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Current Approaches to Metastatic Bone Disease

COA 2017Annual Meeting

Anna A. Kulidjian MD, FRCSC
Chief Orthopaedic Oncology Moores Cancer Center UCSD

Scope of the problem

- 1,437,180 new cases of cancer in USA annually
- 60% of these breast, prostate, lung or kidney primary
- 50% - 70% of all cancer patients develop bone metastases during course of their disease
- 80% of patients with prostate, breast, lung kidney and thyroid
- 10% develop pathologic fracture

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Breast

- 50-75% develop bone metastases
- Mixed lesions
- Median survival with bone mets – 2007 - 32 months 2007
- 2013 - 55.5 months
- 5 year survival 20% - trending up 22%
- 63% of cost of caring for metastatic breast cancer due to skeletal disease

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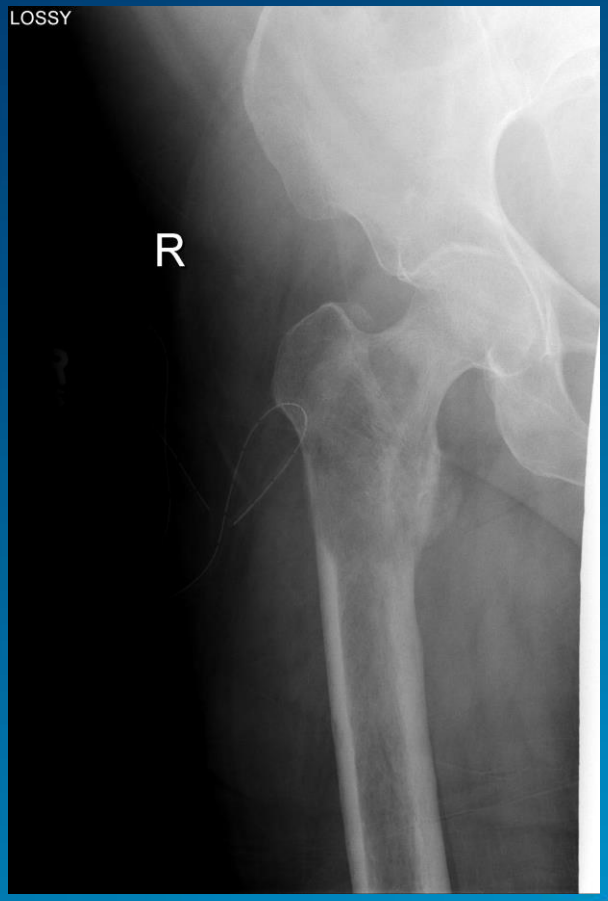
Prostate

- 90% incidence of bone mets in patients who die from prostate cancer
- Commonly mixed Median survival 40 months
- 5 year survival 25%



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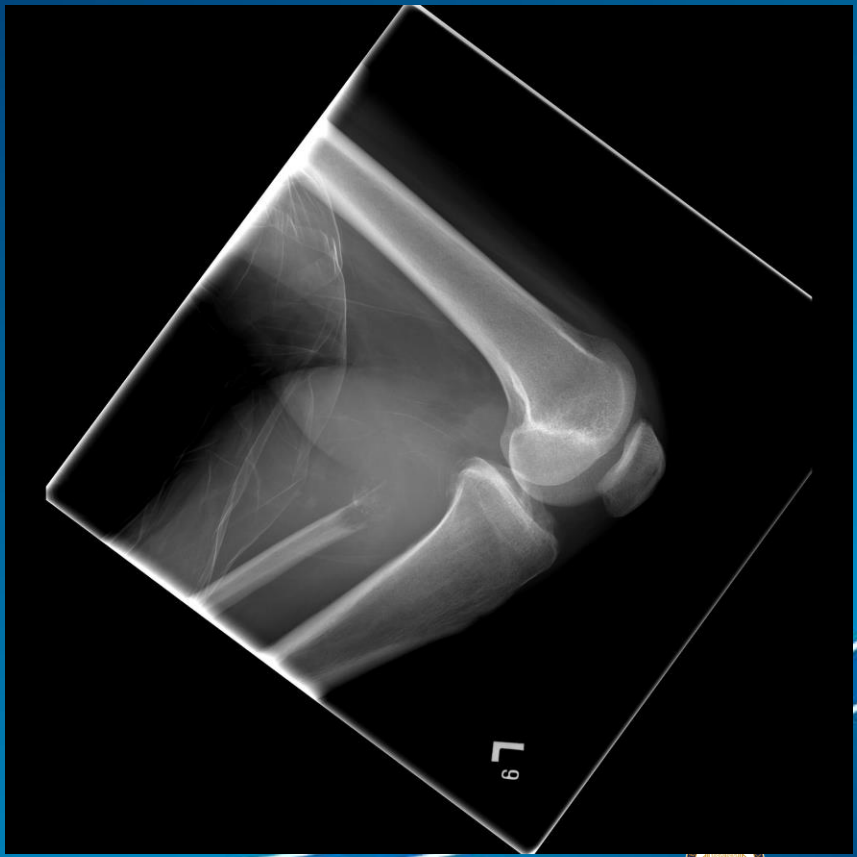
Lung

- 50% incidence of bone metastases
- Typically lytic
- Prognosis with bone metastases generally poor, with median survival 6 months



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Renal

- 50% incidence of bone metastases - lytic
- High incidence of hardware failure and local recurrence with intralesional procedure
- In RARE circumstances excision of solitary bone metastasis may have curative intent

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Bone metastases not a preterminal event

- Patients with bone mets from prostate ca – median survival 40 months and 5 year survival 25%
- Patients with bone mets from breast ca – median survival now 32 months and 5 year survival over 20%
- Patients with liver mets from breast ca – median survival 3 months

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Modes of Presentation

- Skeletal pain
- Hypercalcemia
- Pathological fracture
- Spinal cord compression

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Etiology of pain in skeletal metastases

- Inflammatory (COX-2)
- Neuropathic
- Tumorigenic (endothelin-1)
  - All these usually constant pain, regardless of activity
- Mechanical
  - Often worse with activity, but may be at rest

Investigation of patients with suspected metastatic bone disease (known ca)

- Serum Ca, Mg, Phos, Albumin, ALP
- Plain radiograph of affected region
- Total body bone scan/bone survey/PET
- CT for pelvic/acetabular lesions
- MRI for spine or assessment of soft tissue masses
- If considering surgery, should have c-spine x-rays

4 TENETS OF MANAGEMENT

- 1) Relieve pain
- 2) Preserve/Restore Function
- 3) Maintenance of patient independence
- 4) Control disease progression

- When to NOT operate: when these goals are attainable without OR

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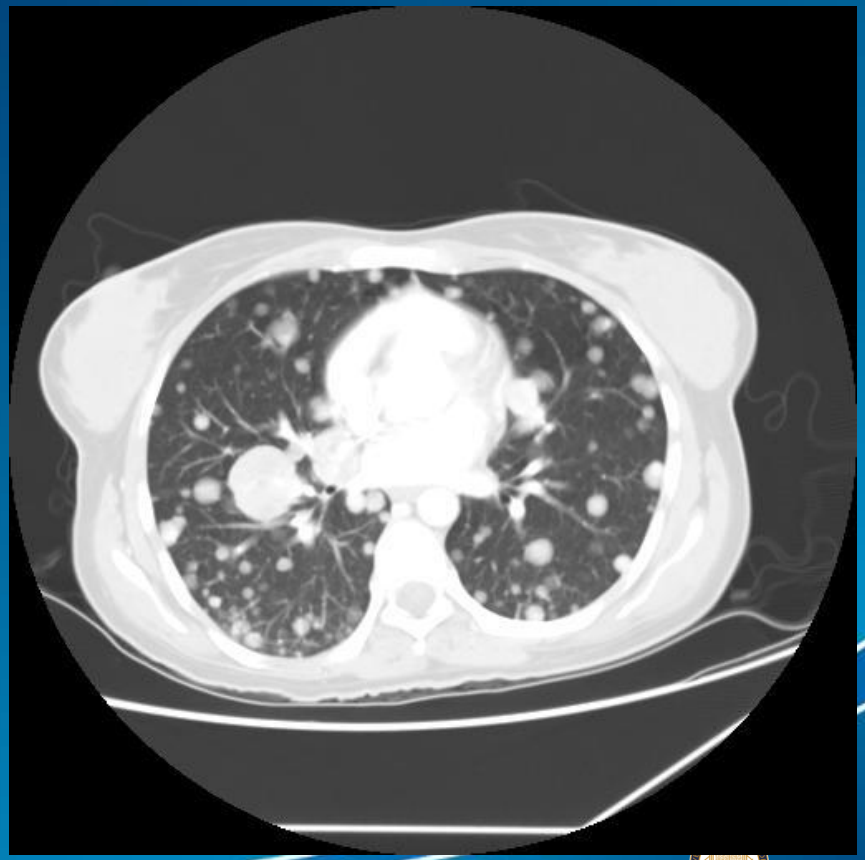
Overall Health of Patient

- Assess visceral and metabolic health
- Consider prior treatment and effect of prior therapy
- Assess longevity



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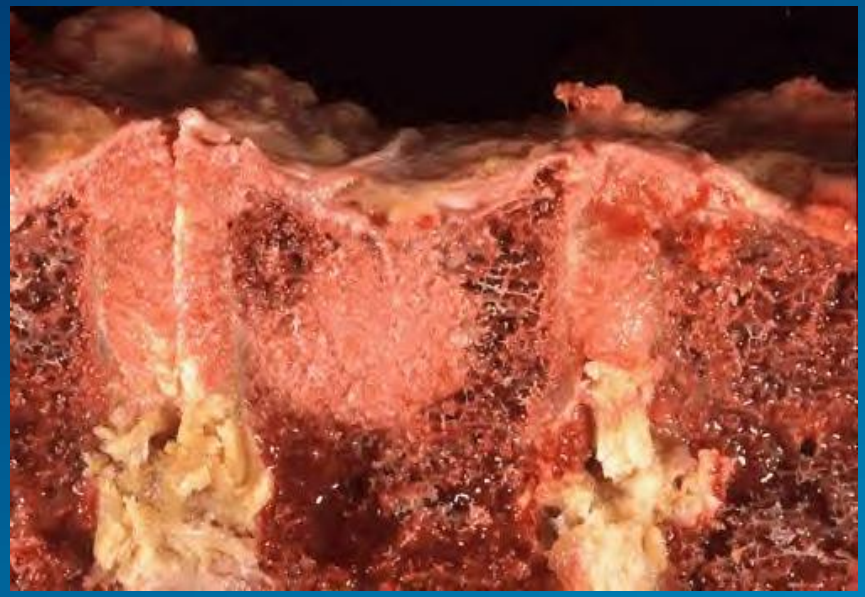
Non-surgical Therapy

- Hormones
- Radiation
- Chemotherapy
- Bisphophonates
- Novel Therapies



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Radiotherapy

- Very effective in breast and prostate cancer
- Extremely effective in hematological cancer
- Less effective in renal cell ca
- One dose (8Gy) vs. 5 doses (20Gy)

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Role of Post-op Radiation after ORIF of Pathologic Fractures

Functional status 1 or 2 (normal use +/- pain)

- 53% S+RT vs 11.5% SA

Second orthopaedic procedures

- 2.9% S+RT vs 15% SA

Overall survival

- median 12.4 mos S+RT vs 3.3 mos SA

Multivariate analysis

- only RT associated with function (p=0.04)

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Take home messages

- Anybody with metastatic bone disease needs radiation
- If the lesion is at risk of pathologic fracture in the lower extremity, operate first, irradiate after
- Otherwise, irradiate first and operate later if necessary

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Hormones

- Prostate and Breast ca
- Effective at various stages of disease
- Effective prior to chemotherapy

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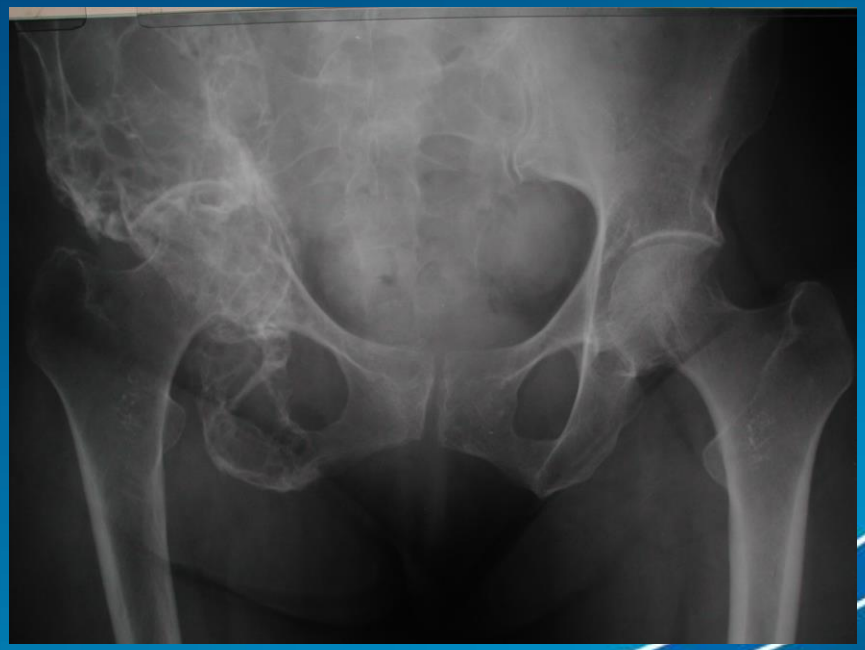
Chemotherapy

- Extremely effective in lymphoma, myeloma
- Very effective in breast & prostate
- Effective in small cell ca
- Ineffective in squamous lung or renal cell



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Bisphosphonates

- Effective in myeloma, breast, prostate
- Effective in hypercalcemia

Bisphosphonates: Mechanisms of Action

- Inhibition of osteoclast maturation, recruitment, and function
- Reduced production of cytokines (eg IL-6)
- Direct anti-tumor activity (static and lytic)
- Inhibition of tumor cell dissemination, invasion, and adhesion to bone matrix
- Antiangiogenic effects
- May be synergistic with chemotherapy
- Additive effect with radiation

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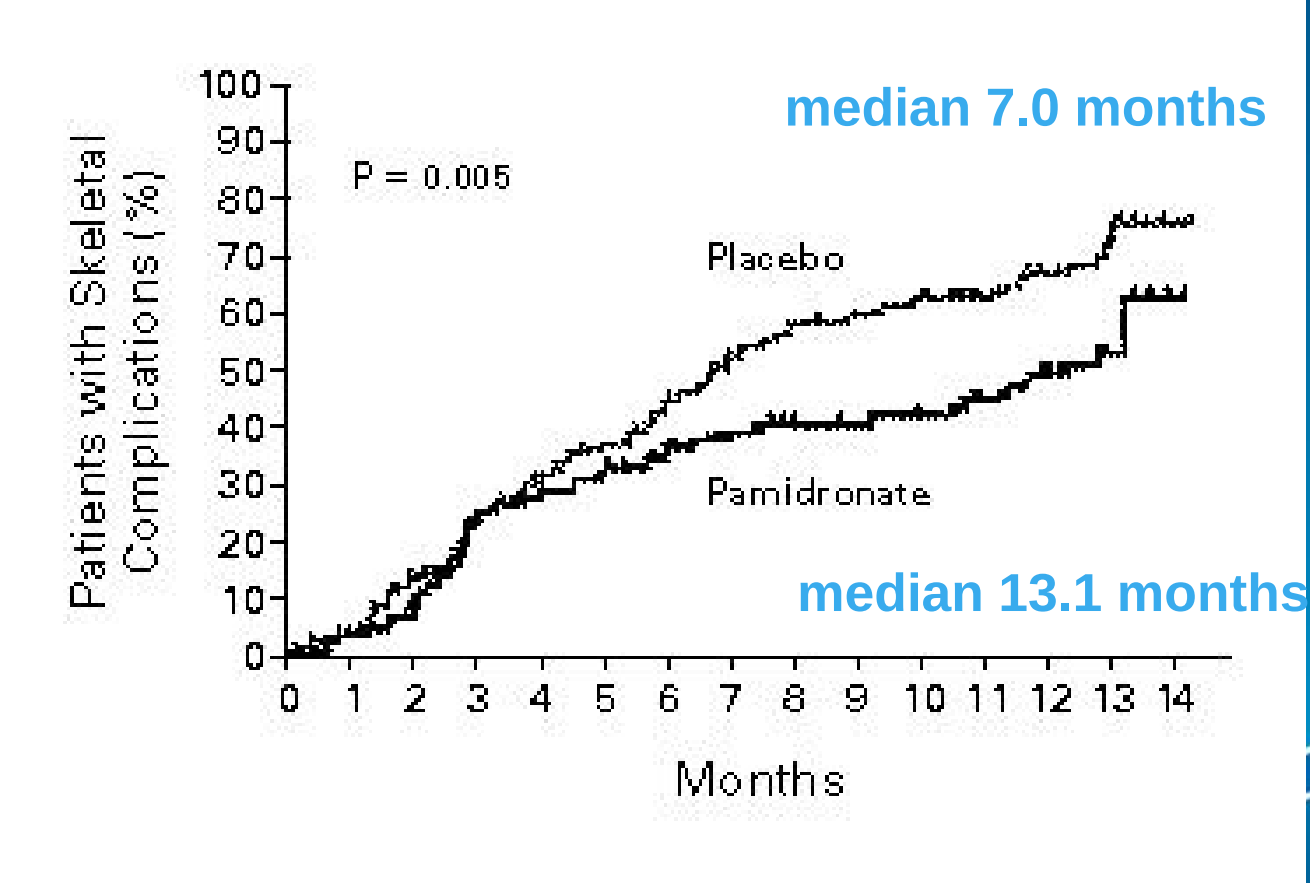
Bisphosphonates: Breast Carcinoma



Hortobagyi et al, NEJM 1996

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Reduction in New Metastases in Breast Cancer with Adjuvant Clodronate Tx

Endpoint	Clodronate	Control	P-value
Distant Mets	21	42	<0.001
Bone Mets	12	25	0.003
Visceral Mets	13	27	0.003
Deaths	2	22	0.001

Diel et al, NEJM 1998

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Bisphosphonates cont'd

- ASCO Recommendation
- For patients with plain radiographic evidence of bone destruction, 90 mg IV pamidronate over 2h, q monthly
- Zometa-also monthly but in 15 minutes – more $
- Denusimab – better?? – mAb against RANK-L

  Lipton etal. "Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomized, phase 3 trials.". European journal of cancer 48 (16): 3082–92. doi:10.1016/j.ejca.2012.08.002
- Bone destruction on other imaging is reasonable evidence to commence Rx
- Likely all patients with metastatic bone disease, regardless of primary, should commence therapy

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Novel Therapies

- Metastases likely arise due to receptor ligand interaction in bone – targeted therapies
- RANK –RANK l interaction
- Expression of certain integrin subtypes (αvβ3) in breast cancer cells lead to 20-fold increase in bone metastases anti – integrin trials are ongoing
- Anti-angiogenic factors in renal cell ca
- Stimulation of COX-2 production in breast cancer cells enhances bone metastases

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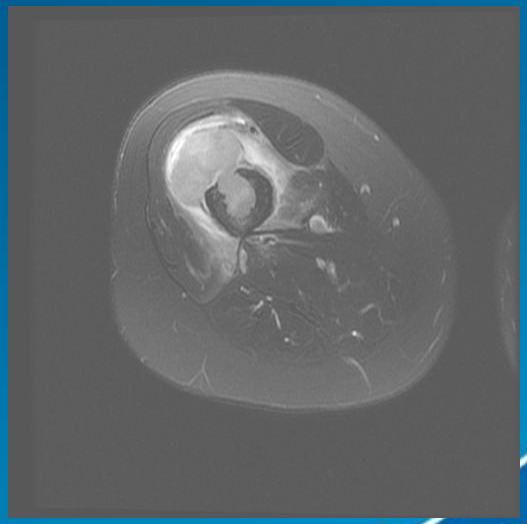
Pain in Bone Metastases

- Important to discern pattern and therefore likely cause of pain
- Mechanical pain – stabilization
- Tumorigenic or inflammatory pain – radiation/chemo or removal of tumor



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Predicting Pathologic Fracture Risk

Indications for Prophylactic Fixation:

- > 2.5 cm
- >50% cortical destruction
- pain unresponsive to radiation
- pathologic lesser trochanter fracture

Bertin, JBJS 1984, 66A:770
Harrington, JBJS 1981, 63A:653

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Predicting Impending Pathologic Fractures: Mirels Scoring System

	Score		
Variable	1	2	3
Site	UE	LE	prox femur
Pain	mild	moderate	functional
Lesion	blastic	mixed	lytic
Size (dia)	<1/3	1/3-2/3	>2/3

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Predicting Impending Pathologic Fractures: Mirels Scoring System

Score	Fracture Risk	Treatment
7	4%	Radiate
8	15%	?
9	33%	Operate
10	72%	Operate

score > size > pain > lesion > site

Prophylactic fixation improves outcomes

	Prophylactic	Completed Fracture
Blood Loss	438cc	636cc
Length of Stay	7d	11d
% discharge home	79%	56%
% ambulatory	35%	12%
1 year survival	35%	25%
2 year survival	19%	10%

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Metastatic Bone Disease Orthopaedic Considerations

- Assume the Fracture Will NEVER Heal
- Plan for Immediate Unrestricted Activities
- 1 Operation Per Bone
- Cement
- If Secure Fixation is Not Possible, RESECT and RECONSTRUCT
- Ask yourself – if I fix this fracture, will I allow the patient to get up and walk on it – if not, consider replacement

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Femoral Neck Lesions

- Is there any point in fixing prior to fracture?
- If the lesion is painful, should you do a fixation operation?

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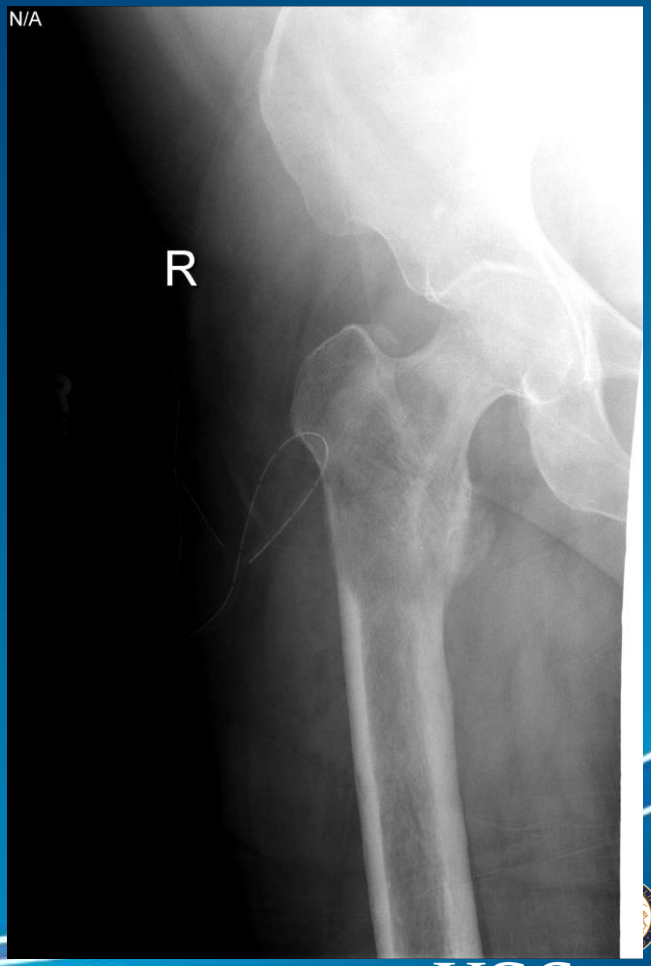
Inter-trochanteric Zone

- High risk of fracture- especially if lesser is off
- Generally disease spreads into head
- Fixation device with cement for early disease
- Usually arthroplasty



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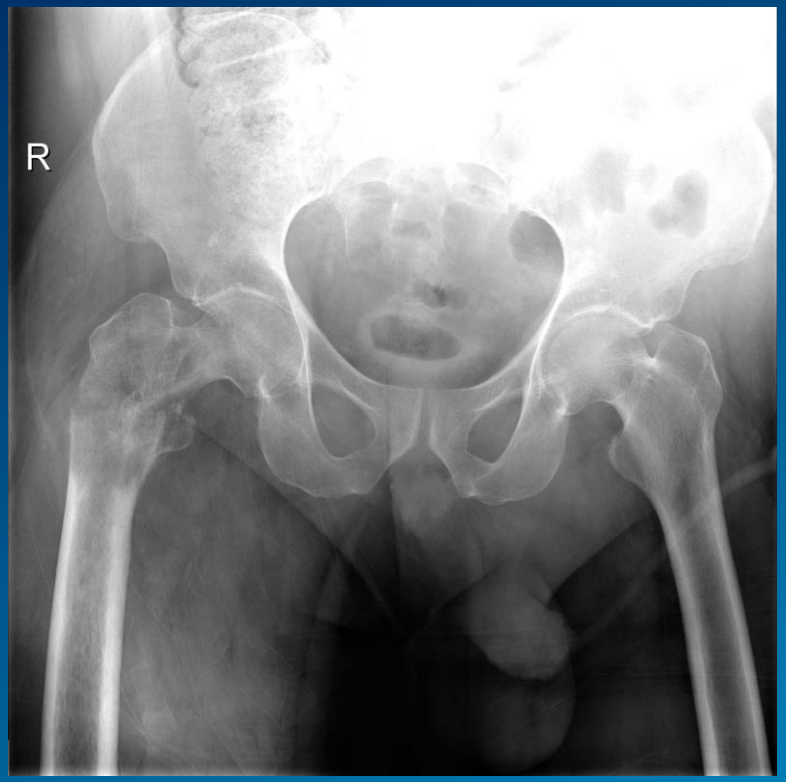

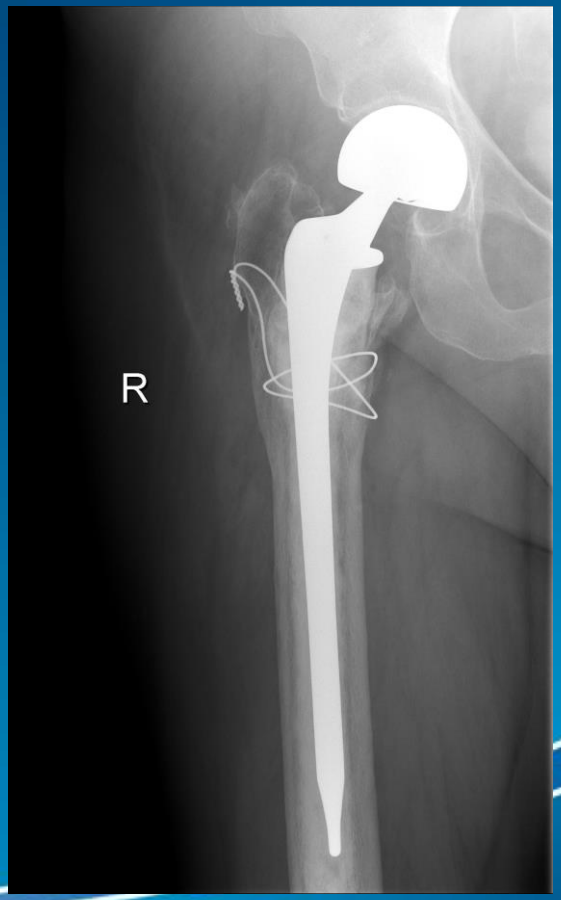

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Subtrochanteric

- Major risk for fracture
- Most important to recognize lesion prior to fracture
- If no fracture, can stabilize with recon nail if neck not involved

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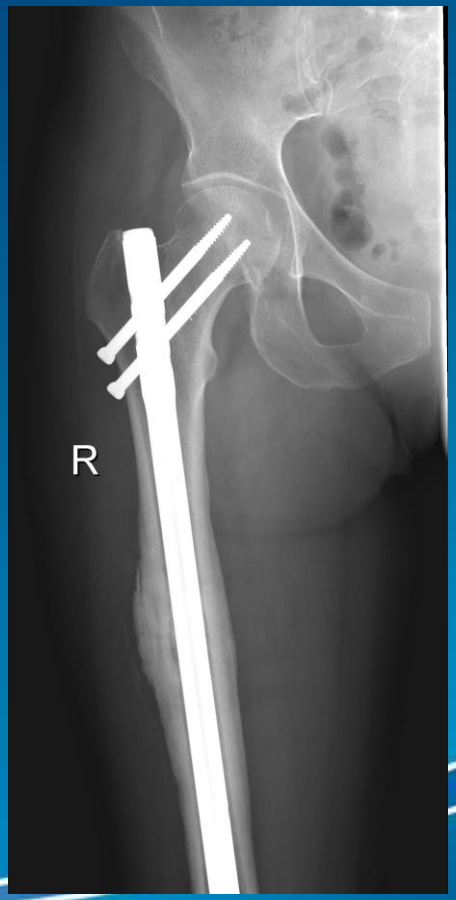

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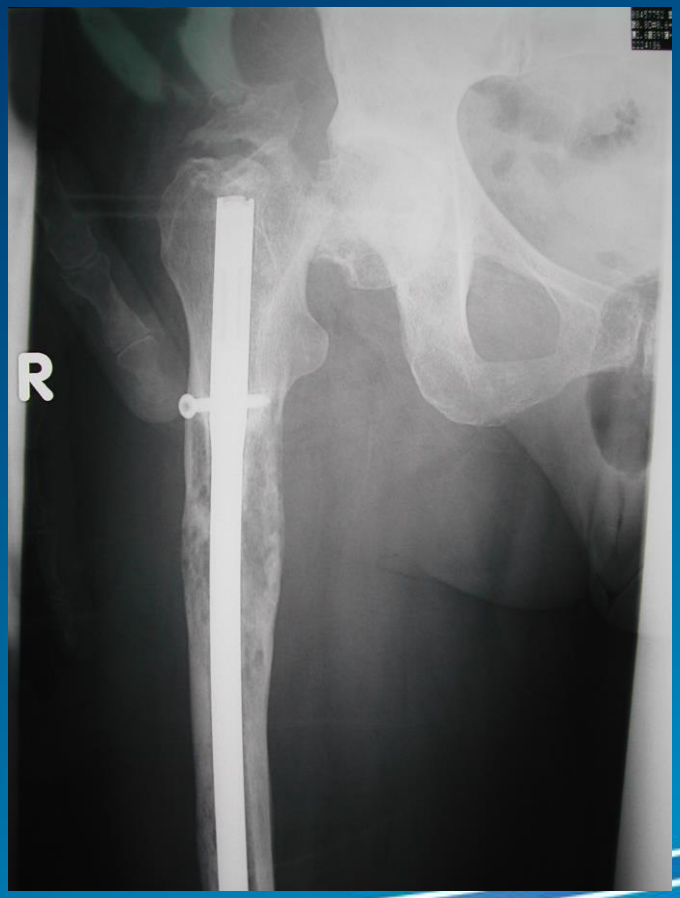
Always use a recon nail…



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Subtrochanteric

- Extension to femoral neck
- Can replace with standard hip implant
- If lesion extends down femur use a long stem

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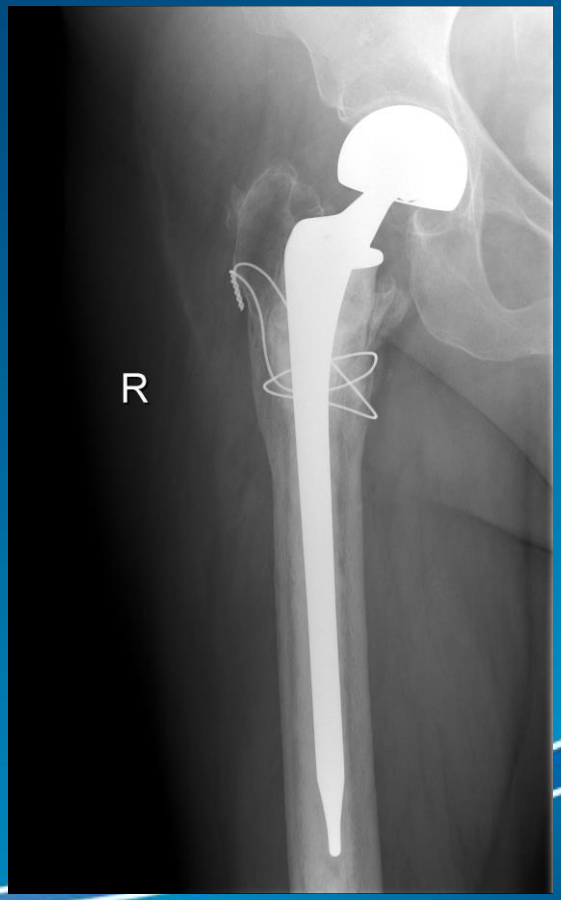

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Beware of metastatic renal cell carcinoma

- Significantly higher likelihood of hardware failure
- Should consider curettage, cement after embolization
- Alternative - replacement

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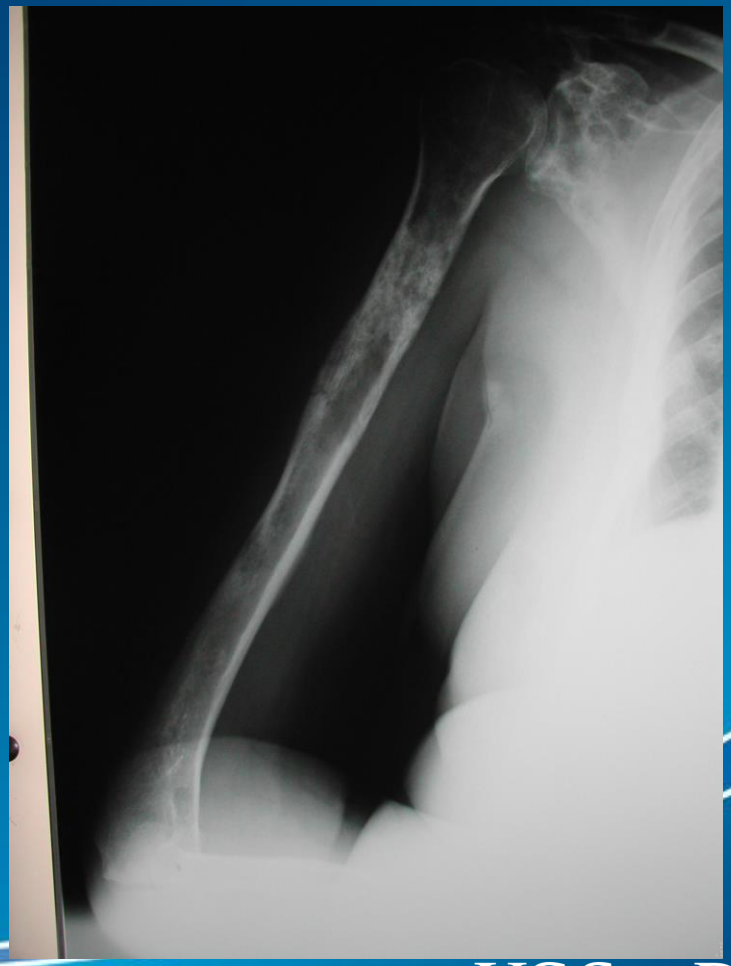
Impending fractures

- Unlike in femur, impending fractures in humerus can be treated with radiation and sling/brace
- Reserve surgical management for symptomatic lesions refractory to radiation/chemo



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Pathologic fractures

- Treatment controversial
- In undisplaced fractures through lesions responsive to radiation (lymphoma, myeloma, breast) functional bracing can occasionally be associated with successful healing
- Majority require surgical management

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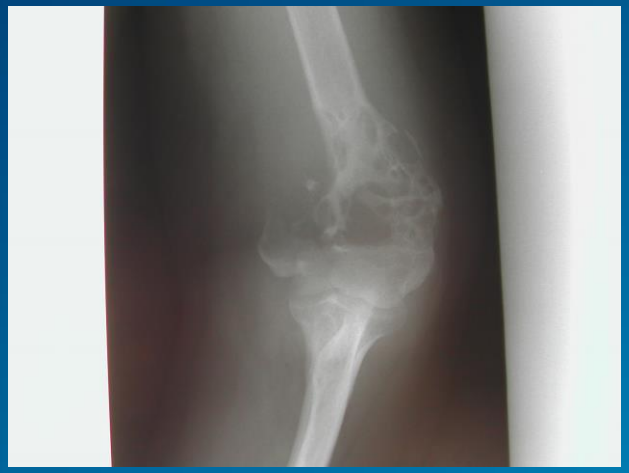
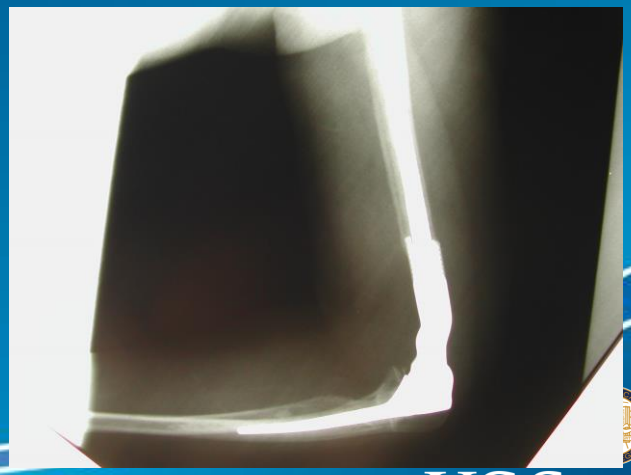
Proximal & distal fractures

- Can usually be managed by prosthetic replacement
- Retention of humeral head with tuberosities associated with better function





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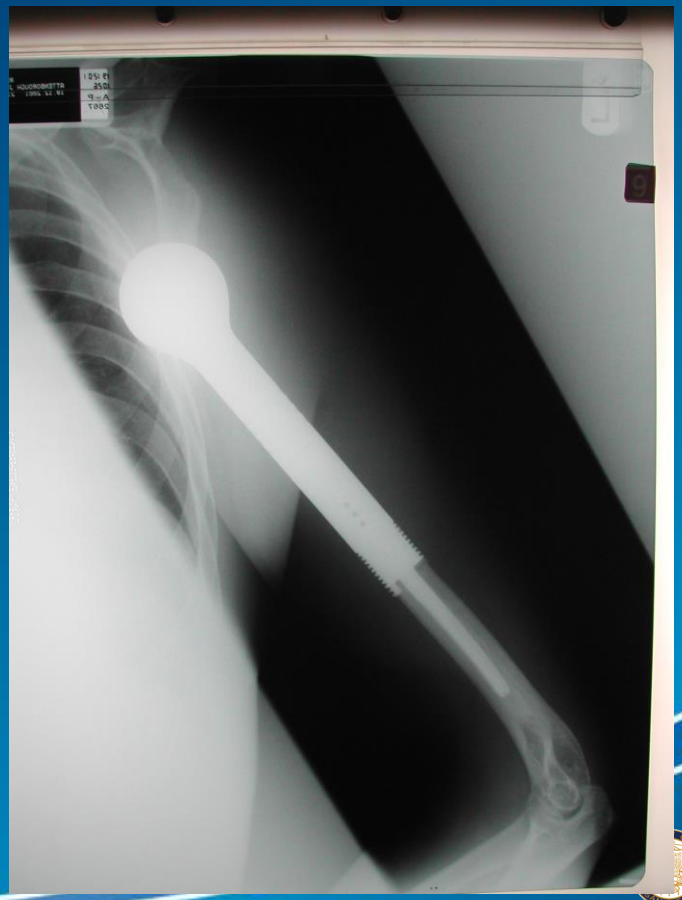

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Diaphyseal fractures - Nail vs. plate

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Remember – not every pathologic fracture in someone over 50 is from metastatic disease!
Biopsy if unclear prior to nailing

The Dilemma

- Because of better treatment of metastatic disease, patients are living longer, and therefore are likely to present with more advanced skeletal disease and pathologic fractures
- Longer survival also means that implant choice has to account for the expected function and life expectancy
- These patients should be treated aggressively to provide maximal quality of life for their entire lifespan

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Future Directions

- Better understanding of the bone-tumor interface biology and the specific drivers that allow homing of tumor and metastasis to bone
- 3D reconstructive software to predict fractures
- Human diseases xenografts are key to advancing our understanding of disease in niche specific environments
- First successful human prostate cancer metastatic to bone model

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