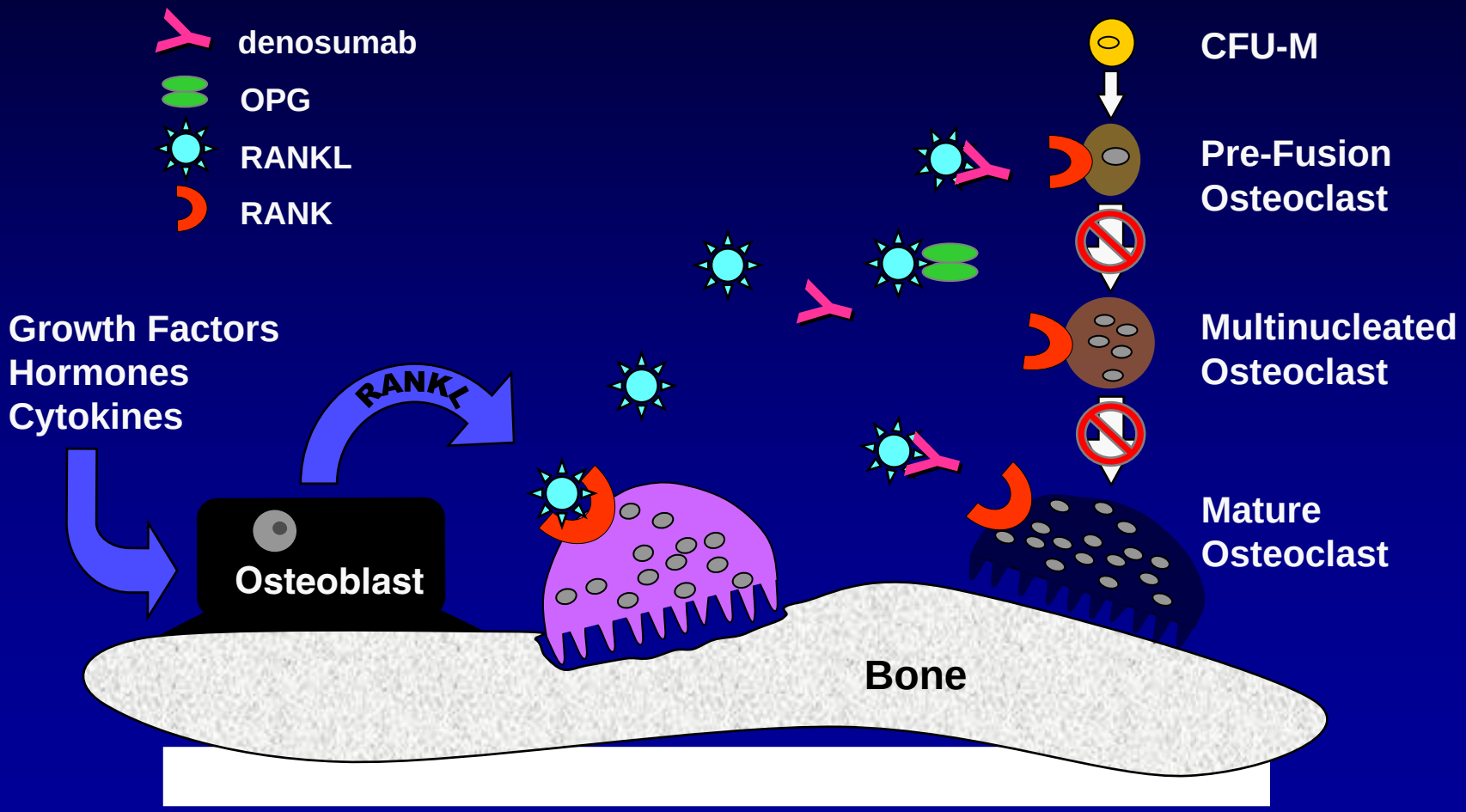


CFU-M = colony forming unit macrophage

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

Denosumab Mechanism of Action

Denosumab inhibits osteoclast formation, function and survival

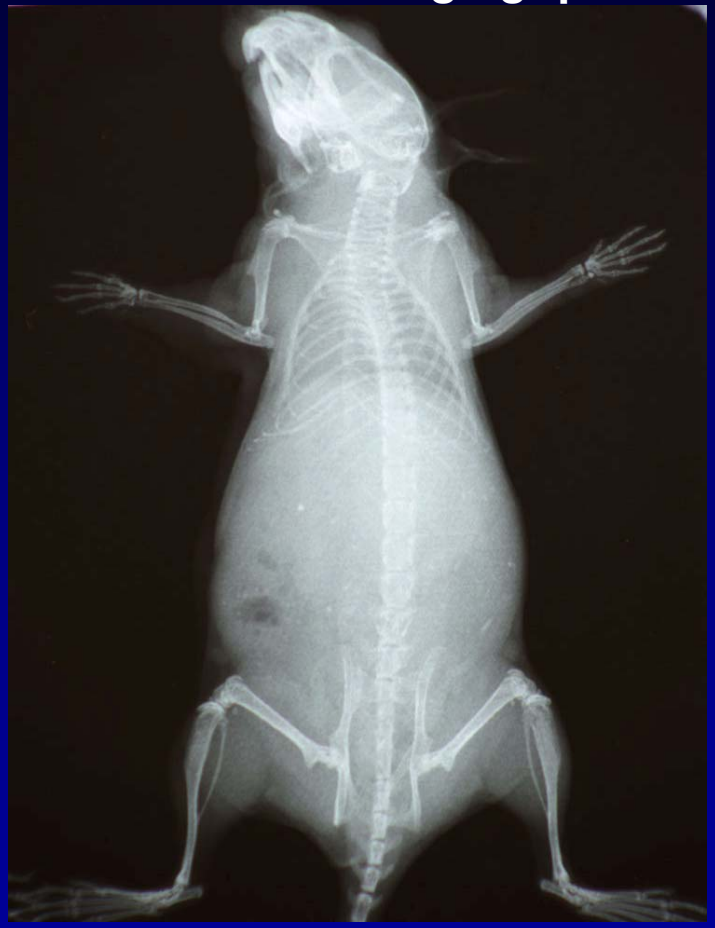


Summary

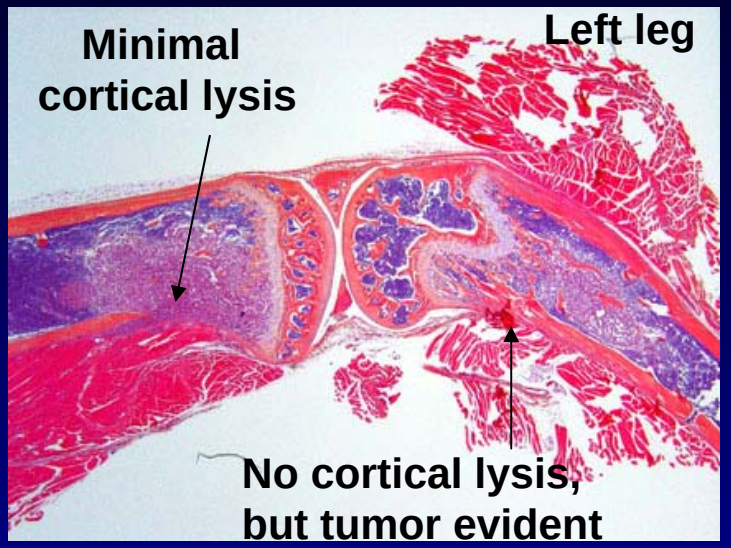
- Denosumab is a fully human monoclonal antibody to RANK Ligand
- RANK Ligand is essential for osteoclast formation, function, and survival
- Denosumab inhibits osteoclast bone resorption in osteoblastic and osteolytic tumors
- Denosumab in preclinical models prevented bone metastasis and delayed progression of established metastases in breast and prostate cancer

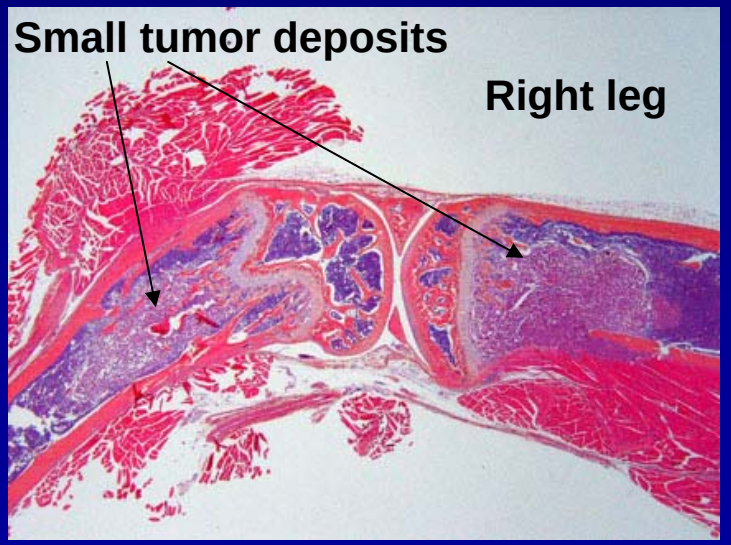
Rapamycin inhibitor
Minimal Bone Destruction in AP24170-Treated Mouse

AP24170 14 mg/kg qw

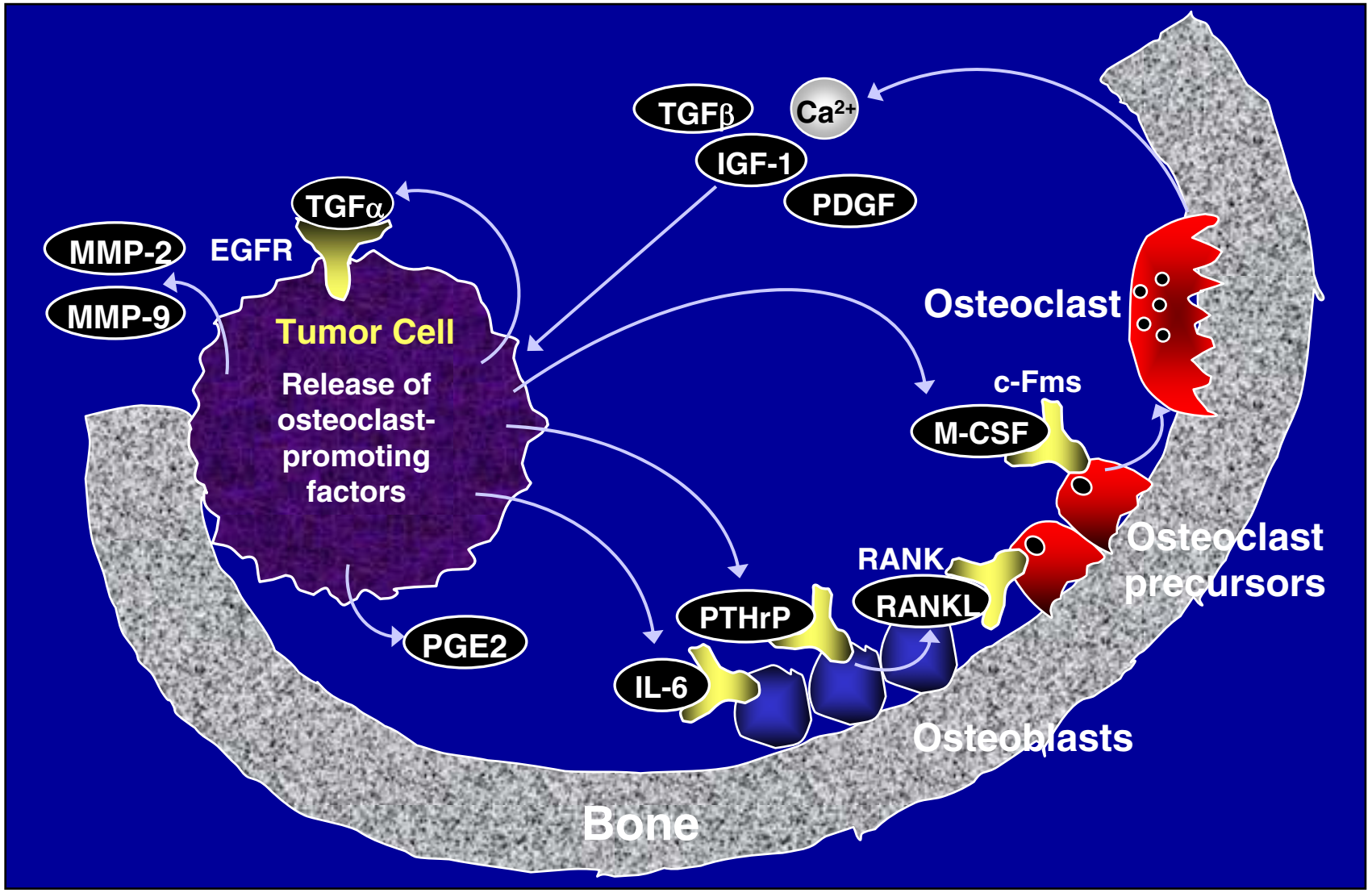


Rt leg





Osteolytic Bone Metastasis "Vicious Cycle"



Opportunities and Challenges

- Need for standardization of care to all research-driven clinical care
- Mechanism-based preclinical research
  - More potent bisphosphonates
  - More targeted specific drugs
  - Need for preclinical model
- Bone, homing ground for bad cancer cells?
- Prevention of recurrence?
- Improved imaging and response criteria?
- Need for Multidisciplinary approach

Acknowledgment

- Breast Cancer Bone Metastasis Working Group
  - Eric Rohren, Stacie Moulder, Colleen Costelloe, Massimo Cristofanilli, Richard L. Theriault, Tse-Kuan Yu, Valerae O. Lewis, John Madewell, Edna Mora, Naoto Ueno, Eric L. Chang, Mark F. Munsell, Michelle L. Davis,
  - Gabriel N. Hortobagyi
- St. Luke International Hospital, Tokyo, Japan
  - Tsuyoshi Hamaoka, MD

It takes a team to take care of bone-related problems.

Thank you !

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