Living Beyond Breast Cancer
Bone Metastases

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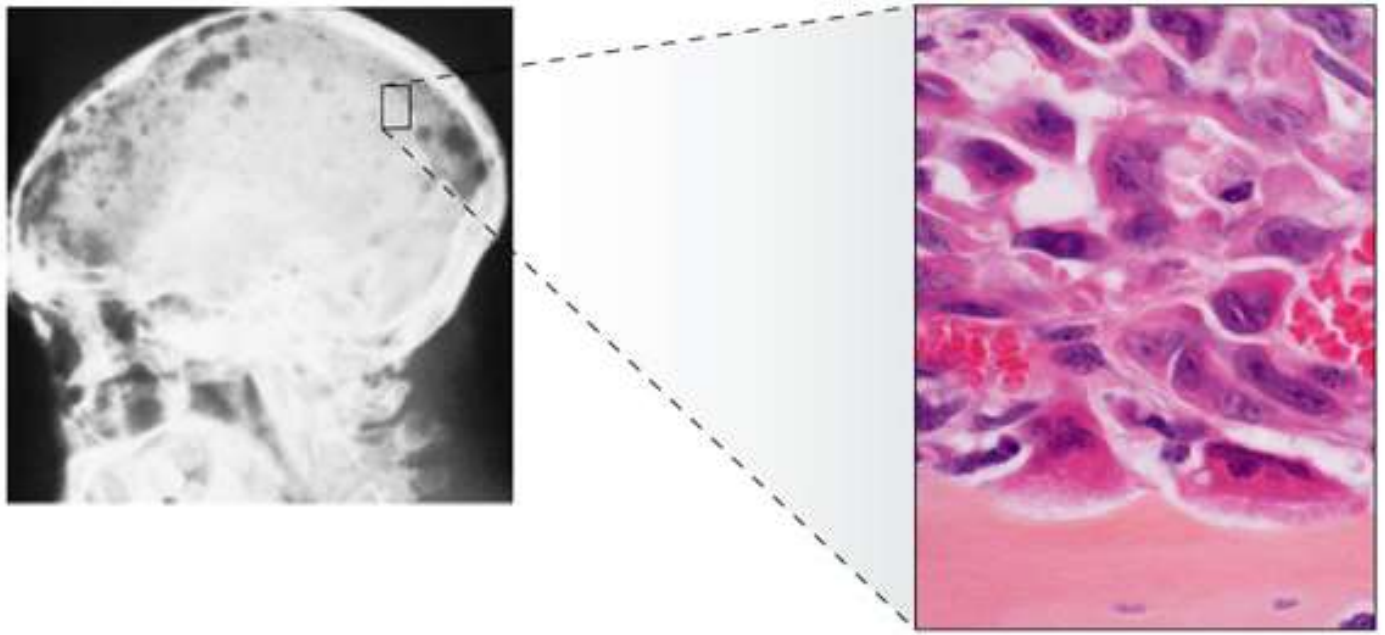
Outline for presentation

- Introduction to bone as an organ
- Epidemiology of bone metastases
- Clinical management of bone metastases
  - Imaging
  - Interventions
- Potential side effects from bone directed therapies
- Research directions
- Dialog together, questions and answers

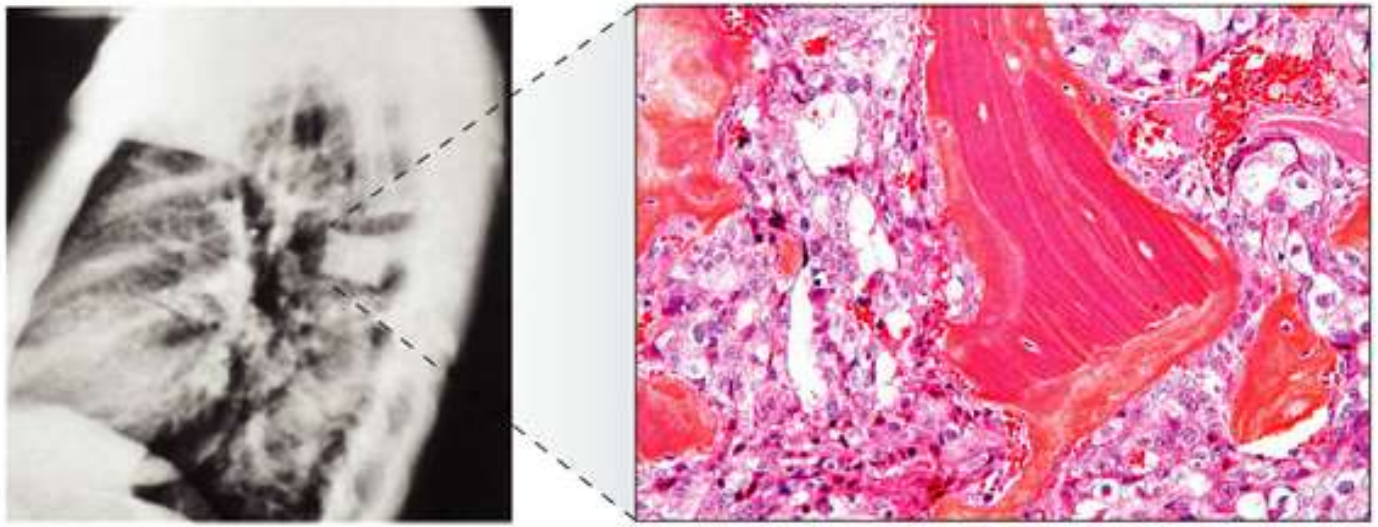
Importance of Bone Integrity

- Structural framework
- Mineral balance
- Bone marrow cells
- Bone metastases: morbidity & mortality:
  - Pain
  - Anemia
  - Compromised mobility
  - Skeletal Related Events (SRE)
  - Bone matrix elaborates growth factors that may promote cancer growth

Osseous Metastases



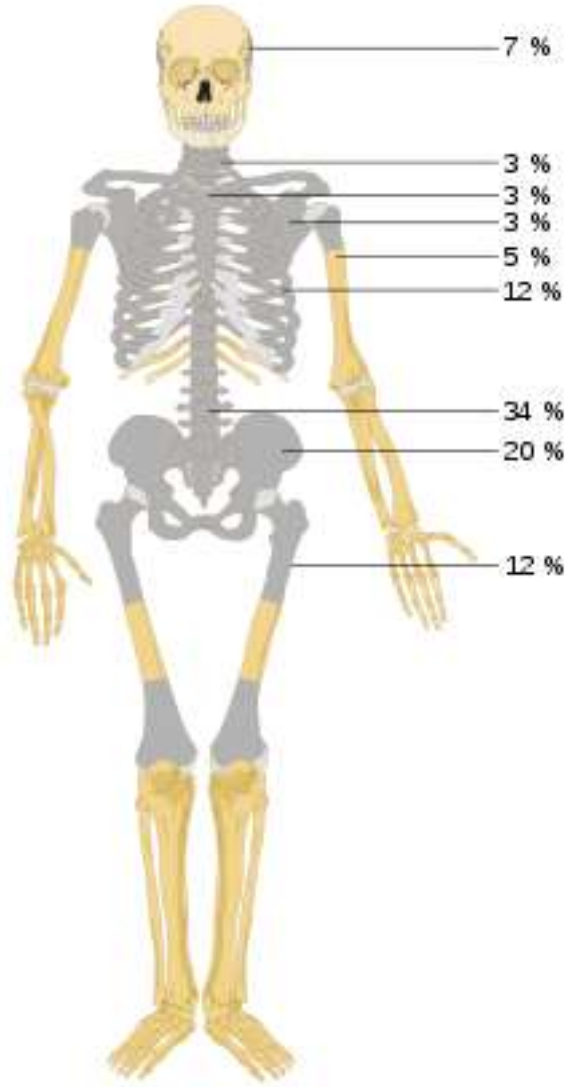
Osteolytic



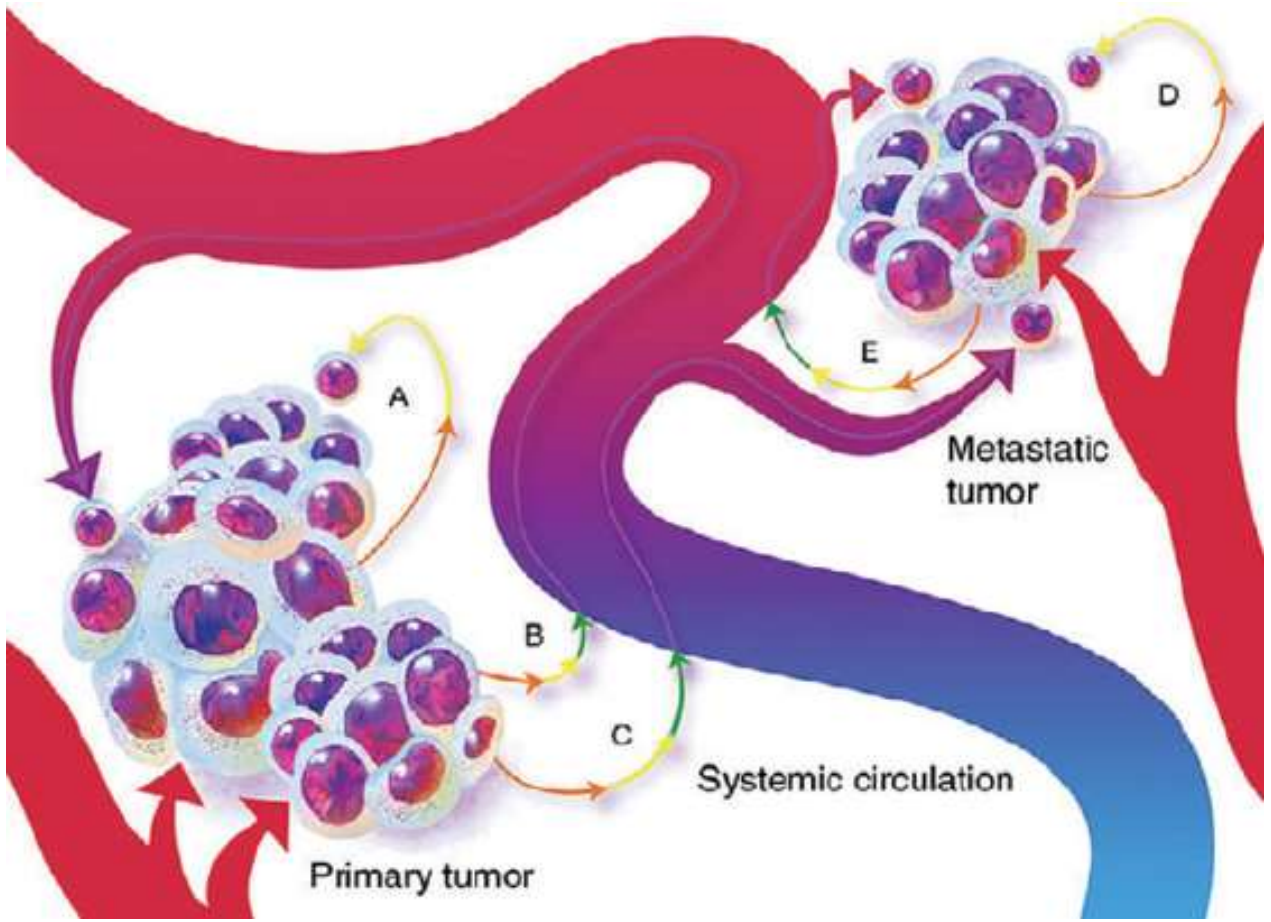
Osteoblastic

Mundy, Nature Reviews Cancer 2002

Common Sites of Bone Metastases



How did the breast cancer get to the bone?



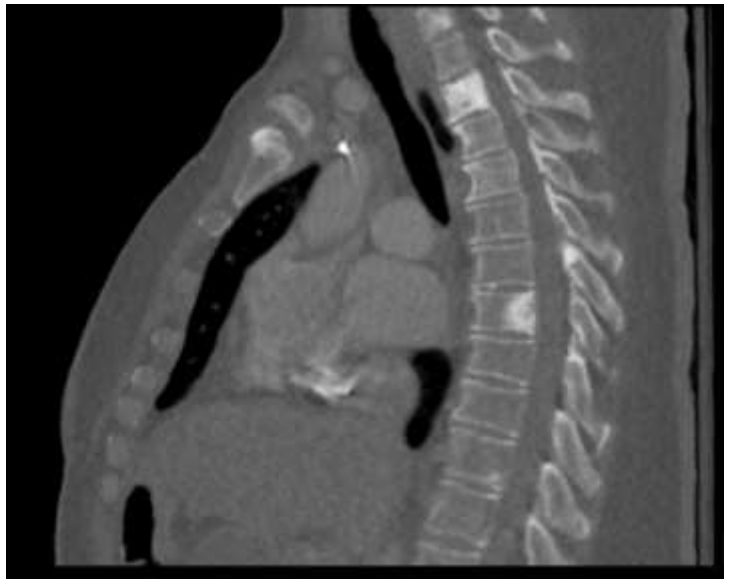
- Pre-metastasis Niche in Organ-specific Metastasis ?
- Homing by what mechanisms?
- Osteomimicry?

Is cancer a disease of self-seeding?

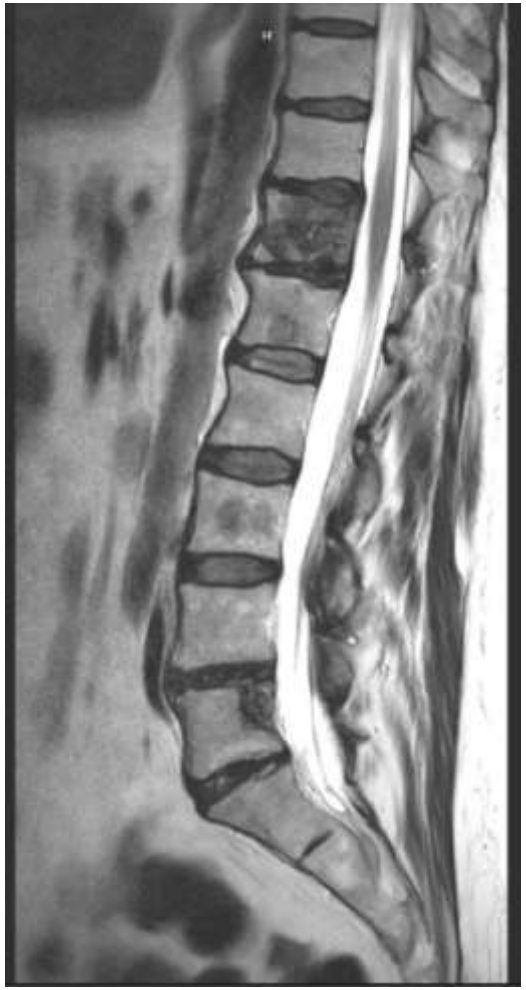
Norton & Massagué
Nature Medicine 2006

Imaging Bone Metastases

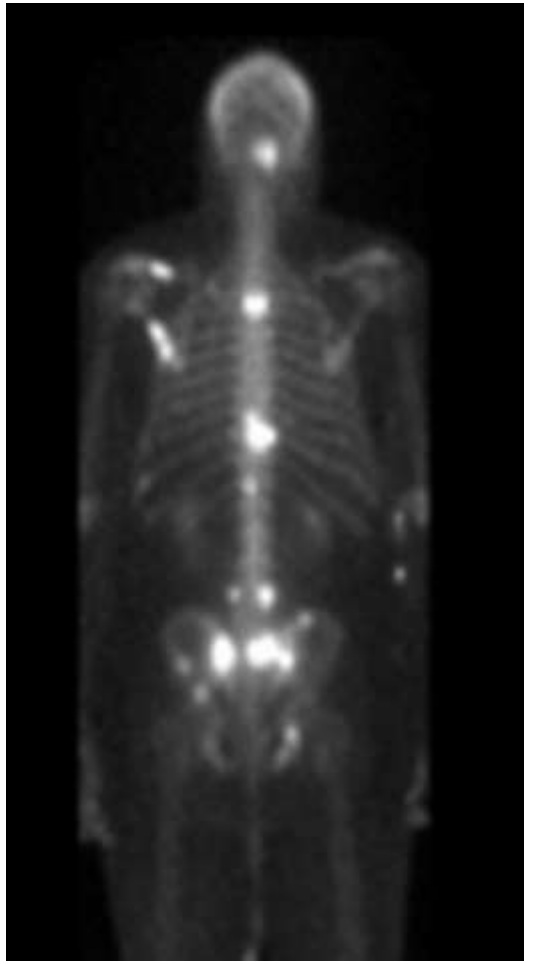
Xray



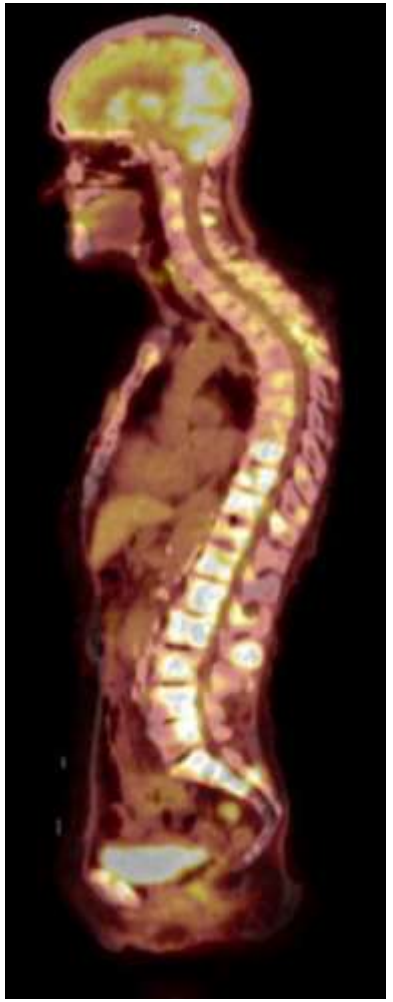
CT



MRI

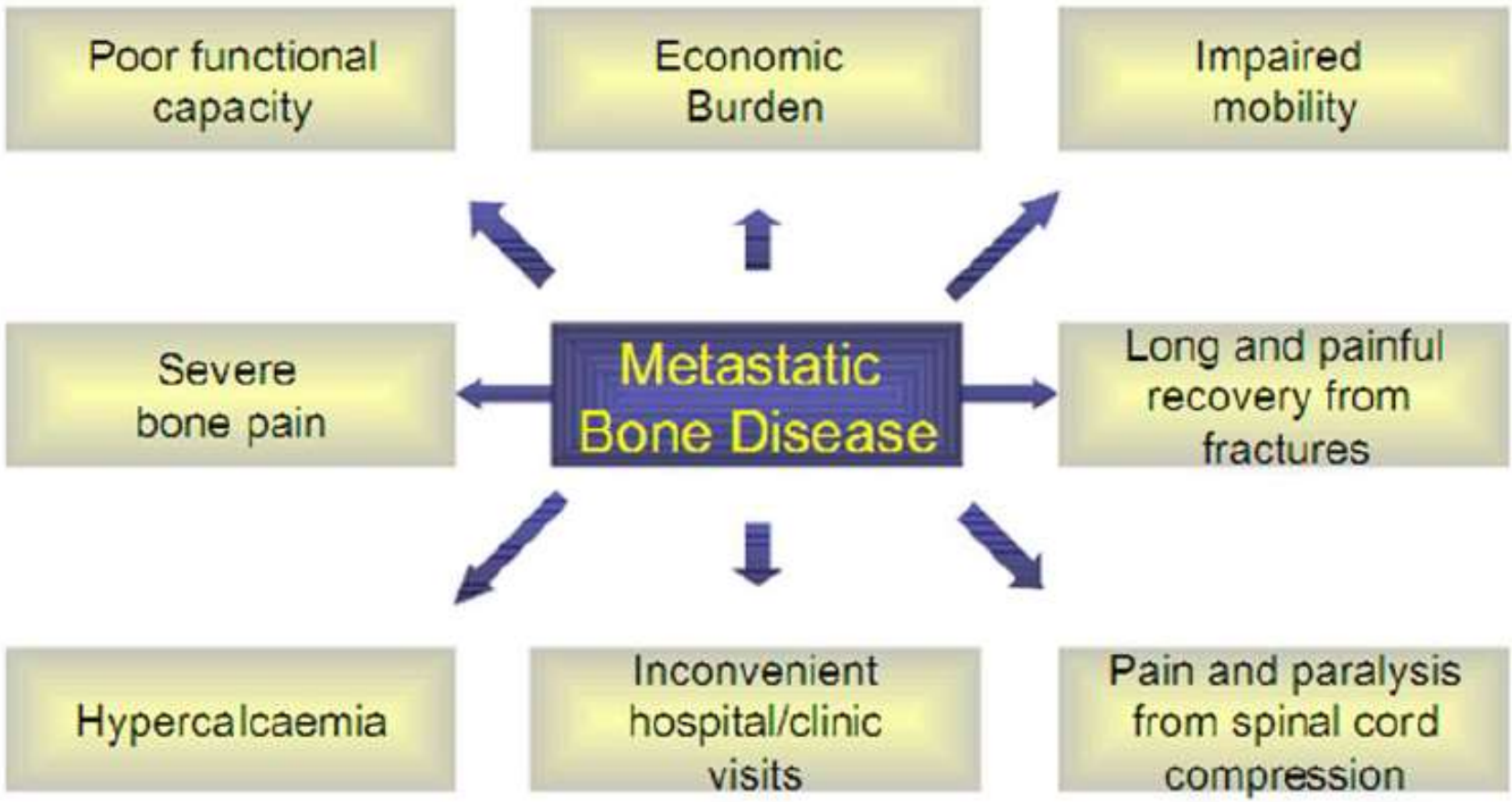


Bone Scan



PET-CT scan

Personal Impact of Bone Metastases



Bone Pain

- Often worsened by motion, weight bearing
- Fracture risk
- Interventions
  - Analgesics (NSAIDs, Tylenol, Opiates, Lidoderm, etc)
  - Physical therapy
  - Radiation therapy
  - Procedures (kyphoplasty, vertebroplasty, etc)
  - Bisphosphonates
  - Other

Bone Metastases in Breast Cancer

Skeletal Related Events (SREs)

- Fracture
- Need for radiation to bone
- Need for surgery to bone
- Spinal Cord Compression
- Hypercalcemia of malignancy

} Oncologic Emergency

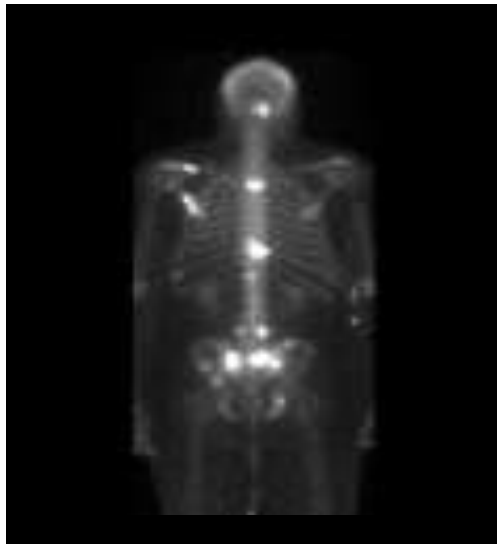
Bone metastases also effect:

- Pain
- Mobility
- Quality of life
- Anemia secondary to compromised marrow

Cancer Induced Bone Disease

Local

- Surgery
- Radiation Therapy
- Clinical Trials



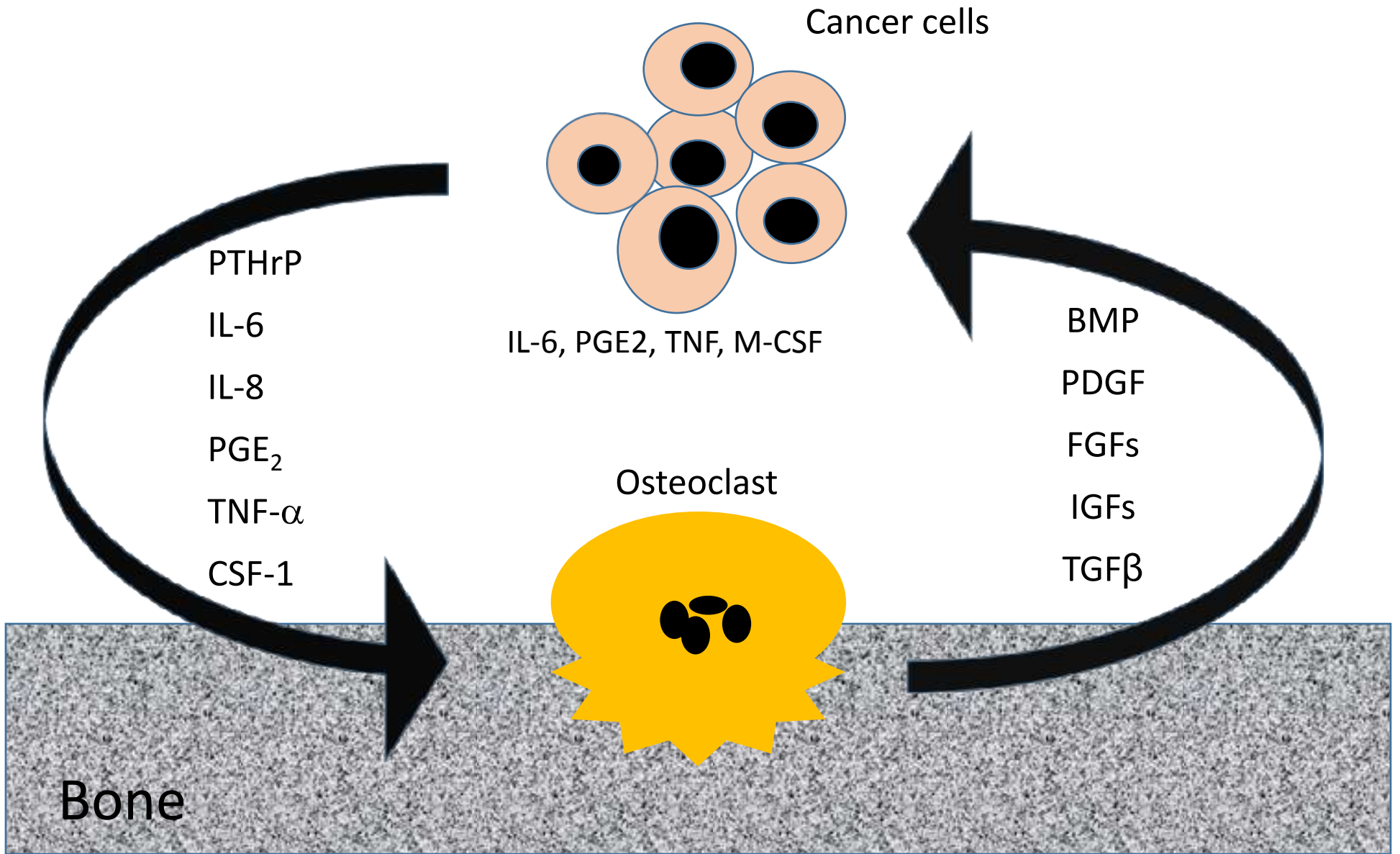
Anticancer therapy

Systemic

- Analgesics
- Osteoclast inhibition
- Clinical Trials

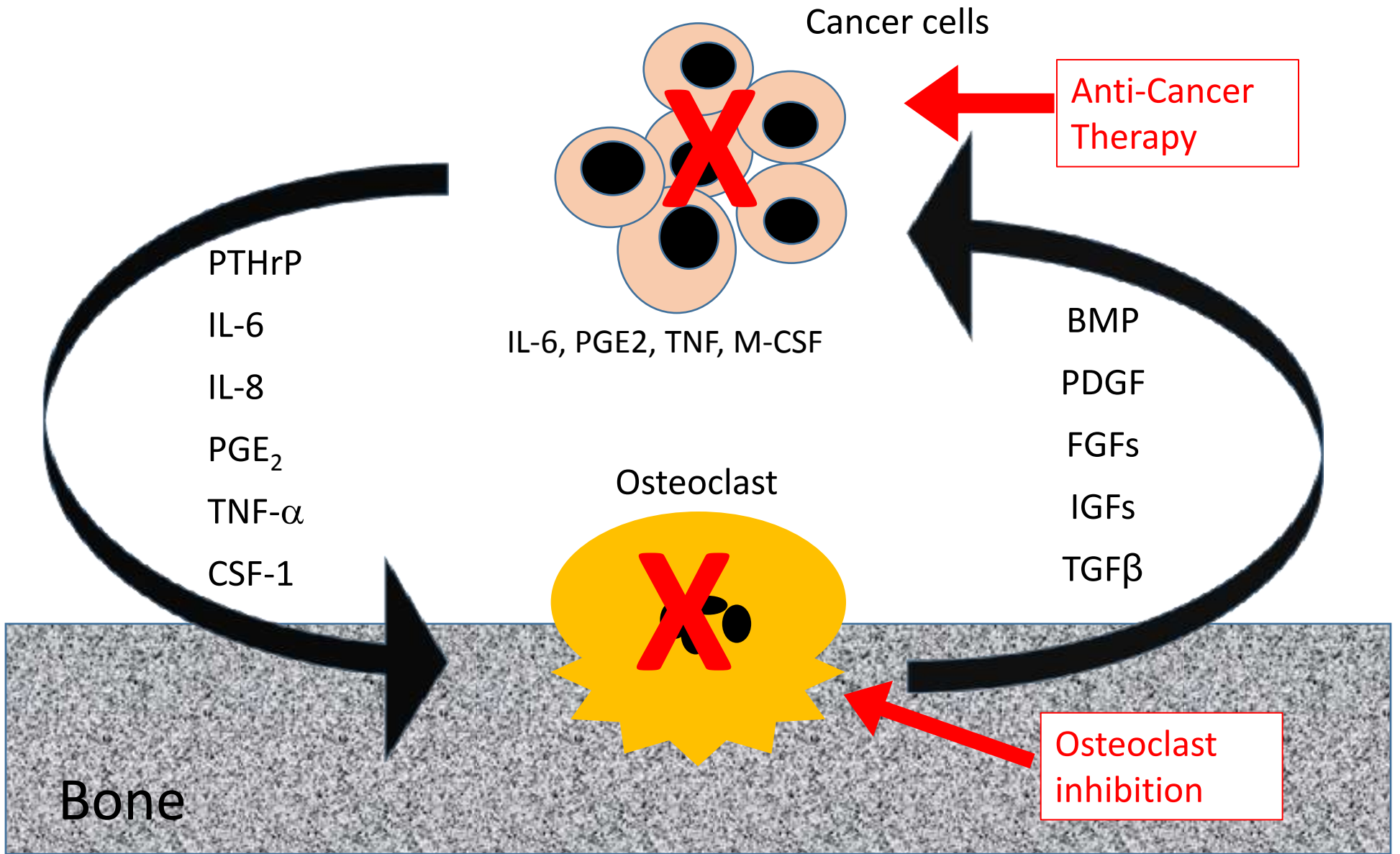
Vicious Cycle (1)

Roodman NEJM 2004



Vicious Cycle (2)

Roodman NEJM 2004



Bone Modifying Agents (Metastatic Bone Disease Osteoclast Inhibitors)

Skeletal Related Events (SRE) rates are reduced by BMA

- Denosumab
- Pamidronate (IV)
- Zoledronic acid (IV)

} Approved in USA & outside of USA for MBD

- Clodronate (IV, oral)
- Ibandronate (IV, oral)

} Approved for MBD Outside USA

Hypercalcemia of Malignancy (HCM):

Zoledronic acid > pamidronate (Major JCO 2001)

Denosumab for bisphosphonate refractory (HCM) (Hu JNCI 2013)

SRE Efficacy of BMA in Metastatic Breast Cancer

Pamidronate versus Placebo (Hortobagyi NEJM 1996): SRE in 1 y

- 43% versus 56% p = 0.046

Pamidronate versus Zoledronic acid (Rosen J.Cancer 2001)

- Breast chemotherapy SRE in 1 y: 44% versus 43%
- Breast hormonal therapy SRE in 1 y: 42% versus 47%

Zoledronic Acid versus Placebo (Kohno JCO 2005)

- SRE in 1 y
  - 29.9% versus 49.6% p=0.003

Denosumab versus Zoledronic acid

- 0.45 events (denosumab) versus 0.58 events (zoledronic acid) per patient per year

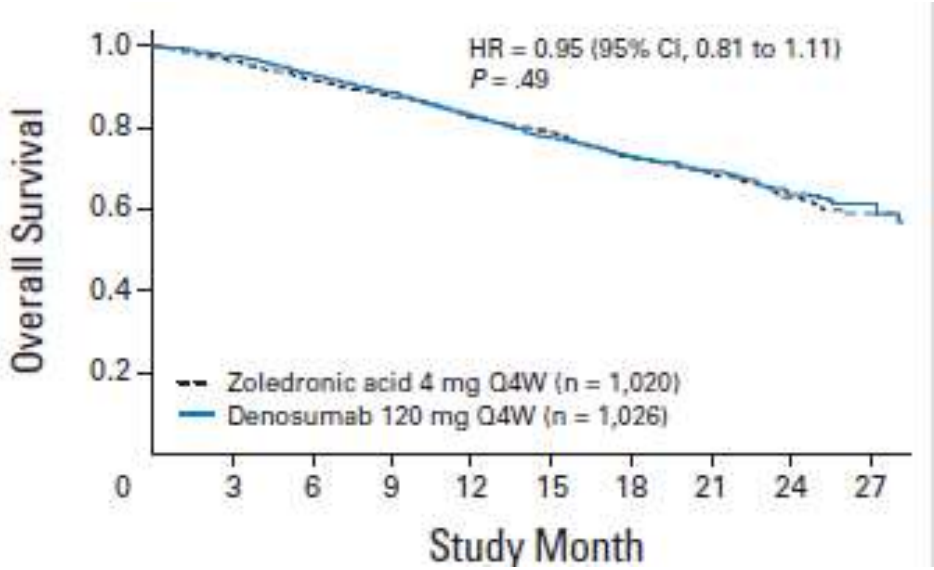
Zoledronic acid every 4 weeks or every 12 weeks: CALGB 70604, ZOOM, & OPTIMIZE-2

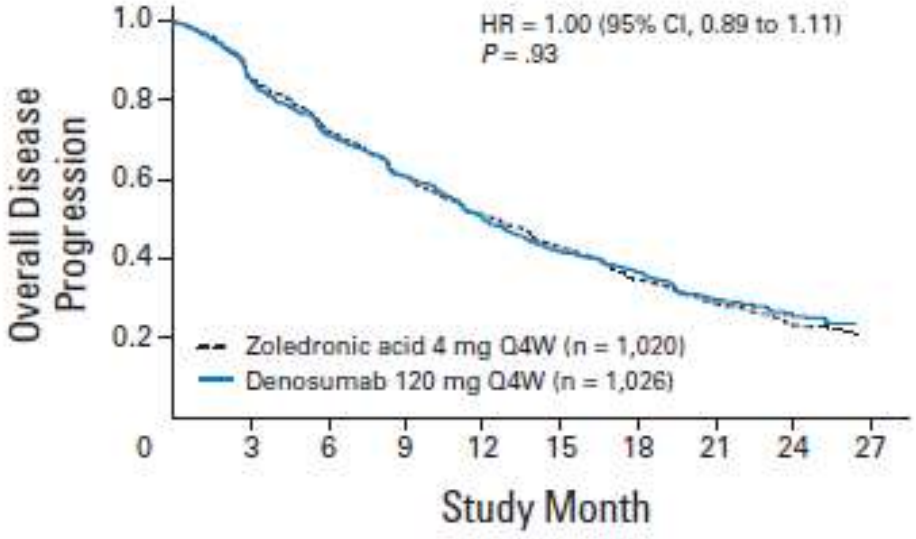
- SRE in 2nd y of dosing Ranges 15% to 29% p=0.004

No Anticancer Efficacy of BMA in Metastatic Breast Cancer

Stopeck JCO 2010

- No change to cancer outcomes in metastatic breast cancer
- No survival difference between zoledronic acid and denosumab

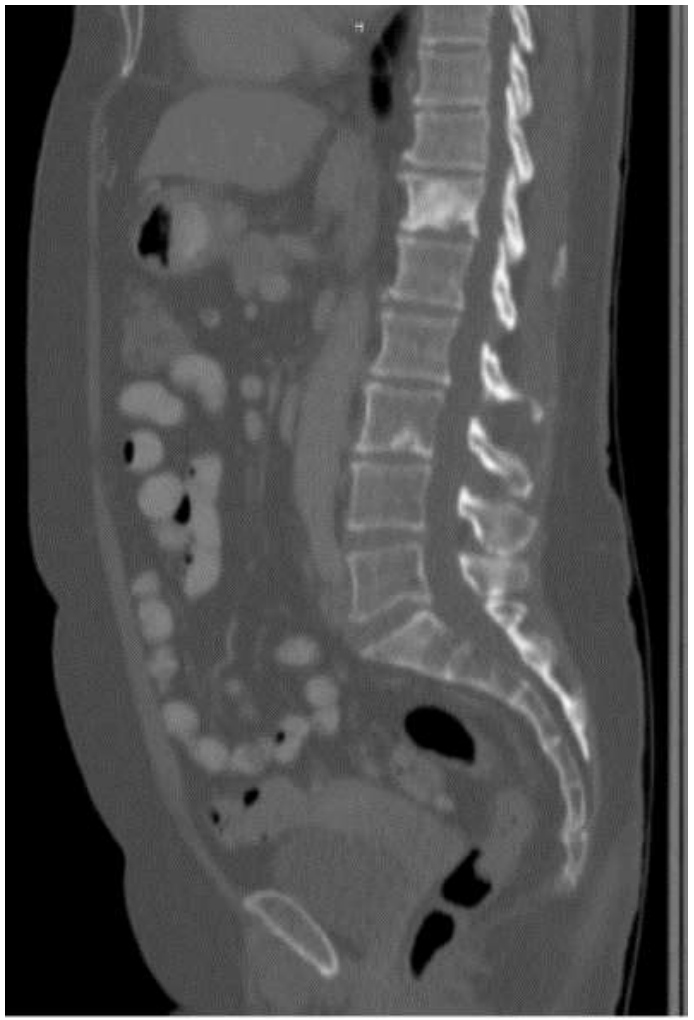




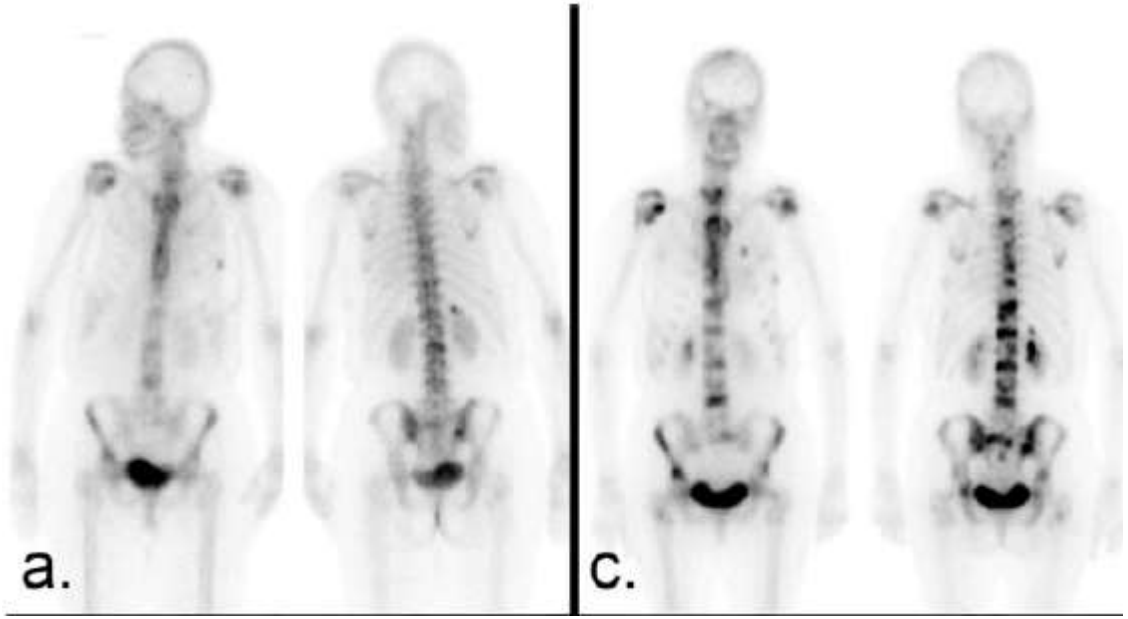
Dose Interval Phase III/IV Breast Cancer Studies

Study name	Drug All intervals are 4w versus 12w	Tumor Type Prior BMA (yes/n0)	Primary Endpoint % SRE 4w/12w	Ref
ZOOM	Zol (open label) 4w v 12w Non-inferiority	MBC Yes, 9 dose pre-study exposure	SRE per patient per year (4w) 15 (12w) 15	Amadori Lancet Oncology 2013
Optimize 2	Zol (placebo) 4w v 12w Non-inferiority	MBC Yes, 9 dose pre-study exposure	SRE rate (4w) 22 (12w) 23.2	Hortobagyi JAMA Onc 2017
CALGB 70604	Zol (open label) 4w v. 12w Non-inferiority	MBC, MPCA, MM No prior BMA	SRE within 2 years (4w) 29.5 (12w) 28.6	Himmelstein JAMA 2017
SAKK 96 /12	Denosumab 4w v 12w	MBC, MPCA No prior BMA	Time to first SSRE	Open to enrollment, NCT 02051218

Choice & Dosing of Bone Modifying Agent

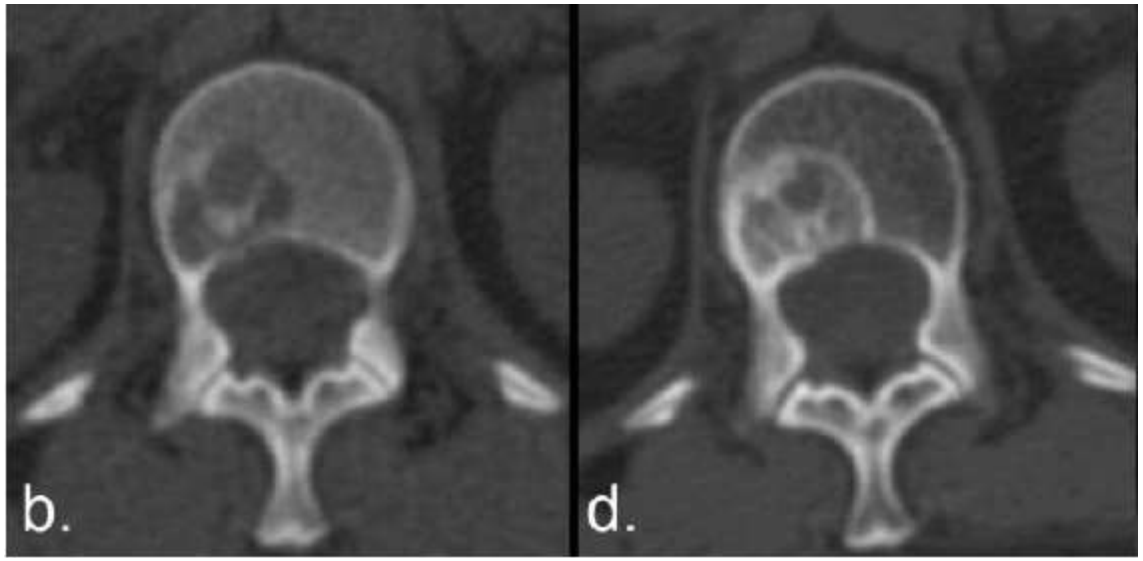


Challenges in Evaluating Bone



Bone Scan

- Flare (response) ?
- Progression?



CT Vertebral Body

Lytic to sclerotic

- Healing?
- Progression?

Osteoclast Inhibitors (cancer dosing)
Side Effects

IV administration (bisphosphonates):

- Acute phase reactions
- Hypocalcemia [5% ≥ grade 2]
- Renal insufficiency
- Osteonecrosis of the jaw (ONJ) [1.3%]
- Atypical fracture [rare]

Subcutaneous administration (denosumab)

- Hypocalcemia [12% ≥ grade 2]
- Osteonecrosis of the jaw (ONJ) [1.8%]
- Atypical fracture [rare]

Coleman Ann Onc 2005; Conte Oncologist 2004; Ross BMJ 2003; Stopeck JCO 2010, Saad Ann Onc 2012; Body EJC 2015

Uncommon Adverse Events Associated with Bone Modifying Agents but Cause(s) Unknown

Atypical Fractures

Osteonecrosis of the Jaw (ONJ)

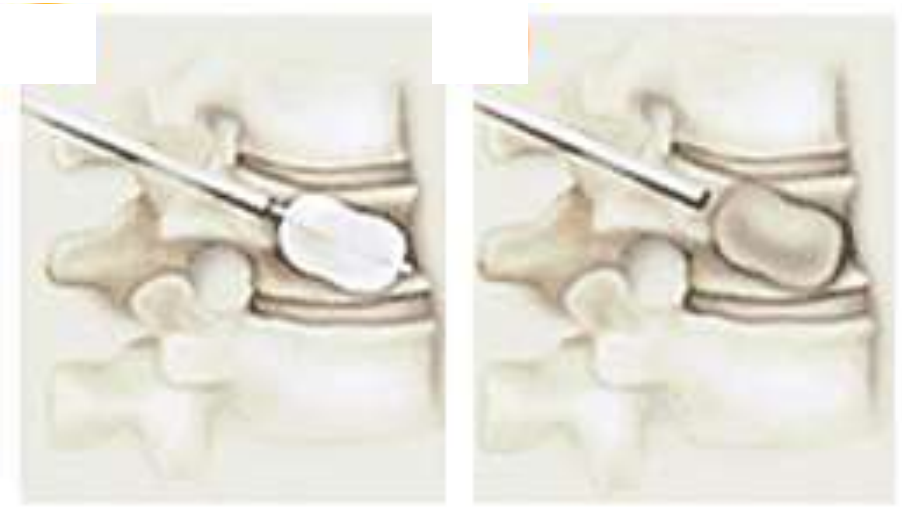
Vertebroplasty & Kyphoplasty: Compression Fracture

polymethylmethacrylate (PMMA)

Vertebroplasty
- Needle + Cement/PMMA

Vertebroplasty

Kyphoplasty
- Balloon + Cement/PMMA



Kyphoplasty

To Operate, Most Surgeons Consider:

Consider surgery:

- Size of lesion: ≥ 2.5 cm
- Lesion: ≥ 50% bone diameter
- Lesion is a Lesser trochanter avulsion
- Patient has ≥ 6 weeks life expectancy

Lesion
At risk
For Fracture

Scoring system to predict pathologic fractures: clinically not often used

Preemptive surgery for impending fracture vs. surgery for completed fracture (favors pre-fracture tx)

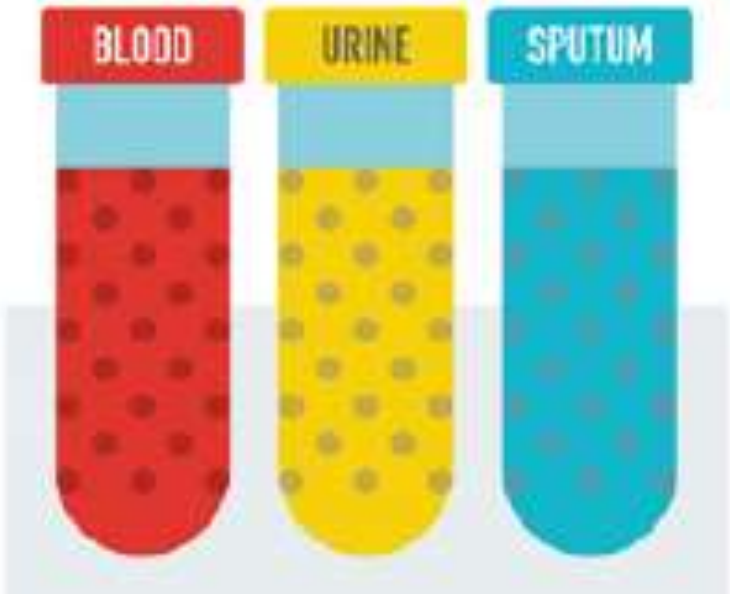
- Shorter hospital stays (7 vs11 days)
- Greater likelihood of discharge home (vs extended care) (79% vs 56%)
- Greater likelihood of support-free ambulation (35% vs 12%)

Mirels Clin Ortho 2003
Ward CORR 2003

Research

LIQUID BIOPSY

A new, nonirvasive technique that can detect disease biomarkers in:



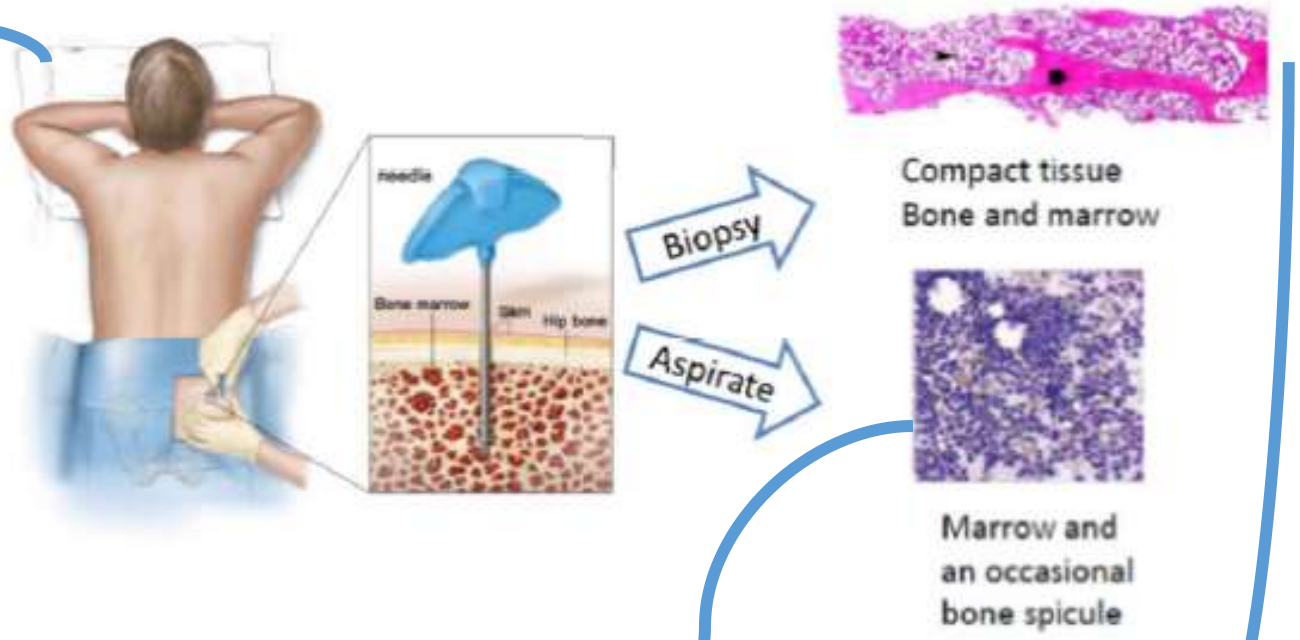
LIQUID BIOPSY CAN BE USEFUL WHEN:

- not enough tissue sample is available
- not enough tumor tissue is in a sample
- a tumor is hard to reach
- regular monitoring is needed

LIQUID BIOPSIES CAN BE ANALYZED FOR:

- the presence of cancer cells
- DNA
- other materials released by cancer cells

Research



<u>Blood</u>

- CTCs
- Plasma

<u>Marrow</u>

- DTC
- Hematopoietic cells
- Aspirate fluids
- Bone cells

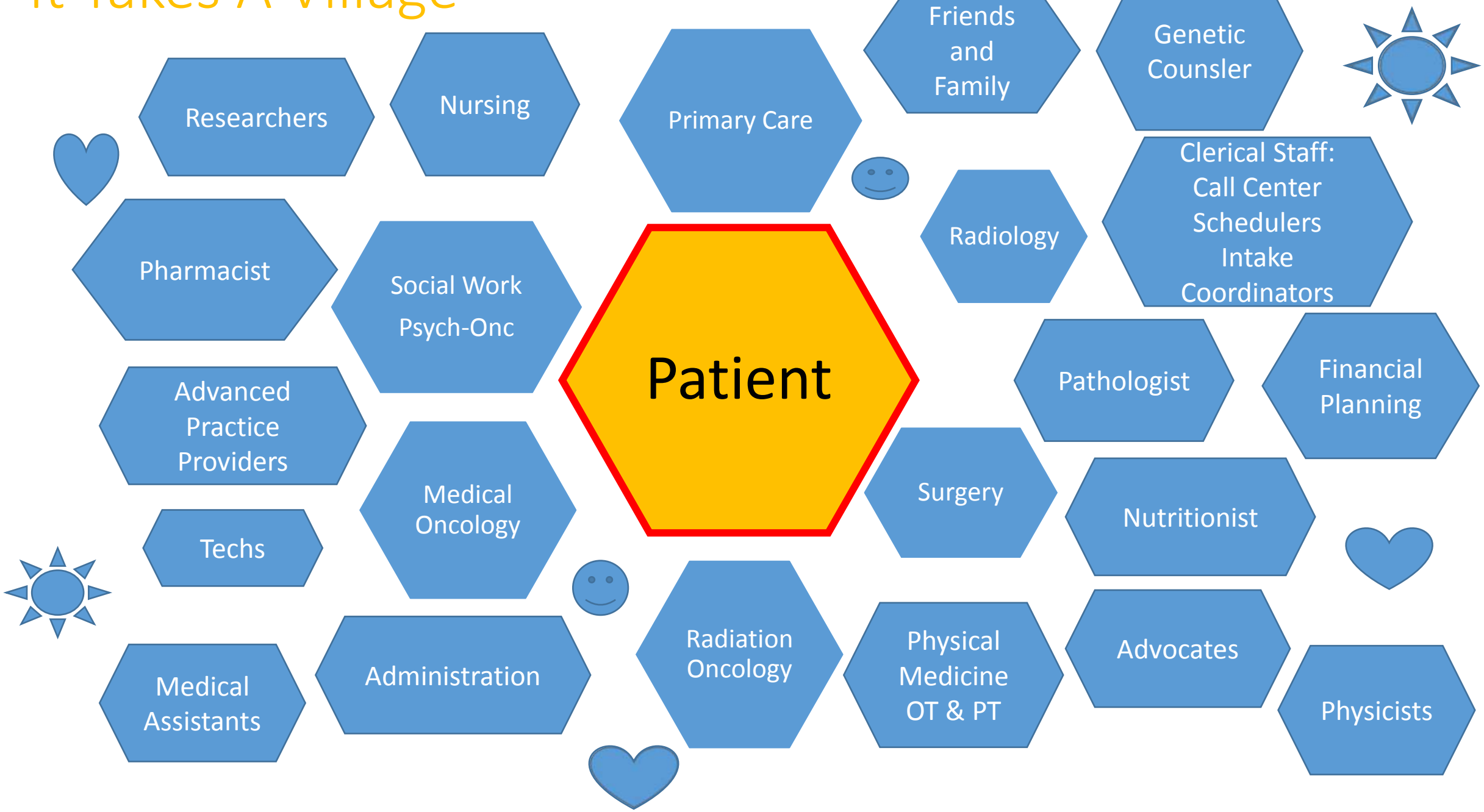
<u>Bone</u>

- Bone cells
- Imaging bone
- Imaging Matrix
- Bone strength

Take Home Points

- Metastatic Bone Disease → interdisciplinary approach
  - Pain control
    - RX: NSAIDs, Opiates
    - External beam radiation & Radiopharmaceuticals
    - Osteoclast inhibition (supportive therapy)
  - Skeletal Related Events
    - Can be emergencies
    - Can be prevented by use of a BMA
  - Quality of Life & Survival
    - SREs carry significant morbidity & mortality
    - Osteoclast inhibition has not been associated with increased survival
    - Duration of osteoclast inhibition therapy is generally indefinite
- Problems/questions remain → Design & participate in trials

It Takes A Village



Thank you!

Now it’s time for Questions