Recent Advances in Metastatic Bone Disease

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Metastasis is the culmination of numerous highly regulated sequences of steps that results in the migration and proliferation of cells from the primary site to a distant location. The biologic consequence of skeletal metastasis is focal bone sclerosis or osteolysis that leads to pain, pathologic fracture, and biochemical derangement.

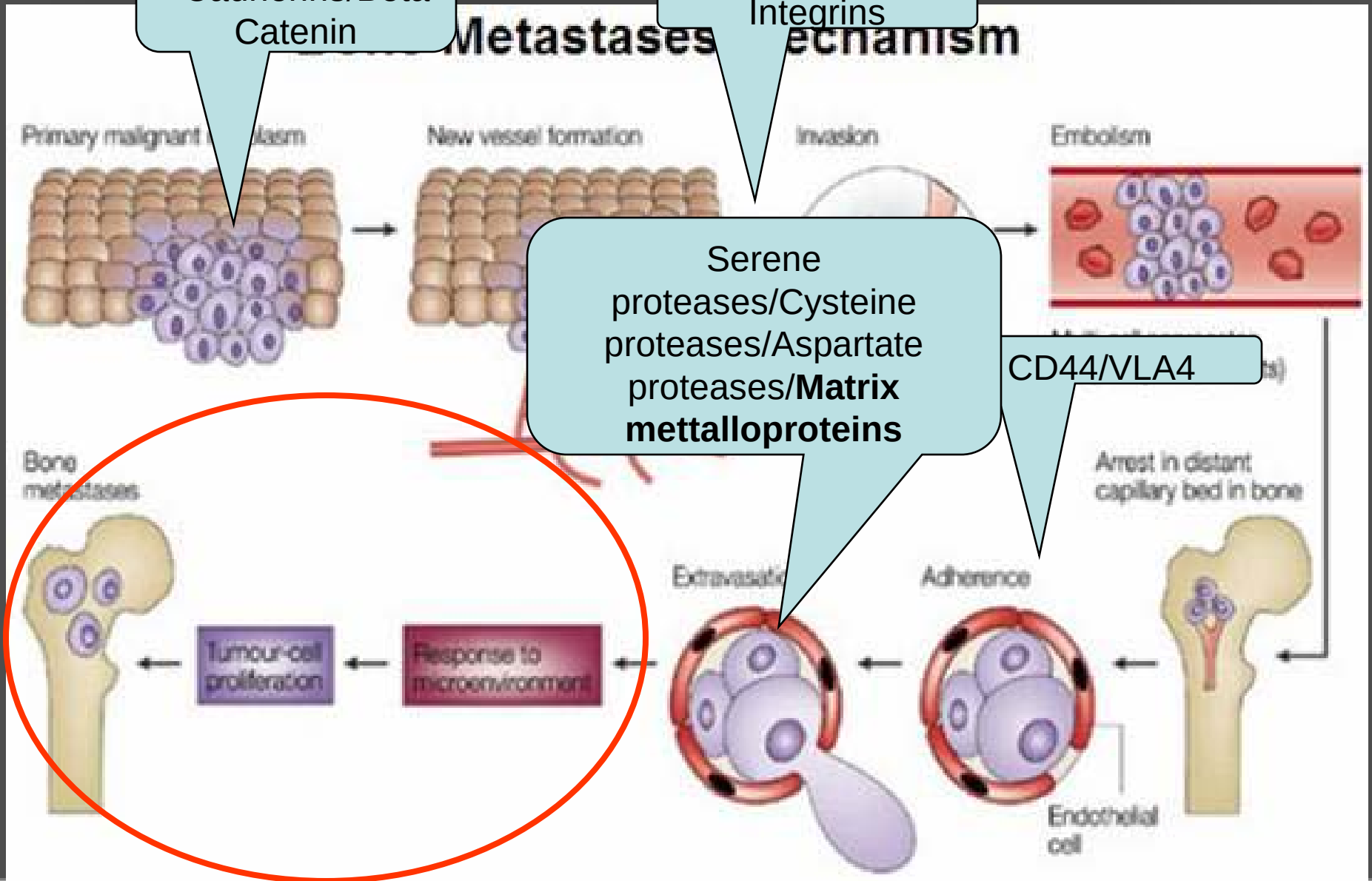
- Pathogenesis – Seed and Soil theory*
- Diagnosis – Bone Markers
- Prognostication
- Treatment
  - Medical
  - Surgical

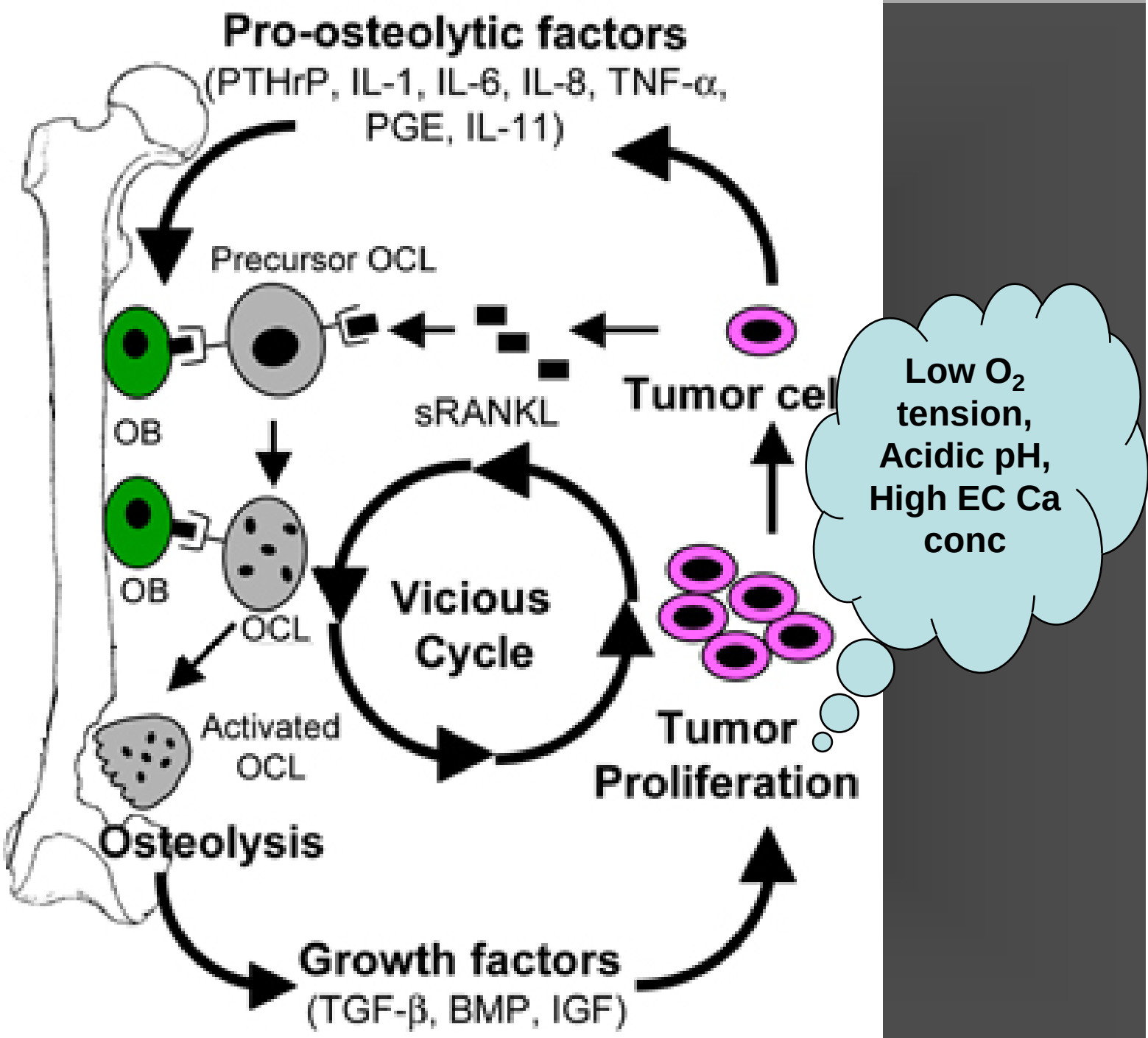
*Dr. Stephen Paget 1889

Pathogenesis

- "Seed & Soil"
- Organ-specific pattern of metastasis
  - colon carcinomas – liver, lung, skin, brain and almost never to kidneys, intestine or muscle.
  - breast carcinomas - most of these organs.
  - Prostate - Bone

Pathogenesis




Pro-osteolytic factors
(PTHrP, IL-1, IL-6, IL-8, TNF-α, PGE, IL-11)
Precursor OCL
OB
OB
OCL
sRANKL
Tumor cell
Low O_2 tension, Acidic pH, High EC Ca conc
Vicious Cycle
Activated OCL
Tumor Proliferation
Osteolysis
Growth factors
(TGF-β, BMP, IGF)

Implicated factors

- Cell adhesion molecules: osteopontin, fibronectin, thrombospondin
- Matrix metalloproteinases (MMP)
- Growth Factors (TGF-b, PDGF, IGF-1, GFG, M-CSF)
- Calcium binding proteins: osteonectin, bone sialoprotein
- Osteoclastogenesis factors: RANK-L, OPG
- Cytokines: IL-1, IL-6, IL-8, IL-11)
- Eisosanoids: PGE2, PGI2, TXA2
- Tumor factors: PTH-rp
- Enzymes: cathepsin K, collagenase, alkaline phosphatase

Diagnosis

- Detection
- Progression
- Recurrence

Diagnosis

- Bone Markers
  - Bone resorption markers
    - Urine hydroxyproline
    - Pyridinoline & deoxy pyridinoline
    - C & N Telopeptides
  - Bone formation markers
    - Bone specific ALP
    - Carboxy & Amino terminal procollagen extension peptides

Demers et al. CORR:2003

Prognostication

- Prognostic Factors
  - Primary lesion
    - Rapid growth
    - Moderate growth
    - Slow growth
  - Visceral mets
  - Performance status
  - Previous chemotherapy
  - Multiple Skeletal mets

Katagiri et al. JBJS B: 2005

Rapid growth	Liver, Gastric, Lung
Moderate Growth	Other CA & SA
Slow growth	Breast, Prostate, Lymphoma, Myeloma, Thyroid

Performance status

- ECOG – Eastern Cooperative Oncology Group

Asymptomatic	0
Symptomatic fully ambulatory	1
Symptomatic. In bed for < 50% of the day	2
Symptomatic. In bed for > 50% of the day. But not bedridden.	3
Bedridden	4

Scoring

Primary (growth rate)	V. Mets	Perf Status	Chemo	Multiple Skel. Mets
0	0	0	0	0
2	2	1	1	1
3	-	-	-	-

Survival

Score	6M	12M	24 M
0 - 2	0.98	0.89	0.75
3 - 5	0.71	0.49	0.29
6 - 8	0.31	0.11	0.02

- 52 yr Female
- Breast CA
- Confined to bed
- Has had full chemo
- No visceral mets

Treatment Strategies

- Strategies
  - Target Tumour cells

  Local drug delivery* (Cement/HAP loading)
    - Methotrexate
    - Cisplatin
    - Doxorubicin

*Rosa et al. JBJS B:2003

Treatment Strategies

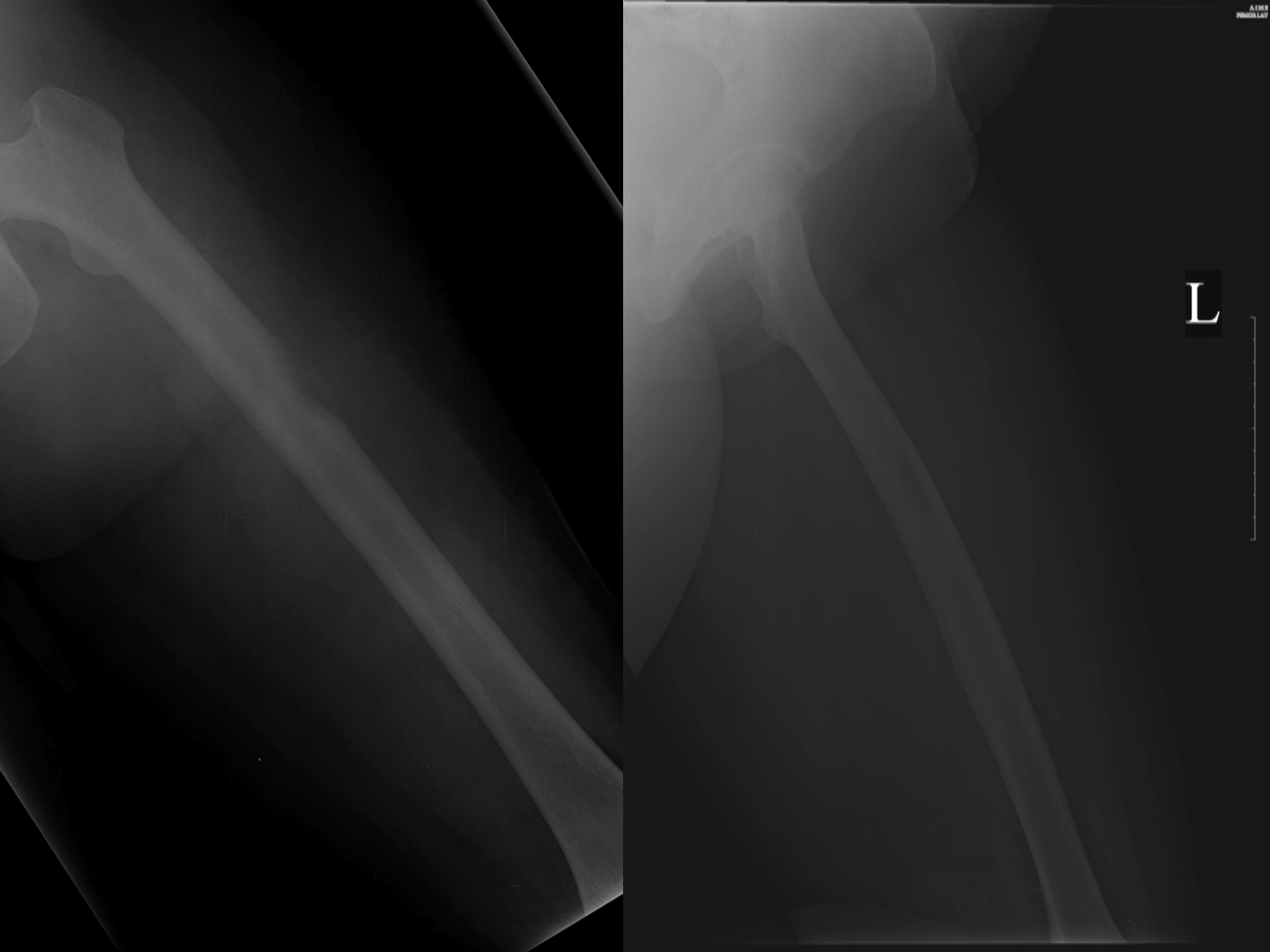
- Target osteoclasts
  - Bisphosphonates
- Target osteoblasts
  - Epigallocatechin 3 gallate (EGCG)
  - BMPs
- Target the bone microenvironment
  - Bisphosphonates
  - Anti MMPs – Runx2
  - Anti CaSR - shRNA

Treatment Strategies

- Chemotherapy
- Hormonal Manipulations
- Radiotherapy

The targets mentioned have overlapping functions to drive the vicious cycle. Therefore a multi pronged strategy should be developed inhibiting different sites and stages of the cycle for therapy to be effective.

Surgical treatment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Mirels Scoring

	1 Point	2 Points	3 Points
Type of lesion	Blastic	Mixed	Lytic
Size (Diameter)	< 1/3	1/3 - 2/3	> 2/3
Site	UL	LL	PT
Pain	Mild	Moderate	Severe

7 or less	Low risk
8	Moderate risk
9 -12	High Fracture

Mirels et al. CORR:1989

Surgical Strategies

- IM Nailing/Plating
- Arthroplasty

PMMA or HAP loaded with anticancer drugs

Challenges

- Prevention of Metastasis
- Treatment of Metastasis

A journey of thousand miles must begin with a single step.